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TITLE: "Benefits, Harms, and Costs of Osteoporosis Screening in Male Veterans."

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7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

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14. ABSTRACT

This is a longitudinal cohort study of approximately 5,000,000 screened and non-screened for osteoporosis, older veterans who received care within the VA system during the study period, followed for up to 10 years to measure fracture rates, mortality rates, treatment-related harms, and cost. In the past year variable definitions and data comparisons has been completed. Identification of the screened cohort is complete. The propensity score model has been developed and analysis to estimate the impact of osteoporosis screening and treatment on fracture and mortality rates has been completed. Analyses have begun to determine whether bisphosphonate treatment is associated with a change in fracture rates or mortality. Analysis has begun for treatment-related harms using time to event modeling with receipt of bisphosphonate as the time varying covariate of interest. The process of defining harms variables is complete. Costs will be measured prospectively for all subjects in the cohort, and adjusted for important covariates. A cost differential for screened and unscreened populations will be calculated. To estimate health system costs under varying screening thresholds and conditions we have employed modeling analyses. Cost variables have been defined.

15. SUBJECT TERMS

Osteoporosis, Males, Screening

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1. INTRODUCTION:

Osteoporotic fractures are a major and under-recognized problem in older men.[1] Osteoporosis is particularly prevalent in the VA system; more than half of male veterans over age 50 years have osteopenia or osteoporosis, and nearly 12% of those over age 75 years have osteoporosis, a rate nearly double the non-veteran population.[6] Despite the widespread recognition that osteoporosis is an important disease in men, there is no clear consensus on the appropriate approach for the primary prevention of osteoporotic fractures. While clinical practice guidelines in women uniformly endorse osteoporosis screening beginning at age 65 years,[11] clinical practice guidelines for men vary substantially in the recommended selection of the screening population, and indeed, on whether or not sufficient evidence exists to support osteoporosis screening at all. Current recommendations include screening all men at a given age [National Osteoporosis Foundation (NOF), Canadian Medical Association (CMA)], or selecting men based on the presence of osteoporosis risk factors [VA HSR&D, American College of Physicians (ACP)].[12-15] In the U.K., clinical risk factor scoring systems such as the Fracture Risk Assessment Tool (FRAX) are used to stratify patients; high risk groups receive treatment without further screening, intermediate risk groups go on to Dual Energy X-ray Absorptiometry (DXA) screening, and low risk groups receive no further screening.[15] Most recently, the United States Preventive Services Task Force (USPSTF) completed a systematic review of osteoporosis screening and treatment in men, and concluded that there was insufficient evidence to recommend for or against screening.[16] This conclusion was also adopted by the VA National Center for Health Promotion and Disease Prevention. This project has developed a large database combining Veterans Affairs and Centers for Medicare and Medicaid Services (CMS) data to quantify the benefits, costs, and harms of osteoporosis screening among men. We will use this database to determine the benefits of osteoporosis screening, including rates of fractures and mortality. We will quantify the harms of osteoporosis screening and treatment, including rare but important side effects such as heart disease, esophageal cancer, and atypical fractures. We will prospectively measure healthcare costs in the screened and unscreened individuals, and model the impact of different screening selection criteria on healthcare system costs. The goal is to develop evidence-based male osteoporosis screening recommendations that optimize benefits to patients, while minimizing harms and health system costs.

2. KEYWORDS:

Osteoporosis
Males
Veterans
Screening
Harms
Costs
Treatment
Fractures
Benefits
Propensity

3. Accomplishments:

What were the major goals of the project? The major goals are to quantify the benefits, harms, and costs of osteoporosis screening in a large cohort of older male Veterans. Specifically the goals were: 1) to create the largest dataset currently available about osteoporosis in men, including medications, co-morbidities, bone mineral density, fractures, and costs; 2) identify Veterans who were screened for osteoporosis and use Natural Language Processing to determine screening results; 3) compare fracture rates and mortality between screened Veterans and a propensity matched group of unscreened Veterans with similar baseline risk. The phases of the project, target dates, and completion status are listed below.

Task	Methods	Outcome/Deliverable/Product	Status
Milestone 1. Regulatory Approval, CMS and VA data requested and obtained. (months 1-6)			
Submit IRB and Human Subjects initial and continuing reviews at Durham VAMC and Salt Lake City VAMC (month 1-4)	Regulatory document completion, human subjects training	Maintenance of IRB approval at all sites engaged in research, study binder, personnel training up to date	Complete Jan_2013
Request Corporate Data Warehouse (CDW), and 1994-1999 Austin data (month 1-3)	Data Access Request Tracker (DART) system	Finder file of all Veterans in study period meeting eligibility criteria developed	Complete Dec_2012
Request Medicare (CMS) data from VA Information Resource Center (VIReC) (month 4-6)	Per VIReC Medicare data request process, using finder file developed from Austin data	Medicare data on eligible subjects downloaded to Durham VA server	Complete Dec_2012
Develop data management and security standard operating procedures (SOPs) (month 1-6)	Modification of existing and creating new SOPs as needed to describe data management practices	• Secure server files created and maintained • Clear procedures for data cleaning and management tasks documented	Complete Feb_2013
Milestone 2. Dual Energy X-ray Absorptiometry (*DXA*) data extracted and cleaned, VA and CMS data cleaned and ready for merge with DXA data (months 1-12)			
Extract DXA data from eligible subjects (month 1-6)	Natural language processing used to extract DXA results from text notes in radiology and	Dataset containing DXA results from all eligible subjects assembled.	Sep_2013

	consultation records		
Clean and validate DXA data (month 6-12)	Random subset of records hand pulled to calculate validations statistics	• Accuracy, Precision, Recall, and F measure calculated for DXA dataset. • DXA dataset is cleaned a ready for merge with VA and CMS files	Jan_2014
VA database variables cleaned and validated (month 6-12)	Outlier variables are identified using graphical and numerical methods, and confirmed, replaced or deleted per the SOPs developed above. Missing variables are imputed if indicated.	Clean database of VA variables created and ready to merge with CMS and DXA files	Dec_2013
CMS database variables cleaned and validated (month 6-12)	Outlier variables are identified using graphical and numerical methods, and confirmed, replaced or deleted per the SOPs developed above. Missing variables are imputed if indicated.	Clean database of CMS variables created and ready to merge with CMS and DXA files	Mar_2014
Milestone 3: Utilization and cost measures constructed for both VA and CMS data, and VA and CMS data files merged. (months 9- 18)			
Construct utilization and cost measures for VA database. (months 9-15)	Fracture related costs will be summarized across VA and non-VA contracted care using ICD9 and CPT codes and aggregated across inpatient and outpatient fields annually for each subject	Fracture-related costs to VA calculated for eligible subjects	Jul_2015
Construct utilization and cost measures for CMS database. (months 9-15)	Fracture-related costs to Medicare will be identified using ICD-9 codes and surgical procedure codes. Total costs to Medicare will be aggregated using the Beneficiary Annual Summary File, and aggregating the positive values from each of the following	Fracture related costs to CMA calculated for eligible subjects	Jul_2015

	variables for the year.		
VA and CMS data files merged (month 15-18)	Using unique subject identifiers, CMS and VA data files will be merged, and cleaned using SOPs.	Cleaned database containing relevant VA and CMS variables created for all eligible subjects	Sep_2015
Milestone 4: Final analytic file completed. (month 21)			
DXA data merged with combined VA and CMS files (month 18-19)	Using unique subject identifiers, DXA data files will be merged with the main analytic file, and cleaned using SOPs.	Database containing all VA, CMS, and DXA result variables ready for cleaning	Jul_2015
Merged file cleaned, data inconsistencies identified and cleaned using SOPs. (month 20-21)	Contradictory or multiple variables across files are identified using graphical and numerical methods, and confirmed, replaced or deleted per the SOPs developed above. Missing variables are imputed if indicated.	Cleaned database containing relevant VA and CMS variables and DXA results is ready for analysis	Aug_2015
Data de-identification of merged file completed according to SOPs (month 21)	Using current VA Information Security Officer guidance, merged datafile will be stripped of HIPAA key identifiers to create a limited data set	Cleaned dataset created with risk of subject identification and loss of privacy minimized	Sep_2015
Milestone 5: Analyses for specific aims completed. (month 30)			
Analyses for specific aims 1-2 (benefits and harms) completed. (months 21-30)	A "propensity to be screened" model will be developed for each VAMC (strata) based on their osteoporosis and fracture risk factors. This screening propensity score will be used as a further stratification variable in Cox Proportional Hazards models, with receipt of DXA as a time-varying covariate, to estimate the impact of osteoporosis screening and	• Hazard ratio reflecting risk of fracture and all-cause mortality (dependent variables) in screened and unscreened individuals, adjusting for important covariates including bisphosphonate treatment • Hazard ratio reflecting risk of harm in treated vs. untreated individuals, adjusting for important covariates (dependent variables include cardiovascular events, esophageal cancer, atypical fractures)	80% complete

	treatment on fracture rates, mortality rates, and treatment-related harm outcomes.		
Analyses for specific aim 3 (costs) completed. (months 21-30)	We will calculate VA and Medicare fracture related resource utilization costs as well as total VA and Medicare resource utilization costs for subjects in five year increments. Costs to the VA and costs to Medicare will be modeled separately and also aggregated to understand overall costs across the two public insurers.	• Cost to VA, Medicare, and total costs of different strategies of osteoporosis screening in male veterans	80% complete
Milestone 6: Result dissemination, final report completed. (month 36)			
Summary results (technical reports) of specific aims 1-3 written. (month 30-33)		Executive summary and technical report created for presentation to relevant stakeholders	50% complete
Technical reports presented to key stakeholder groups identified by advisory board members. (months 33-36)		• Report presented to VA National Center for Health Promotion and Disease Prevention • Report presented to VA Pharmacy Benefits Management	Pending
Scientific presentations and articles for peer review drafted on specific aims 1-3. (months 30-33)		• Results presented at American Society of Bone and Mineral Research, VA Health Services Research and Development, or other professional meetings	First paper published, 4 scientific meeting abstracts

What was accomplished under these goals?

Major Activities and Specific Objectives. In the last report year, major activities can be divided into the following categories:
1) Database development: Natural Language Processing was completed with excellent validation measures on the DXA results. The main analysis database which includes pharmacy, lab, diagnoses, FRAX, BMD, cost, and outcome data has been cleaned and assembled. It is now ready for both primary and secondary analysis.
2) Main analysis activities: Propensity scores predicting likelihood of osteoporosis screening have been developed for all 4.9 million Veterans in 1 year increments, stratified by geographic

region and VA Center complexity score. A meta-analysis of the resulting 484 propensity score models was completed, and accepted for presentation at the 2016 AGS meeting (see below). Optimal matching was used to match up to 3 similar controls to each screened subject to create the final analytic file. Analyses to ensure covariate balance are underway, and when complete, will allow for the primary analysis to be completed by April, 2016.
3) Secondary analysis activities: Four secondary analyses were completed or had major findings that have been submitted to scientific meetings, with results described below. First, we used the large number of Veterans with multiple fractures to identify fracture types correlated more strongly with hip fracture than anticipated, so that rational combined hip fracture endpoints can be used in clinical trials to improve power and reduce required sample size. Second, we used the propensity scores above to identify major drivers of osteoporosis screening in men to identify provider education needs, and clarify clinical practice guidelines. Third, we examined the impact of kidney function on fracture risk, and found that it was a strong independent predictor above FRAX alone (the currently used clinical fracture prediction model) and may need to be added to current guidelines to identify men who need treatment. Finally, we confirmed that Type 2 Diabetes is an independent predictor of fractures in men as it is in women, despite higher BMD in patients with diabetics. Ongoing analyses are identifying potential mediators of the fracture risk including fall-related co-morbidities, medications, and glycemic control.

Significant results, Major Findings. Full copies of published papers are also found in the appendices.

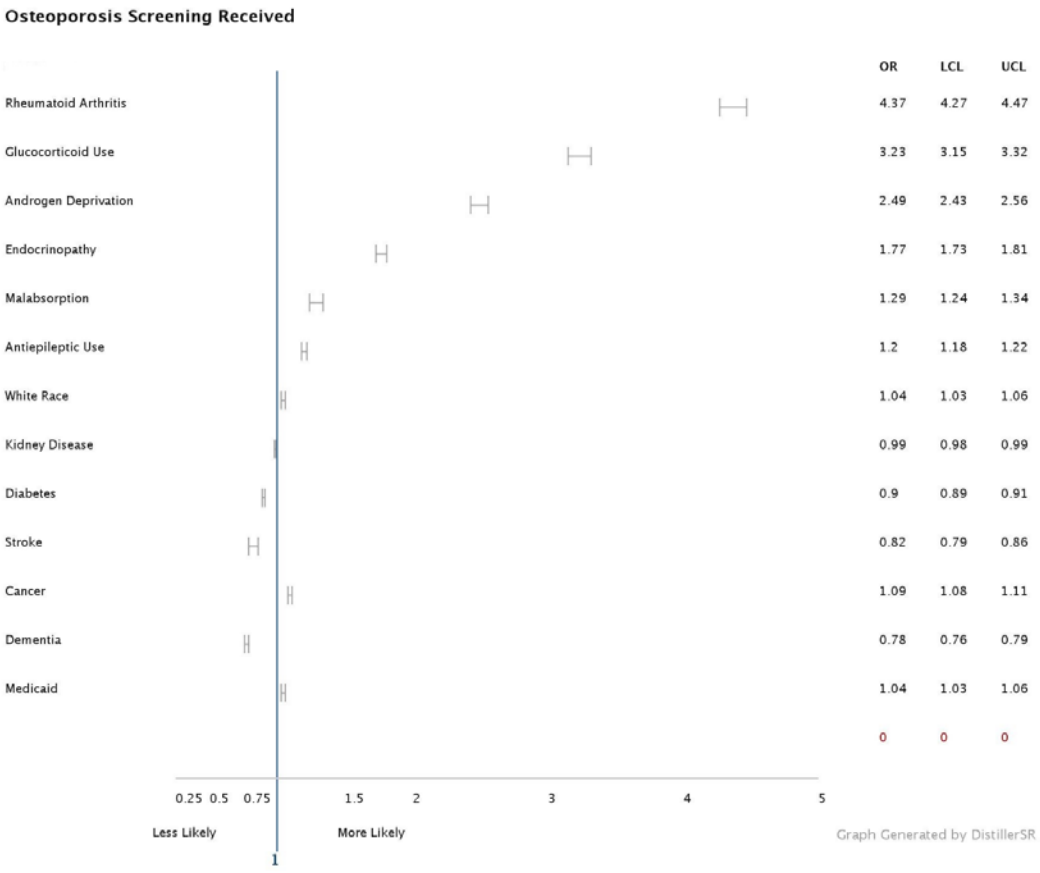
Correlation of Hip Fracture with Other Fracture Types: Toward a Rational Composite Hip Fracture Endpoint ***Colón-Emeric C, Pieper CF, Grubber J, Van Scoyoc L, Schnell ML, et al. Correlation of hip fracture with other fracture types: Toward a rational composite hip fracture endpoint. Bone. 2015; 81:67-71. PubMed [journal] PMID: 2615112***
Purpose: With ethical requirements to enroll lower risk subjects, osteoporosis trials are underpowered to detect reduction in hip fractures. Different skeletal sites have different levels of fracture risk and response to treatment. We sought to identify fracture sites which cluster with hip fracture at higher than expected frequency; if these sites respond to treatment similarly, then a composite fracture endpoint could provide a better estimate of hip fracture reduction.
Methods: Cohort study using Veterans Affairs and Medicare administrative data. Male Veterans (n=5,036,536) aged 50-99 years receiving VA primary care between1999-2009 were included. Fractures were ascertained using ICD9 and CPT codes and classified by skeletal site. Pearson correlation coefficients, logistic regression and kappa statistics, were used to describe the correlation between each fracture type and hip fracture within individuals, without regards to the timing of the events.
Results: 595,579 (11.8%) men suffered 1 or more fractures and 179,597 (3.6%) suffered 2 or more fractures during the time under study. Of those with one or more fractures, rib was the most common site (29%), followed by spine (22%), hip (21%) and femur (20%). The fracture types most highly correlated with hip fracture were pelvic/acetabular (Pearson correlation coefficient 0.25, $p<0.0001$), femur (0.15, $p<0.0001$), and shoulder (0.11, $p<0.0001$).
Conclusions: Pelvic, acetabular, femur, and shoulder fractures cluster with hip fractures within individuals at greater than expected frequency. If we observe similar treatment risk reductions within that cluster, subsequent trials could consider use of a composite endpoint to better estimate hip fracture risk.

Determinants of Osteoporosis Screening in Men. C Colon-Emeric, R Adler, K Lyles, J LaFleur, C VanHoutven, C Pieper – *accepted to American Geriatrics Society Annual Meeting, May 2016*

Background: Practice guidelines vary widely on which men to select for osteoporosis screening. We sought to describe screening predictors and disparities.

Methods: Retrospective cohort using 2000-2010 CMS and VA data for 4,987,440 men aged 50-99 who were eligible for osteoporosis screening (no prior fracture, osteoporosis diagnosis or medication). Logistic regression was used to calculate separate propensity scores for screening in the next calendar year, stratified by region and hospital complexity. Predictor variables included fracture risk factors, co-morbidities, social and access factors. Meta-analysis of the resulting odds ratios (OR) across strata was completed. Analyses restricted to men with a 10 year fracture risk of >20% examined interactions by race, rural status, and region.

Results: The mean age was 66 years, 32% were non-white. Selected summary ORs for receiving osteoporosis screening are presented in the figure below. While most fracture risk factors that guidelines suggest should prompt screening increased the odds of screening in the expected direction, the influence of many was modest, and some were negatively associated with screening (diabetes, stroke, kidney disease). Co-morbidities had a modest impact on screening, but not always in the expected direction; higher Charlson scores were associated with more screening. Social and access variables had modest expected effects, except that Medicaid status was associated with modest increased odds of screening. Differential screening receipt by race, geographic region, hospital complexity level, and rural residence will be presented.



Conclusion: Screening for osteoporosis in men is affected by fracture risk factors, co-morbidities, and access to care, but not always in expected directions. Greater clarity around osteoporosis screening guidelines is needed.

Association of Kidney Function with Fracture Risk among Older Male Veterans. Rasheeda K. Hall, Richard Sloane, Carl Pieper, Cathleen Colón-Emeric – *accepted to American Geriatrics Society Annual Meeting, May 2016*

Background

Older adults develop age-related decline in kidney function and are increasingly diagnosed with chronic kidney disease (CKD). We do not know if age-related decline in kidney function or mild reductions in estimated glomerular filtration rate (eGFR) increases fracture risk, or predicts fracture risk above and beyond currently used prediction models (FRAX).

Methods

This is a longitudinal cohort study using linked Veteran Affairs (VA) and Medicare administrative data of 4.3 million. The cohort included male Veterans (n=4,338,189) over age 50 receiving primary care in the VA who had no prior diagnoses of fracture or osteoporosis therapy. Estimated glomerular filtration rate (eGFR) was estimated using baseline creatinine values and calculated with the Modification of Diet in Renal Disease equation. Subjects were followed to capture any fracture event up to 10 years. Association of baseline eGFR with fracture risk was evaluated with a Cox Proportional Hazards model controlling for known fracture risk factors (race, body mass index, tobacco use, alcohol dependence, chronic steroid use, androgen deprivation therapy, rheumatoid arthritis, hyperthyroidism, diabetes, obstructive lung disease, chronic liver disease, and malabsorption). To account for time at risk for fracture prior to cohort entry, age was included in the model as a time scale.

Results

In this cohort, 808,525 Veterans (X%) had eGFR < 60 ml/min/1.73m^2, of which 17.7%, 0.83%, and 0.13% had eGFR in ranges of 30-59, 15-29, < 15 ml/min/1.73m^2, respectively. Over up to 10 years, 522,448 (12.0%) Veterans experienced at least one fracture. Compared to Veterans with eGFR > 60 ml/min/1.73m^2, unadjusted hazard ratios (95% CI) for fracture were 0.99 (0.96, 1.03), 1.48 (1.37, 1.59), and 2.13 (1.86, 2.40) for Veterans with eGFR in ranges of 30-59, 15-29, < 15 ml/min/1.73m^2, respectively. After adjusting for fracture risk factors, the hazard ratios (95% CI) for fracture slightly decreased to 0.98 (0.94, 1.01), 1.37 (1.26, 1.49), and 1.91 (1.64, 2.19) for Veterans with eGFR in ranges of 30-59, 15-29, < 15 ml/min/1.73m^2, respectively. When eGFR is added to a fracture prediction model including FRAX, it remains a strong independent predictor above the clinically used fracture prediction model.

Conclusion

Among older male Veterans, eGFR < 30 increases fracture risk irrespective of age or length of time at risk for fracture prior to cohort entry. Older Veterans who develop mild reductions in eGFR (30-59) may not experience an increase in fracture risk due to CKD. Adding eGFR to current fracture prediction models improves accuracy.

Type 2 Diabetes, Glycemic Control, and Fracture Risk among Older Male Veterans. Richard Lee, Richard Sloane, Carl Pieper, Cathleen Colón-Emeric – *submitted to American Diabetes Association, January 2016*

Older adults with type 2 diabetes mellitus are at increased risk for bone fracture, despite normal to increased bone mineral density (BMD). Studies investigating the mechanism of this paradoxical fracture risk are limited, especially among older males. This study explored the association between fracture risk, hemoglobin A1c (HbA1c), and diabetes-associated comorbidities among male Veterans age 50 years and older. We conducted a retrospective cohort study of 4.3 million Veterans who received primary care from 2000 to 2010 from the Veterans Health Administration, among whom 1.3 million had a diagnosis of type 2 diabetes mellitus. Compared to those without diabetes, Veterans with diabetes were older (66.2 vs 64.7 years, P < 0.0001), with greater BMI (30.9 vs 28.3 kg/m2, P < 0.0001), and more likely Black race (13.4% vs 13.4%, P < 0.0001). Among those who had a DXA ordered in routine clinical care, those with diabetes had a statistically significant higher median femoral neck BMD (T-

score -0.50 vs -0.27, P < 0.0001). During the study period, a total of 522,448 incident fractures occurred, with a higher incidence among those with diabetes (13.2 vs. 11.6%, P < 0.0001). Among those with diabetes, incident fractures were associated with presence of cardiovascular disease (20.8% vs 12.4%, P < 0.0001) and chronic kidney disease (19.7% for eGFR ≤ 15 mL/min vs 12.3% for eGFR ≥60 mL/min, P < 0.0001), as well as use of anticonvulsants (17.3% vs 11.7%, P < 0.0001) and opiates (16.7 vs 9.7%, P < 0.0001). Compared to Veterans with HbA1c 5.5-7.0%, those with HbA1c >9% had a decreased fracture risk (11.2 vs 12.9%), but those with HbA1c less than 5.5% had an increased fracture risk (16.6%, P < 0.0001). In conclusion, type 2 diabetes is associated with increased fracture risk among older males. Among those with diabetes, fracture risk was associated with presence of diabetes-associated comorbidities and low HbA1c level, perhaps indicating that falls are a major driver of the increased fracture risk.

Other Achievements. None this reporting period

Goals not met. The primary analysis has taken longer than anticipated, in large part due to the factors listed below in the problems section. However, these issues have now been resolved or mitigated and the main analysis is near completion. We anticipate having the primary analysis for benefits and costs completed by July, and the harms analysis completed by August. Dissemination of results to relevant stakeholders including the VA NCP, the American Society of Bone and Mineral Research (ASBMR), and the National Bone Health Alliance (NBHA) will occur in September and October.

What opportunities for training and professional development has the project provided? While not a stated goal of the project, this study has provided training and data analysis opportunities for 2 junior faculty members (R. Hall, R. Lee) who are working in the substudies above. Additional funding has been obtained through a NIH K24 award (Colon-Emeric PI) to continue secondary analysis on the project dataset once the DoD funding is complete.

How were the results disseminated to the community of interest? To date, results have been disseminated in scientific meetings (American Society of Bone and Mineral Research, American Geriatrics Society, American Diabetes Association) and the published literature. When primary analyses are complete, technical reports will be disseminated to VA NCP and national stakeholders including ASBMR and NBHA.

Plans for the next reporting period to accomplish the goals. During the no cost extension, plans are progressing for completion of the primary analysis. We continue to fund 2 Masters level and 1 PhD level statistician to complete the analysis.

4. IMPACT

What was the impact on the development of the principal disciplines of the project? To date the bone health community has been impacted by the creation of an evidence-based combined hip fracture endpoint which will reduce sample size requirements in clinical trials. We anticipate that the primary results will have a major impact on clinical practice guidelines for osteoporosis screening in the future.

What was the impact on other disciplines? Other disciplines impacted by the study include: 1) Endocrinology – confirmation of increased fracture rates in men with type 2 Diabetes despite higher bone mineral density, understanding of mediators; 2) Nephrology – quantification of the impact of low kidney function on fracture risk, above and beyond traditional fracture risk factors,

which will inform identification of patients for treatment; 3) Primary care – expected clarification of osteoporosis screening guidelines and identification of risk factors that aren't currently considered so that educational efforts can be targeted..

What was the impact on technology transfer? Not applicable for this study

What was the impact on society beyond science and technology? Nothing to report this cycle.

5. CHANGES/PROBLEMS

Changes in the approach and reasons for change. No changes to the approach were made.

Actual or anticipated problems or delays and actions to resolve them. 1) There was insufficient space on VA servers for the massive dataset, and a new server had to be developed specifically dedicated for this project. 2) NLP validation took a great deal longer than anticipated, but has now been completed. 3) Some key variables (lab results, costs, co-morbidity measures) were corrupted at the Austin site and time-consuming work-around solutions (e.g., calculating Charlson scores rather than using existing VA comorbidity codes) had to be employed. 4) Unexpected personnel issues resulted in the loss of 2 Masters-level statisticians from the project. New staff had to be identified, trained, and gain regulatory approval to restart work each time. Currently we are fully staffed with a PhD level, and 3 Masters level statisticians working on the data.

Changes that had a significant impact on expenditures. None

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents. Not applicable for this study.

6. PRODUCTS

Publications, conference papers, and presentations

Journal Publications

1. Colón-Emeric C, Pieper CF, Grubber J, Van Scoyoc L, Schnell ML, et al. Correlation of hip fracture with other fracture types: Toward a rational composite hip fracture endpoint. Bone. 2015; 81:67-71. PubMed [journal] PMID: 26151123. Acknowledged federal support: Yes

Other publications, conference papers, and presentations.

1. *Correlation of Other Fracture Types with Hip Fracture: Toward a Rational Combined Hip Fracture Endpoint. American Society for Bone and Mineral Research Annual Meeting poster presentation, October, 2014.
2. *Correlation of Other Fracture Types with Hip Fracture: Toward a Rational Combined Hip Fracture Endpoint, American Geriatrics Society Annual Meeting Epidemiology Paper Session, May 2015
3. Determinants of Osteoporosis Screening in Men. C Colon-Emeric, R Adler, K Lyles, J LaFleur, C VanHoutven, C Pieper – accepted to American Geriatrics Society Annual Meeting, May 2016

4. Association of Kidney Function with Fracture Risk among Older Male Veterans. Rasheeda K. Hall, Richard Sloane, Carl Pieper, Cathleen Colón-Emeric – accepted to American Geriatrics Society Annual Meeting, May 2016
5. ADA paper

Websites or other Internet Sites. Nothing to report.

Technologies or Techniques. Nothing to report.

Inventions, Patent Applications, and/or Licenses. Nothing to report.

Other Products. Nothing to report.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name:	*Cathleen Colón-Emeric, MD, MHS*
Project Role:	*Principal Investigator*
Researcher Identifier (e.g. ORCID ID):	orcid.org/0000-0001-7681-8624
Nearest person month worked:	*3*
Contribution to Project:	*Protocol development, personnel oversight, manuscript drafting, results dissemination*
Funding Support:	*VA GRECC 6/8 salary support*

Name:	*Carl Pieper, DrPH*
Project Role:	*Statistician (PhD level)*
Researcher Identifier (e.g. ORCID ID):	n/a
Nearest person month worked:	*1.2*
Contribution to Project:	*Analysis plan development and oversight*
Funding Support:	*DoD W81XWH-12-2-0093*

Name:	*Janet Grubber, MS*
Project Role:	*Statistician (Masters Level)*
Researcher Identifier (e.g. ORCID ID):	n/a

Nearest person month worked:	*5*
Contribution to Project:	*Data analysis for primary and secondary analyses*
Funding Support:	*DoD W81XWH-12-2-0093*

Name:	*Merritt Schnell, MS*
Project Role:	*Statistician (Masters Level)*
Researcher Identifier (e.g. ORCID ID):	n/a
Nearest person month worked:	*6*
Contribution to Project:	*Data management*
Funding Support:	*DoD W81XWH-12-2-0093*

Name:	*Courtney Van Houtven, PhD*
Project Role:	*Co-Investigator*
Researcher Identifier (e.g. ORCID ID):	n/a
Nearest person month worked:	*2.4*
Contribution to Project:	*Oversee economic analysis*
Funding Support:	*DoD W81XWH-12-2-0093*

Name:	*Steven Thomas, PhD*
Project Role:	*Statistician*
Researcher Identifier (e.g. ORCID ID):	n/a
Nearest person month worked:	*1.8*
Contribution to Project:	*Analysis for economic aims*
Funding Support:	*DoD W81XWH-12-2-0093*

Name:	*Richard Sloane, MS*
Project Role:	*Statistician (masters level)*

Researcher Identifier (e.g. ORCID ID):	n/a
Nearest person month worked:	*1.8*
Contribution to Project:	*Secondary analyses*
Funding Support:	*DoD W81XWH-12-2-0093*

Name:	*Megan Pearson, MA*
Project Role:	*Project Manager*
Researcher Identifier (e.g. ORCID ID):	n/a
Nearest person month worked:	*6*
Contribution to Project:	*Regulatory approval and oversight, team communication, report preparation assistance*
Funding Support:	*DoD W81XWH-12-2-0093*

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period? Previously pending grant K24 AG049077-01A1 was received by the PI. This change in active support makes no change to the PI's effort on the project, as her federal (VA) effort remains fixed at 6/8 FTE.

What other organizations were involved as partners?

Organization Name: Salt Lake City VA Medical Center
Location of Organization: *Salt Lake City, Utah*
Partner's contribution to the project: **Collaboration** – partners at this organization provided the Natural Language Processing

Organization Name: Hunter Holmes McGuire VA Medical Center
Location of Organization: *Richmond, VA*
Partner's contribution to the project: **Collaboration** – partners at this organization serve as co-investigators on the project.

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS: *Not applicable.*

QUAD CHARTS: *Not applicable.*

REFERENCES:

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9. APPENDICES:

Appendix 1: Colón-Emeric C, Pieper CF, Grubber J, Van Scoyoc L, Schnell ML, et al. Correlation of hip fracture with other fracture types: Toward a rational composite hip fracture endpoint. Bone. 2015; 81:67-71. PubMed [journal] PMID: 26151123. Acknowledged federal support: Yes

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Correlation of hip fracture with other fracture types: Toward a rational composite hip fracture endpoint

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ABSTRACT

Purpose: With ethical requirements to the enrollment of lower risk subjects, osteoporosis trials are underpowered to detect reduction in hip fractures. Different skeletal sites have different levels of fracture risk and response to treatment. We sought to identify fracture sites which cluster with hip fracture at higher than expected frequency; if these sites respond to treatment similarly, then a composite fracture endpoint could provide a better estimate of hip fracture reduction.

Methods: Cohort study using Veterans Affairs and Medicare administrative data. Male Veterans (n = 5,036,536) aged 50–99 years receiving VA primary care between 1999 and 2009 were included. Fractures were ascertained using ICD9 and CPT codes and classified by skeletal site. Pearson correlation coefficients, logistic regression and kappa statistics were used to describe the correlation between each fracture type and hip fracture within individuals, without regard to the timing of the events.

Results: 595,579 (11.8%) men suffered 1 or more fractures and 179,597 (3.6%) suffered 2 or more fractures during the time under study. Of those with one or more fractures, the rib was the most common site (29%), followed by spine (22%), hip (21%) and femur (20%). The fracture types most highly correlated with hip fracture were pelvic/acetabular (Pearson correlation coefficient 0.25, $p < 0.0001$), femur (0.15, $p < 0.0001$), and shoulder (0.11, $p < 0.0001$).

Conclusions: Pelvic, acetabular, femur, and shoulder fractures cluster with hip fractures within individuals at greater than expected frequency. If we observe similar treatment risk reductions within that cluster, subsequent trials could consider the use of a composite endpoint to better estimate hip fracture risk.

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1. Introduction

Current guidance from both the U.S. Food and Drug Association and the European Medicines Agency requires that new osteoporosis pharmacotherapies seeking registration have anti-fracture efficacy demonstrated in an 18–24 month randomized, placebo-controlled trial [1,2]. However, the ethics of using a placebo control in subjects at high risk for fracture have been widely questioned, since currently available pharmacotherapies reduce fracture risk by 30–75%. A consensus conference sponsored by the American Society for Bone and Mineral Research, the International Society for Clinical Densitometry, and the National Osteoporosis Foundation suggested that enrolling high risk patients in placebo controlled osteoporosis trials could be ethical provided that there was a clear documentation that they understood their risk, that they had failed prior therapy, or did not have access to standard treatment [3]. However, other opinion leaders and ethics boards have concluded that it is difficult to identify and recruit such patients, and point out that investigators have conflicts of interest which render it nearly always unethical to recruit subjects at the highest risk [4,5]. It has therefore been argued that trials should focus on those at lower risk (e.g., those with osteopenia and/or no prior fracture) or compare two active treatment arms to assess non-inferiority.

As a result of this shift, recent osteoporosis trials are frequently underpowered to detect differences in hip fracture rates, because they are enrolling a lower risk population who have fewer events or are utilizing an active comparator arm. This is particularly problematic for trials in special populations such as men, or trials with specific comorbidities in which patient enrollment tends to be lower than in initial registration trials [6,7]. Even in large trials which successfully show a reduction in hip fractures, the estimate for reduction in hip fracture rates

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is imprecise; for example in the FREEDOM trial comparing fracture rates in post-menopausal women with osteoporosis treated with denosumab vs. placebo, the hazard ratio was 0.60, but the 95% confidence interval ranged from 0.37 to 0.97 [8]. Since hip fractures are the most clinically devastating and costly type of fracture, the lack of a precise estimate of reduction in hip fracture rates for a given treatment is problematic for clinicians, patients, and policy makers seeking to make informed care decisions.

We may be able to learn about hip fracture risk by examining other types of fractures. Skeletal sites have differing properties, such as the relative proportions of cortical and trabecular bone, which result in varying fracture risks and differential responses to treatment. For example, population based qCT and finite element analysis studies of bone microarchitecture and strength have revealed that age-related changes in trabecular and cortical bone loss vary by skeletal site and gender [9]. Animal studies have shown differential trabecular and cortical response to treatment with various osteoporosis pharmacotherapies by skeletal site [10]. If we could identify skeletal sites with similar fracture risks and responses to therapy as the hip, then a composite fracture endpoint incorporating hip plus related fracture types could be used to improve the power and precision of the estimate of reduction in hip fracture rates.

The purpose of this study, therefore, was twofold: to identify correlations between hip and other major fracture types in a large population of older men; and to identify major fracture types which clustered with hip fractures at greater than expected frequency. If these fracture types are subsequently shown to have similar response to therapy, a composite fracture endpoint could be used to provide a valid estimate of hip fracture reduction with smaller sample size requirements.

2. Methods

The sample was derived from administrative databases from a population-based retrospective cohort study of all male Veterans ages 50–99 years receiving primary care in the Veterans Affairs (VA) health care system between 1997 and 2010. Subjects were included if they had at least 2 primary care clinic visits within a 2 year period during the observation period (n = 5,036,536) and their VA Medical Center was offering DXA screening. Baseline diagnoses were ascertained in the 3 years prior to and 1 year following the first primary care visit, while fracture assessment began at the first primary care visit and continued until the end of the study period or death (Fig. 1). The database was created to explore the impact of osteoporosis screening on outcomes in older men; therefore subjects with a diagnosis of osteoporosis or a fracture code in the 3 years prior to the study period (1996–1999) were excluded. Subjects who were enrolled in Medicare managed care plans during the study period were also excluded.

While all 5,036,536 of these patients received VA primary care services, a majority of Veterans also use their Medicare benefit, particularly for acute events such as fractures. Therefore administrative data from the VA and Center for Medicare and Medicaid Services (CMS) Medicare Parts A and B was combined with the VA data. Data sources included inpatient and outpatient treatment files, medications (VA only), and elect labs (VA only). Fractures were ascertained using ICD9 and CPT codes from inpatient and outpatient encounters, and classified as hip (femoral neck, intertrochanteric, subtrochanteric fractures; ICD9 codes 820.0–820.9, procedure codes 79.05–79.65, and CPT codes 27235–27269), forearm (radius, ulna, or both; ICD9 codes 813.0–813.93, procedure codes 79.02–79.62, CPT codes 25505–25652 and 24650–24635), spine (thoracic and lumbar only; ICD9 codes 805.2–806.9 and CPT codes 22305–22525 and 22851), shoulder (humerus; ICD9 codes 812.X, procedure codes 79.01–79.61 and CPT codes 23605–24582), pelvic/acetabular (ICD9 codes 808.0–808.9 and CPT codes 27193–27228), rib/clavicle (ICD9 codes 807.0–807.19, 810.0–810.9 and CPT codes 21800–21810, 23500–23515), distal femoral (ICD9 codes 821.0–821.39 and CPT codes 27500–27514), tibial/fibular (ICD9 codes 823.0–823.9, procedure code 79.06, and CPT codes 27530–27828), and other. Skull, facial digital, and pathological fracture codes were excluded. To avoid double counting due to repeated coding of the same event over time, each individual was counted as having a fracture type no more than once. Distal femoral fractures that occurred within 6 months of a hip fracture were excluded to decrease the probability of misclassification of hip fractures as femur fractures. Because high trauma might lead to fracture types occurring together without a common underlying risk, we defined potentially traumatic fractures as those in which more than 1 type of fracture was coded within 7 days of another fracture type. However, these were excluded in sensitivity analyses (Fig. 2).

We calculated frequencies, percentages, means and standard deviations to describe characteristics, including fracture incidence, of the study population. We calculated these statistics overall, and for those who had a hip plus at least 1 other type of fracture (the population used in the latent class analysis). Pearson correlation coefficients for each pair of hip × (femur, forearm, pelvic/acetabular, rib, shoulder, spine, tibia) fracture type were calculated for the full cohort. These correlations reflected the co-occurrence of the fracture types within individuals, and without regard to the order or timing of the events. Kappa statistics were also calculated to describe the proportion of potential agreement beyond chance. The Mantel–Haenszel method was used to calculate the odds of each fracture type among patients with hip fractures compared to the odds of the same fracture type among those without hip fractures, along with associated 95% confidence intervals (95% CIs) around these odds ratios (ORs). Because we were interested in the correlation of fractures within individuals, regardless of their individual characteristics or level of risk, no patient level covariates were adjusted for in the Mantel–Haenszel analyses. Latent class analysis

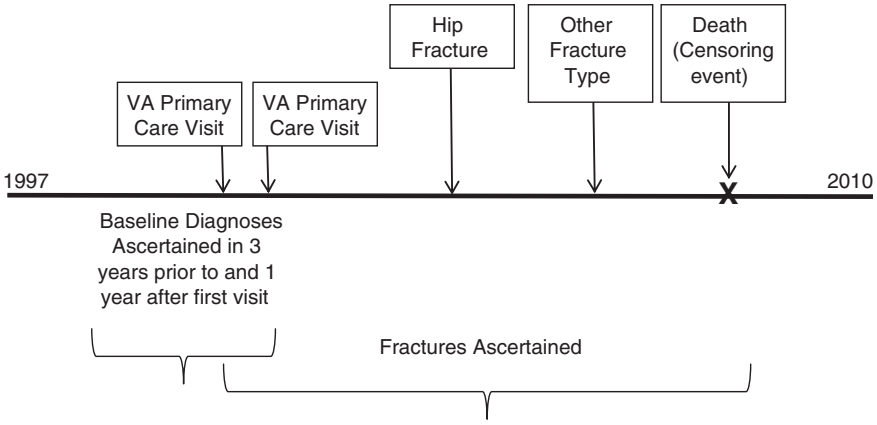

Fig. 1. Cohort schematics for follow-up time and event ascertainment. Note that the order of the fracture events did not matter for this analysis.

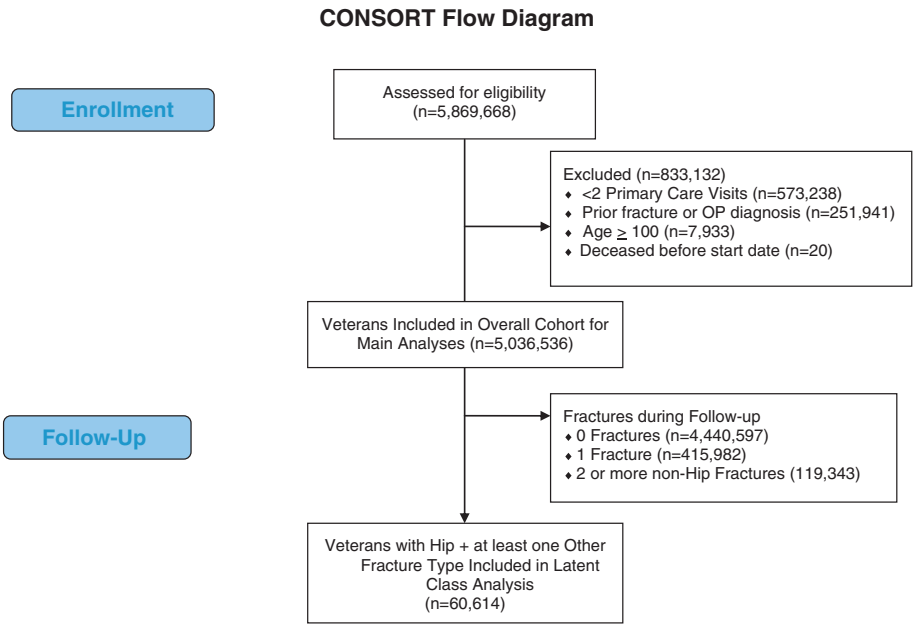

Fig. 2. CONSORT diagram illustrating selection of subjects for analysis.

[11] was used to identify clusters of highly correlated fractures in the group of subjects with hip plus at least one other fracture type; this method is used to identify unmeasured class membership among subjects using categorical or continuous observed variables, and in this case reflected "classes" of fracture types where the conditional probability that groups of fracture types co-occurred in greater than expected rates. All analyses were performed using SAS v9.2 software [12].

3. Results

Characteristics of the study population are described in Table 1. The follow-up time for the n = 5,036,536 men in this study ranged from 0 to 10 years, with an average of 5.4 years (±3.1 std. dev.). During follow-up, 595,579 (11.8%) of men in the study population experienced 1 or more fractures and 179,597 (3.6%) experienced 2 or more types of fractures (range 0–9 fracture types) over the study period. Rib fracture was the most common specific fracture type (29% of individuals with fracture), followed by spine (22%), hip (21%) and femur (20%). Of these fractures, 107,619 (2.1%) were potentially traumatic as defined above. Compared to the full cohort, those with hip and at least 1 other fracture type were older, more likely to be white, have a history of alcohol dependence and glucocorticoid use >90 days; given the large sample size, all comparisons were statistically different.

The fracture types most highly correlated with hip fracture were pelvic/acetabular (Pearson correlation coefficient 0.25, $p < 0.0001$), femur (0.15, $p < 0.0001$), and shoulder (0.11, $p < 0.0001$). Mantel–Haenszel odds ratios for the association between hip fractures and each remaining fracture type, as well as kappa statistics (reflecting the proportion of potential agreement above chance) for each fracture type with hip fracture are reported in Table 2. Latent class analysis revealed good loading onto single factors (rho estimates <0.10 or >0.90) but no convergence over 8 clusters. This suggests a generalized association between all of the fracture types, with no independent fractures which are not related to any other fracture types.

Sensitivity analyses removing potentially traumatic fractures from the analysis decreased the magnitude of the association between hip fracture and each other fracture type by 1.4 to 4.0 times, although the direction of the association remained the same (Table 2). The addition of race to the models resulted in only very minor changes to the odds ratios for the association of each fracture type with hip fracture, indicating that there was no meaningful confounding of the associations between hip and other fracture types by race.

4. Discussion

Accurately estimating the effect of osteoporosis therapies on hip fracture risk is important for clinical decision making and healthcare policy. This estimation is particularly challenging in today's context of

Table 1
Patient characteristics and fracture incidence in the study cohort of Veterans followed from 1999 to 2009.

Characteristic	Overall cohort (n = 5,036,536) N	Male veterans with hip and ≥1 other fracture type during study period (n = 60,614) N
Mean age, years (SD)	66 (10.0)	76 (9.5)
Race/ethnicity (%)		
White, non-Hispanic	3,432,497 (68.2)	44,810 (73.9)
Black, non-Hispanic	575,131 (11.4)	3,271 (5.4)
Other	204,827 (4.1)	1,888 (3.1)
Unknown	824,081 (16.4)	10,645 (17.6)
Mean BMI, kg/m^2 (SD)	29.0 (5.5)	26.7 (5.0)
Alcohol Dependence (%)[a]	1,004,278 (19.9)	13,913 (23.0)
Glucocorticoid use ≥90 days (%)	73,834 (1.5)	1,614 (2.7)
One or more fractures during follow-up (%)		
Any fracture	595,579 (11.8)	60,614 (100)
Hip	125,479 (2.5)	60,614 (100)
Rib	174,859 (3.5)	16,347 (27.0)
Distal femur	120,713 (2.4)	21,498 (35.5)
Forearm	65,617 (1.3)	7,256 (12.0)
Shoulder	58,318 (1.2)	10,357 (17.1)
Tibia/fibula	52,439 (1.0)	5,410 (8.9)
Pelvis/acetabulum	32,906 (0.7)	16,894 (27.9)
Spine	130,950 (2.6)	14,613 (24.1)
Other[b]	92,618 (1.8)	8,258 (13.6)
Potentially traumatic fractures during follow-up	107,619 (2.1)	37,282 (61.5)

All comparisons statistically significant at $P < 0.001$.

[a] Alcohol dependence defined as 1 or more of ICD9 codes 290.X, 291.X, 303.X, 305.00, or CPT code 4320F.

[b] Other includes all other fractures except skull, hand, and foot.

Table 2
Odds ratios (ORs) and 95% confidence intervals (CIs) for the association between specified fracture type and hip fracture, and Pearson correlation coefficients, and kappa statistics for the correlation between hip fracture and other fracture types.

Fracture types	Odds ratios[a] all fractures (95% CI)	Odds ratios[a] excluding potential trauma (95% CI)	Kappa[b] all fractures	Kappa[b] excluding potential trauma	Pearson correlation coefficient[c] all fractures	Pearson correlation coefficient[c] excluding potential trauma
Pelvis/acetabulum n = 32,906	47.6 (46.5, 48.6)	12.0 (11.5, 12.5)	0.21	0.05	0.25	0.07
Femur n = 120,713	10.0 (9.9, 10.2)	4.5 (4.4, 4.7)	0.15	0.05	0.15	0.05
Shoulder n = 58,318	9.1 (8.9, 9.3)	4.6 (4.5, 4.8)	0.10	0.04	0.11	0.04
Spine n = 130,950	5.4 (5.3, 5.5)	3.7 (3.7, 3.8)	0.09	0.05	0.09	0.05
Forearm n = 65,617	5.1 (5.0, 5.2)	3.0 (2.9, 3.1)	0.06	0.02	0.06	0.03
Tibia/fibula n = 52,439	4.7 (4.5, 4.8)	2.8 (2.6, 2.9)	0.05	0.01	0.05	0.02
Rib n = 174,859	4.5 (4.4, 4.6)	3.2 (3.1, 3.2)	0.08	0.05	0.08	0.05
Other n = 92,618	4.0 (3.9, 4.1)	2.3 (2.2, 2.4)	0.06	0.02	0.06	0.02

[a] For the odds of specified fracture in patients with hip fractures compared to the same odds in patients without hip fractures.
[b] The chance adjusted association between specified fracture type and hip fracture.
[c] For the correlation between the specified fracture type and hip fracture.

current trials enrolling lower risk populations, and may become more challenging with a shift toward comparative effectiveness studies in the future. In other fields, such as cardiology, composite clinical endpoints have been used successfully to address this issue [13]. This analysis is the first step in defining a rational composite fracture endpoint that could be used to help approximate the true hip fracture risk reduction rate. We identified several fracture types that are strongly associated with hip fracture within individuals, with odds ratios ranging from 9.1 to 47.6; specifically distal femur, pelvis/acetabular, and humerus fractures are highly correlated with hip fracture. If treatment-related risk reduction is found to be similar among hip and these additional 3 fracture types, the 3 additional fracture types might serve as proxies for hip fractures. Combining these proxies with hip fractures could increase the effective number of 'events' in a trial, reduce sample size requirements, and improve the precision of the estimates of effectiveness of a therapy for reduction in "hip fracture-like" fractures.

We were not able to identify clusters or "latent classes" of fracture types that group with hip fracture and no other fracture types. This is not surprising since osteoporosis affects the entire skeleton, albeit to varying degrees and the underlying risk for falls generally remains elevated within individuals over time and predisposes to all types of fractures. Nevertheless, the odds ratios for pelvic, humerus, and distal femur fracture in association with hip fracture were approximately 10 or more, and were nearly double the odds ratios for other fracture types. The magnitude of these associations suggests that these fracture types are more strongly associated with hip fracture than other sites in the skeleton. While correlation coefficient of 0.25 is usually considered modest, in the context of rare events within individuals, and with consideration of the associated odds ratios, we believe that the observed values are clinically meaningful.

This study has several important strengths. Identifying correlations within fracture types requires a very large sample with adequate follow-up time and nearly complete fracture acquisition. We included more than 5 million older men and merged both VA and Medicare data over 10 years of follow-up. Prior studies have suggested that accurate fracture ascertainment for non-vertebral fractures in administrative data exceeds 95%, with high sensitivity and specificity; for example a recent study found 97% sensitivity for hip fracture in Medicare data alone [14]. While 2/3 of vertebral fractures are clinically silent, others have demonstrated that the positive predictive value of a vertebral fracture claim is 87% [15]. Since clinical vertebral fractures are also an important study endpoint, this cohort provides valuable information despite the lack of availability of silent vertebral fracture information.

There are also limitations which should be considered. The cohort included only men, and these correlations need to be examined in women as there may be important gender-related differences in bone characteristics. Veterans have a higher risk of co-morbidities and other fracture risk factors than non-Veterans [16–19], therefore the generalizability of our findings to populations outside of the VA can be questioned. However, while Veterans' absolute fracture risk may be higher than that of other men due to higher risks of co-morbidities and other factors, this study looked at correlations of fractures within individuals, and there is no clear physiologic rationale as to why the correlations among fracture types should be different in Veterans than non-Veterans. In administrative data there is a possibility of miscoding or double-counting the same fracture; we took steps to minimize potential study bias by limiting coding to a single fracture of each type per individual, and excluding fractures close physical proximity (e.g., hip and distal femur) when they occurred within 6 months. Because this analysis only examined correlations between fracture types and not fracture rates, there is no bias introduced from counting each individual as having a fracture type no more than once, but the total number of fractures reported here for the cohort may be lower than actually occurred. While we excluded pathologic fracture codes, the cohort may have included fractures related to malignancy or infection. There is no accurate way to distinguish high trauma fractures from low trauma fractures in administrative data, and our definition of "potentially traumatic fractures" (2 or more fracture types within 7 days) likely misclassifies some osteoporotic fractures as traumatic. However when we excluded potentially traumatic fractures in a sensitivity analysis, the magnitude of our odds ratios and Kappa values were reduced, but the order was not changed, suggesting that the association between these fracture types remains relevant.

Before a composite fracture outcome could be considered, it will be important to confirm that pharmacologic treatments result in similar fracture risk reductions for all fracture types within the cluster. Because use of pharmacologic therapy for osteoporosis was not randomized, such analysis would be biased within our cohort; meta-analysis of randomized controlled trials will be the most appropriate data to accomplish this task.

In conclusion, we found that pelvic/acetabular, distal femur, and humerus fractures correlate with hip fractures nearly twice as much as with other fracture types. If these 3 skeletal sites are shown to have risk reductions to that of hip upon osteoporosis therapy, a composite fracture endpoint could potentially be used to increase the number of outcomes of interest to provide a more precise estimate of hip fracture risk in clinical trials.

Conflicts of interest

Dr. Colón-Emeric is a consultant to Novartis and Amgen, and receives research support from Amgen. Dr. Lyles is a consultant to Novartis, Amgen, and UCB and receives research support from Amgen, Novartis, and Kirin Pharmaceuticals. Dr. Lyles is co-inventors of US patent applications 20050272707 "Methods for preventing or reducing secondary fractures after hip fracture" and 12532285 "Medication kits and formulations for preventing, treating or reducing secondary fractures after previous fracture". Drs. Colón-Emeric and Lyles are co-inventors of US patent applications 20104717 "Bisphosphonate compositions and methods for treating heart failure" and 61560328

"Bisphosphonate compositions and methods for treating and/or reducing cardiac dysfunction". They are equity owners of BisCardia, Inc. Carl F. Pieper, Janet Grubber, Lynn Van Scoyoc, Merritt Schnell, Courtney Harold Van Houtven, Megan Pearson, Joanne LaFleur, and Robert Adler declare that they have no conflict of interest.

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