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14. ABSTRACT This is a propensity score matched observational study using CMS and VA data from January 1, 2000-December 31, mean follow-up 4.7 years. Men receiving VA primary care aged 65-99 without prior fracture (n=2,539,812) were included. Men receiving DXA were 1:3 matched with untested controls by propensity scores indicating the probability of DXA testing within the next year. Time to first clinical fracture was the primary outcome. Co-morbidities, demographics, medications, DXA results, and osteoporosis treatment were defined using administrative data and natural language processing. Landmark analysis with competing risk compared time to fracture. During follow-up of 183,943 men tested with DXA and 475,449 controls, 9.4% fractured and 20.6% died. DXA testing overall was not associated with a decrease in fractures; conclusions are limited by unmeasured confounders and low medication initiation and adherence in those meeting treatment thresholds (12% of follow-up time). Mortality was 21% lower in DXA tested men, also likely related to unmeasured confounders and selection bias. In contrast, DXA testing in pre-specified subgroups was associated with lower risk of fracture compared to the overall DXA population: androgen deprivation therapy (HR 0.77, 0.66-0.89); glucocorticoids (0.77, 0.72-0.84); age ≥ 80 years (0.85, 0.81-0.90); one or more VA guideline risk factors (0.91, 0.87-0.95); and high FRAX- BMI (0.90, 0.86-0.95). Total costs were slightly higher for DXA treated men than untested men; cost-effectiveness analysis was not completed due to the overall lack of benefit of DXA testing. We conclude that current VA DXA testing practices are ineffective overall; interventions to improve treatment adherence are needed. Targeted DXA testing of higher risk men was associated with lower fracture risk.					
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1. INTRODUCTION:

We analyzed administrative and electronic health record data for all U.S. male Veterans receiving primary care within the VA between 2000-2010 (n=5,869,668). Using propensity score matching, we examined the association between primary osteoporosis screening with DXA and subsequent fractures overall, and in pre-specified high-risk groups in whom screening is recommended by at least 1 practice guideline. We hypothesized that DXA testing would be associated with lower fracture rates in tested relative to untested men with similar likelihoods of being tested, especially when followed by osteoporosis treatment for those meeting recommended treatment thresholds. If DXA was found to be effective we proposed examining the impact on mortality and cost. We measured harms associated with osteoporosis treatment include atrial fibrillation, osteonecrosis of the jaw, and subtrochanteric fractures.

2. KEYWORDS:

Osteoporosis, males, screening

3. ACCOMPLISHMENTS: The PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are significant changes in the project or its direction.

What were the major goals of the project?

The major goals were 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. Milestones and completion dates are listed below.

Task	Methods	Outcome/Deliverable/Product	Status
<i>Milestone 1. Regulatory Approval, CMS and VA data requested and obtained. (months 1-6)</i>			
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
<i>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)</i>			
Extract DXA data from eligible subjects (month 1-6)	Natural language processing used to extract DXA results from text	Dataset containing DXA results from all eligible subjects	Sep_2013

	notes in radiology and consultation records	assembled.	
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 variables for the year.	Fracture related costs to CMA calculated for eligible subjects	Jul_2015
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	Cleaned dataset created with risk of subject identification and loss of privacy minimized	Sep_2015

	key identifiers to create a limited data set		
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 treatment on fracture rates, mortality rates, and treatment-related harm outcomes.	- 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)	Jan_2016
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	July_2016
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	Dec_2016
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	Jan-Sep_2017
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	May-Nov_2017

What was accomplished under these goals?

Methods

Propensity matched observational study using the cohort of 5,869,668 men with any VA outpatient encounters between 2000-2010. We hypothesized that DXA testing would be associated with lower fracture rates in tested relative to untested men with similar likelihoods of being tested, especially when followed by osteoporosis treatment for those meeting recommended treatment thresholds.⁷ Ethical approval was obtained from the Durham and Richmond VA Medical Centers and the Department of Defense.

Data Sources: VA inpatient treatment file, outpatient care file, fee-basis file, pharmacy treatment file, and laboratory files were merged with Centers for Medicare and Medicaid Services (CMS) Part A and B claims. Death was determined from the Vital Status File.

Subjects: Men aged 65-99 years who were eligible for primary DXA testing (no previous DXA, fracture, osteoporosis diagnosis, or osteoporosis medication in the 3 years prior to their start date). Only men with at least 2 VA primary care visits within 2 consecutive years were included to improve ascertainment of co-morbidities and medications.¹⁴

Observation period and follow-up: Each subject's start date was their first primary care visit between January 1, 2000 and December 31, 2010 in the first calendar year after DXA became available at their medical center. Relevant diagnoses and medications were determined for the 3 years prior to their start date, and updated on January 1 of each year thereafter. Subjects were followed until study end or death. Because CMS records were available for all subjects, we did not censor for loss to VA follow-up.

DXA Testing, Results, and Treatment: Current procedural terminology (CPT) codes for DXA were identified from VA and CMS. To supplement this, natural language processing (NLP) identified bone density test results in radiology, primary care, and consult notes. NLP extracted femoral neck T scores and lowest T scores at any site; validation suggested excellent accuracy.¹⁵ Only DXAs done prior to a fracture or osteoporosis medication prescription were considered.

Treatment was defined as at least 1 prescription for a bisphosphonate, calcitonin, or teriparatide. Using U.S. treatment thresholds (osteoporosis by BMD at any site or 10-year FRAX-BMD score $\geq 20\%$ major osteoporotic or $\geq 3\%$ hip fracture),¹⁶ subjects' treatment status was defined 12 months after DXA testing as appropriately treated, appropriately untreated, over-treated, or undertreated. If DXA results were not available, FRAX-BMI was used for classification; prior studies have demonstrated that few patients are classified differently with FRAX-BMI compared to FRAX-BMD.¹⁷ Treatment adherence was estimated using the continuous measure of medication acquisition¹⁸

Co-morbidities and other variables: Co-morbid conditions, medications, and other factors that increase fracture risk were identified using ICD9 codes, laboratory values (hemoglobin A1C, estimated glomerular filtration rate), and medication prescriptions (glucocorticoids, androgen deprivation therapy, hypoglycemics, dopaminergic medications, cholinesterase inhibitors, selective serotonin reuptake inhibitors, opiates, proton pump inhibitors). Charlson co-morbidity scores were calculated using a validated approach.^{19,20} Fall risk factors (neuropathy, stroke, seizure disorder, dementia) and psychoactive medications were included. FRAX 10-year risk for hip and major osteoporotic fracture were calculated at baseline for all subjects using BMI, and updated for those with documented T scores in the 365 days after DXA. Femoral neck scores were used; when unavailable, lowest reported T score was used. Other social and health system factors likely to influence receipt of DXA testing included marital status, co-pay level (financial status), homelessness, rural zip code, receipt of colorectal cancer screening, and number of outpatient visits.

Costs: We combined administrative data from the VA and Center for Medicare and Medicaid Services (CMS) Medicare Parts A and B. VA Data. We used VA data from multiple sources. First, we used the outpatient encounter (OPC) and inpatient encounter (PTF) data for fiscal years 2000-2010. These outpatient encounter data are coded by clinic stop codes, such as primary care, specialty care clinics, outpatient pharmacy, radiology, or laboratory. The corresponding ICD-9 diagnosis codes and CPT-4 procedure codes enable us to define fracture, fracture treatment procedures and co-morbidities. The PTF inpatient utilization data identifies fractures treated as an inpatient, including post-acute care. Second, we used VA Health Economic Resource Center Average Cost (HERC) data to track the VA

expenditures associated with all inpatient stays and outpatient visits for each year. HERC data provides cost estimates at the encounter level using relative value units, and we merged these inpatient and outpatient cost files with the OPC and PTF files using methods described by HERC (Phibbs, Scott, Flores, & Barnett, 2010; Wagner, Chow, & Barnett, 2009) in order to identify fracture and non-fracture related encounters (and associated costs). The appeal of using HERC data is that it makes VA costs comparable to Medicare costs. Third, we obtained fee basis files in order to account for care provided to VA patients by contract providers outside of VA facilities and reimbursed by VHA; this includes inpatient facility (INPT); inpatient ancillary/ physician (ANCIL); and outpatient care, which includes skilled home health and homemaker home health aide services (MED); and outpatient pharmacy (PHR). We employed methods suggested by HERC to find all care provided in a particular fiscal year by searching by treatment date over several years of Fee Basis claims (CITE). Fourth, we used pharmacy benefits management (PBM) files to obtain outpatient pharmacy data for selected drugs and costs (Arnold, Hynes, & Stroupe, 2006). Finally, we obtained the Mini Vitals file from the Austin Automaton Center to track death records in our cohort and Corporate Data Warehouse (CDW) data to calculate body mass index (BMI).

Medicare Data: Since VA enrollees also receive care outside of the VA system (CITES), we obtained Medicare data from the VA Information Resource Center (VIREC) to assess veteran characteristics and healthcare utilization and costs. The Denominator File contains demographic and enrollment information, and determined entitlement status (A/B/Both), participation in Medicare Managed Care, date of death, and Medicaid enrollment status. In addition to inpatient (Part A) and outpatient (Part B) claims, the MedPAR (Medicare Provider and Analysis Review) File was used to identify inpatient and skilled nursing stays, Home Health Agency SAF, and Hospice SAF, including diagnosis codes, procedure codes, and the reimbursement amount. The Outpatient SAF and Carrier SAF were used to identify diagnosis (ICD-9) and procedure codes, dates of service, reimbursement amount, and provider number. We obtained durable medical equipment use and reimbursed amounts from the BASF file. DME that is particularly important for our population may include assistive devices or mobility aids that are commonly used post-fracture. We did not have lab data or drug data (Part D) from Medicare claims, hence, we are missing lab tests ordered as a part of an OP screening workup and lab results determining OP or osteopenia status that occurred during a Medicare-reimbursed visit. The lack of Medicare Part D data means that OP prescriptions that were filled exclusively outside the VA are missing for the later years of our study period, 2006-2010.

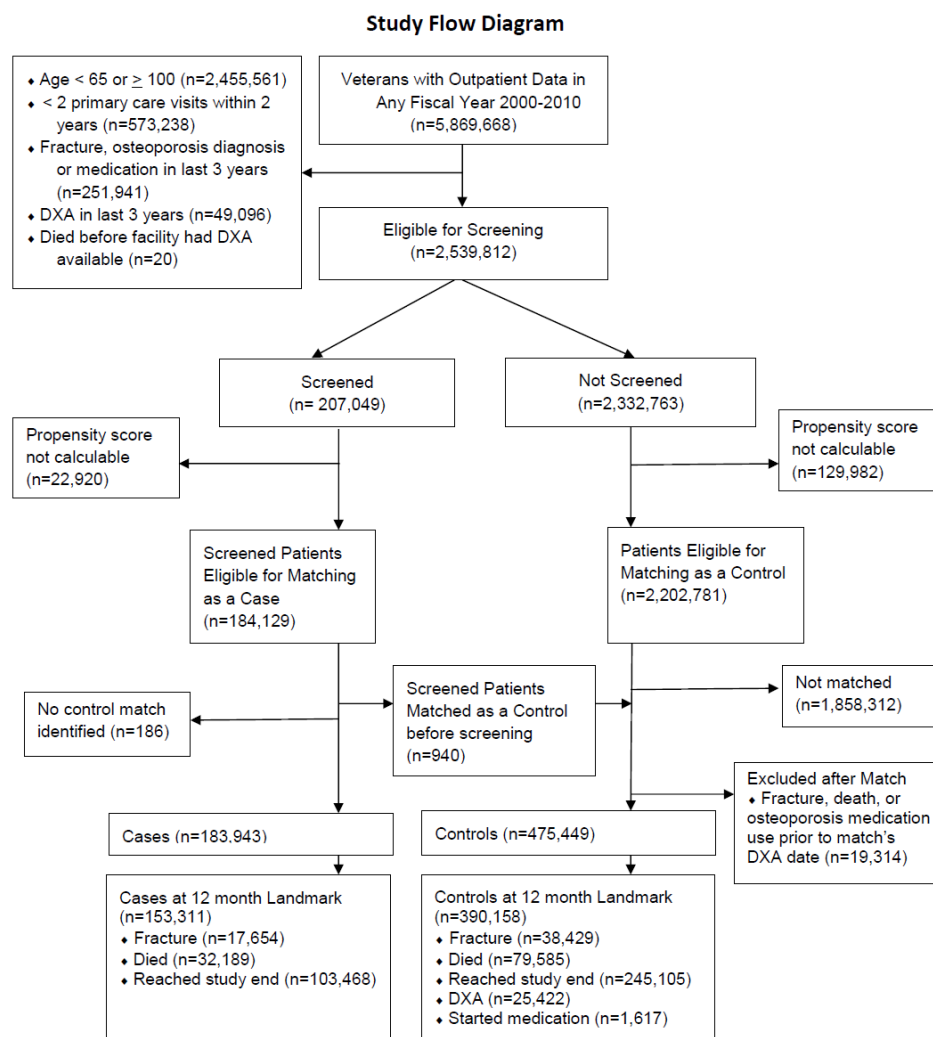
Propensity Score Development: We used propensity scores to match DXA tested “cases” with untested “controls” with a similar likelihood of receiving DXA testing in the next year based on co-morbidities, medications, demographics, health system, and social factors (Table 1). The propensity score contains information on a large number of measured confounders and has a property of balancing them between tested and untested patients.²¹ For this analysis, a 3-year look back period from each subject’s start date was employed to identify baseline risk factors, then new propensity scores were calculated on January 1 of each year incorporating new diagnoses and medications from the prior year. Because DXA testing practices vary by region and medical center complexity level, 80 separate logistic models stratified by year, region, and complexity level were used. Logistic models included all of the potential risk factors for DXA testing listed in Table 1.

Matching: A greedy matching algorithm identified up to 3 untested controls with the closest propensity score to the DXA tested case as of January 1 of the case’s DXA testing year. DXA tested patients were eligible to serve as controls prior to their testing year, at which time they became cases. Controls were excluded after matching if they fractured, began an osteoporosis medication or died between January 1 and the case’s testing date. Matching effectiveness was assessed by ensuring standardized difference <0.1 for all fracture risk factors (figure 2). Propensity score distributions were examined graphically.

Analysis: Proportional Hazards (PH) models, stratifying on the matched groups, assessed the hazard of fracture among DXA tested vs. untested men. Because death could confound the observed effects, Competing Risk analyses as implemented by the methods of Fine and Gray were estimated.²² To allow for the lag time to benefit from an osteoporosis medication,²³ we set a landmark of 12 months after testing (i.e., subjects who died or fractured within 12 months of their DXA testing/match date were censored). Use of this landmark had several additional analytic benefits. First, initial estimates identified that the proportional hazards assumption for fracture risk was not met, with curves crossing around 12 months. Further, we observed a spike in fractures immediately following the first DXA date, suggesting that these likely were post-fracture DXAs with errors in the coding dates. Setting the 1-year landmark removed these misclassified events.

Subjects were censored at fracture, death, or end of study; in addition, controls were censored if they had a DXA (became a case) or started taking an osteoporosis medication. Interaction terms for pre-specified subgroups were examined including age ≥ 80 years, glucocorticoid users, androgen deprivation therapy (ADT) users, high baseline FRAX-BMI score ($\geq 20\%$ major fracture or $\geq 3\%$ hip fracture), and ≥ 1 fracture risk factor per the VA Undersecretary guidelines (glucocorticoids, ADT, traditional anti-epileptic drug, rheumatoid arthritis, alcohol abuse, smoking, BMI < 25 kg/m², hyperthyroidism, hyperparathyroidism, chronic lung disease, chronic liver disease, stroke, Parkinsonism, gastrectomy). All hypothesis tests were 2-sided with significance level of $p < 0.05$. Data were analyzed by authors CFP and JG using SAS 9.4.

Subject Flow Diagram: The figure below shows the number of Veterans at each step of the analysis as described above.



Results

Baseline characteristics are found in Appendix 2, table 1. As expected since they were selected for DXA testing in routine clinical care, matched cases and controls had more fracture risk factors than the overall cohort, but similar proportions of smoking, alcohol abuse, and mean FRAX-BMI scores. Cases and controls were older, more likely to be married, live in non-rural areas, have higher income, prior colorectal cancer DXA testing, and more outpatient visits in the testing year than the cohort overall. After matching, the standardized difference for all risk factors used in calculating the propensity score was < 0.10 (figure 2, below and in Appendix 2), indicating good balance of known fracture risk factors.

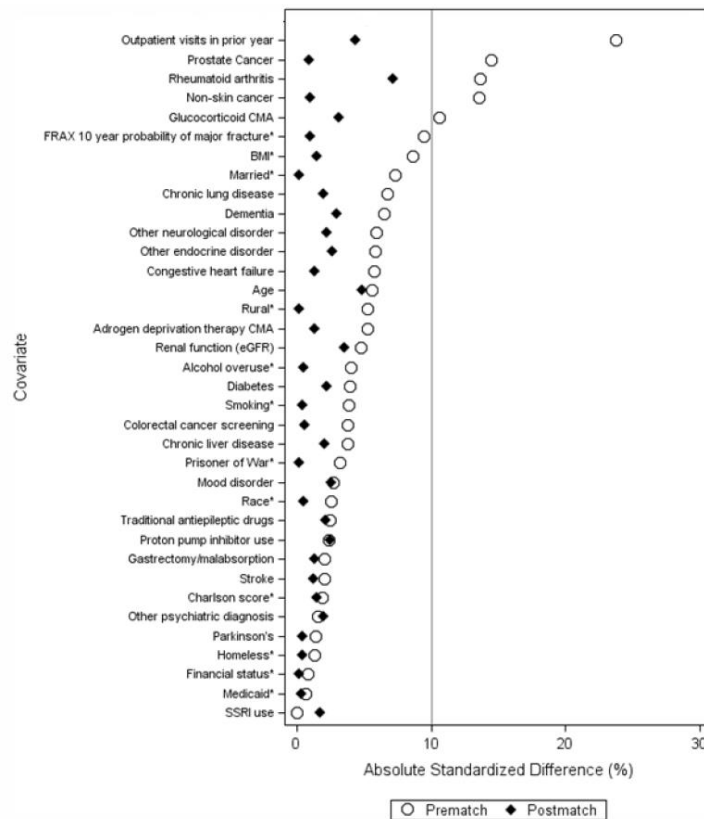


Figure 2. Plot of Standardized Differences between DXA tested and untested individuals (difference in mean values divided by pooled standard deviation) before and after the propensity score match.

Osteoporosis DXA testing, DXA Results, and Follow-up in the Overall Cohort

DXA testing was uncommon (8.2%, $n=207,049$), and varied by region and over time. During a mean follow-up time of 4.7 years after DXA (range 0-10 years), 11.5% sustained a fracture and 22.1% died. Among the subset of individuals in which DXA results were available ($n=81,479$, 39.4% of the DXA tested cohort), 26% had osteoporosis and 46% had osteopenia at any site.

Association of DXA testing with Fracture Risk in the Matched Cohort

DXA testing was associated with a higher fracture risk overall (HR 1.19, 1.16-1.21, figure 3 below and in appendix 2), suggesting the presence of unmeasured fracture risk factors that prompted physicians to order DXA for cases, but were unavailable in administrative data. Assuming a prevalence of 10% in the untested group, these risk factors would have to be fully independent of the 32 risk factors in our model, increase fracture risk by 100%, and be 2.5 times as prevalent in the tested group to have resulted in missing a 10% decrease in the hazards of fracture attributable to DXA testing.

Examining osteoporosis medication use among DXA tested individuals, 43% of those meeting treatment thresholds were not started on medications during follow-up. For those with at least 1 prescription for an osteoporosis medication, the median proportion of follow-up time during which they received medication following the 1-year landmark was 12%. More than 60% of osteoporosis medication use occurred within 90 days of testing, with <10% of prescriptions dispensed 1 year after testing.

DXA testing effectiveness improved over time (3% reduction in hazard of fracture in tested individuals per year, interaction $p<0.0001$). The proportion of cases who were classified as receiving guideline-recommended care was similar over the study period (77% to 82%).

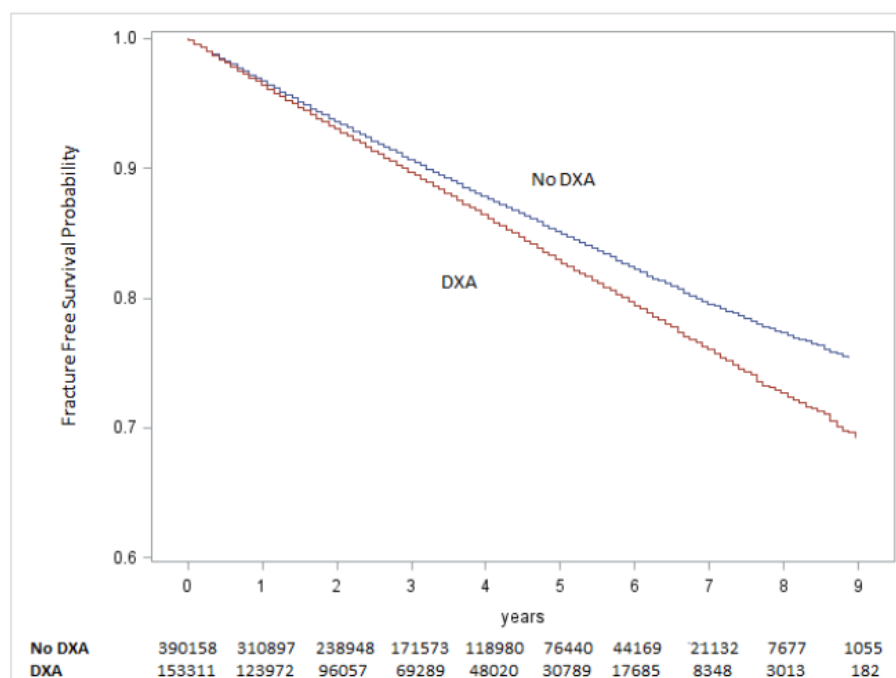


Figure 3. Fracture free-survival for DXA tested and untested men.

Pre-specified subgroups

Interaction terms suggested higher DXA testing effectiveness in all pre-specified groups ($p < 0.0001$), and therefore separate analyses were completed (figure 3). Relative to the risk in the overall tested population, DXA was associated with a 23% lower hazard of fracture relative to untested controls for patients on androgen deprivation therapy (0.77, 0.66-0.89) and glucocorticoids (0.77, 0.72-0.84). Smaller but significant benefits associated with DXA were observed among men aged ≥ 80 years (0.85, 0.81-0.90), those with one or more VA Guideline risk factors (0.91, 0.87-0.95), and those with high 10-year fracture risk by FRAX with BMI (0.90, 0.86-0.95).

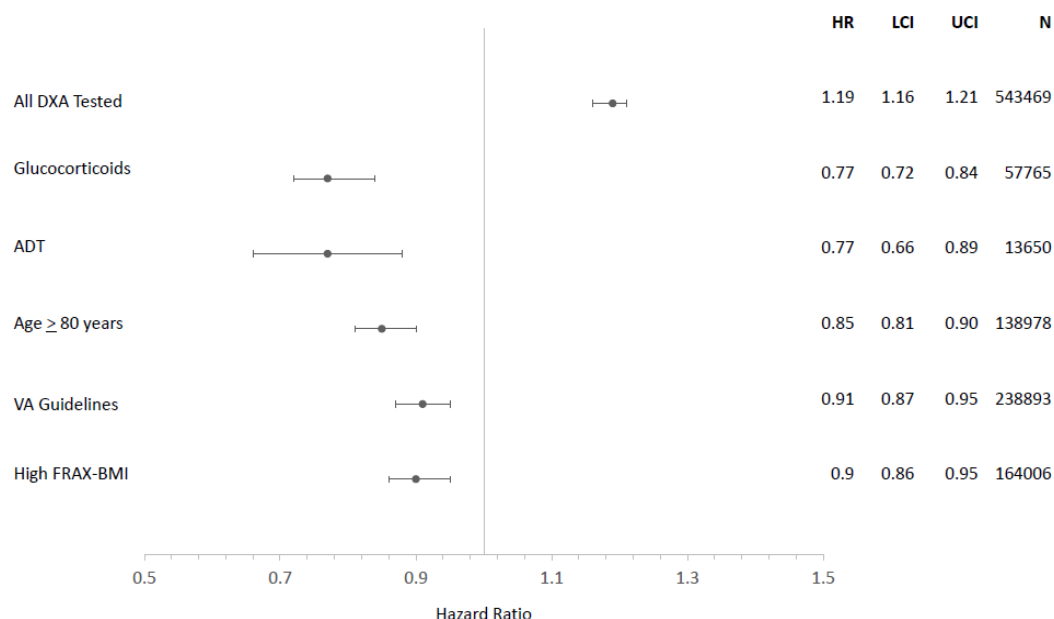


Figure 4. Hazard ratio for fracture in DXA tested relative to untested men. HRs for the pre-specified subgroups are relative to the DXA testing risk in the overall population. High FRAX-BMI score defined as 10-year fracture risk $\geq 3\%$ hip fracture or 20% major osteoporotic fracture before DXA testing. ADT = Androgen Deprivation Therapy; FRAX-BMI = Fracture Risk Assessment Tool using Body Mass Index; HR = Hazard Ratio; LCI = Lower 95% Confidence Interval; UCI = Upper 95% Confidence Interval.

Mortality

The hazard of death in DXA tested men was 21% lower than in unscreened men in the fully adjusted model, suggesting the presence of selection bias with unmeasured confounding (i.e., selection of healthier subjects with longer life expectancy for osteoporosis screening). Use of the competing risk model for the screening analysis did not change results substantively.

Costs

Cost files were assembled as described above, with total expenditures in DXA tested and untested men calculated. However, given the overall lack of DXA testing effectiveness across the cohort, formal cost-effectiveness analyses were rendered uninformative. We conclude that the current overall osteoporosis screening program in VA wastes money without reducing the burden of fractures due to poor targeting and low treatment and adherence rates. The cost file can be used for future modeling analyses of new osteoporosis screening models of care.

Harms

Harms associated with bisphosphonate treatment were compared between cases and controls. There were no significant differences in atrial fibrillation or subtrochanteric fractures. There were insufficient number of osteonecrosis of the jaw for statistical comparison. Given the low treatment rates and short average duration of use observed in this cohort, our ability to detect harms associated with bisphosphonates is low.

Conclusions

Our findings suggest that DXA testing *as it is currently operationalized* in the VA is associated with a lower risk of subsequent fractures among subgroups of men at high fracture risk. However, we were unable to demonstrate a reduction in fractures from DXA testing in the overall cohort in the setting of low treatment and adherence rates, suggesting that major changes in the DXA testing program are needed to avoid waste. Our results are influenced by unmeasured risk factors; the counter-intuitive higher fracture rates associated with DXA testing overall suggests that ordering clinicians are identifying fracture risk factors that were unavailable in administrative data. However, the impact of these risk factors would have to be very large to have resulted in our missing even a modest decrease in fractures with DXA testing generally. These results have important clinical implications for DXA selection and osteoporosis care delivery.

References: See bibliography, Appendix 2.

What opportunities for training and professional development has the project provided?

Three junior faculty mentees led or are leading secondary data analyses (see appendices) as first author, and have gained experience in administrative data analysis, propensity score methodology, and longitudinal studies. Two of these trainees are from underrepresented minority group. 1) Richard Lee, MD, MHS; 2) Rasheeda Hall, MD, MHS; 3) Michael Cary, PhD, RN.

How were the results disseminated to communities of interest?

In addition to dissemination to the community of scholars as described above, we presented results to several VA Stakeholder Groups including VA Office of Specialty Care (Leonard Pogach), VA NCP (Jane Kim), and VA Geriatrics and Extended Care (Richard Allman, Kenneth Shay). With input from these stakeholder groups, results have led directly to the development of 2 new models of primary osteoporosis screening, and a pragmatic randomized trial has been submitted to HSR&D for consideration of funding with a promising score.

4. IMPACT:

What was the impact on the development of the principal discipline(s) of the project?

- 1) The United States Preventive Services Task Force is currently revising their recommendations for the evaluation and treatment of osteoporosis in men, and results from this study are directly informing those guidelines.
- 2) We have identified major issues with osteoporosis medication initiation and adherence across VHA, which we are addressing with 2 proposed new models of care that can be widely disseminated.

What was the impact on other disciplines?

- 1) Nephrology: We found that even early stage chronic kidney disease independently increases fracture risk despite adjustment for competing mortality risk, and that this risk factor should be incorporated into treatment decisions for such patients.
- 2) Diabetes: We found that comorbidities associated with diabetes including congestive heart failure and neuropathy mediate some of the increased fracture risk observed in patients with diabetes. These findings identify new intervention targets for fracture prevention in these patients.

What was the impact on technology transfer?

Nothing to report.

What was the impact on society beyond science and technology?

We anticipate that this project will have a direct impact on the burden of osteoporotic fractures while reducing inefficient practices nationally by focusing screening and treatment efforts on those most likely to benefit.

5. CHANGES/PROBLEMS:

Changes in approach and reasons for change

Nothing to report.

Actual or anticipated problems or delays and actions or plans to resolve them

Nothing to report.

Changes that had a significant impact on expenditures

Nothing to report.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

Significant changes in use or care of human subjects

Nothing to report

Significant changes in use or care of vertebrate animals

Not applicable

Significant changes in use of biohazards and/or select agents

Not applicable.

6. **PRODUCTS:** List any products resulting from the project during the reporting period. If there is nothing to report under a particular item, state “Nothing to Report.”

- **Publications, conference papers, and presentations**

Journal publications.

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
2. Colon-Emeric C, Pieper CF, Van Houtven C, et al. Impact of Primary Osteoporosis Screening in a National Sample of Older Men. *Journal of Bone & Mineral Research*. 2017;32(Suppl 1):Available at <http://www.asbmr.org/education/AbstractDetail?aid=332120e332126-332120cb332124-332124e332128c-332128eb332127-381814f332250e332120>. Published. Acknowledged federal support: Yes
3. Colon-Emeric C, Pieper CF, Van Houtven C, et al. Primary Osteoporosis Screening in U.S. Male Veterans is Effective in High Risk Subgroups, but not Overall. *Journal of Bone & Mineral Research*. 2017;17(Suppl 1):Available at <http://www.asbmr.org/education/AbstractDetail?aid=525168cc-525168f525153-525148b525161-525927d-eea525261fecb525170>. Published. Acknowledged federal support: Yes
4. Colon-Emeric C, Pieper CF, Van Houtven C, et al. Primary Osteoporosis Screening in U.S. Male Veterans is Effective in High Risk Subgroups, but not Overall. Submitted. Acknowledged federal support: Yes
5. Hall R, Sloane R, Pieper CF, Van Houtven C., LaFleur J, Adler R., Colon-Emeric C. Competing Risks of Fracture and Death in Older Adults with Chronic Kidney Disease. *J Am Geriatr Soc*. 2018 Jan 10. doi: 10.1111/jgs.15256. [Epub ahead of print]. Acknowledged federal support: Yes
6. Lee R, Sloane R, Pieper CF, Lyles KW, Adler R., Van Houtven C., LaFleur J., Colon-Emeric C. Clinical fractures among older men with diabetes are mediated by diabetic complications. *J Clin Endocrinol Metab*. 2018 Jan 1;103(1):281-287. doi: 10.1210/jc.2017-01593.. Acknowledged federal support: Yes

Books or other non-periodical, one-time publications.

Not applicable

Other publications, conference papers and presentations.

Other publications, conference papers, and presentations.

1. Colón-Emeric C., Sloane R., Lee R., Lyles KW, Pieper C., Adler R. Age Threshold for Primary Osteoporosis Screening in Men. American Geriatrics Society Annual Meeting, May 2018 (submitted).
2. Colon-Emeric C, Pieper CF, Van Houtven C, et al. Impact of Primary Osteoporosis Screening in a National Sample of Older Men. American Society of Bone and Mineral Research Annual Meeting, September 2017.*
3. Colon-Emeric C, Pieper CF, Van Houtven C, et al. Primary Osteoporosis Screening in U.S. Male Veterans is Effective in High Risk Subgroups, but not Overall. American Society of Bone and Mineral Research Annual Meeting, September 2017.*

- **Website(s) or other Internet site(s)**

Not applicable

- **Technologies or techniques**

Identify technologies or techniques that resulted from the research activities. Describe the technologies or techniques were shared.

Not applicable

- **Inventions, patent applications, and/or licenses**

Identify inventions, patent applications with date, and/or licenses that have resulted from the research. Submission of this information as part of an interim research performance progress report is not a substitute for any other invention reporting required under the terms and conditions of an award.

Not applicable

- **Other Products**

Two clinical interventions to improve primary osteoporosis screening have been developed. Using a modified conceptual framework from Population-based Research Optimizing Screening through Personalized Regimens (PROSPR) we proposed a pragmatic group randomized trial of 36 PACTs to: 1) usual care (no practice management support); 2) PACT Practice Management (robust support with tools and processes to facilitate guideline-based osteoporosis care and adherence promotion, but still within the PACT); 3) Bone Health Service (BHS) (screening and adherence promotion are fully managed by a centralized expert team). Each model has distinct screening promotion and adherence promotion components, which will be evaluated separately to optimize subsequent dissemination and policy decisions. Patient selection for screening leverages real-time use of Electronic Health Record (EHR) tools to identify those with risk factors who most benefit from screening. Treatment adherence components address known patient, provider, and health system barriers to adherence with osteoporosis medications, but utilize evidence-based delivery methods appropriate to the screening model. The 2 new models test fundamentally different primary fracture prevention paradigms and are designed for rapid dissemination across VHA if found to be effective.

Funding to test these models of care has been requested from VA HSR&D (IIR IHX002512A); if granted testing will begin in FY2018, and the interventions will be listed on www.clinicaltrials.gov.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

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

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

Name:	<i>Janet Grubber, MS</i>
Project Role:	<i>Statistician (Masters Level)</i>
Researcher Identifier (e.g. ORCID ID):	<i>n/a</i>
Nearest person month worked:	<i>5</i>
Contribution to Project:	<i>Data analysis for primary and secondary analyses</i>
Funding Support:	<i>DoD W81XWH-12-2-0093</i>

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

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

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

Name:	<i>Richard Sloane, MS</i>
Project Role:	<i>Statistician (masters level)</i>
Researcher Identifier (e.g. ORCID ID):	n/a
Nearest person month worked:	1.8
Contribution to Project:	<i>Secondary analyses</i>
Funding Support:	<i>DoD W81XWH-12-2-0093</i>

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

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

The following support is new this report year:

1UH2-AG056925-01 (PI: Colon-Emeric) 09/30/17-05/31/19 1.92 calendar
\$828,696

Physical Resiliencies: Indicators and Mechanisms in the Elderly Collaborative (PRIME Collaborative)

The overarching objectives of the PRIME Collaborative (Physical Resilience: Indicators and Mechanisms in

the Elderly) are to characterize specific resilience phenotypes, elucidate biological mechanisms, and validate clinically valuable predictive tools and measures of physical resilience. The application focuses on resilience in three systems that are central to older adults' overall health: musculoskeletal, cognitive, and immune.

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.

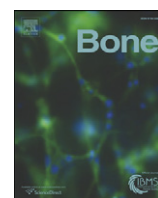
8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS: Not applicable

QUAD CHARTS: Not applicable

9. APPENDICES:

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
2. Colon-Emeric C, Pieper CF, Van Houtven C, et al. Primary Osteoporosis Screening in U.S. Male Veterans is Effective in High Risk Subgroups, but not Overall. Submitted. Acknowledged federal support: Yes
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4. Lee R, Sloane R, Pieper CF, Lyles KW, Adler R., Van Houtven C., LaFleur J., Colon-Emeric C. Clinical fractures among older men with diabetes are mediated by diabetic complications. [J Clin Endocrinol Metab](#). 2018 Jan 1;103(1):281-287. doi: 10.1210/jc.2017-01593.. Acknowledged federal support: Yes



Original Full Length Article

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 $\times$ (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

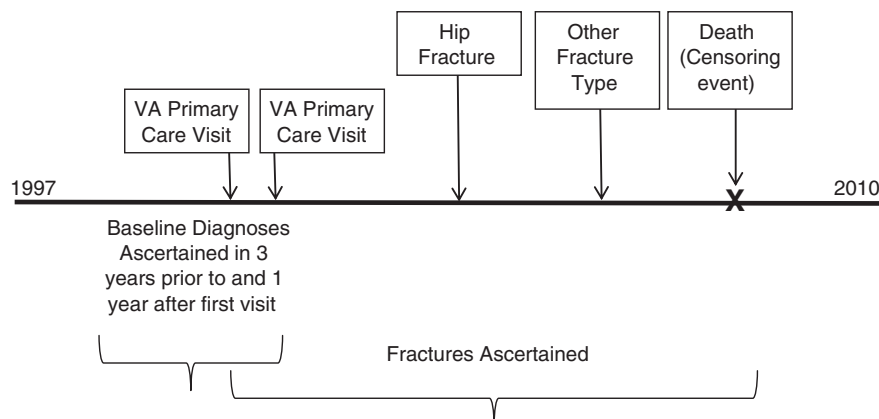


Fig. 1. Cohort schematics for follow-up time and event ascertainment. Note that the order of the fracture events did not matter for this analysis.

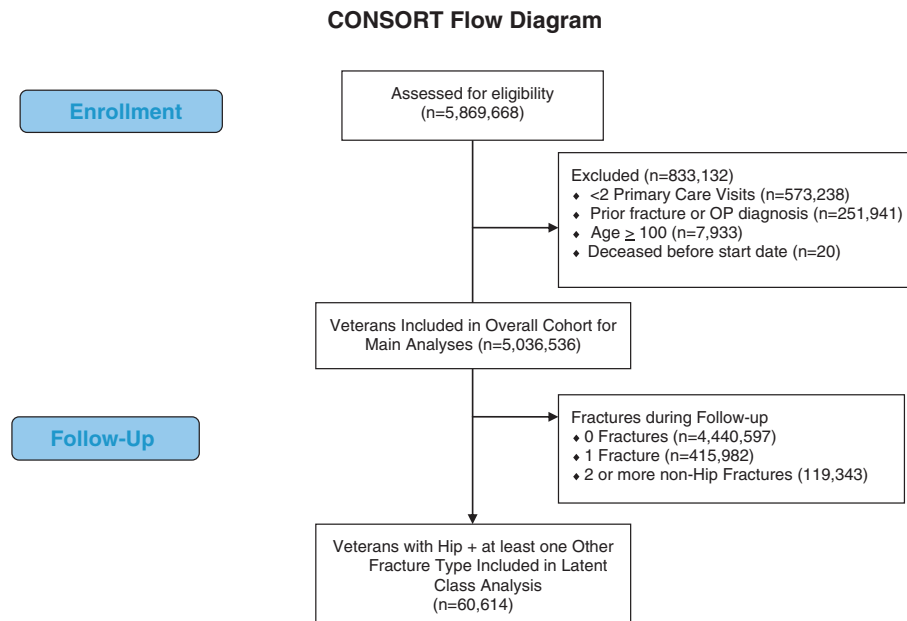


Fig. 2. CONSORT diagram illustrating selection of subjects for analysis.

[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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Primary Osteoporosis Screening in U.S. Male Veterans is Associated with Decreased Fractures in High Risk Subgroups, but not Overall

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Abstract

Primary osteoporosis screening in men is controversial. We examined the association between screening and subsequent fractures in a national sample of Male Veterans using a propensity score matched observational study with mean follow-up 4.7 years. Men aged 65-99 years without prior fracture receiving primary care in VA between 2000-2010 were included (n=2,539,812). Primary screening for osteoporosis with Dual Energy X-ray Absorptiometry was identified in VA and CMS data with administrative codes and natural language processing. Screened men were 1:3 matched with unscreened controls on propensity scores indicating the probability of screening in the next year. Propensity scores included 36 fracture-related comorbidities, social/system factors, medications, and demographic factors. Landmark analysis with competing risk compared time to fracture. During follow-up of 183,943 screened men and 475,449 controls, 9.4% fractured and 20.6% died. While overall screening was not associated with decreased fracture risk, targeted screening of pre-specified subgroups was associated with lower risk of fracture compared to the overall screening population: men on androgen deprivation therapy (HR 0.77, 0.66-0.89); men on glucocorticoids (0.77, 0.72-0.84); men aged $\geq$ 80 years (0.85, 0.81-0.90); men with one or more risk factors defined by the VA Guideline (0.91, 0.87-0.95); and men with high risk for fracture by FRAX using BMI (0.90, 0.86-0.95). Initiation of and adherence to osteoporosis medication was poor, limiting conclusions regarding the efficacy of general screening in men over age 65. We conclude that targeted DXA testing of higher risk men was associated with lower fracture risk. System interventions are needed to improve medication adherence after screening. The results can be used to refine current guidelines for identification of men at risk for fracture.

Keywords: Screening, aging, fracture prevention, health services research, osteoporosis

Introduction

Osteoporosis is under-recognized in older men. At age 50, 13% of white men can to expect suffer a hip, vertebral, or forearm fracture in their remaining lifetime, comparable to the risk of prostate cancer(1). Men are more than twice as likely as women to experience complications after an osteoporotic fracture, and have greater excess mortality after hip fracture(2). It is estimated that hip fractures result in 43 million dollars of excess cost to the Veterans Health Administration (VA) annually(3). Despite this high burden, men are rarely diagnosed and treated for osteoporosis before a fracture occurs(4).

Low diagnosis and treatment is related in part to uncertainty about screening for osteoporosis in men. While guidelines uniformly endorse screening men over age 50 after a low trauma fracture (secondary screening),(5) there is no consensus on screening men who have not had a prior fracture (primary screening)(6) Current recommendations include screening all older men with dual energy x-ray absorptiometry (DXA)(7-9) or selecting men based on fracture risk factors or clinical risk score(10-12) However, the United States Preventive Services Task Force (USPSTF) and VA National Center for Disease Prevention concluded that there was insufficient evidence to recommend for or against primary screening in men(13) citing a lack of direct evidence that it reduces fractures, and concluding that long-term studies were needed.

We analyzed administrative and electronic health record data for all U.S. male Veterans receiving primary care within the VA between 2000-2010. Using propensity score matching, we examined the association between primary osteoporosis screening with DXA and subsequent fractures overall, and in pre-specified high risk groups in whom screening is recommended by at least 1 practice guideline.

Materials and Methods

Propensity matched observational study using the cohort of 5,869,668 men with any VA outpatient encounters between 2000-2010. We hypothesized that primary osteoporosis screening would be associated with lower fracture rates than in unscreened men with a similar likelihood of being screened, especially when followed by osteoporosis treatment for those meeting recommended treatment thresholds(7). Ethical approval was obtained from the Durham and Richmond VA Medical Centers and the Department of Defense.

Data Sources: VA inpatient treatment file, outpatient care file, fee-basis file, pharmacy treatment file, and laboratory files were merged with Centers for Medicare and Medicaid Services (CMS) Part A and B claims. Death was determined from the Beneficiary Identification and Records Locator Subsystem.

Subjects: Men aged 65-99 years who were eligible for primary osteoporosis screening (no previous Dual X-ray Absorptiometry (DXA), fracture, osteoporosis diagnosis, or osteoporosis medication in the 3 years prior to their start date). Only men with at least 2 VA primary care visits within 2 consecutive years were included to improve ascertainment of co-morbidities and medications(14).

Observation period and follow-up: Each subject's start date was their first primary care visit between January 1, 2000 and December 31, 2010 in the first calendar year after DXA became available at their medical center. Relevant diagnoses and medications were determined for the 3 years prior to their start date, and updated on January 1 of each year thereafter. Subjects were followed until study end or death. Because CMS records were available for all subjects, we did not censor for loss to VA follow-up.

Osteoporosis Screening, Results, and Treatment: Current procedural terminology (CPT) codes for DXA were identified from VA and CMS. To supplement this, natural language processing

(NLP) identified bone density test results in radiology, primary care, and consult notes. NLP extracted femoral neck T scores and lowest T scores at any site; validation suggested excellent accuracy(15). Only DXAs done prior to a fracture or osteoporosis medication prescription were considered primary screening.

Treatment was defined as at least 1 prescription for a bisphosphonate, calcitonin, or teriparatide. Using U.S. treatment thresholds (osteoporosis by BMD at any site or 10-year FRAX-BMD score $\geq 20\%$ major osteoporotic or $\geq 3\%$ hip fracture)(16), subjects' treatment status was defined 12 months after screening as appropriately treated, appropriately untreated, over-treated, or undertreated. If DXA results were not available, FRAX-BMI was used for classification; prior studies have demonstrated that few patients are classified differently with FRAX-BMI compared to FRAX-BMD(17) Treatment adherence was estimated using the continuous measure of medication acquisition (CMMA)(18).

Co-morbidities and other variables: Co-morbid conditions, medications, and other factors that increase fracture risk were identified using ICD9 codes, laboratory values (hemoglobin A1C, estimated glomerular filtration rate), and medication prescriptions (glucocorticoids, androgen deprivation therapy, hypoglycemics, dopaminergic medications, cholinesterase inhibitors, selective serotonin reuptake inhibitors, opiates, proton pump inhibitors)(19) Charlson co-morbidity scores were calculated using a validated approach(20,21). Fall risk factors including neuropathy, stroke, seizure disorder, dementia, and psychoactive medications were included. FRAX 10-year risk for hip and major osteoporotic fracture were calculated at baseline for all subjects using BMI, and updated for those with femoral neck T score. Other social and health system factors included marital status, co-pay level (financial status), homelessness, rural zip code, receipt of colorectal cancer screening, and number of outpatient visits.

Propensity Score Development: We used propensity scores to match screened “cases” with unscreened “controls” with a similar likelihood of receiving osteoporosis screening in the next year based on co-morbidities, medications, demographics, health system, and social factors (Table 1). The propensity score contains information on a large number of measured confounders and has a property of balancing them between screened and unscreened patients(22). For this analysis, a 3-year look back period from each subject’s start date was employed to identify baseline risk factors, then new propensity scores were calculated on January 1 of each year incorporating new diagnoses and medications from the prior year. Because screening practices vary by region and medical center complexity level, 80 separate logistic models stratified by year, region, and complexity level were used. Logistic models included all of the potential risk factors for screening listed in Table 1.

Matching: A greedy matching algorithm identified up to 3 unscreened controls with the closest propensity score to the screened case as of January 1 of the case’s screening year. Screened patients were eligible to serve as controls prior to their screening year, at which time they became cases. Controls were excluded after matching if they fractured, began an osteoporosis medication or died between January 1 and the case’s screening date. Matching effectiveness was assessed by ensuring standardized difference <0.1 for all fracture risk factors (figure 2). Propensity score distributions were examined graphically.

Analysis: Proportional Hazards (PH) models, stratifying on the matched groups, assessed the difference in fracture risk between screened and unscreened men. Because death could confound the observed effects, Competing Risk analyses as implemented by the methods of Fine and Gray were estimated(23). To allow for the lag time to benefit from an osteoporosis medication(24), we set a landmark of 12 months after screening (i.e., subjects who died or fractured within 12 months of their screening/match date were censored). Use of this landmark had several additional analytic benefits. Initial estimates identified that the proportional hazards

assumption for fracture risk was not met, with curves crossing around 12 months. Further, we observed a spike in fractures immediately following the first DXA date, suggesting that these likely were post-fracture DXAs with errors in the coding dates. Setting the 1-year landmark removed these misclassified events.

Subjects were censored at fracture, death, or end of study; in addition, controls were censored if they were screened (became a case) or started taking an osteoporosis medication. Models were constructed for the overall cohort, and by the case's status at the 1-year landmark (met or under treatment threshold after screening, and treated or untreated). Interaction terms for pre-specified subgroups were examined including age ≥ 80 years, glucocorticoid users, androgen deprivation therapy (ADT) users, high baseline FRAX-BMI score ($\geq 20\%$ major fracture or $\geq 3\%$ hip fracture), and ≥ 1 fracture risk factor per the VA Undersecretary guidelines (glucocorticoids, ADT, traditional anti-epileptic drug, rheumatoid arthritis, alcohol abuse, smoking, BMI < 25 kg/m², hyperthyroidism, hyperparathyroidism, chronic lung disease, chronic liver disease, stroke, Parkinsonism, gastrectomy). All hypothesis tests were 2-sided with significance level of $p < 0.05$. Data were analyzed by authors CFP and JG using SAS 9.4.

Results

Baseline characteristics are in table 1. As expected, matched cases and controls had more fracture risk factors than the overall cohort, but similar proportions of smoking, alcohol abuse, and mean FRAX-BMI scores. Cases and controls were older, more likely to be married, live in non-rural areas, have higher income, prior colorectal cancer screening, and more outpatient visits in the screening year than the cohort overall. After matching, the standardized difference for all risk factors used in calculating the propensity score was < 0.10 (figure 2), indicating good balance.

Osteoporosis Screening, DXA Results, and Follow-up in the Overall Cohort

Primary osteoporosis screening was uncommon (8.2%), varied by region and over time. Among the subset of screened individuals in which DXA results were available ($n=81,479$, 39.4% of the cohort), 26% had osteoporosis and 46% had osteopenia at any site. During a mean follow-up time of 4.7 years after screening (range 0-10 years), 11.5% sustained a fracture and 22.1% died.

Association of Screening with Fracture Risk in the Matched Cohort

Screening was associated with a higher fracture risk overall (HR 1.19, 1.16-1.21, figure 2), suggesting the presence of unmeasured fracture risk factors that prompted physicians to order screening for cases, but were unavailable in administrative data. Assuming a prevalence of 10% in the unscreened group, these risk factors would have to be fully independent of the 32 risk factors in our model, increase fracture risk by 100%, and be 2.5 times as prevalent in the screened group to have resulted in missing a 10% decrease in the hazards of fracture attributable to screening. Examining fracture risk by treatment status, those who met treatment thresholds and received at least 1 prescription for an osteoporosis medication ($n=22,027$, 14.3% of screened) had a HR of 1.45 (1.39-1.52). Individuals who did not meet treatment thresholds

and were appropriately untreated (n=103,129, 67.3%) nevertheless had a slightly elevated hazard of fracture (HR 1.09; 1.07-1.12) also suggesting unmeasured risk factors. Those classified as “overtreated” (n=11,280, 7.4%, HR1.24; 1.15-1.32) and “undertreated” (n=16,875, 11.0%, HR 1.34; 1.27-1.42) had intermediate hazards (figure 3).

Examining osteoporosis medication use among screened individuals who met treatment thresholds, the median proportion of follow-up time during which they received medication following the 1-year landmark was 12%. More than 60% of osteoporosis medication use occurred within 90 days of screening, with <10% of prescriptions dispensed 1 year after screening.

Screening effectiveness improved over time (3% reduction in hazard of fracture in screened individuals per year, interaction $p < 0.0001$). The proportion of cases who were classified as receiving guideline-recommended care was similar over the study period (77% to 82%).

Pre-specified subgroups

Interaction terms suggested higher screening effectiveness in all pre-specified groups ($p < 0.0001$), and therefore separate analyses were completed (figure 4). Relative to the screening risk in the overall population, screening was associated with a 23% lower hazard of fracture relative to unscreened controls for patients on androgen deprivation therapy (0.77, 0.66-0.89) and glucocorticoids (0.77, 0.72-0.84). Smaller but significant benefits associated with screening were observed among men aged ≥ 80 years (0.85, 0.81-0.90), those with one or more VA Guideline risk factors (0.91, 0.87-0.95), and those with high 10-year fracture risk by FRAX with BMI (0.90, 0.86-0.95).

Discussion

Practitioners and policy makers have little data to inform decisions about primary osteoporosis screening in men. In the Cardiovascular Health Study, 654 men from 2 counties received osteoporosis screening while those in 2 other counties received “usual care”; there was a trend to lower hazard of hip fracture (HR 0.68, 0.32-1.42)(25) which was likely affected by geographic differences in hip fracture rates(26). Other studies have modeled osteoporosis prevalence rates from cohort studies and treatment benefits from clinical trials to estimate screening cost-effectiveness(27,28). Prospective studies such as MrOS(29) have been crucial for establishing osteoporosis prevalence and risk factors, but lack a comparison group. While a randomized controlled trial would be required to establish unbiased estimates of screening’s true effectiveness under optimal conditions, such a study would require a large sample size and long follow-up duration; indeed there is a paucity of data supporting primary osteoporosis screening even in women(30). A single pragmatic trial of more than 12,000 women in the United Kingdom demonstrated a decrease in hip, but not all clinical fractures(31,32). In the absence of clinical trial data, well-done observational studies can provide important insights to guide practice.

Our findings suggest that screening *as it is currently operationalized* in the largest health system in the U.S. is associated with a lower risk of subsequent fractures among subgroups of men at high fracture risk. However, we were unable to demonstrate a reduction in fractures from screening in the overall cohort in the setting of low treatment and adherence rates, suggesting that major changes in the screening program are needed. Our results are influenced by unmeasured risk factors; the counter-intuitive higher fracture rates associated with screening overall suggests that ordering clinicians are identifying fracture risk factors that were unavailable in administrative data. However, the impact of these risk factors would have to be very large to have resulted in our missing even a modest decrease in fractures with screening generally.

These results have important clinical implications for screening selection and osteoporosis care delivery.

Selecting the most appropriate group of men to undergo osteoporosis screening has been controversial. In this cohort, 75% of those receiving screening in routine clinical care did not ultimately meet osteoporosis treatment thresholds and therefore did not benefit from screening. This figure is higher than for women undergoing primary osteoporosis screening(33) although it compares favorably with the yield in colon cancer, aortic aneurysm, and lung cancer screening(34). However, screening was associated with lower hazard of fracture in all subgroups at higher risk relative to the overall population. Therefore, more targeted selection of men at highest risk for fracture would improve screening's impact. Variability in guideline recommendations may be contributing to inefficient selection for screening. Our results support the VA Undersecretary(12) and American College of Physicians(10) guidelines which select older men with 1 or more fracture risk factors. Several guidelines recommend age-based screening, selecting all men over age 65 or 70 years(8,9). Although it remains unclear what the impact of general screening would be among 65-79 year-olds with higher treatment and adherence, our results do support general screening for men over 80 years, at which age fracture rates are increasing exponentially. FRAX with BMI could also be used to focus screening efforts since those with high baseline FRAX-BMI also benefited from screening; in the U.K. only intermediate risk individuals are referred for DXA while high risk individuals go on to treatment(11,32).

In addition to informing selection for primary osteoporosis screening, the results highlight the urgent need to improve treatment rates and adherence monitoring. Among screened men who met treatment thresholds, 43% were never treated, and 90% of those who received an osteoporosis medication discontinued it before it is likely to have provided a benefit. These groups had substantially higher risk of fracture compared to screened men not meeting

treatment criteria (Figure 3), suggesting that screening does provide risk stratification.

However, systems to support patient adherence are needed for men whose DXA indicates high risk. Prior studies outside the VA have shown that 45% of patients on osteoporosis medications discontinue them within 1 year, with men more likely to discontinue than women(35). Poor medication persistence is associated with a higher fracture rate(36) with no evidence of a healthy adherer effect(37).

Challenges with both screening selection and treatment monitoring indicate a need for systems-level approaches. Validated algorithms selecting men for osteoporosis screening based on risk factors found in the electronic health record have been developed(38) but have not been widely adopted due to concerns about provider alert fatigue. Quality improvement interventions targeting primary care providers and patients have had limited success in improving osteoporosis treatment and adherence(39) and these tasks may be best accomplished by a centralized team focused on fracture prevention. Such “Fracture Liaison Service” teams have been effectively deployed worldwide (including within VHA)(40) to improve secondary osteoporosis testing and treatment after a fragility fracture, and are associated with reductions in fracture rates and costs(41). However, this model is not widely used for primary screening before a fracture has occurred.

Limitations

It is important to emphasize that we considered only primary osteoporosis screening in men who have not had a prior fracture; there is broad consensus that “secondary screening” and treatment for osteoporosis is indicated for this high risk group. Recent studies have documented alarming international trends of declining treatment rates after fragility fracture(4).

Although our cohort was large with 10-years of follow-up, the accuracy and completeness of administrative data is limited. Coding for fracture is both sensitive and specific(42), but we

could not distinguish between fragility fractures and high-trauma fractures. Administrative data algorithms for other chronic conditions generally have good specificity but poor sensitivity(43) resulting in unrecognized fracture risk factors. We used mitigating strategies such as including pharmacy records and laboratory results, combining VA and CMS records, and updating propensity scores annually; however unmeasured risk factors clearly remain. We lacked Medicare D prescription data and likely underestimated treatment outside VA, though studies suggest that primary prevention osteoporosis treatment is uncommon in male Medicare beneficiaries(44). Our use of a propensity matched cohort selects a population who is likely to be screened. The generalizability of our findings to non-Veterans should also be considered; because risk factors are common in Veterans, it is estimated that the rate of osteopenia and osteoporosis is nearly double that of non-Veterans and therefore they represent a population more likely to benefit from screening, but with additional adherence challenges(45).

Conclusions

Primary osteoporosis screening high-risk subgroups of men is associated with clinically important reductions in fractures. However, overall screening as currently operationalized in this large national sample of older men is unlikely to yield a clinically meaningful reduction in fractures. Inefficient selection for screening and low treatment and adherence rates should be addressed to improve screening effectiveness.

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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-inventor 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, Courtney Harold Van Houtven, Joanne LaFleur, and Robert Adler declare that they have no conflict of interest.

Authors’ Roles: Study design: CCE, RAA, KWL, CFP, CVH, JL. Study conduct: CCE, CFP, JG, CVH. Data analysis: JG and CFP. Data interpretation: CCE, RAA, KWL, CVH, JL, CFP. Drafting manuscript: CCE. Revising manuscript content: RAA, KWL, CFP, CFH, JL. Approving final version of manuscript: RAA, KWL, CFP, JL, CVH, JG. CFP takes responsibility for the integrity of the data analysis.

Figure Legends

Figure 1. Consort Diagram showing subject flow through the analysis. Exclusion or censoring criteria are shown at diamonds. DXA=dual x-ray absorptiometry (i.e., screening).

Figure 2. Plot of Standardized Differences between screened and unscreened individuals (difference in mean values divided by pooled standard deviation) before and after the propensity score match.

Figure 3. Fracture free-survival for screened and unscreened men.

Figure 4. Hazard ratio for fracture in screened relative to unscreened men. HRs for the pre-specified subgroups are relative to the screening risk in the overall population. Met/under threshold indicates whether or not case met U.S. practice guidelines for treatment after screening. High FRAX-BMI score defined as 10-year fracture risk $\geq 3\%$ hip fracture or 20% major osteoporotic fracture before screening. ADT = Androgen Deprivation Therapy.

Table 1. Characteristics of the overall cohort at baseline, and matched subset on January 1st of year in which the screened patient received DXA.

Characteristic	Overall (at Baseline)	Matched Patients (as of January 1 st of match year)	
		Screened	Unscreened
	N=2,539,812 n (%)	N=183,943 n (%)	N=475,449 n (%)
Demographic, Social and System Factors			
Mean age (sd), yrs	74.5 (6.2)	77.0 (5.7)	76.7 (5.9)
Mean body mass index (sd), kg/m ²	28.2 (4.7)	28.0 (4.4)	27.9 (4.3)
Race			
Black, Non-Hispanic	176,903 (7.0)	13,100 (7.1)	33,610 (7.1)
Other	90,869 (3.6)	8,040 (4.4)	20,538 (4.3)
Unknown	519,216 (20.4)	33,046 (18.0)	83,572 (17.6)
White, Non-Hispanic	1,752,824 (69.0)	129,757 (70.5)	337,729 (71.0)
No co-pay (low income/disability)	1,628,545 (64.1)	113,703 (61.8)	292,091 (61.4)
Medicaid	152,670 (6.0)	11,381 (6.2)	29,826 (6.3)
Married	1,814,547 (71.4)	137,421 (74.7)	355,461 (74.8)
Rural	170,478 (6.7)	10,228 (5.6)	26,281 (5.5)
Homeless	17,953 (0.7)	1,059 (0.6)	2,574 (0.5)
Prisoner of War	25,626 (1.0)	2,478 (1.3)	6,297 (1.3)
Colorectal cancer screened	295,027 (11.6)	102,578 (55.8)	263,640 (55.5)
Median number of outpatient visits (interquartile range)	5.0 (6.0)	8.0 (10.0)	8.0 (11.0)
Fracture Risk Factors			
Chronic lung disease	442,017 (17.4)	68,023 (37.0)	171,166 (36.0)
Diabetes	414,548 (16.3)	63,475 (34.5)	158,970 (33.4)
Hyperthyroid, Cushing's, Hypogonadism	20,057 (0.8)	7,519 (4.1)	16,987 (3.6)
Parkinson's	27,527 (1.1)	3,992 (2.2)	10,012 (2.1)
Prostate cancer	212,223 (8.4)	42,682 (23.2)	108,382 (22.8)

Rheumatoid arthritis	11,843 (0.5)	5,331 (2.9)	8,597 (1.8)
Gastrectomy, malabsorption	6,606 (0.3)	2,209 (1.2)	5,041 (1.1)
Alcohol abuse	407,335 (16.0)	32,487 (17.7)	82,985 (17.5)
Smoking	506,936 (20.0)	33,172 (18.0)	86,505 (18.2)
Mean FRAX-BMI 10 year major fracture risk (sd), %	6.4 (3.0)	6.6 (3.0)	6.5 (3.0)
Medications			
Androgen deprivation therapy	11,078 (0.4)	6,393 (3.5)	13,197 (2.8)
Glucocorticoids	57,448 (2.3)	25,304 (13.8)	58,799 (12.4)
Proton pump inhibitor	187,410 (7.4)	57,674 (31.4)	143,556 (30.2)
SSRI	119,391 (4.7)	27,444 (14.9)	67,921 (14.3)
Traditional anti-epileptic	53,670 (2.1)	17,269 (9.4)	41,732 (8.8)
Other Diagnoses			
Mood disorder	345,200 (13.6)	61,210 (33.3)	152,551 (32.1)
Other psychiatric diagnosis	175,646 (6.9)	30,162 (16.4)	74,535 (15.7)
Dementia	84,154 (3.3)	15,663 (8.5)	36,580 (7.7)
Chronic liver disease	54,162 (2.1)	14,358 (7.8)	34,505 (7.3)
Non-skin cancer	491,142 (19.3)	87,892 (47.8)	224,772 (47.3)
Neuropathy	165,038 (6.5)	38,148 (20.7)	94,287 (19.8)
Congestive Heart Failure	256,692 (10.1)	23,295 (12.7)	58,154 (12.2)
Chronic kidney disease	340,785 (13.4)	97,068 (52.8)	242,350 (51.0)
Stroke	10,174 (0.4)	2,317 (1.3)	5,341 (1.1)
Median Charlson Score (interquartile range)	1.0 (3.0)	0.0 (3.0)	1.0 (3.0)

Because of the large sample size, nearly all comparisons are statistically significant. Clinically important trends are noted in the text. Missing values (overall, screened, unscreened): body mass index (132,909; 8,239; 20,381); co-pay (18,328; 1,080; 2,710) married (8,681; 598; 1,669); rural (40,365; 3,770; 9,509).

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Competing Risks of Fracture and Death in Older Adults with Chronic Kidney Disease

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OBJECTIVES: To examine whether chronic kidney disease (CKD) at any stage is associated with fracture risk after adjusting for competing mortality and to determine whether age or race modify the relationship between CKD and fracture risk.

DESIGN: Prospective cohort study.

SETTING: Department of Veterans Affairs (VA) national healthcare system.

PARTICIPANTS: Men receiving VA primary care aged 65 and older with no history of fracture or osteoporosis therapy (N = 712, 918).

MEASUREMENTS: We determined CKD stage from baseline estimated glomerular filtration rate (eGFR). Participants were followed for up to 10 years for occurrence of any fracture or death. We ascertained fractures and covariates from VA medical records and Medicare claims.

RESULTS: Of the 356,459 older veterans with CKD (defined as eGFR <60 mL/min per 1.73 m²), 15.7% (n = 56,032) experienced a fracture, and 43.0% (n = 153,438) died over a median time at risk of 5.2 years. Veterans with CKD Stages 3 to 5 had a greater risk of death than those without CKD, which biased estimates from traditional survival models. Competing risk models showed that Stage 3 CKD was associated with greater hazard (adjusted subdistribution hazard ratio (sdHR) = 1.07, 95% confidence interval (CI) = 1.02–1.11) of fracture (than those without CKD) and a trend toward greater

hazard for Stage 4 (sdHR = 1.07, 95% CI = 0.94–1.22) and Stage 5 (sdHR = 1.31, 95% CI = 0.97–1.77) CKD. Age, race, and bone mineral density did not modify the relationship between CKD and fracture risk.

CONCLUSIONS: In older male veterans, CKD, including Stage 3, is associated with a moderately greater fracture risk irrespective of age, race, or bone mineral density. *J Am Geriatr Soc* 2018.

Key words: geriatric nephrology; osteoporosis; competing risks

Osteoporotic fractures are a major source of morbidity, mortality, and cost in older adults. Because fracture risk increases exponentially with age, multimorbidity is the norm for most older adults and can complicate assessment of the risks and benefits of osteoporosis screening and treatment. One of the most common but understudied such comorbidities is chronic kidney disease (CKD).

Older adults with CKD have a greater risk of death at worsening levels of kidney function than those without CKD.¹ Because impaired kidney function reduces bone quality and increases risk of falls, CKD has also been associated with fractures,^{2–7} although prior studies did not take into account competing mortality risk, which can bias fracture risk prediction. Furthermore, it is unknown whether CKD in an older adult with mild, age-related decline in kidney function independently increases the risk of fracture or whether the presence of CKD is merely a marker of other chronic illnesses associated with fracture. Precise estimates of the risk of fracture at all levels of CKD, accounting for competing mortality risk and other risk factors, are therefore needed. Finally, we have insufficient evidence to understand whether race or ethnicity modifies the fracture risk associated with CKD. This is especially important because CKD disproportionately affects African Americans, who generally have a lower fracture risk than Caucasians.⁸

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Despite the increasing prevalence of CKD in older adults, current fracture prediction tools, such as FRAX, Garvan, and the Canadian Association of Radiologists and Osteoporosis Canada (CAROC) system,^{9–12} do not include a measure of kidney function, or CKD level, as a risk factor. It is important for clinicians to understand the effect of various CKD levels on fracture risk when making treatment decisions. Therefore, we examined the extent to which various kidney function levels were associated with fracture risk when accounting for competing mortality risk.

METHODS

Study Design

We conducted a retrospective cohort study of male veterans aged 65 and older receiving primary care in the Department of Veterans Affairs (VA) health system between January 1, 2000, and December 31, 2010. We used merged data from VA medical records (including inpatient files, outpatient files, laboratory and pharmacy data) and Medicare claims (Parts A and B) to ascertain clinical characteristics, fractures, and deaths. The Durham VA institutional review board approved this study.

Study Population

This cohort was a subgroup of a larger population-based retrospective cohort study designed to evaluate osteoporosis screening in male veterans. In the parent study, the analytical sample included men aged 65 and older who received primary care at a VA Medical Center equipped to conduct dual x-ray absorptiometry (DXA) screening between 2000 and 2010. Veterans with prior diagnoses of osteoporosis, any fractures (defined as presence of any *International Classification of Diseases, Ninth Revision* (ICD-9) and Current Procedural Terminology (CPT) fracture codes, excluding skull, facial, digital, and pathological fractures), or evidence of bisphosphonate use during a 3-year look-back period were excluded. For this analysis, we also excluded veterans with missing creatinine values during a 3-year look-back period. Using these selection criteria, we identified 356,459 older veterans with CKD, defined as estimated glomerular filtration rate (eGFR) less than 60 mL/min per 1.73 m² on at least 2 occasions at least 3 months apart (Figure 1). We selected this cohort of veterans with prevalent CKD to represent what clinicians would be likely to encounter in clinical practice. Prevalent CKD is more accurately identifiable in administrative data than incident CKD and allows time for CKD-related bone abnormalities to manifest.¹³ For analytical efficiency, we selected a random sample of equal size of subjects without CKD to include in our cohort.

Variables

We assessed for the occurrence of fractures or death from the start of the observation period, defined as the date of a subject's first primary care visit after DXA became available in their facility, through December 31, 2010. Fracture events and types were determined from ICD-9 and CPT codes from inpatient and outpatient encounters in our

merged dataset. We assessed death using the National Death Index and the VA Benefits Identification Records Locator Subsystem death file.

Our primary exposure variable was kidney function as measured according to eGFR. We calculated eGFR from the Modification of Diet in Renal Disease equation using VA laboratory data between 3 years before and after a subject's start date. In the absence of other markers of kidney damage (e.g., abnormal urine composition, kidney imaging test), we used eGFR alone to classify the cohort into four clinically relevant categories: no or mild CKD (eGFR ≥ 60.0 mL/min per 1.73 m²), Stage 3 CKD (eGFR 30.0–59.9 mL/min per 1.73 m²), Stage 4 (eGFR 15.0–29.9 mL/min per 1.73 m²), and Stage 5 (eGFR <15.0 mL/min per 1.73 m²).

We identified covariates associated with fracture or death from clinical data assessed at baseline. These variables included participant demographic characteristics (age, race), region of residence, body mass index (BMI), and additional fracture risk factors listed below. We used ICD-9 and CPT codes from inpatient and outpatient VA and Medicare claims, supplemented with prescription medication use and laboratory values as appropriate, to identify the presence of specific fracture risk factors. To enhance accuracy in identification of each risk factor, these codes had to be identified at two or more visits (inpatient or outpatient) or at one visit accompanied by a relevant prescription for treatment of the risk factor (when applicable). The fracture risk factors included smoking, chronic glucocorticoid use, androgen deprivation therapy, chronic alcohol abuse, rheumatoid arthritis, hyperthyroidism, diabetes mellitus, chronic obstructive pulmonary disease, chronic liver disease, and malabsorption disorder. Additional details regarding operational definitions for these fracture risk factors are available upon request.

Statistical Analysis

We used the FRAX tool with BMI to calculate each subject's 10-year probability of major fracture.¹⁰ In the subset of participants in whom bone mineral density (BMD) was assessed during routine care, results were extracted using a validated natural language processing tool,¹⁴ and FRAX with BMD was also calculated. FRAX scores, along with all other study variables, were reported as proportions for categorical variables and means with standard deviations or medians with interquartile ranges for continuous variables. For descriptive purposes, we conducted bivariate analyses using a 4-level ordinal CKD group definition based on eGFR (described above), with the reference group being no CKD (eGFR ≥ 60.0 mL/min per 1.73 m²), and each covariate using analysis of variance for continuous variables and chi-square tests for categorical variables, with appropriate contrasts to compare each CKD level with the reference group. To evaluate the hazards of fracture attributable to each CKD group, we used Cox proportional hazards regression models, adjusting for demographic characteristics (except for age), region, BMI, and fracture risk factors (listed above). Because cohort members enter the observation period at different ages, data were left-truncated, and age served as the time-to-event scale.¹⁵ Using the Cox models, we performed tests for interaction between eGFR subgroups and baseline age

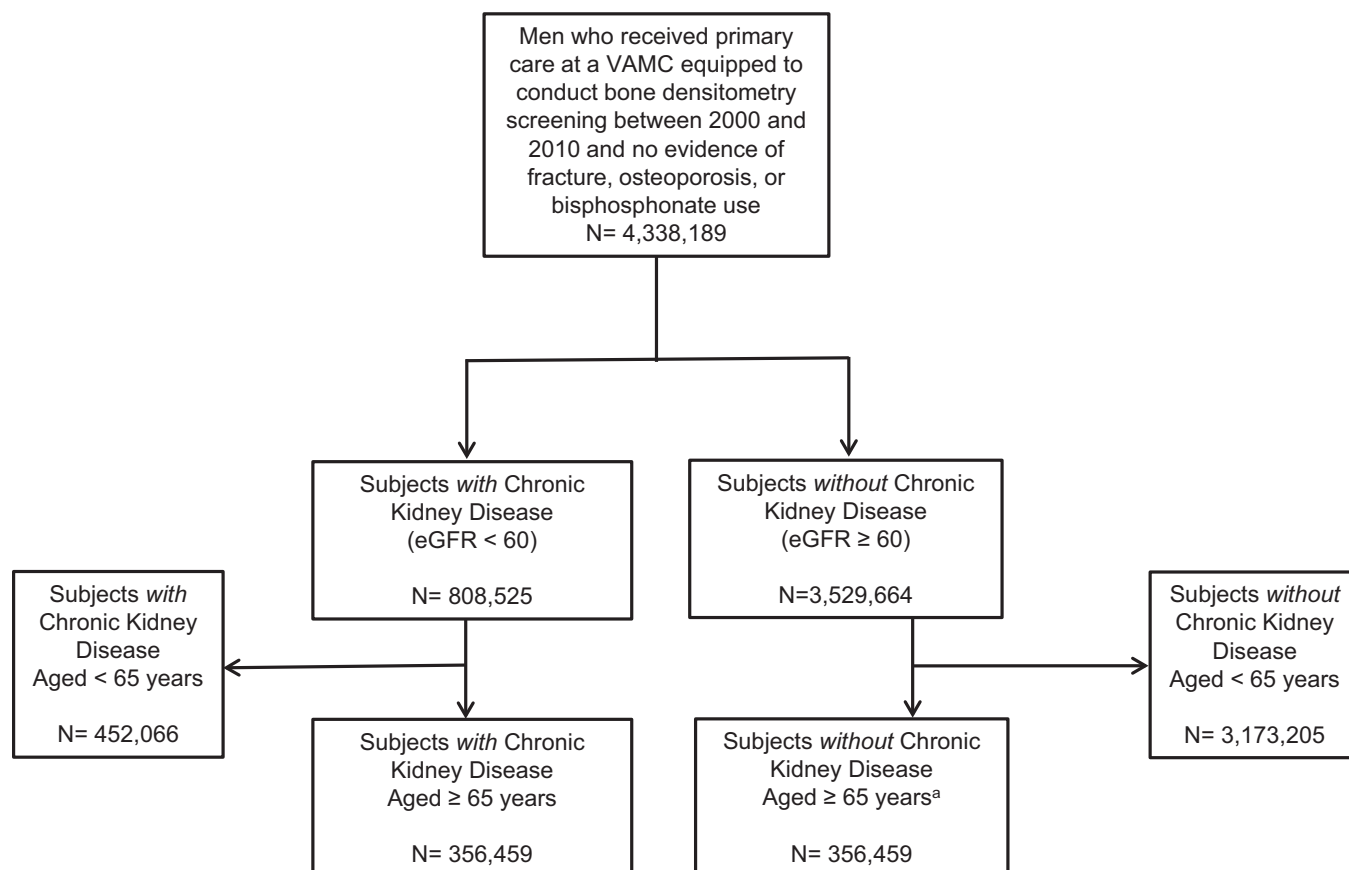


Figure 1. Consort diagram. ^aAn equal random sample of older adults aged ≥ 65 who did not have chronic kidney disease was selected for the analyses. VAMC = Veterans Affairs Medical Center.

groups (65–74, 75–84, ≥ 85) and race (Caucasian, African American, other (Asian or Hispanic ethnicity)). To account for the competing risk of death, we used the Fine and Gray method to estimate unadjusted and multivariable adjusted subdistribution relative hazards of fracture.¹⁶ After confirming the proportional hazards assumption, we performed an additional competing risk analysis adjusting for BMD in cohort members with available BMD data. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Inc., Cary, NC).

RESULTS

Cohort Characteristics

Our analytical sample included 712,918 male veterans (Figure 1). Of the 356,459 subjects with CKD, 95.2% ($n = 339,278$) of cohort members had Stage 3 CKD, 4.3% ($n = 15,167$) Stage 4, and 0.5% ($n = 2,014$) Stage 5. Cohort members without CKD were younger and less likely to have chronic alcohol use, hyperthyroidism, diabetes, chronic obstructive pulmonary disease, chronic liver disease, and malabsorption disorders and had lower FRAX-BMI scores (Table 1).

Fracture and Death Events

Over a median follow-up of 5.2 years, 14.1% ($n = 100,254$) of cohort members experienced fractures;

12.4% ($n = 44,223$) of those without CKD and 15.7% ($n = 56,031$) of those with CKD. The three most common sites of fracture in those with CKD were hip or femur (25.8%, $n = 14,452$), rib or clavicle (22.6%, $n = 12,640$), and vertebra (16.9%, $n = 9,489$) (Supplementary Table S1). Overall mortality over follow-up was 35.5% ($n = 253,415$). In adjusted analyses, Stage 3 CKD was associated with slightly greater hazard of death (hazard ratio (HR) = 1.05, 95% confidence interval (CI) = 1.03–1.08) than no CKD. There was a stepwise increase in hazards of death for Stage 4 CKD (HR = 2.07, 95% CI = 1.94–2.20) and Stage 5 CKD (HR = 2.48, 95% CI = 2.12–2.91).

Association Between CKD and Fracture Risk with and without Competing Mortality

Survival curves demonstrated that the rate of fracture events increased with worsening kidney function (Figure 2—dotted lines). Tests for interaction showed that older age and race did not modify the association between CKD and fracture. In analyses adjusting for fracture risk factors and censoring for death, cohort members with Stage 3 CKD had a significantly lower risk of fracture (HR = 0.95, 95% CI = 0.92–0.99) at any point in the observation period than those without CKD (Table 2). In contrast, fracture risk was greater for those with Stage 4 (HR = 1.32, 95% CI = 1.16–1.49) or Stage 5 CKD (HR = 1.91, 95% CI = 1.45–2.50).

Table 1. Cohort Characteristics According to Chronic Kidney Disease (CKD) Stage

Characteristic	No CKD, n = 356,458	Stage 3, n = 339,278	Stage 4, n = 15,167	Stage 5, n = 2,014
Age, mean±SD	70.9 ± 6.3	75.1 ± 6.4 ^b	75.6 ± 6.8 ^b	73.5 ± 6.4 ^b
Black, n (%)	33,299 (9.3)	18,371 (5.4) ^b	1,507 (9.9) ^a	423 (21.0) ^b
Body mass index, kg/m ² , mean±SD	28.7 ± 5.1	28.7 ± 4.8	28.3 ± 5.1 ^b	27.5 ± 4.9 ^b
Current smoker, n (%)	80,112 (22.5)	64,687 (19.1) ^b	3,085 (20.3) ^b	481 (23.9) ^b
Chronic alcohol use, n (%)	65,185 (18.3)	56,457 (16.6) ^b	2,507 (16.5) ^b	333 (16.5) ^a
Chronic steroid use, n (%)	5,936 (1.7)	5,664 (1.7)	305 (2.0) ^a	45 (2.2)
Rheumatoid arthritis, n (%)	2,315 (0.7)	1,750 (0.5) ^b	61 (0.4) ^a	6 (0.3)
Hyperthyroidism, n (%)	4,060 (1.1)	4,794 (1.4) ^b	245 (1.6) ^b	33 (1.6) ^a
Diabetes, n (%)	108,647 (30.5)	124,345 (36.7) ^b	7,855 (51.8) ^b	1,140 (56.6) ^b
Chronic lung disease, n (%)	85,937 (24.1)	90,906 (26.8) ^b	4,514 (29.8) ^b	585 (29.1) ^b
Chronic liver disease, n (%)	27,378 (7.7)	25,229 (7.4) ^b	1,673 (11.0) ^b	401 (19.9) ^b
Malabsorption, n (%)	1,178 (0.3)	1,453 (0.4) ^b	120 (0.8) ^b	67 (3.3) ^b
FRAX score (10-year probability of major fracture), mean±SD	5.5 ± 2.7	6.6 ± 3.0 ^b	6.8 ± 3.3 ^b	6.3 ± 3.5 ^b

^a*P* < .05, ^b*P* < .001; *P*-value refers to comparison between each CKD stage with the reference group (no CKD, defined as estimated glomerular filtration rate ≥ 60 mL/min per 1.73 m²).

SD = standard deviation.

Accounting for the competing risk of death changed the risk estimates for all levels of kidney function (Figure 2). Specifically, Stage 3 CKD was associated with greater hazard (adjusted subdistribution HR (sdHR) = 1.07, 95% CI = 1.02–1.11) of fracture than no CKD. Stage 4 CKD was also associated with greater hazard (sdHR = 1.07, 95% CI = 0.94–1.22) of fracture than no CKD. Accounting for the high competing risk of death in Stage 4 or 5 CKD (60% died during the observation period) attenuated the association seen in the Cox regression models but still demonstrated a trend toward greater fracture risk (Table 2). When FRAX-BMD was added to a competing risk model with eGFR alone for the subset of patients in whom it was available (*n* = 36,563), the strength of association between eGFR and fracture was relatively unchanged, indicating that the addition of BMD to the model did not mediate the association between eGFR and fracture.

DISCUSSION

It is estimated that 20% to 33% of older adults worldwide will develop osteoporotic fractures,^{17,18} and at least 25% of older adults will also develop CKD in their lifetime.¹⁹ With the high prevalence of osteoporosis and CKD in older adults, it is important for clinicians and researchers to understand how CKD at various stages modifies the risk of fracture. We demonstrated that even moderate (Stage 3) CKD remained associated with fracture risk even in the face of competing mortality.

Our findings demonstrate the importance of considering the competing risk of mortality when estimating the effect of CKD on fracture risk. Most existing observational studies that show an association between CKD and fracture risk did not account for competing mortality and limited analyses to hip fractures.^{2,4} One population-based study that performed competing risk analyses found an 83% greater risk of death and 16% greater risk of hip fracture in individuals with CKD diagnoses, and the risk

of hip fracture was mildly attenuated to 14% in competing risk models.⁷ Adding to this evidence, we examined the association between each CKD stage and risk of any fracture in the face of competing risk of mortality. Although we had a smaller sample of participants with Stage 4 CKD, the effect size was identical to that for Stage 3 CKD (HR = 1.07). Thus, our study provides further evidence that high mortality seen in CKD does not preclude strategic fracture risk prediction and management in these individuals, including those with Stage 3 CKD.

Our findings have implications for osteoporosis screening. Current U.S. practice guidelines recommend DXA screening in men aged 65 and older who have one or more fracture risk factors, but the American College of Physicians Male Osteoporosis Screening Guideline,²⁰ the Endocrine Society Osteoporosis in Men Guideline,²¹ and the Veterans Affairs Male Osteoporosis Screening Algorithm²² do not commonly consider CKD to be a fracture risk factor. Similarly, in the United Kingdom, guidelines recommend that decisions to pursue DXA screening be determined from FRAX (with BMI) estimates of fracture risk, but the FRAX tool does not include a measure of kidney function.²³ The magnitude of the greater risk we observed, especially for Stage 4 and 5 CKD, is comparable with that of well-accepted risk factors, including smoking, chronic lung disease, and chronic liver disease.^{24,25} We identified this greater risk of fracture attributable to CKD, including Stage 3 CKD, despite the inherent limitations of the Modified Diet in Renal Disease estimating equation that cause overestimation of eGFR in older adults.^{26,27} This would tend to bias our analysis against finding a significant effect of Stage 3 CKD, making our positive findings even more compelling. Because many people with Stage 3 CKD will progress to later stages, in which treatment options are more limited, and our results suggest that even moderately reduced kidney function is associated with greater fracture risk after controlling for traditional fracture risk factors, such men should be considered for DXA screening. Although men with advanced CKD may

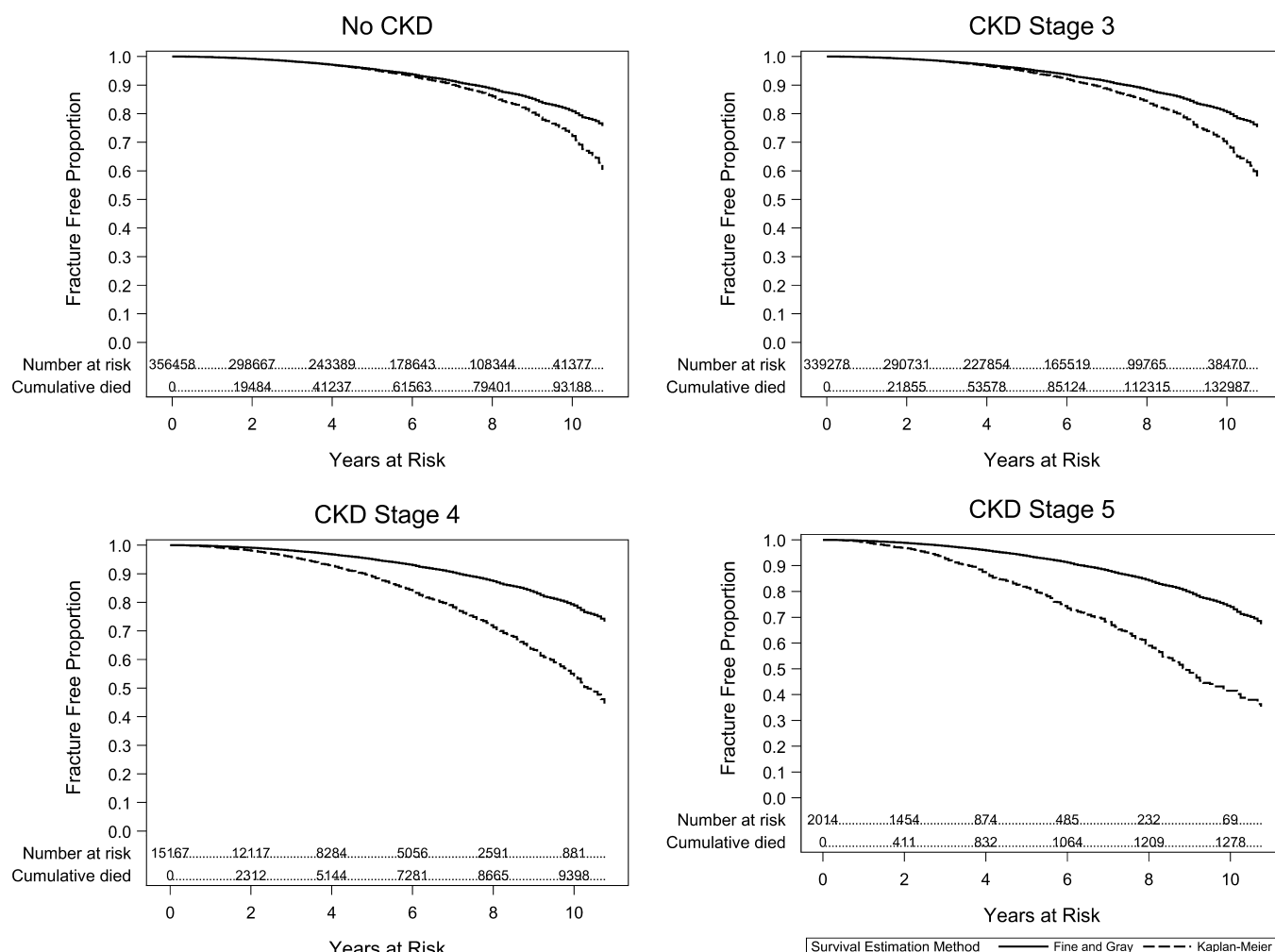


Figure 2. A Comparison of fracture-free survival curve using Kaplan–Meier and competing risk methods according to level of kidney function. For each chronic kidney disease (CKD) stage, there is a panel that demonstrates the Kaplan–Meier survival curve for fracture (dotted line) and a plot of individuals who remain in the risk set (subjects without fracture event and those with death events) of the Fine and Gray analysis (solid line). At higher CKD stages, the Fine and Gray analysis shows a smaller proportion of fractures than the survival curve because individuals who die remain in the risk set of this analysis.

Table 2. Adjusted Hazard of Fracture According to Chronic Kidney Disease (CKD) Stage

CKD Stage	Cox Proportional Hazards, Adjusted HR (95% CI)	Fine and Gray, Adjusted Subdistribution HR (95% CI)
3	0.95 (0.91–0.99)	1.07 (1.02–1.11)
4	1.32 (1.16–1.49)	1.07 (0.94–1.22)
5	1.91 (1.45–2.50)	1.31 (0.97–1.77)

Models were adjusted for baseline demographic characteristics (except for age), region, body mass index, smoking history, chronic corticosteroid use, chronic alcohol use, rheumatoid arthritis, hyperthyroidism, diabetes, chronic obstructive pulmonary disease, chronic liver disease, and malabsorption.

HR=hazard ratio, CI= confidence interval.

not be screened because of concerns about competing mortality risk yielding insufficient time to benefit, our results support screening selected men with advanced CKD given that their fracture risk remains high after considering the

competing risk of mortality. Further research is needed to develop a clinical prediction tool to help clinicians identify men with advanced CKD who may benefit from DXA screening.

Our findings also have implications for osteoporosis treatment in older adults with CKD. Current guidelines recommend osteoporosis treatment for men and women with a 10-year probability of hip fracture of 3% or greater or of major osteoporosis-related fracture of 20% or greater.²⁸ This fracture risk assessment does not consider level of kidney function. We found that level of kidney function, as measured using eGFR, is associated with greater fracture risk independent of BMD. The fact that altered vitamin D metabolism resulting in renal osteodystrophy has a greater effect on bone quality, which DXA does not measure, than on bone density may explain this finding in part. The independent risk of fracture attributable to eGFR could modify treatment decisions. For example, the FRAX tool calculates that a 79-year-old male smoker with a parental history of hip fracture and a BMI of 22.8 kg/m² has a 10-year risk of major osteoporotic

fracture of 14%. From our analyses, his Stage 3 CKD introduces an additional instantaneous risk of fracture of 7%. By accounting for risk attributable to CKD, this individual's actual risk of fracture in any given timeframe is potentially higher, which would influence a clinician's decision to initiate osteoporosis treatment.²⁹ Although many osteoporosis treatments are not approved for use in individuals with advanced CKD, newer agents such as denosumab are options for these individuals. Denosumab, teriparatide, alendronate, and raloxifene all have some evidence of benefit in BMD or fractures in Stage 3 CKD,^{30–33} but additional data regarding benefits and side effects are needed to inform the treatment of older adults with Stage 3 or more-advanced CKD.³⁴

This study's strength derives from its large population-based cohort of male veterans, although administrative data lack important information and introduce study limitations. First, we did not optimally classify participants according to level of kidney function because we did not have urine albumin data or other evidence of kidney damage (renal imaging, clinical notes). As a result, there may have been misclassification of some subjects with Stage 3 as subjects without CKD, although it is likely that this misclassification error would bias our findings toward no significant difference between these groups. Second, we used clinically diagnosed fractures as our endpoint, which is accurate for most fracture types, but misses up to two-thirds of vertebral fractures. The underdiagnosis of vertebral fractures may be more likely in nonwhite men who tend to access healthcare services less and therefore have less opportunity for vertebral fractures to be diagnosed incidentally during other imaging studies. Third, our models did not capture important unmeasured confounders, such as falls, frailty, comorbidity burden, vitamin D status, and markers associated with secondary hyperparathyroidism (serum parathyroid hormone level, calcium, fibroblast growth factor 23, phosphorus levels). Last, associations based on our cohort of male veterans who receive primary care in the VA may not be fully generalizable to the larger population of older men and women with CKD or individuals younger than 65.

Older adults with Stage 3 CKD have a greater risk of any fracture than those without CKD when accounting for competing risk of mortality. Attention to moderate CKD as an independent fracture risk factor could improve osteoporosis screening and treatment decisions.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Table S1. Fracture Site by Chronic Kidney Disease Stage

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Clinical Fractures Among Older Men With Diabetes Are Mediated by Diabetic Complications

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Introduction: Type 2 diabetes mellitus among older women has been associated with increased bone mineral density, but paradoxically with increased fracture risk. Findings among older men have varied, and potential mechanisms have not been fully elucidated.

Methods: A retrospective study of male veterans 65 to 99 years of age who received primary care in the Veterans Health Administration from 2000 to 2010, using administrative data from all 146 Veterans Health Administration medical centers linked to Centers for Medicare and Medicaid Services Medicare fee-for-service data. Potential mediating factors of the diabetes-associated risk were evaluated using negative binomial regression models with the outcomes of any clinical fracture and hip fracture.

Results: Of 2,798,309 Veterans included in the cohort, 900,402 (32.3%) had a diagnosis of diabetes. After adjusting for age, race, ethnicity, body mass index, alcohol and tobacco use, rheumatoid arthritis, and corticosteroid use, the risk of any clinical fracture associated with diabetes was 1.22 (95% confidence interval, 1.21 to 1.23) and that of hip fracture was 1.21 (95% confidence interval, 1.19 to 1.23). Significant mediating factors included peripheral neuropathy, cardiovascular disease, and congestive heart failure, with 45.5% of the diabetes-associated fracture risk explained by these diagnoses.

Conclusions: Older male Veterans with diabetes have a 22% increased risk of incident clinical fracture compared with those without. A significant portion of this risk is explained by diabetes-related comorbidities, specifically peripheral neuropathy and congestive heart failure. Identification of these mediating factors suggests possible mechanisms, as well as potential interventions. (*J Clin Endocrinol Metab* 103: 281–287, 2018)

Diabetes mellitus affects >29 million persons in the United States, with the highest rates among adults >65 years of age (1). At an annual cost of \$245 million, a significant proportion of the burden results from complications of diabetes, including renal and cardiovascular disease. Among its complications, diabetes mellitus has been associated with a significant

increased risk for fracture (2–5). However, type 2 diabetes mellitus among older adults has also been associated with increased bone mineral density (BMD); thus, the increased fracture rate presents a clinical paradox (6–8).

The underlying mechanisms for this paradoxical increased fracture risk remain controversial. A number of

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Abbreviations: BMD, bone mineral density; BMI, body mass index; CI, confidence interval; CMS, Centers for Medicare and Medicaid Services; MrOS, Osteoporotic Fractures in Men; OR, odds ratio; RR, relative risk; VHA, Veterans Health Administration.

complex interactions between bone and diabetes have been previously reviewed (9, 10). Although older adults with diabetes have an increased risk of falls (11–13), several studies have shown that the higher fracture risk persists even after adjusting for fall risk (14, 15). Others have suggested that diabetes-related changes in bone quality also contribute to the increased fracture risk (16, 17). These bone changes could be mediated in part by other diabetes-associated conditions such as impaired renal function or cardiovascular disease, both of which have been associated with lower bone quality and increased fracture risk (18, 19). However, others have postulated that diabetes complications are simply a marker of more severe diabetes and do not indicate a mechanism of action.

Some studies have suggested a differential effect of diabetes on fracture risk by sex, with the increased fracture risk confined to women, whereas others have shown no interaction. Furthermore, there has been substantial variation in the magnitude of the risk estimates (20–24). Therefore, we conducted this study to confirm and precisely quantify the risk of fracture (both clinical and hip) among older men with diabetes, and then to identify potential mediating factors of the fracture risk. We hypothesized that comorbidities, especially those related to complications of diabetes, mediate the observed increase in fracture risk.

Methods

Using administrative data from all 146 Veterans Health Administration (VHA) medical centers, we conducted a retrospective study of a cohort of male veterans aged 65 to 99 years who received primary care in the VHA from 2000 to 2010. Receiving primary care was defined as having two or more visits to a primary care provider in 2 consecutive calendar years. Men with a diagnosis of osteoporosis, osteoporosis medication prescription, or any clinical fracture in the 3 years prior to their start date were excluded. The VHA data sources included the inpatient treatment file, outpatient care file, the fee-basis file, and the Pharmacy Benefits Management Services outpatient treatment file. Because some veterans receive urgent/emergent medical care at non-Veterans Affairs facilities, the cohort was limited to those ≥ 65 years of age, and VHA data were linked to Centers for Medicare and Medicaid Services (CMS) Medicare fee-for-service data for more complete capture of medical care. The Medicare data sources were derived from fee-for-service Medicare, including part A (inpatient, including skilled nursing, home health, and hospice) and part B (outpatient) claims. Data were analyzed on the Veterans Affairs Informatics and Computing Infrastructure. The study was approved by the Institutional Review Board at the Durham Veterans Administration Medical Center.

Diabetes was defined as presence of diabetes-related ICD9 codes (250.xx) on two or more inpatient or outpatient visits, or the presence of one code in addition to prescription for diabetes medication. Birman-Deych *et al.* (25) validated this definition,

showing 75% sensitivity and 99% specificity. Diabetes medications included insulin, metformin, thiazolidinediones, and sulfonylureas/secretagogues. It was not possible to accurately distinguish between type 1 and type 2 diabetes in this administrative dataset; however, $>98\%$ of those classified with diabetes had at least one code indicating type 2 diabetes, and prior studies of veterans have documented low rates of true type 1 diabetes because this diagnosis precludes military service (26).

Clinically apparent fractures were ascertained from ICD9 codes in inpatient and outpatient Veterans Affairs and CMS files, utilizing codes 733.93 to 733.95, 767.3, 800 to 829, and V54.13, as well as CPT codes for fracture treatment. ICD9 codes related to fractures of the fingers, toes, and skull/face were excluded.

Demographic variables included age, race, and ethnicity. Physical measurements included body mass index (BMI) at baseline. Comorbidities included a history of cerebrovascular disease, cardiovascular disease, peripheral vascular disease, myocardial infarction, hypertension, chronic obstructive pulmonary disease, chronic liver disease, prostate cancer, mood disorders, seizure disorders, rheumatoid arthritis, and neuropathy. Presence of a comorbid disease was defined as one or more of the respective ICD9 codes in two or more separate inpatient or outpatient visits. For example, peripheral neuropathy was defined as presence of ICD9 codes 356.x, 357.x, 250.6, 353.5, 713.5, and 354.0 to 355.9, and congestive heart failure was defined as ICD9 codes 425.x and 428.x (additional definitions are available from the authors upon request). Chronic kidney disease was defined as the presence of respective ICD9 codes on two or more inpatient or outpatient visits, or creatinine clearance <60 mL/min on at least two laboratory measurements at least 3 months apart. Chronic corticosteroid use was defined as three or more continuous months of use of glucocorticoid medication at an average daily dose ≥ 10 mg of prednisone equivalents. History of tobacco use was defined as ICD9 codes for tobacco dependence, tobacco use, or presence of a prescription for nicotine replacement.

Natural language processing using a validated extraction process from radiology and consult databases in the Veterans Affairs Informatics and Computing Infrastructure platform was used to extract results from BMD assessments by dual x-ray absorptiometry on individual veterans. The databases were queried for any text fields with keywords such as DEXA, DXA, bone density, BMD, T score, and adjacent text searches that extract site-specific BMD results.

Descriptive statistics were used to characterize the study population, with means and standard deviation values for continuous variables and with frequencies and percentages for categorical variables. The χ^2 test for categorical variables or the Student *t* test for continuous variables was used to examine the difference in distributions of baseline characteristics between those with and without diabetes. The fracture outcomes of interest were any clinical fracture and hip fracture. Association of diabetes with clinical fracture risk was evaluated using negative binomial regression modeling and with hip fracture using logistic regression. The initial model evaluated association of diabetes with the fracture outcome, controlling for fracture-related comorbidities, including age, race/ethnicity, BMI, rheumatoid arthritis, corticosteroid use, tobacco use, and alcohol use, which were then added to the model. Relative risks (RRs) of clinical fracture or odds ratio (OR) of hip fracture

associated with diabetes with 95% confidence intervals (CIs) are presented. To evaluate potential mediating factors, comorbidities associated with both diabetes and metabolic bone disease were added individually to the fracture-related model, specifically cerebrovascular disease, cardiovascular disease, peripheral vascular disease, myocardial infarction, hypertension, chronic obstructive pulmonary disease, chronic liver disease, prostate cancer, mood disorders, seizure disorders, and neuropathy. Mediation factors were identified by comparing CIs for diabetes-associated fracture risk prior to and after inclusion of potential factors in the regression model. Non-overlapping 95% CIs were deemed to be significant factors. A final model was evaluated that included all significant mediating factors into a single model. The percentage of the mediated effect was calculated as the relative change in the parameter estimate after inclusion of the potential mediator to the model. All analyses were done in the SAS System for Windows (version 9.3; SAS Institute, Cary, NC).

Results

Among the 2,798,309 veterans in the cohort, 900,402 (32.3%) had diabetes. Baseline characteristics of the study population stratified by diabetes status are presented in Table 1. Compared with those without diabetes, men with diabetes were slightly older (71.2 vs 70.8 years), with greater BMI (30.1 vs 28.0 kg/m²), and more likely to report Black race (10.2% vs 7.6%). Older men with diabetes were also more likely to suffer from chronic kidney disease, cardiovascular disease, and neuropathy.

Among those with a BMD assessment ordered in routine clinical care during the cohort period (n = 150,026), those with diabetes had a higher femoral neck BMD, compared with those without diabetes (T score −0.51 vs −0.28, $P < 0.001$).

During the study period, there were 56,905 clinical fractures among older men without diabetes and 25,840 among those with diabetes. Of those, there were 7575 hip fractures among those without diabetes and 3601 among those with diabetes. The overall fracture rate was 0.117 per 1000 days at risk, with 0.130 per 1000 days among older men with diabetes compared with 0.111 per 1000 days among those without diabetes. Common sites of fracture among older men with diabetes included vertebra, rib, hip, and lower extremity (Table 2).

After adjusting for age, race, ethnicity, BMI, alcohol and tobacco use, and corticosteroid use, the risk of any clinical fracture associated with diabetes was 1.22 (95% CI, 1.21 to 1.23). Fracture risk was similar between those with diabetes treated without antihyperglycemic agents [RR, 1.17 (1.16 to 1.18)] and those prescribed oral agents only [RR, 1.18 (1.16 to 1.19)]. The most common oral agent prescriptions were sulfonylureas (73.6%), metformin (54.5%), and thiazolidinediones (10.4%). However, fracture risk was significantly higher for those prescribed both insulin and an oral agent [RR, 1.40 (1.37 to 1.43)] and those prescribed insulin only [RR, 1.54 (1.51-1.58)]. Significant mediating factors for

Table 1. Baseline Characteristics by Diabetes Status

	Without Diabetes Mellitus (N = 1,897,907)	With Diabetes Mellitus (N = 900,402)	P
Age, y (mean ± SD)	71.8 ± 6.6	72.1 ± 6.5	<0.001
BMI, kg/m ² (mean ± SD)	28.0 ± 4.7	30.1 ± 5.4	<0.001
Race, %			
White	71.7	71.2	<0.001
Black	7.6	10.2	
Other	3.4	5.0	
Unknown	17.3	13.6	
Femoral BMD T score ^a	−0.51 ± 1.44	−0.28 ± 1.45	<0.001
Comorbidities, %			
Alcohol abuse	18.1	17.5	<0.001
Tobacco use	22.5	20.1	<0.001
Rheumatoid arthritis	0.7	0.5	<0.001
Corticosteroid use	1.7	1.6	0.19
Chronic kidney disease			
Stage 3	22.7	27.7	<0.001
Stage 4/5	0.9	2.0	
Neuropathy	13.6	23.8	<0.001
Cardiovascular disease	8.4	11.2	<0.001
Cerebrovascular disease	0.65	1.00	<0.001
Congestive heart failure	12.6	21.3	<0.001
Chronic lung disease	25.0	24.5	<0.001
Chronic liver disease	7.7	7.9	<0.001
Seizure disorder	3.9	4.8	<0.001

Abbreviation: SD, standard deviation.

^aWhen available (N = 150,026).

Table 2. Fracture Site According to Diabetes Status

Fracture Site, n (%)	Without Diabetes Mellitus (N = 1,897,907)	With Diabetes Mellitus (N = 900,402)
Total	56,905	25,840
Vertebral	15,319 (26.9)	5,745 (22.2)
Rib	10,314 (18.1)	4,677 (18.1)
Hip	7,575 (13.3)	3,601 (13.9)
Other lower limb	6,471 (11.4)	2,983 (11.5)
Tibia/fibula	4,779 (8.4)	2,726 (10.6)
Radius/ulna	4,250 (7.5)	2,024 (7.8)
Humerus	2,421 (4.3)	1,468 (5.7)
Scapula/clavicle	1,568 (2.8)	692 (2.7)
Pelvis	1,464 (2.6)	649 (2.5)
Femur	1,391 (2.4)	619 (2.4)
Patella	921 (1.6)	407 (1.6)
Sternum	194 (0.3)	90 (0.3)
Other upper limb	134 (0.2)	73 (0.3)
Other	23 (0.0)	6 (0.0)

diabetes-associated fracture risk included comorbidities associated with diabetes complications (Table 3): peripheral neuropathy explained 21.1% of the fracture risk, congestive heart failure explained 16.6%, and cardiovascular disease explained 6.9%. However, chronic kidney disease and cerebrovascular disease did not significantly mediate the fracture risk. As expected, comorbidities that are not associated with diabetic complications (*e.g.*, chronic liver disease, chronic pulmonary disease) were not significant mediation factors and were not included in the final model. In the final model, inclusion of peripheral neuropathy, cardiovascular disease, and congestive heart failure resulted in mediation of 45.5% of the total fracture risk.

For hip fracture, the OR associated with diabetes, after adjusting for demographic factors and fracture-related comorbidities, was 1.21 (95% CI, 1.19 to 1.23). As observed with risk of any clinical fracture, peripheral

neuropathy was a significant mediator of the diabetes-associated hip fracture risk (20% of fracture risk explained) (Table 4). Both cardiovascular disease and congestive heart failure trended toward a significant mediation effect; however, the CIs were overlapping with the baseline model. Forty-one percent of the hip fracture risk associated with diabetes was explained with inclusion of peripheral neuropathy, cardiovascular disease, and congestive heart failure.

Discussion

In this large retrospective cohort study of men >65 years of age, after controlling for multiple fracture-related risk factors, diabetes mellitus remained independently associated with a significant 20% increase in any clinical fracture and hip fracture. Our estimate of the magnitude of the fracture risk associated with diabetes in men is largely consistent with, but more precise than, prior prospective studies. The Osteoporotic Fractures in Men (MrOS) cohort had a 22% increased risk associated with diabetes; however, there was not a significant difference in rate of hip fracture associated with diabetes mellitus in the MrOS study [3.3 per 1000-person-years (non-diabetes) vs 3.1 per 1000-person-years (diabetes)] (24). In the Health ABC study, the unadjusted RR was 1.61; the risk was lower in our study compared with that observed in the Health ABC study, but study participants in Health ABC were slightly older than those in MrOS and in the present study (8). A prior population-based study in Ontario, Canada, showed a significant increase in hip fracture risk associated with diabetes, after adjusting for multiple confounders, including age, medical comorbidities, and medication use (hazard ratio, 1.18; 95% CI, 1.12 to 1.24) (5). Interestingly, there was a statistically

Table 3. RR of Any Clinical Fracture Associated With Diabetes and Mediating Effect of Comorbidities on Diabetes-Associated Risk

	RR (95% CI)	% of Diabetes Effect Mediated
Diabetes ^a	1.22 (1.21–1.23)	—
+ Chronic kidney disease	1.21 (1.20–1.22)	NS
+ Neuropathy	1.17 (1.16–1.18)	21.1
+ Cardiovascular disease	1.19 (1.18–1.20)	6.9
+ Cerebrovascular disease	1.21 (1.20–1.22)	NS
+ Congestive heart failure	1.18 (1.17–1.19)	16.6
+ Chronic obstructive lung disease	1.22 (1.21–1.23)	NS
+ Chronic liver disease	1.22 (1.21–1.23)	NS

Abbreviation: NS, not significant.

^aAll models were adjusted for age, race/ethnicity, tobacco use, alcohol use, glucocorticoid use, rheumatoid arthritis, and BMI.

Table 4. OR for Hip Fracture Associated With Diabetes and Mediating Effect of Comorbidities on Diabetes-Associated Risk

	OR (95% CI)	% of Diabetes Effect Mediated
Diabetes ^a	1.21 (1.19–1.23)	—
+ Chronic kidney disease	1.20 (1.18–1.21)	NS
+ Neuropathy	1.16 (1.15–1.18)	20.0
+ Cardiovascular disease	1.18 (1.17–1.20)	NS
+ Cerebrovascular disease	1.21 (1.19–1.22)	NS
+ Congestive heart failure	1.18 (1.16–1.19)	NS
+ Chronic obstructive lung disease	1.21 (1.19–1.23)	NS
+ Chronic liver disease	1.21 (1.19–1.22)	NS

Abbreviation: NS, not significant.

^aAll models were adjusted for age, race/ethnicity, tobacco use, alcohol use, glucocorticoid use, rheumatoid arthritis, and BMI.

significant sex interaction, with men having lower risk than women. Compared with prior studies among older women, our study suggests that the magnitude of both any clinical fracture and hip fracture risk, associated with diabetes, among older men is comparable to that reported in older women.

Nearly half of the increased risk in clinical fracture was mediated by diabetes-related comorbidities, including neuropathy and cardiovascular disease, but not by unrelated comorbidities such as chronic liver or pulmonary disease. There was no mediation observed by chronic kidney disease or cerebrovascular disease. In contrast to our results, diabetes-related comorbidities were not associated with increased fracture risk in the Health ABC study; however, those authors acknowledge that they may not have had sufficient power to observe such an effect. Although some have hypothesized that diabetes is simply a marker of poor health status, our study had ample power to suggest a direct effect of diabetes on incident fracture risk by specific mechanisms.

Peripheral neuropathy was the most important mediator of fracture risk observed in our cohort. Prior studies have shown a significant risk of falls associated with both peripheral neuropathy and type 2 diabetes, as well as a contribution of such falls with regard to fracture risk (11, 12, 27, 28). For example, in the Women's Health Initiative–Observational Study, Bonds *et al.* (14) found that older women with diabetes reported more falls at baseline and during follow-up, compared with those without diabetes (44% vs 32%). Thus, our data reinforce the importance of fall risk reduction interventions for both female and male patients with diabetes, particularly those with peripheral neuropathy.

We also found significant mediation by congestive heart failure, suggesting a direct effect of diabetes on bone and calcium metabolism. Congestive heart failure has been associated with lower serum 25-hydroxyvitamin D levels, increased parathyroid hormone levels, increased magnesium and calcium excretion, and fracture risk (29–32). In animal studies, increased aldosterone (as found in heart failure) stimulated increased calcium excretion and increased parathyroid hormone levels (33, 34). In a case-control study of male veterans, Carbone *et al.* (35) showed fewer fractures in patients prescribed spironolactone, an aldosterone antagonist. Also, studies have shown increased levels of inflammatory cytokines (*e.g.*, interleukin-6 and tumor necrosis factor- α) associated with congestive heart failure (36, 37), which have also been associated with increased fracture risk, as well as frailty and physical performance (38–41). Although this suggests that congestive heart failure may also lead to increased falls risk, the mediation seen in the present study appears to be independent of that seen with peripheral

neuropathy. Our findings suggest that bone density screening and fracture prevention strategies should be emphasized for patients with comorbid diabetes and heart failure.

Our results should be interpreted in light of the study strengths and weaknesses. To our knowledge, this is the largest cohort study among older men of diabetes and fracture risk, allowing for precise estimates of fracture risk within this population. Because of the linkage with the CMS database, there was high ascertainment for clinical fracture, as prior studies have demonstrated good sensitivity and specificity for ICD9 fracture codes (42–44). However, potential weaknesses should be acknowledged. In contrast to prior prospective studies, covariates in this study were limited to those that were available in administrative datasets, and some laboratory (*e.g.*, 25-hydroxyvitamin D, parathyroid hormone levels) and fracture-related risk factors (*e.g.*, falls not resulting in health care utilization, parental hip fracture history) were not measured. We were unable to quantify duration of diabetes, or accurately assess diabetes control in our dataset. Finally, prior studies have shown that veterans have higher risk of fracture compared with nonveterans (45–48). Therefore, the generalizability of the results in this study may be limited. However, the comparison group in this study was also veterans, thus reducing variability between groups and selection bias.

In conclusion, this large cohort study confirmed a 22% increased risk of incident clinical fracture associated with diabetes among older men. This risk was independent of other known risk factors for fracture. A significant portion of this risk was explained by diabetes-related comorbidities, specifically peripheral neuropathy and congestive heart failure. Identification of these mediating factors suggests possible mechanisms for the diabetes effect, as well as potential interventions.

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