TITLE: Increased risk of bone fractures in hemodialysis patients treated with proton pump inhibitors in real world: results from the Dialysis Outcomes and Practice Patterns Study (DOPPS)

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Abstract

Long-term treatment with Proton Pump Inhibitors (PPIs) is associated with an increased risk of fractures in the general population. PPIs are widely prescribed to dialysis patients but to date no study specifically tested, by state-of-art statistical methods, the relationship between PPIs use and fractures in this patient-population. This study aimed to assess whether PPIs use is associated with bone fractures (i.e. hip fractures and fractures other than hip fractures) in a large international cohort of hemodialysis patients. We considered an observational prospective cohort of 27097 hemodialysis patients from the DOPPS study. Data analysis was performed by the Fine & Gray method, considering the competitive risk of mortality, as well as by a cause-specific hazards Cox model dealing death as a censoring event and matching patients according to the prescription time. Out of 27,097 hemodialysis patients, 13,283 patients (49%) were on PPI treatment. Across the follow-up (median:19 months), 3.8 bone fractures x 100 person-years and 1.2 hip fractures x 100 person-years occurred. In multiple Cox models, considering the competitive risk of mortality, the incidence rate of bone (SHR: 1.22, 95% CI: 1.10-1.36, P<0.001) and hip fractures (SHR: 1.35, 95% CI: 1.13-1.62, P=0.001) was significantly higher in PPI treated than in PPI untreated patients. These findings held true also in multiple, cause-specific, hazards Cox models matching patients according to the prescription time (bone fractures, HR: 1.47, 95% CI: 1.23-1.76, P<0.001, hip fractures (HR: 1.85, 95% CI: 1.37-2.50, P<0.001). The use of PPIs requires caution and a careful evaluation of risks/benefits ratio in hemodialysis patients.

Introduction

Proton pump inhibitors (PPIs) are commonly prescribed for gastrointestinal disorders, in which the inhibition of gastric acid secretion is desirable, such as peptic ulcer disease, dyspepsia and gastroesophageal reflux disease. The use of PPIs is widespread and has progressively increased since their introduction.[1] In the ambulatory setting the prevalence of visits in which patients used PPIs increased from 4.0% in 2002 to 9.2% in 2009.[2] Moreover, 63% of the patients using PPIs did not have gastrointestinal complaints or a specific indication for PPI use. Accordingly, PPIs were included among the most common potentially inappropriate medications, identified using the updated Beers criteria. [3] For this reason, while prescribing this class of drugs, an accurate evaluation of the risks/benefits ratio of long term use of PPI is formally recommended by the American Gastroenterological Association.[4] In a Danish nationwide study, the prevalence of PPI use in adults increased from 2% in 2002 to 7.4% in 2014 and prolonged treatment was very common.[5] Remarkably, PPI use increased with age, its prevalence among patients over 60 years old reaching 14.0% in men and 16.3% in women and exceeding 20% among patients aged 80 years and over.[5] In stage 5D chronic kidney disease (CKD) patients, we found that PPI use is even higher, with 76 % of patients receiving long-term treatment.[6] Bone and mineral disorders, including secondary hyperparathyroidism and bone fractures, are more common among CKD patients than in people with normal renal function.[7] In the general population, PPI use is associated with an increased risk of fractures.[8,9]

The aim of this study was to assess the relationship between use of PPIs, and bone and hip fractures in hemodialysis patients of the phases 2-4 of the observational Dialysis Outcomes and Practice Patterns Study (DOPPS) study, which included the systematic collection of fractures requiring hospitalization.

Material and Methods

Patient population

The DOPPS is a prospective cohort study of hemodialysis practices based on the collection of observational longitudinal data for a random sample of patients from dialysis facilities in a

representative and random sample of units in more than twenty countries.[7] DOPPS 1 began in 1996-2001 in the United States, in 1998–2001 in Europe (France, Germany, Italy, Spain, and the United Kingdom) and in 1999-2001 Japan. DOPPS 2 (2002–2004), 3 (2005–2008), and 4 (2009–2011), included the same DOPPS 1 countries, plus Australia, New Zealand, Canada, Belgium, and Sweden. The DOPPS phases 2-4 included 34593 hemodialysis patients, of whom 27857 (i.e. 81%) were hospitalized for various reasons.

Study groups, outcome and exposure definition

From a source population of 27857 hospitalized patients, 75 were excluded because of missing baseline demographic characteristics (such as age, race, time of starting dialysis and gender) and 685 patients were excluded because of missing information on PPI treatment. Thus, 27097 hospitalized patients were available for the present analysis. We specifically focused on hospitalized patients to better capture medication data thus minimizing the possibility of information bias.

The DOPPS investigators identified all first hospitalizations (defined by an overnight hospital stay) with an associated “bone fracture diagnosis code” according to international standards for hospital admissions. Bone fractures were coded as either 'hip' or 'other'; information on other types of fractures (e.g. vertebral fractures) were not available. Thus, bone fractures include “hip-fractures” and fractures other than hip fractures. Hospitalizations and outpatient visits (including fracture-related visits) occurring during the study, along with diagnoses and procedures (i.e. X-ray imaging) relevant to the hospitalization or outpatient visit, were reported chronologically for each patient. Capturing both hospitalization events and outpatient visits provided a reasonable expectation that the vast majority of fracture-related events were recorded in this study. Hip fractures were distinguishable from among all reported fracture-related events, whereas fracture types other than hip fracture were less well defined and consequently analysed collectively. For fracture event rates, follow-up continued until the first of death, fracture hospitalization, transplantation, renal replacement therapy modality switch, recovery of renal function, departure from the facility, or end of follow-up. PPI use was assessed on individual basis, i.e. whether or not the PPI was administered in the patient concerned

at the time of the visit. Prevalent PPI users were those who were already treated with the drug at the date of enrolment. Naïve users or "new users" were those who start the treatment after the enrolment into the study.

Statistical Analysis

Patients' characteristics were summarized as mean ± standard deviation, median and inter-quartile range or as percent frequency, and comparisons between patients' groups were made by independent T-Test, Mann-Whitney Test or Chi Square Test, as appropriate. The frequency of bone and hip fractures requiring hospitalization across Countries was expressed as incidence rate (fractures/100 person-years) and 95% confidence interval. In the 'time to the first event' survival analyses, the index date for naïve PPI users was the date of starting treatment whereas for prevalent PPI users and nonusers the index date was the date of enrollment.

The crude and adjusted relationships between PPI treatment and incidence rate of bone and hip fractures, taking into account the competitive risk of mortality, were investigated by using the cumulative incidence function and the Fine and Gray approach,[10] respectively. The effect of PPI on study outcomes was also investigated by a cause-specific hazards Cox model dealing patient death as a censoring event and stratifying by Country and study phase. To provide further insight into the pathophysiological implications of study results, we calculated the etiological fraction or attributable risk (AR), i.e. the proportion of fractures that would be prevented in our study cohort if the PPI treatment was eliminated in treated patients.

In multiple Cox models, we included PPI treatment as well as a series of potential confounders (i.e. all variables listed in Table 1): age, gender, race, BMI, diabetes, smoking (past and current), background CV comorbidities, dialysis vintage (i.e. the time spanning from the date of dialysis initiation to the date of enrolment into the study), concomitant treatments (any form of Vitamin D, phosphate binders, and calcium-based phosphate binders), and biochemical data [albumin, PTH, calcium, phosphate, alkaline phosphatase and fractional urea clearance (Kt/V)]. To account for prevalent users bias, a sensitivity analysis on naive patients versus no users was also performed.

Concomitant therapies (any form of Vitamin D, phosphate binders, and calcium-based phosphate binders) were defined differentially for the two study outcomes, depending on the fact whether the date of each specific treatment start precedes or not the date of the outcome occurrence.

Missing values for confounding variables were imputed by multiple imputation in which 30 completed data sets were generated and analyzed with standard combination rules for multiple imputation. Each variable was used as a confounder in the imputation model. In Cox models fitted according to the Fine and Gray approach, data were expressed as sub-distribution hazard ratios (SHR), 95% CIs and P values. In cause-specific hazards Cox models dealing patient death as a censoring event, stratifying by Country and study phase and matching patients of the two arms according to the prescription time-distribution,[11] data were expressed as hazard ratios (HR), 95% CIs and P values.

All analyses were performed by two standard statistical packages (SPSS for Windows Version 22, IBM, USA; STATA/IC 13.0 StataCorp P, TX, USA).

Role of the Funding source

None of the authors received any funding for this study.

Patient and Public Involvement

Full details about the involvement of patients and public in the DOPPS data collection are given elsewhere (see https://www.dopps.org/).

Results

The main demographic, clinical and biochemical data of the whole study population (n=27,097) as well as of PPI treated (n=13,283, 49%) and untreated (n=13,814, 51%) patients are given in **Table 1**. In individual countries, the prevalence of PPI treated patients ranges widely from 28.6% in Japan to 73.5% in Spain (**Supplementary Figure 1)**. Overall, patients from western countries represent 77% of the PPI treated population and 60% of the non-PPI treated patients, while the corresponding data for Asians are 12% and 28%. The incidence rates of bone fractures were higher on average in PPI treated than in PPI untreated patients in all countries but Italy and Germany

(Supplementary Figure 2). However, in Italy hip fractures were higher in PPI treated than in untreated patients whereas in Germany the contrary was observed.

Across the follow-up period (median 19 months, IQR: 10-28 months), 1,592 patients experienced bone fractures (3.8 bone fractures/100 person-years, 95% CI: 3.6-3.9) and 528 patients had hip fractures (1.2 hip fractures/100 person-years, 95% CI: 1.1-1.3). Overall, 6,249 patients died. The mortality rate was higher in PPI users than in no users (25.8% versus 20.4%, P<0.001) raising a problem of competitive risks. In crude Cox models (Fine & Gray approach) taking into account the competitive risk of mortality, the incidence rate of bone (SHR: 1.36, 95% CI: 1.24-1.51, P<0.001) and hip fractures (SHR: 1.70, 95% CI: 1.43-2.02, P<0.001) was significantly higher in PPI treated than in PPI untreated patients (**Figure 1-upper panels**). A sensitivity analysis in naïve PPI users (**Supplementary Table I**), confirmed a higher incidence rate of bone and hip fractures in PPI treated than in PPI untreated patients (**Figure 1-bottom panels**). The calculation of the attributable risk (AR) showed an AR of 30% for bone fractures and 44% for hip fractures in the whole study population and an AR of 37% and 52%, respectively, in the sensitivity analysis on naïve users versus untreated suggesting that about one half of hip fractures and more than one third of bone fractures could be avoided if PPI use was eliminated in treated patients. Data adjustment for potential confounders, i.e. for all variables listed in **Table 1**, did not materially affect the PPI-study outcomes links either in the whole study cohort ('prevalent users + naïve users' versus 'no users', see **Table 2**) or in a sensitivity analysis assessing the fractures risk of 'naïve users versus no users' (**Table 3**).

In multiple, country and phase stratified, cause-specific hazards Cox models (adjusting for the same set of variables listed in **Tables 2-3**) in patients of the two arms matched according to the prescription time (n=14136 of whom 3276 treated with PPI and 10860 untreated), PPI treatment confirmed as a strong and independent risk factor of study outcomes [bone fractures, $HR_{\text{Country and phase stratified}}$: 1.47, 95% CI: 1.23-1.76, P<0.001; hip fractures, $HR_{\text{Country and phase stratified}}$: 1.85, 95% CI: 1.37-2.50, P<0.001]. Of note, diabetes consistently emerged as a strong risk factor of bone and hip

fractures in the study population (see **Tables 2-3**) independently of PPI use and other potential confounders.

Discussion

In a large, international cohort of hospitalized hemodialysis patients, the use of PPI associates with an increased risk of bone and hip fractures independently of the competitive risk of mortality and potential confounders including demographic, clinical and biochemical data as well as concomitant therapies. Thus, the study provides evidence supporting the notion that PPI use is a risk factor of bone and hip fractures in the dialysis population.

PPIs are among the most widely prescribed medications worldwide. The average prevalence of PPI use in the DOPPS population is 49%, a figure markedly higher than that in the general population,[6] where several studies have highlighted the association between PPI treatment and bone fractures.[8,9,12] In a meta-analysis including 11 observational studies,[12] the reported relative risk for hip fractures associated with PPI use was 1.30 (95 % CI: 1.19-1.43) and such an association was of similar magnitude of that we found in the whole dialysis population comparing prevalent + naïve users versus no users (SHR: 1.35, 95% CI: 1.13-1.62- Table 2) but lower than that emerged in the sensitivity analysis comparing naïve users versus no users (SHR: 1.62, 95% CI: 1.24-2.11) indicating that the prevalent users bias should be taken into account when investigating the effect of PPI on adverse clinical outcomes in hemodialysis patients. In the same metanalysis,[12] the relative risk associated with PPI users was also increased for spine (RR: 1.56, 95% CI 1.31–1.85) and any-site fractures (RR: 1.16, 95% CI 1.04–1.30). Based on growing and compelling evidences reported in literature, the FDA issued a drug safety communication warning about the possibility of increased risk of fractures of the hip, wrist, and spine with the long-term use of both prescription and over-the-counter PPIs in the general population.[13] This recommendation is of obvious public health importance because fractures *per se* are not only disabling clinical events but also a risk factor of mortality. Indeed, a population-based study highlighted a relationship between bone fractures and an increased risk of death and reported a mortality rate of 20% in the first year after a hip fracture.[14] Similar data

on mortality associated with hip fractures were also reported in hemodialysis patients: post-fracture mortality rates exceeded 500/1000 patient years and fractured patients had higher unadjusted rates of death (3.7-fold) than the overall non-fractured dialysis population.[7] On the other hand, mortality is exceedingly higher in hemodialysis patients than in the general population and for this reason it could act as a competitive risk while investigating the relationship between PPI use and bone fractures. Remarkably, in our study the relationship between PPI use and bone fractures remained significant also considering the competitive risk of death for both bone and hip fractures, either on univariate or on multivariable Cox analyses.

Mechanisms linking PPI use and bone fractures are still poorly understood, but there are several potentially plausible explanations. Importantly, fractures may be facilitated not only by reduction in bone density, but also by derangement of bone quality, and both bone quantity and quality could be affected by PPI use. Inhibition of gastric acid secretion can adversely affect the absorption of several nutrients, vitamins and drugs.[15] A reduced intestinal absorption of calcium and magnesium could lead to osteoporosis and fractures. However, in our study blood biochemistry results did not affect the association between PPI and fractures. Our results are consistent with accurate metabolic studies showing that PPI-associated hypochlorhydria does not decrease fractional calcium absorption following 30 days of continuous PPI use.[16] Although we did not measure magnesium level in the study cohort, the homeostasis of this cation seems to be crucial for bone health. Magnesium deficiency, a well known adverse effect of PPI use,[17] contributes to bone impairment, both directly by acting on crystal formation and on bone cells, and indirectly by interfering with the activity of parathyroid hormone and 1,25$(OH)_2$-vitamin D synthesis, as well as by promoting low grade inflammation.[18] Magnesium is also deposited in large quantities in bone, being essential for bone health. In addition, since magnesium is acting as inhibitor of extra-skeletal calcification, PPI-induced hypomagnesemia may worsen vascular calcifications in patients with CKD.[19] Interestingly, in the DOPPS cohort treated with PPIs peripheral artery disease was more common (34% of patients) compared to untreated patients (26%). Proton pump inhibitors interfere with the active transport of

magnesium, and clinically significant phenomena are observed in the carriers of heterozygotic mutations of the ion channels TRPM6 and TRPM7 (transient receptor potential melastatin), which have a relevant role in the maintenance of magnesium homeostasis.[17,19] Recently, Sakaguchi et al investigated 113,683 patients undergoing hemodialysis over a 2-year follow-up, finding an incidence of 2% for new hip fractures. The crude incidence rate was significantly higher among patients in the lower quartiles of serum magnesium levels (2.63%, 2.08%, 1.76%, and 1.49% in Q1–Q4, respectively). After adjustment for demographic and clinical factors, patients in Q1 had a 1.23-fold higher risk for hip fracture than those in Q4 (95% confidence interval, 1.06 to 1.44; P=0.01).[20] Of course, given the fact that we did not dose magnesium levels in the DOPPS patients, these considerations, although biologically plausible, are purely speculative.

Vitamin B12 deficiency has been associated with PPI use.[21] Low vitamin B12 levels increase homocysteine levels, impairing cross-linking of bone collagen,[22] and might increase the risk of bone fractures.[23] In addition, peripheral neuropathy is also a consequence of vitamin B12 deficiency, increasing the risk of falls and, consequently, of bone fractures. The association between PPI use and increased risk of falls has been clearly demonstrated.[24] Moreover, a direct PPI action on bone is also a possibility.[25] Osteoclast function is dependent on proton pumps, which may be directly inhibited by PPIs, reducing bone resorption and turnover. This action was initially considered a potential treatment for osteoporosis,[26] but altering bone turnover can deteriorate bone quality and increase the risk of fractures.

PPI treatment has been associated with other relevant side effects, supporting the concept of significant adverse biologic effects on the body, besides the intended effects in the gastrointestinal system.[27] Microbiome alterations with bacterial overgrowth may affect absorption of nutrients, including proteins and vitamin K, with potential long-term adverse effects on bone health and increased fracture risk.[28] The potential interaction between PPIs and vitamin K is of interest, as vitamin K intake is associated with a protective effect on bone fractures.[29]

The large difference in the incidence rates of bone fractures among different countries, as well as the finding that in Italian and German patients the side effect of PPI was not visible, remain unexplained and they deserve further studies, in order to identify which factors might prevent bone fractures.

Study strengths and limitations

Strengths of our study are the large patient-population and the fact that the PPI-fractures relationship remains significant in Cox models including potential confounders and taking into account the competitive risk of death by the Fine and Gray approach[10] as well as in multiple, cause-specific hazards Cox models dealing patient death as a censoring event, stratifying by Country and study phase and matching patients of the two arms according to the prescription time-distribution. Furthermore, the potential distortion attributable to prevalent users' bias on the study results was investigated by performing a detailed analysis in naïve patients versus no treated. Remarkably, such a sensitivity analysis provides results even more convincing than those obtained in the whole study population comparing prevalent + naïve PPI users versus no users. Lastly, the observational nature of our cohort represents another strength, rather than a weakness, of our study, because observational studies are recognized to be essential for investigating the safety profile of medications.[30] Although in Cox models we adjusted for a series of well-known potential confounders (including demographic and clinical variables and bone biomarkers), the possibility that we did not adjust for 'unmeasured confounders' (including other tattribdrugs) cannot be excluded. However, the magnitude of the excess risk of bone and hip fractures (ranging from +22% to +62%) in PPI treated patients as compared to those untreated indicates that such a possibility is rather unlikely. Furthermore, it is important noting that the hazard ratio of PPI for bone fractures we found in our study (see Table 2) was very similar (1.22 versus 1.19) to that reported in a secondary analysis of the EVOLVE trial investigating the effect of Cinacalcet and other risk factors on the risk of bone fractures in dialysis patients.[31] In this post-hoc analysis,[31] in a multiple Cox model adjusting for a series of potential confounders, the effect of PPI on bone fractures did not achieve the formal statistical significance (P=0.09) most likely because of the low number of patients treated with PPI in the experimental EVOLVE trial (only 1141

patients versus 13283 patients in our real-life study). Our results are also in keeping with those reported in a recent case-control study by Vangala et al.[32] in hemodialysis patients included in the USA Renal Data System. This study shows that the odds ratio of hip fractures is higher in PPI treated than in untreated patients, independently of a series of potential confounders. In the Vangala's study, the adjusted excess risk of hip fractures of PPI use versus nonuse ranged from +16% to +21% (dependent on the frequency of PPI administration), figures lower than those found by us in primary (+35%) and sensitivity (+62% and +85%) analyses. This underestimation of the PPI effect on hip fractures may depend on the fact that Vangala et al.[32] did not take into account the potential distortion due to prevalent users bias, did not include into multivariate models circulating levels of bone biomarkers and did not collect time to event data, all methodological issues which we specifically considered in our study, which also has the strength of including an international cohort of hemodialysis patients.

Conclusions

Considering the major health and economic burden of bone fractures, it is of utmost importance to adopt strategies for bone fractures prevention in a fragile population such as hemodialysis patients. The growing and convincing evidence of a harmful effect of PPI on bone health[33-34], the internal coherence of the results emerged in our study as well as the magnitude of the negative effect of PPI use on the risk of bone and hip fractures in hemodialysis patients suggest caution and a careful evaluation of risks/benefits ratio while prescribing this class of drugs in this patient population.

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Legends to figures

Figure 1 Cumulative incidence of bone and hip fractures in PPI treated and untreated patients in the whole study cohort (upper panels) as well as in the sensitivity analysis (bottom panels) comparing naïve PPI users versus no users. See Methods-Statistical Analysis for more details.

Supplementary Figure 1 Percentage of DOPPS patients on PPI treatment according to Countries.

Supplementary Figure 2 Country-stratified **i**ncidence rate of bone and hip fractures (and 95% CI) in PPI treated and untreated patients.

Table 1 Demographic, clinical and biochemical characteristics of the whole cohort of patients and as divided according to PPI treatment.

		PPI treatment	
	Whole cohort (n=27097)	**No users (n=13814)**	**Prevalent users + naive patients (n=13283)**
Age (years)	63.9±14.4	63.1±14.6	64.8±14
BMI (kg/m^2)	25.2±5.9	24.9±5.8	25.6±5.9
Dialysis vintage (months)	24 (5-64)	23 (4-66)	24 (5-62)
Male gender (%)	58.4%	59.7%	57.1%
Caucasians (%)	68.6%	60.0%	77.5%
African descent (%)	7.2%	8.1%	6.3%
Asian/Indian (%)	20.1%	27.5%	12.4%
Native American (%)	0.8%	0.72%	0.76%
Other (%)	3.3%	3.6%	3.0%
Smoking (%)	48.4%	46.8%	50.1%
Background CV comorbidities			
Diabetics (%)	40.6%	39.0%	42.4%
Coronary Artery Disease (%)	46.8%	43.4%	50.4%
Chronic Heart Failure (%)	32.9%	30.6%	35.3%
Cardiovascular Disease (%)	36.7%	34.5%	38.9%
Cerebrovascular disease (%)	18.0%	16.4%	19.8%
Peripheral Artery disease (%)	29.9%	26.0%	34.0%
Biochemical data			
Albumin (g/dl)	3.7±0.4	3.7±0.4	3.6±0.5
PTH (pg/ml)	199(104-340)	187(96-329)	209(114-349)
Calcium (mg/dl)	9.1±0.7	9.1±0.7	9.0±0.6
Phosphorus (mg/dl)	5.2±1.3	5.4±1.3	5.1±1.3
Alkaline phosphatase (units/l)	109(77-185)	114(77-202)	106(77-170)
**Kt/V	1.48±0.28	1.45±0.28	1.50±0.28
Concomitant therapies*			
***Any Vitamin D (%)	65.2%	62.9%	67.5%
Phosphate binders (%)	91.3%	92.1%	90.5%
Calcium-based phosphate binders (%)	74.1%	77.7%	70.5%

Data are mean ± SD, median and interquartile range, or as percent frequency, as appropriate.
*Concomitant therapies when investigating the hip fractures are as follows:
whole cohort, any Vitamin D: 65.4%; phosphate binders: 91.4%; calcium-based phosphate binders:74.3%.
no users, any Vitamin D: 63.2%; phosphate binders: 92.2%; calcium-based phosphate binders:77.8%.
prevalent users + naïve users, any Vitamin D: 67.7%; phosphate binders: 90.5%; calcium-based phosphate binders:70.6%.
**Fractional urea clearance (a dimensionless index of dialysis adequacy).
*** Includes either intravenous (alphacalcidol, paricalcitol, doxercalciferol, calcitriol, and other) or oral vitamin D.

Table 2 Multiple Cox regression analyses in all study sample (prevalent users + naive patients versus no users, n=27097)

	Multiple Cox regression models taking into account the competing risk of death (Fine & Gray approach)	
Variables (units of increase)	**Bone fractures** *SHR (95% CI) and P value*	**Hip fractures** *SHR (95% CI) and P value*
PPI treatment (0=no users; 1=prevalent users + naïve users)	**1.22(1.10-1.36), P<0.001**	**1.35(1.13-1.62), P=0.001**
Age (1 year)	**1.02(1.01-1.02), P<0.001**	**1.04(1.03-1.05), P<0.001**
Gender (0=F; 1=M)	**0.64(0.57-0.71), P<0.001**	**0.68(0.58-0.83), P<0.001**
African descent (0=caucasians;1=yes)	**0.61(0.47-0.79), P<0.001**	0.72(0.46-1.11), P=0.13
Asian/Indian (0= caucasians;1=yes)	0.89(0.77-1.04), P=0.15	**0.41(0.29-0.56), P<0.001**
Native American (0= caucasians;1=yes)	1.07(0.62-1.85), P=0.80	1.66(0.74-3.72), P=0.22
Other (0= caucasians;1=yes)	**0.68(0.47-0.97), P=0.03**	0.65(0.32-1.30), P=0.22
BMI (kg/m^2)	0.99(0.98-1.01), P=0.14	0.98(0.96-1.00), P=0.05
Diabetes (0=no; 1=yes)	**1.29(1.16-1.44), P<0.001**	**1.23(1.01-1.50), P=0.04**
Smoking (0=no; 1=yes)	1.09(0.98-1.23), P=0.12	1.10(0.90-1.34), P=0.34
CV comorbidities (0=no; 1=yes)	1.03(0.91-1.17), P=0.66	1.21(0.95-1.56), P=0.13
Dialysis vintage (years)	**1.02(1.01-1.03), P<0.001**	**1.04(1.02-1.05), P<0.001**
Any Vitamin D (0=no; 1=yes)	**0.87(0.78-0.97), P=0.01**	0.94(0.78-1.14), P=0.54
Phosphate binders (0=no; 1=yes)	0.91(0.77-1.08), P=0.27	0.88(0.67-1.17), P=0.38
Albumin (1 g/dl)	**0.73(0.65-0.83), P<0.001**	**0.62(0.50-0.77), P<0.001**
PTH (100 pg/ml)	1.01(1.00-1.03), P=0.05	1.02(0.99-1.04), P=0.15
Calcium (1 mg/dl)	1.01(0.93-1.09), P=0.80	1.05(0.92-1.20), P=0.49
Phosphate (1 mg/dl)	**0.92(0.88-0.97), P=0.001**	0.93(0.85-1.01), P=0.08
Alkaline Phosphatase (1 unit/l)	**1.01(1.00-1.02), P=0.006**	1.00(0.99-1.01), P=0.23
Kt/V (1 unit)	**1.33(1.09-1.61), P=0.004**	1.27(0.91-1.77), P=0.16

Data are sub-hazard ratios (SHR), 95% CI and P value.
Cox analyses including calcium-based phosphate binders instead of phosphate binders provided similar results (data not shown).

Table 3 Multiple Cox regression analyses in naïve PPI users versus no users (n=17090).

	Multiple Cox regression models taking into account the competing risk of death (Fine & Gray approach)	
Variables (units of increase)	**Bone fractures** *SHR (95% CI) and P value*	**Hip fractures** *SHR (95% CI) and P value*
PPI treatment (0=no users; 1=naïve users)	**1.29(1.10-1.51), P=0.002**	**1.62(1.24-2.11), P<0.001**
Age (1 year)	**1.02(1.02-1.03), P<0.001**	**1.06(1.04-1.07), P<0.001**
Gender (0=F; 1=M)	**0.56(0.49-0.65), P<0.001**	**0.56(0.43-0.73), P<0.001**
African descent (0=caucasians;1=yes)	**0.49(0.35-0.70), P<0.001**	0.74(0.43-1.28), P=0.28
Asian/Indian (0= caucasians;1=yes)	**0.79(0.66-0.95), P<0.001**	**0.34(0.23-0.51), P<0.001**
Native American (0= caucasians;1=yes)	1.41(0.74-2.68), P=0.30	2.78(1.14-6.79), P=0.03
Other (0= caucasians;1=yes)	0.72(0.46-1.12), P=0.15	0.42(0.13-1.32), P=0.14
BMI (1 kg/m^2)	**0.99(0.97-0.99), P=0.04**	**0.96(0.94-0.99), P=0.01**
Diabetes (0=no; 1=yes)	**1.26(1.09-1.46), P=0.002**	**1.31(1.01-1.70), P=0.04**
Smoking (0=no; 1=yes)	1.13(0.96-1.32), P=0.15	1.05(0.80-1.38), P=0.74
CV comorbidities (0=no; 1=yes)	1.05(0.89-1.23), P=0.58	1.24(0.89-1.73), P=0.20
Dialysis vintage (years)	**1.02(1.01-1.04), P<0.001**	**1.03(1.01-1.06), P=0.002**
Any Vitamin D (0=no; 1=yes)	0.92(0.80-1.07), P=0.28	1.19(0.91-1.54), PP=0.20
Phosphate binders (0=no; 1=yes)	0.83(0.66-1.05), P=0.12	0.79(0.53-1.19), P=0.26
Albumin (1 g/dl)	**0.79(0.67-0.93), P=0.005**	**0.72(0.53-0.99), P=0.04**
PTH (100 pg/ml)	1.01(0.99-1.03), P=0.32	0.99(0.94-1.03), P=0.57
Calcium (1 mg/dl)	0.95(0.86-1.05), P=0.34	1.01(0.84-1.23), P=0.88
Phosphate (1 mg/dl)	**0.92(0.86-0.97), P=0.005**	0.94(0.85-1.06), P=0.30
Alkaline Phosphatase (1 unit/l)	1.00(1.00-1.01), P=0.03	1.00(0.99-1.01), P=0.41
Kt/V (1 unit)	1.24(0.95-1.61), P=0.11	0.97(0.60-1.57), P=0.90

Data are sub-hazard ratios (SHR), 95% CI and P value.

Cox analyses including calcium-based phosphate binders instead of phosphate binders provided similar results (data not shown).

Supplementary table I Demographic, clinical and biochemical characteristics of the whole cohort of patients and as divided according to PPI treatment (no users versus naïve users).

	PPI treatment	
	No Users (n=13814)	**Naive patients PPI treated (n=3276)**
Age (years)	63.1±14.6	64.5±13.8
BMI (kg/m2)	24.9±5.8	25.5 ±5.9
Dialysis vintage (months)	23.5 (4-66)	24 (5.5-67)
Male gender (%)	59.7%	57.7%
Caucasians (%)	60.0%	69.1%
African descent (%)	8.1%	7.7%
Asian/Indian (%)	27.5%	19.0%
Native American (%)	0.72%	0.79%
Other (%)	3.6%	3.3%
Diabetics (%)	39.0%	42.2%
Smoking (%)	46.8%	49.2%
Background CV comorbidities		
Coronary Artery Disease (%)	43.4%	48.5%
Chronic Heart Failure (%)	30.6%	33.2%
Cardiovascular Disease (%)	34.5%	35.3%
Cerebrovascular disease (%)	16.4%	17.7%
Peripheral Artery disease (%)	26.0%	31.2%
Biochemical data		
Albumin (g/dl)	3.7±0.4)	3.6 ±0.4)
PTH (pg/ml)	187 (96-329)	208(113-352)
Calcium (mg/dl)	9.1±0.7	9.1±0.6
Phosphorus(mg/dl)	5.4 ±1.3	5.2±1.2
Alkaline phosphatase (units/l)	114 (77-202)	110 (79-195)
Kt/V	1.45±0.28	1.50 ±0.29
Concomitant therapies*		
Any Vitamin D (%)	62.9%	71.7%
Phosphate binders (%)	92.1%	93.3%
Calcium-based phosphate binders (%)	77.7%	74.8%

Data are mean ± SD, median and interquartile range, or as percent frequency, as appropriate.

*Concomitant therapies when investigating the hip fractures are as follows:

no users, any Vitamin D: 63.2%; phosphate binders: 92.2%; calcium-based phosphate binders:77.8%.

naïve users, any Vitamin D: 71.9%; phosphate binders: 93.4%; calcium-based phosphate binders:74.9%.