WP2 Framework for pharmacoepidemiological studies

WG1 Databases

Study Protocol

Calcium Channel Blocker Treatments and Cancer Risk. A methodological protocol to compare the results between databases, across designs: Evaluation of the impact of design/database/population differences on the outcome of the studied association

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WG1 Drug AE group

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Contents

1. Context of the studies

The studies described in this protocol are all performed within the framework of PROTECT (Pharmacoepidemiological Research on Outcomes of Therapeutics by a European ConsorTium) Workpackage 2 and Workgroup 1. Primary aim of these studies is to develop, test and disseminate methodological standards for the design, conduct and analysis of Pharmacoepidemiological (PE) studies applicable to different safety issues and using different data sources. To achieve this, results from PE studies on 5 key adverse events (AEs) performed in different databases will be evaluated. Therefore, emphasis will be on the methodological aspects of the studies in this protocol and not on the clinical consequences of the association under investigation. The standards to develop will contribute to decrease the discrepancies in results from different studies in the future and increase the usefulness and reliability of these studies for benefit-risk assessment in the EU.

2. Background

Within WP2, five possible adverse event – drug pairs have been selected for analyses; one of these includes the possible role of calcium channel blockers (CCBs) in the risk of cancer. Analyses will address the hypothesis that CCBs modify the risk of cancer (all forms of cancer combined and various groups of cancers).

This hypothesis will be investigated using two sources of data: the UK General Practice Research Database (GPRD) and the Danish national databases. Investigations in the UK may also use The Health Improvement Network (THIN). The databases are described in more detail in the 'Sources of data' section below.

Conducting studies on the possible association between CCBs and cancer using a pharmaco-epidemiological approach based on data collected in existing databases and cancer registries is challenging. The challenge lies in working within the limitations of the available data (in terms of quality and completeness) and simultaneously maximizing the value of the available data through thoughtful study design and statistical analysis.

CCBs represent a chemically and pharmacologically diverse group of agents that are widely used for the treatment of hypertension and angina. It has been proposed that CCBs may interfere with apoptosis, leading to an increased potential for abnormal cell proliferation and tumor growth (1). The underlying biological mechanism for this effect is thought to be linked to the role of transmembrane Ca2+. This hypothesis has been critically reviewed and results have shown that the action of CCBs on apoptosis are complex with both increases and decreases in intracellular Ca2+ linked to this form of programmed cell death (2). CCBs have also been shown to inhibit apoptosis in certain non-transformed cell lines but promote apoptosis in other non-transformed and transformed cell lines. The results from non-human genotoxicity studies have shown no link between CCB use and tumor development (2).

Epidemiologic studies have also provided inconsistent results. While only a few follow-up analyses reported an increased risk for all cancer (3-5) or breast cancer (6-9), further observational studies have so far provided no evidence to support the hypothesis that long-term use of CCBs might be carcinogenic (10-17). As a whole, these studies have been limited by lack of statistical power and/or inadequate methods for defining the exposure window of antihypertensive treatment in relation to the index date (cancer outcome), making the establishment of a causal relationship between CCBs use and risk of cancer problematical. Studies often assumed a relatively short period of CCB use (usually between 2 months and 1 year) before entering the study as users. In other cases, information on the use of CCBs was only available at study entry or during follow-up. Overall, most studies were limited by follow-up periods that could be considered too brief to measure a carcinogenic effect. The vast majority of studies collected information from electronic medical or administrative databases.

In 1996, Pahor et al. reported an overall 2-fold increase in cancer risk associated with use of CCBs in a cohort of 750 elderly subjects with hypertension (3). When compared against non-users, the risk of developing cancer increased approximately 1.7 times for CCB users in a subsequent reanalysis of the same cohort using different inclusion criteria (1.72 (95% CI 1.27-2.34) (5). Fitzpatrick et al., in a study including 3,198 women aged 65 years or more, reported a 2.6-fold increased risk of breast cancer for CCBs users compared with non CCB users, with a higher relative risk (RR) reported for women exposed to both CCBs and estrogen replacement therapy (hazard ratio, 4.48; 95% CI, 1.58 - 12.75; based on four exposed cases) (6). While these studies were limited to varying degrees, several features are worth noting: (i) the strength of the association appeared to be dependent on daily dosage or cumulative dose, ranging from no association in users of low dosages to a 2-fold (or possibly higher) increased risk in users of higher dosages; (ii) the time period to the appearance of this association appeared to be at least 2 to 3 years; (iii) an association with a higher risk of cancer was found primarily for verapamil (4), while no such relationship has been reported for diltiazem; and (iv) no highly consistent associations were shown with specific cancer sites or histological types (7). Li et al. found that the use of particular types of antihypertensive medications, including immediate-release CCBs and certain diuretics, were associated with a modest increased risk of breast carcinoma among 975 women aged 65-79, with an odds ratio of 1.5 (95% CI, 1.0 - 2.1) for CCBs (8). Some studies involved a large number of multiple comparisons which were not accounted for in the analysis, so that some of the positive associations may have been chance findings.

A more recent case-control study on commonly prescribed medications and breast cancer, primarily anti-hypertensives and anti-depressants, described a slightly increased risk of breast cancer associated with use of CCBs, but there was no dose response relationship with increasing duration. Breast cancer risk was not associated with use of antidepressants, beta blockers, corticosteroids, or non-steroidal anti-inflammatory drugs (9). However, most case-control analyses comparing the risk of developing cancer among patients with hypertension on treatment with CCBs or other antihypertensive medications such as angiotensin-converting enzyme (ACE) inhibitors or β-blockers have shown a similar risk for malignancy among users and non-users of CCBs (9-16). The study by Jick et al. (11) found a relative risk for all cancers combined of 1.27 (95% CI 0.98-1.63) among CCB

patients with hypertension and 0.79 (0.58-1.06) among ACE inhibitor patients with hypertension (the comparison group in both cases were patients using β-blockers). This result was considered unlikely to be causal since there was no increase in risk with increasing duration of CCB use.

Consecutive large-scale, population-based cohort studies conducted in Denmark (18-20) contributed to the increasing evidence of a lack of association between the use of CCBs and cancer, supported by additional cohorts available to date (21-24). Limitations of these studies included the use of self-reported exposure data (21,23) and lack of covariate information on important confounders, such as smoking, BMI and alcohol use (18-20; 24).

Cohen et al. carried out three successive interviews in a cohort of community dwelling individuals aged 65 - 105 years in North Carolina (22). The proportion of individuals who reported having taken a CCB in the previous two weeks (3 CCB classes included) was 3.8% (133/3511) in 1986, 8.5% (259/3048) in 1989 and 13.9% (343/2126) in 1992. Our study will differ from the Cohen et al. interviews in several respects, notably the ethnic composition of the study population, the more recent time period covered and the definition of CCB user status (first-time users).

The current study aims to learn from the experience, strengths and limitations of previous research to present a best-practice approach to addressing the hypothesis in question. Combined with the objectives of the PROTECT program, we hope that this study will help to provide a framework for guiding methodological choices in future research and contribute to increasing the usefulness and reliability of pharmacoepidemiological studies for benefit-risk assessment and decision making.

3. Objectives

The primary objective of the study is to investigate the possible association between use of CCBs and risk of all forms of cancer combined, among adult patients (18 to 79 years of age during the study period, 1 January 1996 and 31 December 2009). The study will be conducted using three databases with different study designs (descriptive, cohort, population based cohort study and nested case-control) across different databases (GPRD, THIN, Danish databases) and to compare the results between databases, across designs to evaluate the impact of design/database/population differences on the outcome of the studied association.

However, a CCB drugs descriptive analysis will be conducted in the 7 databases to be studied in the WP2-WG1.

Secondary objectives are to investigate the potential association between use of CCBs and risk of all forms of breast cancer in women; all forms of prostate cancer; and all forms of colon cancer using the same age groups and databases).

4. Methods

4.1Data Sources

Three databases are proposed in this study protocol: GPRD (and the National Cancer Registration System linkage) and the Danish databases as a high priority databases and THIN as a low priority database to hold this study.

From GPRD and THIN patients will be identified from general practices in England, Scotland, Wales and Northern Ireland.

From Denmark patients will be identified using the Register of Medicinal Products Statistics.

In addition, a CCB drugs descriptive study will be also conducted in the other databases studied in WP2-WG1, that are the Mondriaan database (Netherlands), the Bavarian claims database (Germany) and the BIFAP database (Spain).

4.1.1 General Practice Research Database (United Kingdom)

The GPRD is the largest ongoing health care database available in the UK since 1987. The database contains more than 4.8 million active research quality patient data from more than 590 general practices in the UK (England, Scotland, Wales and Northern Ireland). The validity of a wide range of drug exposure data is routinely tested. External record linkage is available to other NHS datasets.

The National Cancer Registration System covers the whole of the UK and currently involves 11 cancer registries, each covering populations of between approximately 1.65 and 13.8 million people. Cancer registration in England is conducted by eight regional registries, which also submit a standard dataset of information to the Office for National Statistics (ONS), for collation of national cancer incidence data. Northern Ireland, Scotland and Wales each have one, national cancer registry. The information is acquired from a variety of sources including hospitals, cancer centers, treatment centers, hospices, private hospitals, cancer screening programs, other cancer registers, general practices, nursing homes, death certificates and Hospital Episode Statistics (HES). In many instances, more than one source of information is available to cancer registries from a single organization, for example hospital patient information systems (PAS), pathology laboratories, medical records departments and radiotherapy databases. Processing of the data involves checking the validity and completeness of the data and a complex process of clinical data linkage and consolidation. For this current study, we aim to explore the feasibility of using data from the English and Scottish Cancer Registration regions.

4.1.2 Danish National Database (Denmark)

The Danish national databases can provide computerized records of: sociodemographic factors, visits to general practitioners and to hospital, the dispensing of medication by pharmacies, and mortality for the Danish population (5.5 million people). All registers can be linked using the civil registration person number, which is given to all inhabitants of Denmark. All registers are nationwide and the coverage is close to a 100 percent, and the validity is very high.

Statistics Denmark keep a register with records of income, degree of education, working status, and marital status. The National Board of Health keeps registers as: 1) the Danish Civil Registration

System, the National registration of patients which covers all inpatient stays from 1977 to 1994 and from 1995 it also includes all outpatient visits to hospitals, outpatient clinics, and emergency rooms. Upon discharge, the physician codes the reason for the contact using the ICD system. 2) The National Health Insurance Service Registry. The register does not contain ICD codes for the contacts but codes for the nature of the contact (regular check-up visit, routine vaccination in children). 3) The Cause-of-death Register. The Danish Medicines Agency keeps a National Pharmacological Database of all drugs sold throughout the country from 1994 onward. Prescription medicines include information concerning the individual who redeemed the prescription. The register does not contain information at an individual level of medicines dispensed hospitals. Any drug bought is registered with ATC code, dosage sold, and date of sale.

4.1.3 The Health Improvement Network (United Kingdom)

The Health Improvement Network (THIN) is collaboration between two companies; In Practice Systems Ltd. (INPS), developer of Vision software used by general practices in the UK, and EPIC, provider of access to data for use in medical research. THIN data are collected during routine medical practice and regularly delivered to a central database. THIN data collection started in 2003, and the database currently contains the electronic medical records of almost 8 million patients (more than 3 million active patients) collected from over 386 general practices in the UK. THIN database consequently covers more than 5.7% of the UK population.

Patient data are arranged in five standardized files per practice: patient, medical, therapy, additional health data and a file to enable data linkage containing postcodes. Additional data can be collected using the Additional Information Service which includes: questionnaires completed anonymously by the patient or general practitioner, copies of patient-related correspondence, a specified intervention (e.g. a laboratory test to confirm a diagnosis) and death certificates.

4.1.4 Mondriaan (The Netherlands)

The Dutch Mondriaan project is a private-public collaboration funded by the Dutch TOP Institute Pharma. Under the umbrella of Mondriaan, the participating databases currently include: the Dutch General Practitioner (LINH) database, The Almere Health Care (ZGA) database, The General Practitioners of Utrecht (HNU) database and The Leidsche Rijn Julius Health Centre (LRJG) database. The cumulative number of persons having data in Mondriaan reached around 1.4 million comprising mainly of GP data complemented by pharmacy dispensing data and linkages to survey data. The four databases within Mondriaan have different starting dates and scope of data. LINH is the Netherlands Information Network of General Practice and it holds a longitudinal data on morbidity, prescription, and referrals. The GPs record data on all patient contacts, including diagnoses, referrals and prescriptions. The ZGA is a GP and pharmacy database. The HNU is a GP database set up in 1995 and includes data dating till the end of 2005. The LRJG is a GP database with a linkage to additional survey records. Survey information is periodically up-dated through follow-up, including information on a wide range of health and lifestyle related variables.

4.1.5 BIFAP (Spain)

BIFAP (Base de datos Informatizada para estudios Farmacoepidemiologicos en Atencion Primaria – A computerized database of medical records of Primary Care) is a non-profit research project operated by the Spanish Medicines Agency (AEMPS), a public agency belonging to the Spanish Department of Health, with the collaboration of the Spanish Centre for Pharmacoepidemiological Research (CEIFE). The project has started in 2003 having the goal to achieve a pool of collaborators in the range of 1000 general practitioners and pediatricians. Currently, 1190 physicians (995 GPs and 195 pediatricians) from 9 different autonomous communities in Spain collaborate with BIFAP and send their data to BIFAP every 6 months. BIFAP database includes clinical and prescription data from around 3.1 million patients covering around 6.8% of Spanish population. The AEMPS has renewed its funding to BIFAP for project consolidation, for validation of information included in the databases, in addition to performing epidemiological studies.

4.1.6 Bavarian Claims Database (Germany)

The Bavarian statutory health insurance physicians' association is based on accounting information of the Bavarian physicians. This German database includes a population-based data on diagnosis and medical services, covering 10.5 million people. It is a pharmacy (claims) database linked to outpatient treatment data through general practitioners and specialists. The database exists since 2001 and covers 84% of the Bavarian population excluding those with private insurance.

4.2Period of valid data collection

The study population will consist of CCB first-time users and non-users from 1 January 1996 to 31 December 2009, aged 18 to 79 years. CCB use before 1994 is not known, and patients without CCB use during 1994 and 1995 will be considered as non-users user prior to the study and therefore eligible to the study. Concerning GPRD and THIN/BIFAP patients are included if they have Primary Care Practice history of at least two years and at least one year's computerized GPRD/GP prescription history.

Patients with any cancer recorded in the GPRD or The Danish National registration of patients prior to cohort entry will also be excluded from the analysis. Cancer diagnoses will be determined using Read codes (refer to 'Definition of outcomes' below), ICPC codes and ICD-10 codes.

We will consider defining further selection criteria for the cohort study, to balance CCB user and non-user cohorts with respect to a number of key variables such as age, sex, date of study entry, and health services utilization.

4.2.1 Definition of exposure

Treatment with CCB will be assessed using the GPRD product code, multilex code, drug substance name and British National Formulary (BNF) code and ATC-codes in the Register of Medicinal Products.

The descriptive study will require one prescription to define exposure. Exposure in the cohort study and the nested case-control study will be defined as cumulative use of CCB. The cumulated exposure will be derived from the total amount of DDD, the number of prescriptions and the period the prescriptions covers (package size).

CCBs will be divided into three exposure types, depending on the main treatment effects. Table 1 describes these exposure groups.

4.2.2 Definition of outcomes

Outcomes will include all forms of cancer combined, as well as breast cancer in women, prostate cancer and colon cancer analyzed separately. Cancer diagnoses will be determined using Read codes, ICPC codes and ICD-10 codes.

Initial case definition criteria have already been assessed in the GPRD, by a medical review of all Read codes attributable to cancer outcome (blinded to exposure status). Our review found that 2,688 out of 4,154 (64.7%) Read codes were appropriate for use in this study. The unused Read codes were principally excluded where: (i) the tumor was benign, (ii) the site of the primary cancer was unknown, (iii) the tumor was metastatic.

We strongly believe that the study design using the GPRD database can be improved further by validation of cancer outcomes using the HES and/or National Cancer Registration System. This validation would strengthen the basis of case identification, as well as potentially flagging cases that may not have been recorded in the GPRD. As all cancer are recorded in the Danish database, this is not a problem in the Danish data.

5. Study Designs

5.1Descriptive study

The period prevalence and point prevalence of CCB use (defined as ≥ 1 prescription for a CCB) will be described by age group (0-9,10-19,20-29, 30-39, 40-49, 50-59, 60-79) and sex or by indication for the period 2000 to 2009 (ten years). Period prevalence and point prevalence will also be presented for the years 2000, 2004 and 2009. Period prevalence of patients having ever used a CCB will be presented by number of prescriptions (1, 2-4, 5-11, 12-23, >23) for 2000 to 2009.

The period prevalence of cancer will be presented by age group (10 year categories) and sex for the period from Jan 1999 to Dec 2001 inclusive. The yearly incidence of cancer will be presented by age group (10 year categories) and sex from 2000 to 2009. Incidence and prevalence will be presented for all forms of cancer combined, as well as for breast cancer, prostate cancer and colon cancer described separately. The table below shows in which databases descriptive studies on drugs in the one hand and on cancer in the other hand will be held.

Table 1. Databases where descriptive studies will be held

Calcium channel blockers and cancer		
	Descriptive studies on drugs	Descriptive studies on disease
Mondriaan	yes	No
GPRD	Yes	Yes
THIN	Yes	Yes
Bavaria	Yes	No
Denmark	Yes	Yes
BIFAP	Yes	Yes
IMS Germany	Yes	No

5.2 Cohort study

We will use a cohort study design identifying CCB first-time users and CCBs non-users between 1 January 1996 and 31 December 2009. Left censoring date will be the latest of the following: the date the practice became up to research standard, the date the patient was enrolled in the practice or the date the practice was enrolled in the database. The Danish database: 1996.

Index date will be the date of the first registration of cancer, in the Danish data this will be the registration in The National Registration of patients, whereas in GPRD the index date might be at the GP or as in the Danish data in a cancer registry registered during hospitalization. CCB non-users will be drawn as a random sample matched on age and gender. Members of each cohort will be followed from entry to the study until the earliest of: diagnosis date of study outcome (cancer), date of disenrollment from database, reaching 80 years of age, date of death, or end of study period.

The cohort study will employ various methods to assess the risk of cancer outcomes by CCB user status. CCB users will be compared with CCB non-users in terms of their incidence of cancer outcomes. Initial analysis will be made comparing cancer occurrences from a period of six months to one year of cohort entry. We will also analyze duration and dose of CCB treatment in relation to cancer outcomes as well as the cumulative number of prescriptions.

As different medicines are with different amount of DDD as well as there is a different amount of tablets in a package a new treatment episode will be considered when an interval of days derived from prescribed medicine pr. day timed the number of tablets in the package (package size) timed the number of packages (treatment period) from one prescription to the next exceeds more than:

Treatment period of 30 days; 10 days

Treatment period of 60 days; 20 days

Treatment period of 90 days; 30 days (no treatment period can exceed 90 days).

We will compare cancer outcomes occurring six months – 1 year, 1-4 years and >5 years following initiation of CCB therapy. This will take into account the lag-time for clinical onset of cancer and the diagnose delay.

Preliminary data analysis will employ standard methods such as non-parametric univariate and bivariate analyses. Further analyses will include Cox proportional hazard models with time-dependent covariates.

Patients who changed therapy during follow-up will present a challenge to the analysis. All CCB prescription data will be collected together with dates of use and change. This will allow periods of different exposures to be pieced together for the analysis. We plan to employ state-of-the-art statistical methods including Cox-regression analysis (including use of time dependent models) and ridge regression (useful when dealing with co-linearity).

If CCB use is fairly ubiquitous, it may be difficult to obtain sufficient patients to form a reference group of CCB non-users. Therefore, we may need to perform an analysis based on internal comparison between quartiles of CCB exposure to demonstrate possible dose response effects.

To account for switching of CCB exposure, we could conduct an analysis that estimates the relative risk of cancer(s) according to cumulative exposure to CCB. We may use the number of CCB prescriptions during the follow-up period to provide an estimate of the cumulative CCB exposure, and pool person-time with similar exposure categories (defined as number of prescriptions) together. This analysis will account for changes in CCB exposure over time by assigning follow-up time to categories defined by the accumulated number of prescriptions. We will incorporate covariate adjustment in these analyses, since changes in therapy may have been related to covariates. Multiple CCB prescriptions and unexposed person-time will be summed to make the total observation time for each subject and for all subjects together.

Since CCB therapy may vary over time as there may periods without therapy another approach will be to try to treat each interval between waves as one observation (subject interval). This approach is equivalent to the algorithm that all subject intervals are pooled as if the information recorded at each interval is a new observation for evaluating cancer risk. “The technique is a generalized person-years approach in that it treats each observation interval (of equal length) as a mini-follow-up study in which the current risk factor measurements are employed to predict an event in the interval”(25).

5.3Population based Cohort study

The population-based study will describe prevalence of CCB use and prevalence and incidence of cancer outcomes within the study population defined above, over the study period. In order to be more representative of the population, all patients with a history of cancer before the start of the study will be included in the analysis.

Cox proportional hazard analysis with time dependent covariates will be used to calculate RR and 95 % Cl to compare cases and controls. The analysis will face the same challenges as the cohort study. Exposure will be as in the cohort study:

Patients with >= 1 one prescription of CCB

Cumulated exposure to CCB

Analysis on the three main treatment groups

Outcome will be cancer occurring six months – 1 year, 1 – 4 years after exposure and >5 years after beginning of treatment.

The challenges with patients changing treatment will be addressed as in the cohort study.

5.4Nested case-control study

We will use a nested case control study design identifying cases of cancer outcomes between 1 January 1996 and 31 December 2009, and matching them on a ratio of 1:4 with controls that had not yet developed any form of cancer before the date of cancer diagnosis of the case. Cases will be matched to controls on same age (years) and gender.

Analysis will be made regarding length of use as well as number of prescriptions. Cancer outcome will be defined as six months – 1 year, 1-4 years and >5 years.

Conditional logistic regression analyses will be used to calculate odds ratios (ORs) and 95% CIs to compare cases and controls in terms of exposure to CCBs (<1-year, 1-4 years and >5 years before the date of cancer diagnosis of the case) and duration of CCB use, as well as other potential risk factors for cancer outcomes. If CCB use is fairly ubiquitous, analyses will be based on internal comparisons between quartiles of CCB exposure.

The table below summarizes in which databases the different methodologies will be conducted.

Table 2. Summary of databases and methodologies used for the calcium channel blockers and cancer study

	Cohort*	Nested CC	Pop based CC
GPRD	High	Low	High
THIN	Low	Low	Low
Denmark	High	High	Low
*Cohort of users of CCB initiators and matched cohort of non-users / matched cohort of other antihypertensive users			

6. Covariates

Key variables in the Cox proportional hazards regression and conditional logistic regression analyses will include antihypertensive treatment other than CCB, cardiovascular medication other than antihypertensives, co-prescription data (e.g. post-menopausal hormone treatment, NSAID, immunosuppressants) (see table 9 in the data specification document for description of cardiovascular medication), Body Mass Index (BMI), smoking, alcohol consumption and co-morbidities (e.g. diabetes and asthma / pulmonary disease). Co-morbidity is particularly important

since calcium channel blockers may be differentially prescribed to hypertensive patients in some circumstances (e.g. in patients with asthma, for whom beta-blockers are contraindicated, calcium channel blockers may be preferentially prescribed). We may be able to use socio-economic (SES) status based on ward-level (or postcode) deprivation (Carstairs or Townsend Score) as a proxy for smoking and other health-related behavior, as these variables are known to be highly correlated (25). In the Danish data we intent to use employment status as SES.

Confounders will be treated as time-dependent covariates in the Cox proportional hazard model, in the case-control confounders will be defined at index-date (date of case occurrence). The degree to which covariate data are missing in GPRD will need to be carefully evaluated. Some data consolidation may be achievable through data linkage to the HES database, which would be a valuable exercise. Due to the lack of information in the Danish data on BMI, alcohol and smoking prevalence will be estimated based on Health Interview Surveys according to age, gender, marital status, employment status and geographical location.

7. Adjustment for confounding

7.1 Multivariable model

The multivariable regression models presented for the cohort study and the nested case control study will be adjusted for all potential confounders associated with an increased risk of cancer according to the literature. The model can only be applied if, as a rule of thumb, there are at least 10 events per independent variable in the model. If the number of variables in the model would be too large (<10 events per variable), analysis will be made in order to investigate which parameters have the least impact on the model according to the change in estimation method (26). In order not to exclude any possible confounders we will not rely completely on the change in estimation method. We will make stratified analysis on potential confounders from the literature, even if the normal definition of confounding is not met (27). Analysis for co-linearity will be done.

We will also explore the possibility of using a multivariable technique (propensity score analysis and matching) to achieve a high degree of balance between comparison groups. Propensity scores can be estimated by unconditional logistic regression analyses that incorporate potential predictors of therapy as independent variables in the regression and group status (CCB or comparator) as the outcome. The propensity score can be estimated for each person as the probability of being a member of the CCB group, given membership in the study population and the covariate pattern as predicted by the propensity score model.

7.2 Propensity score modeling

We will also explore the possibility of using a multivariable technique (propensity score analysis and matching according to gender, age) to achieve a high degree of balance between comparison groups. Propensity scores can be estimated by unconditional logistic regression analyses that incorporate potential predictors of therapy as independent variables in the regression and group

status (CCB or comparator) as the outcome. The propensity score can be estimated for each person as the probability of being a member of the CCB group, given membership in the study population and the covariate pattern as predicted by the propensity score model.

8. Instrumental variable analysis

A method that potentially controls for both observed and unobserved confounding is instrumental variable (IV) analysis (25), (26). An IV is a variable that is strongly related to exposure, and only related to the outcome through exposure. Hence, an IV should neither directly nor indirectly through (unobserved) confounders be associated with the outcome. Importantly, if the IV is independent of observed confounders, it is assumed to be independent of unobserved confounders. This is in analogy with the comparability of observed and unobserved prognostic variables between the intervention and control group achieved by randomization in a trial.

A key example of instrumental variable approach in pharmacoepidemiology for the assessment of gastrointestinal complications in relation to COX-2 inhibitors compared to non-selective non-steroidal anti-inflammatory drugs (NSAIDs) has illustrated this approach (27). It may however not be possible to identify valid IVs for every pharmacoepidemiologic research question (28).

We aim to apply IV analysis to assess the unconfounded association between prescriptions for calcium channel blockers and cancer. Several potential IVs will be evaluated, including physician preference (e.g. as indicated by the prescription to the previous patient with a prescription for the same indication), regional variation (e.g. different regions or countries, possibly with different prescribing guidelines), and calendar time (e.g., periods prior to and after establishment of new guidelines) (29), (30). These variables may be related to prescriptions of calcium channel blockers, yet are unlikely to be directly related to cancer risk, nor indirectly through the potential confounder(s) listed in the paragraph “potential confounders”. Estimation will be conducted via a two-stage instrumental variable model (31). This analysis will be a separate from the main analyses described in this proposal and focuses on the (methodological) application of IV analysis in pharmacoepidemiology.

9. Limitations of study designs, Datasources and analytical methods

The most important (potential) limitation to this study relates to the challenge of obtaining quality information on important confounder data (such as smoking, BMI, and alcohol consumption). Pharmaco-epidemiological studies involving cancer as an outcome always have the potential to be confounded by smoking in particular. For breast cancer, analysis will be restricted to women; it is unlikely that we will be able to obtain data on age at menopause and information on oral contraceptive use may be limited. For colon cancer, we are unlikely to obtain information concerning dietary habits (relating to the consumption of fiber, fruit, vegetables and red meat) or

physical activity. The extent to which we will be able to obtain data on family history of cancer is also a major limitation.

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11. Tables of codes

Table 1. CCB exposure assessment

CCB – Main treatment effects (ATC-code[+])	CCB use*
CCBs with direct cardiac effects (ATC-code C08D)	Diltiazem
	Gallopamil
	Verapamil
Non-Selective CCBs (ATC-code C08E)	Bepridil
	Fendiline
	Lidoflazine
	Perhexiline
Selective CCBs with mainly vascular effects (ATC-code C08C)	Amlodipine
	Barnidipine
	Benidipine
	Cilnidipine
	Felodipine
	Isradipine
	Lacidipine
	Lercanidipine
	Manidipine
	Mibefradil
	Nicardipine
	Nifedipine
	Nilvadipine
	Nimodipine
	Nisoldipine
	Nitrendipine

* Defined using BNF categories 2.6.2

[+]http://www.whocc.no/atc_ddd_index/?code=C08

Table 2. ICD-10 codes for Cancer outcome

All cancer types are defined in the ICD-10 as all subgroups of group "C" and some of group "D"

Cancer according to ICD-10 coding	C00 - D48	
Lips, oral cavity and pharynx	C00 - C14	
Digestive organs	C15 - C26	
- Colon	C18	*
Respiratory and intrathoracic	C30 -C39	
Bone and articular cartilage	C40 - C41	
Skin	C43 - C44	
Mesothelial and soft tissue	C45 - C49	
Breast	C50	*
Female genital organs	C51 - C58	
Male genital organs	C60 - C63	
- Prostate	C61	*
Urinary tract	C64 - C68	
Eye, brain and other parts of the central nervous system	C69 - C72	

Thyroid and other endocrine glands	C73 - C75	
Ill-defined, secondary and unspecified sites	C76 - C80	
Stated or presumed to be primary, of lymphoid, haematopoietic and related tissue	C81 - C96	
Independent (primary) multiple sites	C97	
Carcinoma in situ	D00 - D09	
Benign neoplasms	D10 - D36	+
Neoplasm of uncertain or unknown behaviour	D37 - D48	+
* seperate analysis		
+ exluded from the analysis		

(*) separate analysis

(+) excluded from the analysis

Table 3. READ codes for Cancer outcome

Cancer according to Read coding	**Include**	
Malignant neoplasm of lip, oral cavity and pharynx	B0...00, Byu0.00	
Malignant neoplasm of digestive organs and peritoneum	B1...00, , Byu1.00, B803.00, 4M1….,9Ow1.00	
- Malignant neoplasm of colon	B13..00, B803.00, 4M1….	*
Malignant neoplasm of respiratory tract and intrathoracic organs	B2...00, Byu2.00, H51y700	
Malignant neoplasm of bone and articular cartilage	B30..00, Byu3.00	
Malignant neoplasm of connective and other soft tissue	B31..00, Byu0.00, B933.11, A789500	
Malignant neoplasm of skin	B32..00, , Byu4.00, B935.11, Byu5A00, Byu5B00, 4M7…., 7G03…	
Basal cell carcinoma	B33..11	
- Malignant neoplasm of female breast	B34..00, B825000, B83..00, Byu6.00, ByuFG00	*
Female genital organs	B40..00, B41..00, B42..00, B43..00, B44..00, B911…, Byu7.00, K551000	
Male genital organs	B46..00, B47..00, B48..00, Byu8.00, 4M0….	
- Prostate	B46..00, B834.00, 4M0….	*
Urinary tract	B49..00, B4A..00, Byu9.00,7B2C700	
Eye, brain and other parts of the central nervous system	B50..00, B51..00, B52..00, ByuA.00	
Thyroid and other endocrine glands	B53..00, B54..00, ByuB.00, 5A1….	
Ill-defined, secondary and unspecified sites	B55..00, B592.00, B593.00, ByuC.00	
Stated or presumed to be primary, of lymphoid, hematopoietic and related tissue	B6...00, B934…, B937.12, B937.13, B937.14, B935.11, B935.12, B936.11, B936.12, ByuD.00, C37…., 713…., 4M2…., 7D023.., A789600, A789700, AyuC600, B937…	
Independent (primary) multiple sites	ByuE.00, ByuF…, A789800	
Carcinoma in situ	B8...11, B8...12, B8...13, B80..00	

(*) separate analysis

Cancer according to Read coding	**Include**
Excluded codes	14….., Z….., 5A….., 7H….., 7L….., 8B….., 9b….., 9N….., 9Ok…., A788…, B5…00, B5…11, AyuC900, B057.00, B30..11, B30..12, B470300, B471100, B47z.12,

	B7z0.00, B831.12, B833311, B833400, B833500, B90…., B91..00, B910.00, B911.00, B911z00, , B912.00, B913…, B914…, B915…, B916, B917…, B91z…, B92…., B93..00, B930…, B931.00, B932.00, B933.00, B935.00, B936.00, B937.00, B937.11, B937W00, B937W11, BA….., BB….., ByuH, B937100, B937200, B937300, 1O0..00, AyuC800, 5A15.00, 5A15.00, B153.00, B55yz00, B55z.00, B56…., B57…., B58…., B59..00, B590.00, B590.11, B591.00, B594.00, B59z.00, B5y..00, B5z..00, B8...00, BB02.00, BB03.00, BB03.11, ByuC700, ByuC800, ByuF.00, C1z2.00

Table 4. ICPC-2 codes for Cancer outcome

Cancer according to ICPC-2 coding		
Malignancy NOS	A79	
Hodgkin's disease/lymphoma	B72	
Leukaemia	B73	
Malignant neoplasm blood other	B74	
Malignant neoplasm stomach	D74	
Malignant neoplasm **colon**/rectum	D75	*
Malignant neoplasm pancreas	D76	
Malignant neoplasm digest other/NOS	D77	
Neoplasm of the eye/adnexa	F74 (include malignant neoplasm)***	
Neoplasm of ear	H75 (include malignant neoplasm)***	
Neoplasm cardiovascular	K72 (include malignant neoplasm)***	
Malignant neoplasm musculoskeletal	L71	
Malignant neoplasm nervous system	N74	
Malignant neoplasm bronchus/lung	R84	
Malignant neoplasm respiratory, other	R85	
Malignant neoplasm of the skin	S77	
Malignant neoplasm thyroid	T71	
Neoplasm endocrine other/unspecified	T73 (include malignant neoplasm)	
Malignant neoplasm of kidney	U75	
Malignant neoplasm of bladder	U76	
Malignant neoplasm urinary other	U77	
Malignant neoplasm relate to pregnancy	W72	
Malignant neoplasm cervix	X75	
Malignant neoplasm **breast** female	X76	*
Malignant neoplasm genital other (f)	X77	
Malignant neoplasm **prostate**	Y77	*
Malignant neoplasm male genital other	Y78	
Benign neoplasm/unspecified	B75,D78,L97,N75-76,R86,R92,S78-S80,T72,U78-79,W73,X78-81,Y79	+
* separate analysis		
+ excluded from the analysis		

NOTE: ***F74, H75, K72 ICPC codes are the only available codes for the eye, ear and cardiovascular, and those codes include benign or malignant neoplasms.

12. Appendix 1: Amendment 1

Protocol: PROTECT_WP2 Final Protocol_CCB_Cabcer_22Nov2011
Amendment number: Nº 1
Amendment date: 2 Feb 2012
Protocol Owners: Lead: Lamiae Grimaldi (LASER), Backup: Ulrik Hesse (DKMA)
Reviewers: Marieke de Bruin (UU)

1. Reason(s) for Amendment:

Adding descriptive study on outcome(Cancer) as well as exposure (CCB use)by BIFAP for this drug event pair.

2. Protocol Section(s) Amended

The protocol sections that were amended are detailed below. The format is as follows:

- The "change from" section represents the current text in the protocol.
- Red text is used to indicate the addition of information to the current text
- Strikethrough formatting option (e.g., ~~text~~) is used to show the deletion of information from the current text.
- The "change to" section represents the revised text, with the revisions shown in the "change from" section in normal text.

Section 4.2 :Period of valid data collection

The study population will consist of CCB first-time users and non-users from 1 January 1996 to 31 December 2009, aged 18 to 79 years. CCB use before 1994 is not known, and patients without CCB use during 1994 and 1995 will be considered as non-users user prior to the study and therefore eligible to the study. Concerning GPRD and THIN/BIFAP patients are included if they have Primary Care Practice history of at least two years and at least one year's computerized GPRD/GP prescription history.

Patients with any cancer recorded in the GPRD or The Danish National registration of patients prior to cohort entry will also be excluded from the analysis. Cancer diagnoses will be determined using Read codes (refer to 'Definition of outcomes' below), ICPC codes and ICD-10 codes.

Section 4.2.2 Definition of outcomes

Outcomes will include all forms of cancer combined, as well as breast cancer in women, prostate cancer and colon cancer analyzed separately. Cancer diagnoses will be determined using Read codes, ICPC codes and ICD-10 codes.

Section 5.1 descriptive study :Table 1. Databases where descriptive studies will be held

Calcium channel blockers and cancer		
	Descriptive studies on drugs	Descriptive studies on disease
Mondriaan	yes	No
GPRD	Yes	Yes

THIN	Yes	Yes
Bavaria	Yes	No
Denmark	Yes	Yes
BIFAP	Yes	Yes
IMS Germany	Yes	No

Table 1. CCB exposure assessment

CCB – Main treatment effects (ATC-code[+])	**CCB use***
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	Verapamil
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* Defined using BNF categories 2.6.2

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Table 4. ICPC-2 codes for Cancer outcome

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* separate analysis		
+ excluded from the analysis		

NOTE: ***F74, H75, K72 ICPC codes are the only available codes for the eye, ear and cardiovascular, and those codes include benign or malignant neoplasms.