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BisCK study

Risks and benefits of bisphosphonate use in patients with chronic kidney disease: a population-based cohort study

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Substantive changes to version 3.0:

- Management plan: rearrangement of tasks according use CPRD and HES data instead of UK Renal Registry data.
- Data sources: addendum.
- Further clarifications in the statistical analysis plan.

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SUMMARY OF RESEARCH

AIM/S

Although osteoporosis and fragility fractures are common amongst CKD patients, the effectiveness and safety of first-line anti-fracture therapies (bisphosphonates) for this population are still unclear. We therefore aim to study the association between oral bisphosphonate (OB) use in stage ≥3B CKD patients and the following outcomes: CKD progression (stage worsening or entering renal replacement therapy or transplant) (WP1), clinical fracture/s (WP2), adverse events (hypocalcaemia or hypophosphatemia, upper gastro-intestinal events, and acute kidney injury) (WP3), and axial bone mineral density (WP4).

METHODS

Data sources: the primary data source for WP1-3 of our study will be the Clinical Practice Research Datalink (CPRD), linked to the Hospital Episodes Statistics (HES). Data from the Danish Odense University Hospital Database (OUHD) will be used for WP4.

Study participants: all patients registered in CPRD or in OUHD, aged ≥40 years, with an eGFR<45, and with ≥1 years of follow-up data available will be included. Users of bisphosphonates in the year before eGFR testing, as well as CPRD participants with no possible linkage to HES data will be excluded.

Exposure: Users of oral bisphosphonates will be identified from primary care prescriptions (CPRD) or pharmacy dispensations (OUHD).

Outcomes: WP1: CKD progression will be defined as stage worsening (according to eGFR as recorded in CPRD) or initiation of renal replacement therapy/transplant (HES).

Study outcomes for WP2-3 will be ascertained using previously validated lists of READ/OXMIS (CPRD) (1-3) or ICD-10/OPCS (HES) (4) codes. The main study outcomes will be: all clinical fractures excluding the skull/face and digits, which are not considered to be osteoporotic (WP2), and adverse events (hypocalcaemia/hypophosphatemia requiring hospital admission, upper gastro-intestinal events, and hospitalization for acute kidney injury) for WP3. WP4: annualized hip bone mineral density percentage change, as measured using DXA scan, will be measured.

Confounders: pre-defined lists of confounders will be identified for each of the study outcomes. These will be included in separate propensity score logistic equations to minimize confounding by indication. Propensity scores (ps) represent the probability that a patient will receive a specific treatment based on his/her baseline characteristics (5).

Power: according to feasibility counts from CPRD, 4,127 eligible (eGFR<45) bisphosphonate users and 204,528 eligible non-users are available. These numbers provide >90% power to detect as significant a HR of ≥1.20 for the association between bisphosphonate use and the outcomes in WP1 and WP3, and a HR o ≤0.85 for the association between bisphosphonate use and fracture risk (WP2). Regarding WP4, the numbers provided by OUHD (>500 bisphosphonate users and >3,000 non-users with eGFR<45 available in the dataset at 31/12/2012) ensure 80% power to detect as significant an expected >25% difference in bone loss between bisphosphonate users and non-users.

Statistical analyses: firstly, logistic equations will be fitted to estimate ps for each of the study outcomes. Secondly, each bisphosphonate user will be ps-matched to 5 non-users using caliper-matching methods. Ps-matching has been shown to be useful to minimize confounding by indication in observational studies involving drugs (i.e.pharmacoepidemiology) (6). Missing confounders will be handle with 10 multiple imputation by chained equations. Finally, time-varying Cox regression models stratified by ps matched sets will be used to study the association between bisphosphonate use and each of the study outcomes in WP1-3; similarly, linear regression modeling will be used to study the relationship between bisphosphonate use and hip bone density change in WP4.

BACKGROUND AND RATIONALE

There are 300,000 fragility fractures per year in the UK and reducing the burden of fragility fractures is a key health priority within the NHS. Osteoporosis is a silent disease of bone that causes bone fragility and increases the risk of fracture. Over 1 in 4 people with osteoporosis have moderate or severe chronic kidney disease (CKD) (7). Further, CKD has been shown to predict not only low bone mass due to accelerated bone loss (8), but also fracture risk, with a doubled risk in patients with stage 3 CKD (9), a 2.5-3-fold risk in those with stage 3B CKD (10), and an 4 times higher fracture incidence amongst patients with stage 4 CKD (11) or in renal replacement therapy (12).

While there are effective therapies to reduce the risk of fracture, the use of first line anti-osteoporosis therapies (i.e. oral bisphosphonates) is restricted in patients with CKD for two main reasons: 1.there are safety concerns related to the risk of bisphosphonates worsening kidney function and other adverse events which are already increased in patients with CKD such as severe hypocalcaemia or hypophos-phaetemia (which has been observed in about 8% of cancer patients treated with powerful intravenous bisphosphonates (13)), upper gastro-intestinal events, or acute kidney injury; and 2. given the biological mechanism of how CKD weakens bone differs from osteoporosis, it is far from established that bisphosphonates will have a similar beneficial effect in reducing fracture rates. Efficacy data for bisphosphonates is scarce in CKD, as the numbers of patients with moderate or severe CKD recruited for the pivotal trials were low, with only 301 patients with an eGFR<30 being recruited in the risedronate arm from a total of 9 randomized controlled trials (14). Importantly, participants in these trials with CKD are likely to be healthier and have fewer co-morbidities compared with patients with CKD in the real life setting as we have previously shown [Prieto-Alhambra D et al. "RCT Participants and Real Life Drug Users: A Population-Based Cohort Study". Poster presentation at ISPE 2014 Conference, Taiwan]. Another concern is that about 40%-45% of patients with end-stage renal disease (15, 16), and an unknown proportion of those with stage 4 CKD, may suffer adynamic bone disease where there is a marked reduction in activity of the cells in bone. Given the mechanism of action of bisphosphonates is to further reduce activity of bone cells (osteoclasts), there remains a concern that use of anti-resorptive medications such as bisphosphonates in this setting would increase and not decrease the risk of fracture.

Given all this, and despite good safety data from randomized trials for both risedronate (14) and alendronate (17), NICE guidelines (TA160 and 161) do not support the use of bisphosphonates in patients with eGFR<35, and oral bisphosphonates are not recommended with eGFR<35 (alendronate (18)), or eGFR<30 (ibandronate (19) and risedronate (20)), mainly due to a lack of experience rather than evidence demonstrating worse outcomes (see Fosamax SPC EMC). This leaves this patient group with a very high fracture risk effectively untreatable.

EVIDENCE EXPLAINING WHY THIS RESEARCH IS NEEDED NOW

Formulae to estimate eGFR based on serum creatinine are increasingly popular: according to routinely collected data on biochemistry tests in NHS settings, the number and proportion of UK patients tested for serum creatinine, for whom eGFR measurements are estimated, increased by almost 30% between 2004 and 2009, leading to a raise in the number of patients diagnosed with CKD (21). In addition, socio-demographic factors, such as an increasing elderly population, will magnify this problem.

With bisphosphonates being contraindicated in the CKD population, new and more expensive treatments may be used instead but a good proportion of CKD patients at high risk of fracture are not offered any treatment. However, the safety data that led to the contraindication of oral bisphosphonates in patients with eGFR<30 comes from the combination of 1.adverse events induced by intravenous zoledronate, the most powerful of all bisphosphonates, which due to its pharmacokinetics reaches a much higher maximal concentration in the blood when compared with oral bisphosphonates, and 2.the relatively low number of patients with eGFR<45 included in the pivotal trials of oral bisphosphonates, and the lack of additional data on the safety of these for patients with stage ≥3B CKD. All this calls for urgent data on the risks and benefits of bisphosphonates in these patients. However, before embarking on a randomised trial (the gold standard design to answer these questions) it is prudent to fully explore existing resources given the concerns of randomizing patients to treatments that are formally not recommended, or even contraindicated.

Our proposal will make the most of the readily available information collected in NHS routine practice and other routine datasets and use novel modelling methods to inform the future use of anti-osteoporosis medications in these patients and/or prioritise further clinical trials in this field.

AIMS AND OBJECTIVES

Our proposal is addressed to answer a relevant question identified by the NIHR HTA Commissioning Board: what are the risks and benefits of the use of bisphosphonates amongst patients with chronic kidney disease?

To answer these questions, we have designed a retrospective cohort study using routinely collected data from large electronic health records databases from primary, secondary and specialist renal unit care. The proposed linkage of GP, hospital admission, and renal replacement therapy/transplant data will constitute a unique dataset in the UK.

The specific aims are to study, in the population with stage ≥3B CKD (eGFR<45 ml/min/1.73m2), the following:

Workpackage 1: the association between the use of oral bisphosphonates and the progression (stage worsening or entering renal replacement therapy/transplant) of kidney disease.

Workpackage 2: the relationship between oral bisphosphonate use and incident symptomatic fractures.

Workpackage 3: the risk of adverse events (upper gastro-intestinal events, hypocalcaemia/hypophosphatemia, or acute kidney injury) amongst users of oral bisphosphonates, compared to matched non-users.

Workpackage 4: the annual changes in DXA-measured hip bone mineral density in oral bisphosphonate users, compared to matched non-users.

RESEARCH PLAN

METHODS

As recommended in the commissioning brief, we will use routinely collected (observational) data. We have planned a propensity score-matched cohort study, with the intention to minimize confounding. Propensity score matching is considered one of the best methods available to approximate the results from randomized controlled trials in pharmaco-epidemiology (5, 22). Such studies are suboptimal compared to RCTs due to the lack of random treatment allocation, but they are the gold standard when RCTs are not possible. That is indeed the case in scenarios where the drug is contraindicated for the target population, like the use of bisphosphonates in patients with moderate-severe kidney failure.

In addition, novel statistical modeling methods will be used: 1.multiple imputation with chained equations (23, 24) will be performed to minimize the bias introduced by missing information, a common issue in routinely collected data sources; and 2.Rosenbaum boundaries analyses (25) will be carried out to account for the potential impact of unobserved (and therefore unadjusted for) confounders.

The availability and breadth of routinely collected data in the UK, including both primary (CPRD) and secondary (HES) care clinical information, makes this study possible at an affordable cost, and much faster than alternative observational study designs. Further, the use of these multiple datasets ensures the findings from this study will be both generalizable across the UK but also robust in terms of data quality and completeness. However, data linkage and intensive data management are required to obtain the detailed information necessary to answer the research question of interest. In addition, advanced statistical modeling methods (including multivariate logistic and linear regression, propensity score caliper-matching (6), and time-varying survival analyses) will be needed to adjust for confounding by indication, and to avoid biases intrinsic to pharmaco-epidemiological studies, such as the immortal-time bias (26).

TARGET AUDIENCE

Patients with CKD and a history of osteoporosis or fragility fractures, as well as NHS clinicians involved in their care (general practitioners, nephrologists, rheumatologists, and orthopaedic surgeons) will be our primary target audience.

Relevant charities will be involved in the dissemination of our study results to the lay audience: 1.the National Osteoporosis Society health sector relations manager (Mrs F Thompson) is a co-applicant in our grant, and has been involved in the drafting and review of the current application; and 2.a patient representative and executive member of the National Kidney Federation (Mrs D Abbott) is also a listed co-applicant of this grant.

Drug regulators (MHRA in the UK and EMA at a European level) will be informed of our study results, as these may change the current restrictions of use of first-line therapies for the

prevention of fragility fractures in the CKD population.

NICE will also receive the results of our study, as these might have an impact on future guidance for the prevention of osteoporotic fractures: current guidelines (TA 160/161) do not support the use of bisphosphonates in patients with CKD, as recommended by MHRA.

Finally, the findings of this study will inform the need for formal clinical trials within the NIHR network.

HEALTH TECHNOLOGIES BEING ASSESSED

The current proposal will assess the risks and benefits of the use of oral bisphosphonates to prevent fragility fractures amongst patients with stage ≥3B CKD. Oral bisphosphonates are the first line therapies for the primary and secondary prevention of osteoporotic fractures, as recognized by NICE guidelines (TA 160 and 161), but they are contraindicated in patients with eGFR<30-35. The drugs assessed will be the currently recommended ones: oral alendronate, risedronate, and ibandronate.

Use of oral bisphosphonates will be identified using pre-specified lists of the British National Formulary (BNF) within CPRD, and Anatomic Therapeutic Classification (ATC) codes for OUHD (Appendix 1).

There is no approved alternative bone medication for patients with severe CKD, and therefore oral bisphosphonate users will be compared to those not on anti-osteoporosis therapy (i.e. drug non-users).

EXPOSURE PERIODS

As the data sources include information on drug prescribing (CPRD) or dispensing (OUHD) as opposed to drug consumption, the prescription duration may not reflect the true number of days over which a prescription was used. As a result, assumptions will be made to account for non-adherence (or non-compliance) in order to define periods of continuous exposure.

We will assume that any overlap between two prescriptions of the same bisphosphonate represent early collection of a repeat prescription. Hence, any overlapping days between two prescriptions of the same drug will be added to the end of the period covered by the two prescriptions. In order to define periods of continuous use of study drugs, any two prescriptions of the same drug will be concatenated if the gap between the end of the first of the two prescriptions and the start of the second of the two prescriptions was less than 30 days apart.

DESIGN AND THEORETICAL/CONCEPTUAL FRAMEWORK

CONCEPTUAL FRAMEWORK

An observational cohort study using routinely collected data will be performed to evaluate the potential risks (CKD progression, hypocalcaemia/hypo-phosphatemia, and a number of adverse events) and benefits (bone density improvement, and fracture protection) observed amongst patients with stage ≥3B CKD in actual 'real life' NHS practice.

STUDY DESIGN

The chosen study design is a propensity score-matched retrospective cohort study. This is one of the best pharmaco-epidemiological designs available for the assessment of intended (benefits) and unintended (risks) effects of drugs in observational data. Propensity score-matching will therefore be used to match each eligible bisphosphonate user to 5 non-users, producing matched comparable (in terms of observed baseline characteristics) cohorts.

TARGET POPULATION

The target population of this study will be patients with an eGFR<45 (based on serum creatinine) aged 40 years or older at the age of biochemistry testing.

EXCLUSION CRITERIA

From the population described above, we will exclude those with any of the following exclusion criteria:

- Less than 1 year of follow-up data available within the data source/s.
- CPRD participants with no possible linkage to HES.
- Use of anti-osteoporosis medication/s in the previous year (except calcium and/or vitamin D supplements).
- Use of any (except calcium and/or vitamin D supplements) other anti-osteoporosis medication/s (other than bisphosphonates).

SETTING/CONTEXT

Setting: The proposed study will obtain data from both primary (CPRD) and secondary (HES) care.

Study period: Currently used oral bisphosphonates (alendronate, risedronate and ibandronate) were approved and launched to the market in 1996 onwards. Our study period will therefore cover from 1996 to the latest data extraction for the identified data sources, likely 31/12/2014.

Follow-up: Data from randomized placebo-controlled trials have shown that bisphosphonates are effective to reduce fracture risk only after at least 6 months of continuous use (27). That is not the case though for adverse events, which can be observed immediately after bisphosphonate therapy initiation (14, 17, 28). Therefore, different follow-up windows will be established, as follows:

- Safety outcomes (WP1 and WP3): Patients will be followed from the latest of the following dates

a) Start of study period
b) One year of valid data in database
c) Date of incident prescription of bisphosphonate (after one year of non-use)

until the earliest date of:

a) The end of enrolment in the database (due to moving out or death)
b) Date of last data update in the database
c) Stopping of treatment +30 days (no repeat prescription within 1 month)
d) Switch of treatment to other (non-bisphosphonate) osteoporosis medication
e) Outcome of interest (different date for each study outcome)

- Effectiveness outcomes (WP2 and WP4): Patients will be followed from the latest of the following dates

a) Start of study period
b) One year of valid data in database
c) Date of continued prescriptions of an oral bisphosphonate for 6 months after the date of therapy initiation

until the earliest date of:

a) The end of enrolment in the database (due to moving out or death)
b) Date of last data update in the database
c) Stopping of treatment +180 days (no repeat prescription within 6 months)
d) Switch of treatment to other osteoporosis medication, with no repeat prescription of oral bisphosphonates within the next 6 months
e) Incident recorded fracture (WP2) or last BMD measurement available (WP4)

SAMPLING

One of the advantages of routinely collected datasets is that the contained information is readily available, not needing active recruitment. Therefore, all patients eligible (see target population and exclusion criteria above) registered in the chosen data sources will be included.

Sample size/power: According to feasibility counts provided by CPRD, the number of eligible patients (with an eGFR<45 and possible to link to HES) would be of 204,528 subjects, and 34,127 (16.7%) of these received oral bisphosphonate prescriptions. These numbers would provide statistical power to reliably answer each of the study aims, as it can be seen below:

Work-package 1: In a survival analysis (log-rank 2-sided test), accepting 5% type I error and 20% attrition from propensity score matching and loss to follow-up in 2 years, and assuming CKD stage progression rates of 12/100 person-years (29), the available number of participants would provide 90% power to detect an excess risk of CKD progression of 10% or more (HR ≥1.10) associated with oral bisphosphonate use.

Work-package 2: In a log-rank (2-sided) test, and accepting 5% type I error and 20% drop-out, with 2 years of follow-up and an expected fracture rate of 103/10,000 person-years in CPRD data (30), the available sample size would provide 90% power to detect a fracture reduction of at least 15% (HR≤0.85) amongst oral bisphosphonate users (compared to non-users).

Work-package 3: In a log-rank 2-sided test with an alpha risk of 0.05, and assuming a 20% drop-out rate, the number of patients available would provide >90% power to detect as significant a ≥20% excess risk (HR ≥1.20) for any clinical event with a cumulative incidence of ≥2% in 2 years follow-up. Less common adverse events or weaker associations would require bigger numbers (Table 1).

Table 1. Number of eligible bisphosphonate users needed to ensure 90% statistical power to detect as significant the described associations in a 2-sided survival model (log-rank test), assuming 5 bisphosphonate non-users will be matched to each user.

2-year cumulative incidence of adverse event/s	HR 1.1	HR 1.2	HR 1.3	HR 1.4	HR 1.5
0.50%	330,529	86,234	39,840	23,218	15,353
1%	165,288	43,130	19,929	11,617	7,683
2%	82,667	21,578	9,974	5,817	3,849
3%	55,217	14,394	6,657	3,883	2,570
4%	41,357	10,802	4,997	2,917	1,932
NOTE: cells in bold indicate characteristics of associations we would have 90% power to detect					

The incidence of each of the identified adverse events amongst bisphosphonate users is as follows:

a) Upper gastro-intestinal events: according to data from the pivotal randomized trial for oral alendronate, 11% of the patients allocated to the active treatment arm developed upper gastro-intestinal events, with 1.6% developing serious events (perforation/ulcer/bleeding) (31);
b) Hypocalcaemia/hypophosphatemia: although the incidence of bisphosphonate-induced hypocalcaemia/hypophosphatemia in the target population (stage ≥3 CKD

patients) is unknown, data from the UK Renal Registry 2013 report suggest that hypocalcaemia and hypophosphatemia are relatively frequent in end-stage renal disease, with a prevalence of 11% and 12% amongst patients on haemodialysis respectively. In addition, data from cancer patients suggest that 8% of them develop hypocalcaemia requiring medical attention following an infusion of intravenous zoledronic acid (13);

c) Acute kidney injury (AKI): the population-based incidence of AKI has been estimated at 209 cases per million person-years (32), therefore making a 2-year cumulative incidence of 0.04%. Therefore, the available sample size would ensure power to detect as significant an excess risk of ≥40% (HR ≥1.4) of AKI associated with bisphosphonate use. It is however well known that the risk of AKI is higher amongst patients with previous CKD (33).

In summary, the proposed study would have ≥90% power to detect as significant an excess risk of ≥10% between bisphosphonate use and both upper GI and hypocalcaemia/hypophosphatemia events, and of (in the most conservative scenario) ≥40% between use of bisphosphonates and risk of AKI.

Work-package 4: The Danish OUHD included 35,025 patients in the year 2012. We expect to identify at least 500 CKD patients defined as oral bisphosphonate users, matched 1:5 to 2,500 non-users. Accepting type I error of 5% in a two-sided test, and a common mean (standard deviation) hip BMD loss of 0.61% (1.23%) per year (34), this sample size would provide >80% power to detect as significant a >25% difference in bone loss change between bisphosphonate users and non-users.

DATA COLLECTION

Data linkage and management: As stated above, one key advantage of routinely collected data is the immediate access to large and representative samples of patients with no need for prospective data collection. In our proposal, over 200,000 eligible patients (with an eGFR<45) have been identified in CPRD, with >34,000 of them starting bisphosphonate use in the study period.

More challenging is however the workload involved in the linkage and data management required for the current study, where 2 different data sources (CPRD and HES) will be linked to answer the aims of WP1-3. For this reason we have included co-applicants with extensive experience in linkage between these data sources as described above (see "Response to feedback points"). The data management needed to produce a final working dataset will be carried out by a senior data manager at Oxford with expertise in such procedures. With supervision from the PI and the appointed statistician, she will develop ad-hoc code in Python and SQL to produce a dataset that can be analyzed using standard statistical packages such as Stata.

For WP4, investigators at the Odense Patient Data Exploratory Network (OPEN) initiative will carry out the linkage of clinical (including bone mineral density), biochemistry (i.e. serum

creatinine), and pharmacy dispensations data, as well the needed data management. The funding for these are either included in the requested data license fee (linkage and data management) or provided at no cost by external collaborators (supervision by Prof Bo Abrahamsen and Prof Kim Brixen).

Mapping of outcomes of interest: All events/outcomes will be ascertained using pre-specified lists of either validated or agreed READ/OXMIS (CPRD) and ICD/OPCS (HES) codes. The proposed lists of codes have been created following a number of steps:

1. Literature review of validation studies of CPRD or HES data. When validation studies were found showing a good quality of recording within CPRD/HES (all the cases in the current proposal), the list/s of validated codes were pulled from the manuscript or online (supplementary) appendices and used as the proposed list of codes for this study.
2. Where no such studies were found for any of the study outcomes (here only for hypocalcaemia/hypophosphatemia (WP3)), the following steps were followed in Stata, as recommended by Dave S et al (35):
    a. Identifying a list of key words and synonyms for the outcome of interest.
    b. Converting the ICD/OPCS code dictionaries into Stata files containing the ICD/OPCS code and description fields, and dropping duplicate codes.
    c. Sorting the code dictionary and browsing to identify relevant code stems for hypocalcaemia/hypophosphatemia.
    d. Converting the ICD/OPCS code dictionary 'code description' field to lower case and searching for key words (identified in step (1)) using the Stata for each command.
    e. Sorting the code dictionary and browsing to identify further code stems.
    f. Searching the code dictionary 'ICD code' field for relevant codes using the Stata foreach command.
    g. Excluding irrelevant codes.

DATA ANALYSIS

Propensity Score matching: Propensity scores represent the probability that a patient will receive the drug of interest (i.e. oral bisphosphonates) according to their baseline socio-demographics and clinical characteristics. Multivariable logistic regression equations will be used to calculate one propensity score for each of the study outcomes of interest (36). Pre-specified predictors of each of these outcomes will be included in each of these equations (37). Finally, the created propensity scores will be used to match bisphosphonate users to comparable non-users with a caliper matching technique with a maximum caliper width of 0.02 standard deviations (SDs). In short, this means that bisphosphonate non-users will only eligible to be matched if their propensity score falls within a bandwidth of 0.02 SDs of the bisphosphonate user subject's propensity score. This method has been shown to be the most efficient to minimize confounding by indication in pharmacoepidemiological studies (6) and typically excludes the small proportion of patients with extremely high or extremely low risk

for the outcome that are not present in both intervention and comparator patient samples. Covariate balance achieved through PS matching will be assessed using absolute standardized difference in means or proportions.

Some confounders, such as smoking, alcohol drinking, body mass index might not be completed. We will impute them for the propensity score (logistic) models using multiple imputation by chained equations (MICE) methods. 10 imputed datasets will be used. For each imputed dataset, a ps matched dataset will be identified and analysed as per study outcome separately. Outcome estimates of 10 ps imputed datasets will be then combined using Rubin's rules to obtain an overall outcome estimate (46).

Absolute rates of study outcomes: The crude and age and sex specific incidence rates (and 95% confidence intervals) of each of the events will be estimated separately in the cohort of oral bisphosphonate users and amongst propensity score-matched non-users assuming a Poisson distribution. Kaplan-Meier plots will be created to show the predicted cumulative probability of each of the study endpoints according to bisphosphonate use.

In addition, annualized eGFR (secondary outcome in WP1) and BMD (WP4) changes and 95% confidence intervals will be reported.

Immortal time bias and time-varying exposure: Immortal time bias (ITB) is a common issue in pharmaco-epidemiology. In brief, ITB appears when in a study the event of interest cannot occur for a certain time span due to study design and/or data analysis methods used (26). In cohort studies, immortal time typically arises when the definition of drug use involves a delay or wait period during which follow-up time is accrued—for example, waiting for a prescription or drug dispensation after discharge from hospital when the discharge date represents the start of follow-up (38).

A number of methods are available to avoid ITB. We will, in our study, use time-varying exposures, where in a survival analysis the time previous to index date for drug users (i.e. the time before first prescription of oral bisphosphonates) is reclassified as drug non-user person-years. We have extensive expertise using this method (39-41), which has been shown to be the most efficient to avoid ITB in pharmaco-epidemiological studies (42).

Hazard ratios: We will use proportional hazards Cox regression modelling to estimate the Hazard Ratio (HR) and 95% Confidence Intervals for each of the outcomes of interest according to bisphosphonate use. To account for the matched cohort approach proposed, we will use Cox regression stratified by matched sets.

The proportional hazards assumption will be checked using clog log plots. Alternative models, e.g. parametric survival models and weighted Cox regression(43) will be considered. The final decision of the alternative modelling techniques will depend on the availability of a suitable function to describe the hazards distribution.

If mortality rates are different amongst bisphosphonate users and matched non-users, Fine and Gray survival analyses (44) will be used instead, to account for a competing risk with death.

Failing to do so would results in a biased estimation of the excess/reduced risk of the events of interest amongst bisphosphonate users (45).

Beta coefficients: Longitudinal analysis will be used to study the association between bisphosphonate use and annualized changes of both eGFR (secondary outcome in WP1) while linear regression modelling will be used to study the association between bisphosphonate use and changes of BMD between two observed time points (WP4). Beta coefficient and 95% confidence intervals will be reported for the effect of bisphosphonate use on both outcomes.

Sensitivity analyses: Three pre-defined interactions will be tested for, and if significant, stratified analyses will be reported: 1.by gender; 2.by history of previous fracture; and 3.by CKD stage.

In addition, a sensitivity analysis will be carried out to test whether the observed association/s between bisphosphonate use and each of the outcomes follows a gradient, one of the Bradford-Hill criteria of causality (46). To do this, bisphosphonate users will be categorized according to their medication possession ratio (MPR). MPR is calculated as the number of defined daily doses prescribed over the total number of days of follow-up, and it is therefore an approximation of adherence in CPRD and similar datasets.

Bisphosphonate users will then be grouped into: low adherence (MPR <0.4), intermediate adherence (MPR 0.4 to <0.8) and high adherence (MPR ≥0.8), and HRs will be estimated for each of these categories when compared with matched bisphosphonate non-users.

A post-hoc analysis has been proposed to study the association between bisphosphonate use and hypocalcaemia/hypophosphataemia: given the low number of study participants with the proposed outcome of interest (hospital admission for calcium/phosphate alterations), data has been extracted on laboratory values of serum calcium and phosphate as available in primary care records (CPRD). Hypocalcaemia/hypophosphataemia as defined by these values will be analysed as a secondary outcome for WP3 in addition to the proposed main outcome.

DISSEMINATION AND PROJECTED OUTPUTS

OUTPUTS

A detailed report of our study, including all the work undertaken, will be published in the NIHR HTA Journal. A number of research papers will also be published to report key findings in national and international scientific journals including the Lancet, the British Medical Journal, the Journal of Bone and Mineral Research, Osteoporosis International, Journal of the American Society of Nephrology, or Kidney International, amongst others. Where available, we will publish our findings in open access, and we have requested funding to cover related fees, which range from £1,800 (Osteoporosis International) to £3,000 (BMJ).
Our results will also be presented at national (National Osteoporosis Society, British Society of Rheumatology, UK Renal Association) and international (American Society of Bone and Mineral Research, International Osteoporosis Foundation, European Renal Association, European Dialysis and Transplant Association, American Society of Nephrology) scientific conferences. We will preferably report our findings in such forums in the format of oral presentation/s.

The involved charities (National Kidney Federation and National Osteoporosis Society) will organize meetings between study investigators (including their representatives listed as co-applicants of this grant, Mrs D Abbott and Mrs F Thompson) and both local and national groups. Also, our findings will be reported in the format of pdf or paper leaflets for patients, in collaboration with these charities.

Our collaborators from the UK Renal Registry and the CPRD will also disseminate our findings in their websites and internal newsletters/publications.

DISSEMINATION

As the study progresses, we will collaborate with relevant charities (the National Osteoporosis Society, the National Kidney Federation), scientific societies (the American Society of Bone and Mineral Research, the International Osteoporosis Foundation, the European Renal Association, the British Society of Rheumatology), NHS managers, healthcare professionals, patients and the public for direct communication of our findings. This will be facilitated by existing collaborations with patient representatives, members of the UK Renal Registry board (Dr Fergus Caskey), the lead investigator of the FRISCY network as a co-PI (Dr Kassim Javaid), involvement of the National Osteoporosis Society health sector relations manager as a listed co-applicant (Mrs Fizz Thompson), and representation on their Clinical Scientific Committee (Dr Kassim Javaid & Professor Cyrus Cooper), and patient representation (Mrs D Abbott). Further, from the international perspective, we will work with the International Osteoporosis Foundation Clinical Scientific Advisory Committee structure to inform an international guidance document.

We expect our findings to impact on future guidelines for the treatment of osteoporosis and prevention of fragility fractures in CKD patients. We will do so by informing NICE and the MHRA

of our findings as soon as they are published.

Changes in clinical guidelines as well as potential re-evaluation of drug contraindications would change clinical practice by modifying the use of bisphosphonates in CKD patients.

The chosen PPI representatives (Mrs Fizz Thompson and Mrs D Abbott) are co-applicants of this grant, and will be directly involved in the dissemination of our results to the general audience. . Depending on the strength of the findings, this would involve as an output the production of UK guidance documents for patients and health care professionals in both primary and secondary care involved in this topic area as has been done for the vitamin D testing and treatment in adults.

Finally, should the findings from this work lead to equipoise, they may inform the need for a formal application for an RCT from the research community.

MANAGEMENT PLAN

-Months -3 to 0: Writing job descriptions for required staff (Project Coordinator and Statistician) by the study Principal Investigator (PI); Co-investigators teleconference; Contract negotiations (NIHR and University of Oxford Research Services).
-Month 0: Project Coordinator (PC) interviews and appointment by PI and Human Resources (HR);
-Month 1: Co-applicants kick-off meeting.
-Months 1-3: Re-formatting and submission of the study protocol to the CPRD/MHRA Independent Scientific Advisory Committee (ISAC) by the study PI+PC; evaluation/feedback by ISAC, changes/modifications requested and resubmission by PI+PC.
-Month 3: Interview for Statistician and appointment by HR and PI.
-Months 4-6: Data linkage and data extraction for CPRD/HES and Danish data sources by data providers.
-Months 8-10: Data management of CPRD/HES dataset: conversion of the extracted data in working datasets, ready for their analysis by funded Data Manager (supervised by study PI and in collaboration with appointed Statistician).
-Months 11-13: Data management of Danish dataset.
-Months 10-15: Submission and approval of Confidentiality Advisory Group (CAG) and Research Ethics Committee (REC) applications to link UKRR data to CPRD data.
-Months 11-16: First round of data analyses of CPRD/HES dataset (Months 10-16) and Danish (Months 15-16) datasets by appointed Statistician (supervised by study PI).
-Month 17: Internal discussion of preliminary results and co-investigators (co-applicants and external international collaborators) meeting, organised by PC (supervised by PI).
-Months 18-20: Second round of data analyses by Statistician (supervised by PI): CPRD/HES data for WP1-3 in Months 18-19, and Danish dataset for WP4 in Month 20.
-Months 21-30: Data analysis of renal outcomes using CPRD and HES data.
-Month 30: Internal discussion of final study results and dissemination plan, and co-investigators meeting, organised by PC (supervised by PI).
-Months 31-33: Writing of study report (PI, PC), related abstracts/manuscripts (PI, Statistician, and coinvestigators), dissemination to lay audience, and study closure

REGULAR COMMUNICATION

A Steering committee formed by an external chair, the study PI, PPI representatives, a pharmacoepidemiologist, and a clinician will meet in November 2016, May 2017, and May 2018 to evaluate the study progress and adherence to governance policies.
A Study Investigators Group constituted by the PI, all study co-applicants (including PPI representatives) and international collaborators will have regular meetings/teleconferences every 3 months to ensure effective communication between investigators at different sites, and to monitor study progress.
There will be:

- Five Co-applicants and external collaboration meetings: months 1, 10, 17, 30 and 33 ('kick-off'

meeting, 'data management discussion' meeting, 'internal discussion on preliminary results' meeting, 'final results and dissemination plan' meeting and 'study closure' meeting).

- Co-applicants and external collaborators teleconferences: when no meeting is planned, a teleconference will be held every 3 months.

More meetings will be planned if necessary.

APPROVAL BY ETHICS COMMITTEES

The proposed study will only use retrospective, routinely collected data. The identified data sources (CPRD, HES, and the Odense University Hospital Database) do not request ethics committee approval to access/extract their data. Instead, approval by internal independent data access committees is required, including the Independent Scientific Advisory Committee (ISAC) at MHRA for CPRD and linked HES data.
We have wide experience in the submission (and subsequent approval) of protocols to ISAC: the PI has been successfully approved 4 protocols for different studies, and other listed co-applicants like Dr A Judge and Prof NK Arden have obtained approval for 3 and 2 protocols respectively. In addition, support will be available from internal investigators for each of the identified data sources, who are listed co-applicants in this grant or external collaborators (Bo Abrahamsen, consultant endocrinologist and professor, and Kim Brixen, medical director of the Odense University Hospital).
Addendum: A first application to the Confidentiality Advisory Group (CAG) for the linkage of CPRD data to the UK Renal Registry was rejected. Following from this, an ad-hoc application (for a one-off linkage for this piece of research) was submitted for approval from the Research Ethics Committee (Oxford C REC) and CAG, which were both approved in March/2017.

An application was submitted to NHS Digital in August/2017 to act as a third trusted party in the linkage of CPRD and UK Renal Registry data. In June/2018 it was decided that, given the relevance of the preliminary study results, the final results of the study will be obtained using data from the CPRD linked to HES, as the NHS Digital application to link the CPRD and the UK Renal Registry was still pending approval. This has been discussed with and approved by the NIHR HTA.

PATIENT AND PUBLIC INVOLVEMENT

The proposed study affects mainly patients with osteoporosis and chronic kidney disease, and two charities provide the natural environment for the dissemination of our results to the target lay audience: the National Osteoporosis Society (NOS), and the National Kidney Federation (NKF). Two key patient and public representatives have been identified and included as co-applicants of the current proposal from its early stages: Mrs Fizz Thompson, health sector relations manager at the NOS, and Mrs Denny Abbott, patient representative and executive member at the NKF. The overarching aims of their involvement are: 1.to assist the study investigators in identifying the most relevant study outcomes (adverse events) from a patients' perspective, 2.to collaborate in the drafting of the grant lay summary, 3.to participate in the study steering committee to monitor and discuss study progress and preliminary results, and 4.to organize dissemination to the lay audience.

Both AT and DA were contacted using existing links between listed co-applicants and the named charities (Dr Kassim Javaid with the NOS, and Dr Fergus Caskey with the NKF), and have participated in the following aspects of the study outline and full application: 1.drafting and reviewing lay summary, 2.narrowing down study outcomes (i.e. relevant adverse events), 3.reviewing and commenting on the application form and "Detailed Project Description".

AT and DA, as listed co-applicants in the grant, will be part of the study steering committee as well as they will be invited to all of the 3-monthly teleconferences.

The two PPI representatives will be instrumental in the dissemination of study findings to the lay audience, in the format of workshops, meetings with local/regional and national groups, communication of results to groups of expert patients, and if relevant dissemination in the format of pdf or paper leaflets for patients.

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APPENDIX 1

BNF and ATC codes for the identification of drugs of interest.

DRUG NAME	ATC (Denmark)	BNF (UK)
ALENDRONIC ACID (AS SODIUM SALT) oral soln 70mg/100ml	M05BA04	06.06.02.00
ALENDRONIC ACID (AS SODIUM SALT) tabs 10mg	M05BA04	06.06.02.00
ALENDRONIC ACID (AS SODIUM SALT) tabs 10mg	M05BA04	06.06.02.00
ALENDRONIC ACID (AS SODIUM SALT) tabs 10mg	M05BA04	06.06.02.00
ALENDRONIC ACID (AS SODIUM SALT) tabs 5mg	M05BA04	06.06.02.00
ALENDRONIC ACID (AS SODIUM SALT) tabs 70mg	M05BA04	06.06.02.00
ALENDRONIC ACID (AS SODIUM SALT) tabs 70mg	M05BA04	06.06.02.00
ALENDRONIC ACID (AS SODIUM SALT) tabs 70mg	M05BA04	06.06.02.00
ALENDRONIC ACID (AS SODIUM SALT) tabs 70mg	M05BA04	06.06.02.00
ALENDRONIC ACID (AS SODIUM SALT) tabs 70mg	M05BA04	06.06.02.00
ALENDRONIC ACID (AS SODIUM SALT) tabs 70mg	M05BA04	06.06.02.00
ALENDRONIC ACID 10mg tablets	M05BA04	06.06.02.00
ALENDRONIC ACID 5mg tablets	M05BA04	06.06.02.00
ALENDRONIC ACID 70mg tablets	M05BA04	06.06.02.00
IBANDRONIC ACID 50mg tablets	M05BA06	06.06.02.00
IBANDRONIC ACID conc soln inf 2mg/2ml	M05BA06	06.06.02.00
RISEDRONATE SODIUM 30mg tabs	M05BA07	06.06.02.00
RISEDRONATE SODIUM 35mg tabs	M05BA07	06.06.02.00
RISEDRONATE SODIUM 35mg tabs	M05BA07	06.06.02.00
RISEDRONATE SODIUM 5mg tablets	M05BA07	06.06.02.00
RISEDRONATE SODIUM tabs 30mg	M05BA07	06.06.02.00
RISEDRONATE SODIUM tabs 35mg	M05BA07	06.06.02.00
RISEDRONATE SODIUM tabs 5mg	M05BA07	06.06.02.00

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