Incidence of Fractures in Patients With Type 2 Diabetes in the SAVOR-TIMI 53 Trial

DOI: 10.2337/dc15-1068

OBJECTIVE
Patients with type 2 diabetes have an increased risk of bone fractures, the predisposing factors for which are unknown. Treatment with thiazolidinediones (TZDs) further increases the incidence of osteoporotic fractures. In the Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus (SAVOR-TIMI 53) trial, fractures were considered an adverse event of special interest, and information regarding fractures was collected.

RESEARCH DESIGN AND METHODS
We compared the incidence of fractures among the 8,280 patients who were assigned to treatment with saxagliptin with that in the 8,212 patients who were assigned to placebo. We further analyzed the participants’ baseline characteristics and fracture risk.

RESULTS
During a median follow-up of 2.1 years, 241 patients (2.9%) in the saxagliptin group and 240 (2.9%) in the placebo group experienced a fracture (hazard ratio [HR] 1.00 [95% CI 0.83–1.19]). Event rates for fractures were the same in both treatment arms: 14.7 per 1000 patient-years in the entire population and 14.0 in the on-treatment population (first event only). Fracture risk was similar in patients treated with saxagliptin or placebo across different subgroups defined by race, cardiovascular risk, and renal function. A multivariable Cox regression analysis showed that risk of fracture was associated with female gender (P < 0.0001), longer diabetes duration (P < 0.0001), older age (P = 0.002), major hypoglycemic events (P = 0.01), noncompliance with study drug (P = 0.01), and treatment with TZDs (P = 0.03).

CONCLUSIONS
In a large population of older patients with type 2 diabetes, treatment with saxagliptin was not associated with an increased risk of fractures. The association between longer diabetes duration and increased risk of bone fracture is an intriguing finding.

There is a growing body of evidence that type 1 and type 2 diabetes both predispose to bone fractures (1,2). A recent nested cohort study demonstrated a hazard ratio (HR) of 1.66 (95% CI 1.6–1.72) for the risk of fractures requiring surgery in patients with diabetes compared with age- and sex-matched control subjects (3). The same study also demonstrated increased risk for postfracture complications among the population with diabetes, including deep wound infection, septicemia, and mortality.
Recent findings indicate that bone strength is closely linked to the regulation of energy metabolism and insulin sensitivity (4). Bone and glucose homeostasis are controlled by common regulatory factors, including insulin (5), peroxisome proliferator activated receptor-γ (6,7), and gastrointestinal hormones such as glucose-dependent insulinotropic peptide (8) and glucagon-like peptide (GLP) (9).

Owing to the frequent coexistence of type 2 diabetes and osteoporosis and the higher incidence of fractures among patients with type 2 diabetes, it is important to investigate any interaction between antidiabetic drugs and fracture risk. Thiazolidinediones (TZDs) are strongly associated with a decrease in bone mineral density (BMD) and a twofold increase in the risk for fractures in women (10–12). Although the evidence linking TZD use and fractures is strong, evidence supporting the effect of other, older, antidiabetic drugs on bone strength is much weaker (protective: metformin (12–14), or deleterious: insulin (13,14) and sulfonylurea (13–15)). In a 4 year follow-up of the Look Action for Health in Diabetes (AHEAD) substudy (16), intensive lifestyle intervention led to weight loss that was associated with a modest increase in bone loss at the hip in men.

Animal models indicate that incretins may have beneficial effects on bone mass and bone quality (8,9). A meta-analysis of phase 2 and 3 clinical trials enrolling 20,000 patients treated for 24 weeks or longer, in which dipeptidyl peptidase-4 (DPP-4) inhibitors were compared with placebo or active treatment, showed that treatment with DPP-4 inhibitors was associated with a reduced risk of fractures (17). In a recently published retrospective population-based cohort study in which DPP-4 inhibitor (sitagliptin) users were compared with patients treated with other antidiabetic drugs (excluding insulin) and control subjects without diabetes matched for age and sex, no association was found between DPP-4 inhibitor use and osteoporotic fracture risk (18). We report here the results of the predefined outcome of the adverse event of special interest (AEOSI) of fractures in the Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus (SAVOR-TIMI 53) trial.

**RESEARCH DESIGN AND METHODS**

**Study Design and Patient Population**

SAVOR-TIMI 53 was a multicenter, randomized, double-blind, placebo-controlled trial that randomized 16,492 patients at 788 sites in 26 countries. Patients had type 2 diabetes with HbA1c between 6.5% and <12.0% within 6 months of randomization and a history of established cardiovascular (CV) disease (CVD) and age >40 years or multiple risk factors for CVD, including age >55 for men or >60 for women. Patients were randomized to receive saxagliptin, 5 mg daily (2.5 mg daily in patients with an estimated glomerular filtration rate [eGFR] of ≤50 mL/min), or matching placebo. Other background glucose-lowering and CV therapies were administered at the discretion of treating physicians. Open-label titration of glucose-lowering therapies was allowed throughout the trial in both arms, excluding the use of DPP-4 inhibitors or GLP-1 receptor agonists. During the trial, systemic steroid use at baseline and/or for more than 3 months was reported in 6 patients (1.2%) who had a fracture and in 272 patients (1.7%) who did not have a fracture (P = 0.59). The study protocol was approved by the relevant institutional review board at each participating site, and written informed consent was obtained from all patients. The primary and secondary outcomes of this trial were previously described (19).

**Fractures As Predefined AEOSI and Their Collection**

In the protocol, 10 categories were defined as AEOSI, including bone fractures. Investigators were specifically trained to collect all data regarding AEOSI and record them on a specific page in the electronic case report form (eCRF). Fractures were identified by two criteria:

- events reported by the investigator as an AEOSI on the eCRF searching the full adverse event database for all patients with a diagnosis matching a prespecified Medical Dictionary for Regulatory Activities (MedDRA) version 15.1 list of preferred terms (excluding "tooth fracture")

Analysis was done on the entire population ("overall") and on the population that was "on treatment." Overall categories included all subjects who were randomized (intention-to-treat [ITT] population), including subjects who never took the study medication, and included all AEs that occurred on or after the date of enrollment. "On treatment" refers to AEs occurring while the subject was receiving treatment. AEs were deemed on treatment if, for nonserious AEs, the event occurred on or before the first day after the last blinded drug dosing date, or for serious AEs (SAEs), the event occurred on or before the 30th day after the last blinded drug dosing date. For those who did not experience bone fracture, the on-treatment window ended at the last dose date + 30 days.

**Statistical Analysis**

Baseline characteristics of subjects were examined, and subjects with any fracture event were compared with those without such an event. Analyses were conducted on an ITT basis among patients who underwent randomization and by on-treatment analysis among randomized patients who took at least one dose of the study medication. Categorical variables were compared using the χ² or Fisher exact test and continuous variables with the t test. A P value ≤0.05 was considered statistically significant. P values were not adjusted for multiple testing. Kaplan-Meier estimates of cumulative risk for the first occurrence of bone fracture were plotted. For the subgroup analysis, the risks of bone fracture by baseline characteristics were examined using the Cox proportional hazards regression model, with each baseline variable only as the model term. The 95% CIs for the hazard ratios (HR) are based on profile likelihood. Forest plots were used to show HR estimates and 95% CIs by baseline variables. The multivariate Cox regression model was used for analyses of strength of baseline characteristics association with bone fracture. The model included treatment and clinically meaningful baseline covariates as the model terms. Baseline covariates, either continuous or categorical factors, were evaluated for association with bone fracture as measured by the Wald χ² statistical test corresponding to their contribution to the model. Statistical software SAS 8.2 or higher (SAS Institute, Inc., Cary, NC) was used.

**RESULTS**

**Incidence of Fractures**

Fractures occurred in 241 of the 8,280 subjects (2.9%) randomized to the
saxagliptin arm and in 240 of the 8,212 subjects (2.9%) randomized to the placebo arm (HR 1.00; 95% CI 0.83–1.19). Both groups developed 14.7 fractures per 1,000 patient-years. Kaplan-Meier analysis of the time to the first event of bone fracture in the ITT population, by different treatment arms, is shown in Fig. 1A.

On-treatment analysis showed that there were 222 (2.7%) and 220 (2.7%) incident fractures in the saxagliptin and placebo arms, respectively. The exposure-adjusted rate of subjects with on-treatment AEs of bone fracture per 1,000 years of follow-up (based on the first event only) was 14.0 in both groups.

Of the fracture AEOSI, some were also classified as SAEs, mainly due to hospitalization. In the saxagliptin arm overall, there were 95 (1.1%) SAE fractures (88 [1.1%] on treatment), and in the placebo arm overall, there were 84 (1.0%) SAE fractures (79 [1.0%] on treatment; P = 0.53).

The proportions of subjects with an AE or SAE of bone fracture were similar between the saxagliptin and placebo groups across the following subgroups: sex, age, race, regions of residence, baseline CV risk, and baseline renal function categories (Fig. 2A).

The occurrence of multiple fractures in the same subject was similar between the two treatment arms: In the saxagliptin group, 24 subjects (0.3%) had two to three events and 2 subjects (<0.1%) had four or more events. In the placebo group, 27 subjects (0.3%) had two to three events, and 1 subject (<0.1%) had four or more events.

Kaplan-Meier accumulation curves according to diabetes duration in the combined two treatment arms (ITT population) showed a gradual increase in the risk of fractures with longer diabetes duration (Fig. 1B).

Baseline Characteristics and Multivariable Analysis of Subjects Who Had Fractures
Baseline characteristics of subjects who had fractures during follow-up is summarized and compared with those without fractures (Table 1). Subjects with fractures were older, more likely to be female, Caucasian, and non-Hispanic or Latino, had longer diabetes duration, lower eGFR, and were more likely to have had a history of dyslipidemia or heart failure and less likely to have had a prior myocardial infarction. Patients with fractures were also more likely to use diuretics, insulin, and TZDs at baseline and less likely to use metformin.

The HR of the time to first event for bone fracture was calculated for the ITT population of the combined two treatment arms, according to the following baseline characteristics: CV risk, renal function strata, demographic subgroups (Fig. 2B), diabetes duration, HbA1c at baseline, the occurrence of hypoglycemia, and albumin-to-creatinine ratio at baseline (Fig. 2C), and by baseline diabetes medications (Fig. 2D). The HR for fracture was increased in the following subgroups: moderately reduced renal function versus normal renal function, older age (≥65, ≥75) versus younger, female versus male, residents of North America versus Europe or Latin America, longer diabetes duration, patients with any and with major hypoglycemic events, insulin users, and those who did not use metformin.

On multivariable Cox regression analysis, fractures were associated with the following characteristics: female versus male gender (HR 1.84 [95% CI 1.53–2.21], Wald $\chi^2 = 41.96$, $P < 0.0001$), longer diabetes duration (HR 1.02 per year [95% CI 1.01–1.03], Wald $\chi^2 = 19.24$, $P < 0.0001$), older age (HR 1.02 per year [95% CI 1.01–1.03], Wald $\chi^2 = 9.93$, $P = 0.002$), noncompliance with study medication (saxagliptin or placebo) (HR 1.50 [95% CI 1.10–2.03], Wald $\chi^2 = 6.64$, $P = 0.01$), major hypoglycemic events during the study (HR 1.76 [95% CI 1.13–2.74], Wald $\chi^2 = 6.22$, $P = 0.01$), and the use of T2Ds (HR 1.44 [95% CI 1.03–2.01], Wald $\chi^2 = 4.63$, $P = 0.03$). There was no statistically significant association between increased risk of fractures and the following parameters: eGFR (HR 1.00 [95% CI 0.99–1.00], Wald $\chi^2 = 3.56$, $P = 0.06$), HbA1c (HR 0.93 [95% CI 0.87–1.00], Wald $\chi^2 = 3.51$, $P = 0.06$), or insulin use (HR 1.24 [95% CI 0.99–1.56], Wald $\chi^2 = 3.37$, $P = 0.07$). Variables that were not associated with the risk for fractures were the use of sulfonylurea ($P = 0.84$) or metformin ($P = 0.92$), BMI ($P = 0.63$), and the randomized treatment arm ($P = 0.95$).

Location of Fractures
The distribution of the location of the fractures at the different regions of the skeleton was generally similar between the two treatment arms (Fig. 3). A major osteoporotic fracture was defined, according to the World Health Organization definition (20), as a fracture of the hip, vertebrae, radius/ulna, or humerus. The difference between the total number of fractures at these locations between saxagliptin (110 fractures) and placebo (102 fractures) was not significant ($P = 0.62$).

CONCLUSIONS

Saxagliptin Versus Placebo

The SAVOR-TIMI 53 trial was a large randomized controlled trial performed in relatively old (mean age 65.1 ± 8.5) patients with type 2 diabetes, in whom fracture incidence was prespecified as AEOSI and actively collected. Over a median follow-up of 2.1 years, the incidence of fractures was equally distributed between saxagliptin- and placebo-treated arms, in the ITT population (14.7 fractures per 1,000 patient-years), and also in the on-treatment population (14.0 fractures per 1,000 patient-years). Further, no differences were found in the incidence of fractures between the different treatment arms in various predefined subgroups. This is especially important considering some of the high-risk groups that were included in the study: sizeable female population of 5,455, large elderly population of 8,561 aged ≥65 years old and 2,330 aged ≥75 years old, and a large population with renal dysfunction, with 2,240 with moderately decreased renal function (eGFR 30–50 mL/min) and 336 with severely decreased renal function (eGFR <30 mL/min).

Increased risks of fractures among patients with type 2 diabetes were previously reported in the hip (1,2,21,22), proximal humerus (1,2,21), vertebra (23), and all nonvertebral fractures (1,21,22,24). No significant differences were found between treatment arms in the distribution of the location of fractures in the SAVOR-TIMI 53 patients (Fig. 3). There was also no difference in major osteoporotic fracture as classified according to the World Health Organization definition (20). Therefore, in conclusion, saxagliptin therapy does not influence the risk of fractures among patients with type 2 diabetes.

The Incretin System and Bone Metabolism

Despite the abundant evidence regarding the interaction between the incretin
system and bone health, the results of the SAVOR-TIMI 53 trial do not support a correlation between the use of the DPP-4 inhibitor saxagliptin and the risk of fractures.

In animal models, intermittent administration of glucose-dependent insulinovertropic peptide had an anabolic effect and prevented bone loss, similar to parathyroid hormone (25). GLP-1 appears to have a double-inhibitory effect on bone resorption, one direct and another indirect, via the thyroid C cells (9,26). A beneficial effect on bone structure was observed in rats with impaired glucose metabolism treated with exendin-4 (27).

Considering data derived from incretin-based therapy in patients with type 2 diabetes, a 44-week treatment with exenatide versus insulin glargine did not affect BMD (28). After 1-year treatment with the DPP-4 inhibitor vildagliptin, levels of markers of bone resorption and calcium homeostasis were unaffected compared with baseline and placebo (29). A meta-analysis of 28 phase 2 and 3 clinical trials enrolling 20,000 patients treated for 24 weeks or longer showed that treatment with DPP-4 inhibitors was associated with a reduced risk of fractures compared with placebo or active treatment (17). Several factors weaken this meta-analysis compared with the current study: its retrospective nature, post hoc analysis, the inclusion of only fractures that were reported as SAEs, comparison of various interventions, short duration of follow-up (median 35 weeks), and small number of fractures (11 of 5,877 in the DPP-4 inhibitors vs. 21 of 4,928 in the comparators).

However, the discrepancy between the meta-analysis and this report cannot fully be explained by the limitations of the meta-analysis and remains puzzling. The discrepancy is further supported by the difference between the findings in this trial and the results of a post hoc pooled analysis of 20 phase 2 and 3 trials (n = 9,156) comparing saxagliptin with placebo or active comparator, which found an increased risk for fractures with saxagliptin treatment (HR 1.81 [95% CI 1.04–3.28]) (30). The patient population in the pooled analysis was younger, with a shorter duration of diabetes, better renal function, less concomitant medication, and generally healthier compared with the SAVOR TIMI-53 patient population. The difference in patient population may explain the discrepancy between the pooled analysis and the current study results. In a retrospective population-based cohort that compared 22,510 DPP-4 inhibitor (sitagliptin) users out of 216,816 patients treated with other antidiabetic drugs (excluding insulin) and 216,816 control subjects without diabetes matched for age and sex, no association was found between DPP4-I use and osteoporotic fracture risk (18). Despite the large number of patients, that study had a few inherent weaknesses compared with our study, including its retrospective unrandomized nature (differences in the distribution of age, sex, etc. between the groups), and shorter duration of DPP-4 inhibitor treatment (median 1.3 years).

Patients With Type 2 Diabetes, Baseline Characteristics, and the Risk of Fractures
To help define factors that were associated with increased risk of fractures in our population, we conducted a Cox multivariable regression analysis. The following parameters were independently associated with a higher risk for fractures: female sex, longer diabetes duration, older age, noncompliance with study medication (saxagliptin or placebo), major hypoglycemic events
during the study, and the use of TZDs. The following parameters were not significantly associated with the risk of fractures, although they were somewhat borderline: lower eGFR, lower HbA1c, and insulin use. BMI and the use of metformin, sulfonylurea, or saxagliptin were not associated with the risk of fractures in our population.

Female sex, older age, and TZD use are well-known risk factors for fractures. Longer diabetes duration was previously shown to increase fracture risk in retrospective cohort studies (13,31,32) and in prospective population-based studies: among women (21) and in previously known and treated patients with diabetes but not in newly diagnosed diabetes, in patients with impaired glucose tolerance, (22) or in the Chinese population (33). This association is strengthened by the similar findings in our randomized controlled trial. The recently published analysis of nonvertebral fractures from the Action To Control Cardiovascular Risk in Diabetes (ACCORD)-bone sub-study (34) also demonstrated longer diabetes duration among participants with fractures compared with those without fractures; however, that trial was not controlled for age. As opposed to this finding, a case-controlled, nationwide study from Denmark did not find any association between diabetes duration and the risk of fractures (35); however, that study was done in a very different population with a mean age of 43 years.

Longer diabetes duration might be associated with greater tendency to fall due to sight disturbances, peripheral and autonomic neuropathy, impaired proprioception and/or postural hypotension. Another possible explanation is that in patients with longer duration of diabetes, the bone is more fragile and more likely to break. A possible mechanism for this includes prolonged exposure to advanced glycation end products that damage bone collagen and affect bone metabolism (36) and increased visceral fat tissue, which is associated with ongoing inflammation that might also damage bone structure (37).

We found no significant association between baseline eGFR and the risk of fractures in the Cox multivariable analysis. Our findings are strengthened by the ACCORD-bone analysis (34), which also did not demonstrate an association between the risk of fracture and baseline eGFR, but rather, found an association between the slope of deterioration of eGFR and the risk of fractures among women. We found a significantly increased risk for fractures among participants who had a major hypoglycemic event (HR 1.76 [95% CI 1.13–2.74]). This strengthens findings in two previously published studies, a case-controlled nationwide study from Denmark (35) that demonstrated an increased risk for hip fractures and a retrospective observational study that demonstrated an increased risk for fall-related fractures.
Fractures Incidence in SAVOR Trial

Diabetes Care

Antidiabetic Drugs and the Risk of Fractures

Our study found that the only antidiabetic drugs that had a statistically significant effect on the risk of fractures were TZDs. Although only ~5% of our patient population was using TZDs at any time during the trial (19), the use of TZDs was associated with an increased risk for fractures, which further demonstrates the strong effect of this group of drugs on the risk of fractures. TZDs are strongly associated with a decrease in BMD and up to twofold increases in the risk for fractures among postmenopausal women (10–12). TZDs increase the risk of fractures by multiple mechanisms, including an increase in lineage allocation of the stem cells toward adipocytes at the expense of osteoblasts in the marrow, resulting in reduced bone formation (6).

In our study, metformin was used in ~70% of the entire study population (19). There was a significantly higher percentage of patients who used metformin at baseline among patients who did not have a fracture compared with those that had a fracture (69.4% vs. 64.4%, P = 0.021) (Table 1) as well as decreased a HR of 0.77 (95% CI 0.64–0.93) (Fig. 2D). However, multivariable analysis found that metformin use was not independently associated with a reduction in fracture risk (P = 0.92). This might partly be explained by the lower use of metformin among the large population of patients with renal dysfunction.

Although the Rochester cohort suggests that metformin decreases fracture risk in patients with type 2 diabetes (with a HR of 0.7) (13), the A Diabetes Outcome Progression Trial (ADOPT) study did not demonstrate similar beneficial effects of metformin on fracture risk (12). It did show decreased levels of both bone resorption markers (C-telopeptide cross-linked collagen type 1) and, contrary to animal studies, decreased levels of bone formation markers (procollagen type 1 N propeptide) (15). No bone metabolic markers were measured in our study, and the follow-up might be too short to show any clinical difference with the use of metformin.

More than 40% of the patients in our study were using insulin at baseline. The univariate Cox regression analysis showed that insulin was associated with an increased risk for fractures (HR 1.45 [95% CI 1.21–1.73]) (Fig. 2D). However, at the multivariate Cox regression analysis, insulin use was not associated with a significant change in the risk for fractures in our population, possibly due to the association between insulin use and diabetes duration. Contrary to our findings, in another study, insulin-treated women with diabetes had an almost doubled fall incidence (odds ratio 2.78 vs. 1.68) (14), which might lead to a higher risk for fractures. In the Rochester cohort, insulin use slightly but significantly increased the fracture rate (13). A prospective study demonstrated that insulin-treated older women with diabetes had more than double the risk of foot fractures (multivarate-adjusted risk ratio of 2.66) compared with patients without diabetes and noninsulin-user patients with diabetes (19).

In our study, ~40% of the population was using sulfonylureas (19). The use of sulfonylureas was associated with increased risk for hypoglycemic events in

<p>| Table 1—Baseline characteristics of subjects with or without fracture during follow-up by ITT analysis |</p>
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Fracture during follow-up</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes (n = 481)</td>
<td>No (n = 16,011)</td>
</tr>
<tr>
<td>Baseline measurements</td>
<td></td>
<td></td>
</tr>
<tr>
<td>eGFR, median (SD) mL/min</td>
<td>66.3 (31.3)</td>
<td>71.8 (29.3)</td>
</tr>
<tr>
<td>Albumin-to-creatinine ratio, median (SD) mg/mmol</td>
<td>2.1 (9.7)</td>
<td>1.8 (6.9)</td>
</tr>
<tr>
<td>HbA1c, median (SD) %</td>
<td>7.5 (1.6)</td>
<td>7.6 (1.8)</td>
</tr>
<tr>
<td>Fasting glucose serum, median (SD) mg/dL</td>
<td>142 (60)</td>
<td>145 (64)</td>
</tr>
<tr>
<td>Baseline cardiovascular medications, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>349 (72.6)</td>
<td>12,055 (75.3)</td>
</tr>
<tr>
<td>Statins</td>
<td>392 (81.5)</td>
<td>12,525 (78.2)</td>
</tr>
<tr>
<td>β-Blockers</td>
<td>284 (59.0)</td>
<td>9,878 (61.7)</td>
</tr>
<tr>
<td>Diuretics</td>
<td>232 (48.2)</td>
<td>6,833 (42.7)</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>252 (52.4)</td>
<td>8,688 (54.3)</td>
</tr>
<tr>
<td>Baseline antihyperglycemic medications, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metformin</td>
<td>310 (64.4)</td>
<td>11,113 (69.4)</td>
</tr>
<tr>
<td>Sulfonylurea</td>
<td>179 (37.2)</td>
<td>6,407 (40.0)</td>
</tr>
<tr>
<td>TZD</td>
<td>39 (8.1)</td>
<td>931 (5.8)</td>
</tr>
<tr>
<td>Insulin</td>
<td>239 (49.7)</td>
<td>6,548 (40.9)</td>
</tr>
</tbody>
</table>

Categorical variables were compared using the χ² or Fisher exact test and continuous variables with the t test. P < 0.05 was considered to be statistically significant. P values were not adjusted for multiple testing. IQR, interquartile range.
the saxagliptin arm compared with the placebo arm. Hypoglycemia and, specifically, major hypoglycemic events were associated with increased risk of fracture, and major hypoglycemia was an independent risk factor for fractures in the multivariate Cox regression analysis. However, sulfonylurea use was not associated with an increased risk of fractures in the single-variable analysis (Fig. 2D) or in the multivariate Cox regression analysis. Similar to our findings, the use of sulfonylurea (glyburide) did not have an effect on bone mass and fracture risk in the ADOPt clinical trial and in the Rochester cohort study (13).

Study Strengths and Weaknesses
The strength of the study presented here is the large and diverse population of patients with type 2 diabetes monitored prospectively in the SAVOR-TIMI 53 trial. This population includes a large prespecified subset of patients at a considerably high risk for fractures, including women, elderly patients, and patients with renal dysfunction. The diversity of the population regarding HbA1c at baseline, duration of diabetes, and antidiabetes treatment improves the external validity of this research. Fractures were predefined AEOSI, and information was actively collected throughout the study, which enhances the confidence in the data presented here. A large percentage of fractures were also classified as SAE due to hospitalization, and more data were collected for these cases.

The weakness of our study is that fractures were exploratory end points in this trial. Therefore, this study was not designed to collect the data necessary to properly and thoroughly evaluate fractures in general and osteoporotic fractures in particular. All fractures, regardless of their mechanism, were classified together, and any evidence regarding BMD or bone turnover markers was missing. The lack in fracture ascertainment might attenuate the possible association between treatment arms and fracture risk. Another weakness is the relatively short duration of follow-up (median 2.1 years, with interquartile range of 1.8–2.3) (19), which was just barely longer than 1–1.5 years of use, which is the length of time needed for drugs used for the treatment of osteoporosis (such as bisphosphonates) to show a diminishing effect on the risk of fracture. Lastly, even though the SAVOR-TIMI 53 is one of the largest trials done in this population of patients

Figure 3—Distribution of the location of fractures at the ITT population for saxagliptin vs. placebo arms (Subjects with events in more than one category are counted in each category. Subjects with multiple events in the same category are counted only once in that category). (A high-quality color representation of this figure is available in the online issue.)
with type 2 diabetes at high CV and fracture risk, the power of the trial was designed by the primary combined CV outcome and not by the fracture risk and, therefore, may not completely exclude possible change in fracture risk under saxagliptin treatment.

Summary
Saxagliptin neither increased nor decreased the incidence of fractures in a large, diverse population at high risk for fractures. Because fractures are highly prevalent among patients with type 2 diabetes, this is an important safety issue to consider when choosing antidiabetic treatment. We found a strong association between longer diabetes duration and the risk of fractures. This is a significant factor for clinicians to consider, especially because BMD underestimates the risk for fractures among patients with type 2 diabetes. Further data collected through ongoing large outcome studies, as well as by observational studies, may further shed light on this important overlap between two of the largest epidemics of our time: type 2 diabetes and osteoporosis.

APPENDIX
SAVOR-TIMI 53 Executive Committee: Eugene Braunwald (Study Chair), Deepak L. Bhatt (Co-Principal Investigator), Itamar Raz (Co-Principal Investigator), Jaime A. Davidson, Robert Frederich (nonvoting), Boaz Hirshberg (nonvoting), Gabriel Steg.

Funding. The SAVOR-TIMI 53 trial was funded by AstraZeneca and Bristol-Myers Squibb.

Duality of Interest. O.M. discloses the following relationships—advisory board: Novo Nordisk, Eli Lilly and Company, Sanofi, Merck Sharp & Dohme, Boehringer Ingelheim, Janssen Pharmaceuticals, Novartis Pharmaceuticals AG, AstraZeneca; grants paid to institution as study physician: AstraZeneca and Bristol-Myers Squibb; research grant support through Hadassah Hebrew University Hospital: Novo Nordisk; speaker’s bureau: AstraZeneca and Bristol-Myers Squibb, Novo Nordisk, Eli Lilly and Company, Sanofi, Novartis Pharmaceuticals AG, Merck Sharp & Dohme, and Boehringer Ingelheim; C.W. is an AstraZeneca employee. A.C. discloses the following relationships—honorary advisor for advisory work and lectures: AstraZeneca, Boehringer Ingelheim, Eli Lilly and Company, Merck Sharp & Dohme, Novartis Pharmaceuticals AG, Novo Nordisk, and Teva. C.S. is an AstraZeneca employee. K.S. discloses the following relationships—honorary advisor for speaking engagements: Eli Lilly and Company, Novo Nordisk, Sanofi, Servier, and Janssen-Cilag; participation in clinical trials: Astra Zeneca. D.L.B. discloses the following relationships—advisory board: Cardax, Inc., Elsevier Practice Update Cardiology, Medscape Cardiology, and Regado Biosciences; board of directors: Boston VA Research Institute, Society of Cardiovascular Patient Care; chair: American Heart Association Get With The Guidelines Steering Committee; data monitoring committees: Duke Clinical Research Institute, Harvard Clinical Research Institute, Mayo Clinic, and Population Health Research Institute; honoraria: American College of Cardiology (Clinical Trials and News senior associate editor, ACC.org), Belvoir Publications (Harvard Heart Letter editor in chief), Duke Clinical Research Institute (clinical trial steering committee); Harvard Clinical Research Institute (clinical trial steering committee), HMP Communications (Journal of Invasive Cardiology editor in chief), Journal of the American College of Cardiology (associate editor, section editor, pharmacology), Population Health Research Institute (clinical trial steering committee), Slack Publications (Cardiology Today’s Intervention chief medical editor), WebMD (continuing medical education steering committees), Clinical Cardiology (deputy editor); research funding: AstraZeneca, Bristol-Myers Squibb, Sanofi, Ethicon, Forest Laboratories, Ischemix, Medtronic, Pfizer, Roche, Sanofi, and The Medicines Company; unfunded research: FlowCo, PLX Pharma LLC, and Takeda Pharmaceutical Company Ltd. I.R. discloses the following relationships—advisory board: AstraZeneca/Bristol-Myers Squibb, Eli Lilly and Company, Medscape, LLC, Merck Sharp & Dohme, Novo Nordisk, Sanofi, Sanofi, Novartis, and Orgenesis Inc.; speaker’s bureau: AstraZeneca, Bristol-Myers Squibb, Insuline Medical Ltd, Gil Medical Ltd, Kamada Ltd, and FuturRx Ltd; speaker’s bureau: AstraZeneca/Bristol-Myers Squibb, Eli Lilly and Company, Johnson & Johnson, Merck Sharp & Dohme, Novartis Pharmaceuticals AG, Novo Nordisk, Sanofi, and Teva; stock/shareholder: Insuline Medical Ltd, LabStyle Innovations, SmartZyme Innovation Ltd, Orgenesis Inc., and GlucoMe Ltd. No other potential conflicts of interest relevant to this article were reported.

Author Contributions. O.M. acquired, analyzed, and interpreted the data, drafted the manuscript and revised the manuscript for important intellectual content, corrected the manuscript according to reviewer comments, and approved the final version of the manuscript submitted. C.W. was part of the executive committee and helped to design the trial, acquire and analyze, and interpret the data, and approved the final version of the manuscript submitted. J.D. and K.S. reviewed the manuscript for important intellectual content and approved the final version of the manuscript submitted. B.M.S., B.H., and C.S. conceived and designed the study, helped to acquire, analyze, and interpret the data, reviewed the manuscript for important intellectual content, and approved the final version of the manuscript submitted. I.Y. and A.R. helped to acquire, analyze, and interpret the data, revised the manuscript for important intellectual content, and approved the final version of the manuscript submitted. I.R. conceived and designed the study, helped to acquire, analyze, and interpret the data, reviewed and revised the manuscript for important intellectual content, and approved the final version of the manuscript submitted. I.R. conceived and designed the study, helped to acquire, analyze, and interpret the data, reviewed and revised the manuscript for important intellectual content, and approved the final version of the manuscript submitted. D.L.B. conceived and designed the study, helped to acquire, analyze, and interpret the data, reviewed and revised the manuscript for important intellectual content, and approved the final version of the manuscript submitted. L.B., K.S., and I.R. are the guarantors of the work and, as such, had full access to all the data in the study, and take responsibility for the integrity of the data and the accuracy of the data analysis.

Prior Presentation. Parts of this study were presented at 74th Scientific Sessions of the American Diabetes Association, San Francisco, CA, 13–17 June 2014.

References
1. Nicodemus KK, Folsom AR; Iowa Women’s Health Study. Type 1 and type 2 diabetes and incident hip fractures in postmenopausal women. Diabetes Care 2001;24:1192–1197
differentiation and bone formation. Endocrinology 2005;146:1226–1235
23. Yamamoto M, Yamaguchi T, Yamauchi M, Kaji H, Sugimoto T. Diabetic patients have an increased risk of vertebral fractures independent of BMD or diabetic complications. J Bone Miner Res 2009;24:702–709
25. Bollag RJ, Zhong Q, Ding KH, et al. Glucose-dependent insulinotropic peptide is an integrative hormone with osteotropic effects. Mol Cell Endocrinol 2001;177:35–41