Bisphosphonate Prescriptions in Men With Androgen Deprivation Therapy Use

Androgen deprivation therapy (ADT) is an effective, widely used therapy for men with prostate cancer. Adverse effects include bone loss and increased fracture risk.1 Canadian guidelines recommended bisphosphonate use in men with osteoporosis or fragility fracture as early as 2002 and in men on ADT in 2006.2,3

Rates of bone mineral density testing in men starting ADT were previously examined;4 however, bisphosphonate prescribing patterns are relatively unknown and have likely changed over time because of increasing awareness of bone effects of ADT and evidence of bisphosphonate efficacy. We examined rates of bisphosphonate prescriptions in men initiating ADT in Ontario, Canada, between 1995 and 2012.

Methods | Linked administrative databases at the Institute for Clinical Evaluative Sciences in Ontario, Canada (population of about 13 000 000), and the Ontario Cancer Registry were used, as previously described.1 These databases have an error rate of 0.7% for drug claims, a specificity of 95% for prior osteoporosis, and a positive predictive value of 94% for fractures.5,6

Men aged 66 years or older starting ADT for prostate cancer comprised the study cohort. Individuals diagnosed between January 1, 1995, and December 31, 2012, who had undergone orchiectomy or received at least 6 months of continuous medical ADT (ie, with luteinizing hormone-releasing agonists) and survived at least 1 year after ADT initiation were included.

Any bisphosphonate claim within 12 months of ADT initiation was captured through drug database claims; bisphosphonates have been available under the public health plan for all seniors (age >65 years) since 1996. A comprehensive set of covariates was obtained from inpatient and outpatient claims using specific procedure, diagnostic, and claims codes as previously described.1 Frailty fractures were defined as those occurring at the wrist, hip, or spine.

Counts (per 100 persons) and Poisson regression using SAS version 9.2 (SAS Institute Inc) were used to evaluate bisphosphonate prescription over time in 3 groups: all nonusers of bisphosphonates, those with prior osteoporosis, and those with prior fragility fracture. The latter 2 groups represent individuals at high risk for subsequent fracture. For all 3 groups, we excluded men with any bisphosphonate claim in the 12 months prior to ADT initiation (3.1% of total population).

Level of significance was $P < .05$ and statistical tests were 2-sided. Informed consent was waived due to use of anonymized population-level data; the study was approved by the University Health Network research ethics board.

Results | A total of 35,487 men with prostate cancer who began ADT during the study period were identified. Baseline characteristics appear in the Table.

Bisphosphonate claims among all nonusers increased from 0.35 (95% CI, 0.17-0.53) per 100 persons in 1995-1997 to 3.40 (95% CI, 2.88-3.92) per 100 persons in 2010-2012 ($P < .001$). Even among those with prior osteoporosis or fragility fracture, rates remained low.

Among all 3 groups, peak bisphosphonate claims occurred in 2007-2009 (Figure), with a high of 11.89 (95% CI, 7.23-16.55) per 100 persons in those with prior osteoporosis.

Discussion | Our results show that bisphosphonate prescriptions among men receiving ADT remained low during the study period, even for those at high risk of subsequent fractures. As the most widely used class of prescription drugs for osteoporosis, this suggests limited awareness among clinicians regarding optimal bone health management.

The decrease in bisphosphonate prescriptions after 2009 may be partly due to recent negative media regarding the association of bisphosphonates with rare osteonecrosis of the jaw and atypical femoral fractures. This is appropriate for groups at low risk for fractures, but the decrease in use for high-risk patients is concerning.

Although the optimal rate of bisphosphonate use in men on ADT is unknown, it is reasonable that most men with prior osteoporosis or fracture should be taking a bisphosphonate or other effective bone medication.
Key study limitations include a lack of access to bone mineral density results to determine a patient’s risk for future fracture, examination of prescription claims and not actual drug use, and unclear generalizability to other geographic regions.

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COMMENT & RESPONSE

Assessment of Heterogeneity in Meta-analyses

To the Editor Dr Dechartres and colleagues1 investigated the association between analytic strategy and estimates of treatment outcomes in meta-analysis. In view of the emphasis that Dechartres and colleagues placed on the risk of bias in selecting trials for meta-analysis, it is unfortunate that their meta-analyses relied on the method of DerSimonian and Laird. Evidence of its shortcomings has been accumulating for many years, and Cornell et al3 provide an accurate summary: “the most widely used method for pooling heterogeneous studies—the DerSimonian-Laird (DL) estimator—can produce biased estimates with falsely high precision.” This reliance on the DerSimonian-Laird estimator weakens the study.

Dechartres and colleagues reported that “when appropriate, we used a continuity correction to deal with zero counts in 1 group only.” Sweeting et al5 compared several meta-analytic methods for combining odds ratios on sparse-event data, with emphasis on continuity corrections, and concluded that “the inverse variance [fixed-effect] method performed consistently badly, irrespective of the continuity correction used.” The DerSimonian-Laird method obtains its initial estimate from the inverse-variance-weighted fixed-effect method.