Supplemental Data-Table B.-Summary of the Human Studies Reviewed

PPI product	Study	Number of pts	Results
Omeprazole	O'Connel 2005 (18) US Short-term- 1wk A randomized, double-blind, placebo-controlled, crossover trial	18 women mean age was 76 ± 7 years (range 65–89 years)	Omeprazole & calcium absorption Omeprazole markedly decreased fractional calcium absorption from 9.1% (95% CI): 6.5% to 11.6%) on placebo to 3.5% (95% CI): 1.6% to 5.5%, P = 0.003) The absolute difference in fractional calcium absorption between placebo and omeprazole was −5.5% (95% CI: −2.1% to −9.0%). This difference represented an average percentage decrease of 41% (95% CI: −86% to 3%).
Any PPIs	Vestergaard 2006 (30) Denmark Jan-Dec 2000 Case-control	124,655 cases with fractures; 373,962 matched Controls Last PPI use of ≤ 1 year ago and > 1 year ago were analyzed	Risk of fracture & PPI use ≤ 1y ago Overall fracture risk, aOR= 1.18 (95% CI, 1.12–1.43) Risk of hip fracture, aOR = 1.45 (95% CI, 1.28–1.65) Risk of spine fracture, aOR = 1.60 (95% CI, 1.25–2.04) Risk of forearm fracture, aOR = 0.95 (95% ci, 0.82-1.11) Multivariate adjustment. No adjustment for smoking, physical activity, the use of calcium /vitamin D supplements.
Any PPIs	Yang 2006 (31) UK 1987-2003 Nested case-control	13,556 cases with fractures; 135,386 matched controls Exposure of PPI > 1 year	Risk of hip fracture & PPI use > 1 year, aOR = 1.44 (95% CI, 1.30–1.59) Risk of hip fracture increased with high-dose PPI: (dose defined as dose/day, >1.75 doses/day), aOR = 2.65 (95% CI, 1.80-3.90) Risk of hip fracture increased with longer duration of PPI use, 1 yr, aOR = 1.22 (95% CI, 1.15-1.30); 2 years, aOR=1.41 (95%CI, 1.28-1.56); 3 years, 1.54 (95% CI, 1.37-1.73), 4 yr, aOR = 1.59 (95% CI, 1.39-1.80) Multivariate adjustment.
Any PPIs	Yu 2008 (32) US Two prospective cohorts of men and women >65yo W- 5339 M-5755	Women (4,574 non-PPI/ H2RA users, 234 PPI Users, 519 H2RA users); Men (4,920 non-PPI/H2RA users, 487 PPI users, 335 H2RA users)	Risk of hip fracture & PPI and/or H2RA use Risk of hip fracture (multivariate adjusted) Women: aRH = 1.16 (95% CI, 0.80-1.67) Men: aRH = 0.62 (95% CI, 0.26-1.44) Risk of non-spine fracture (multivariate adjusted) Women: aRH = 1.34 (95% CI, 1.10-1.64) Men: aRH = 1.21 (95% CI, 0.91-1.62) Multivariate adjustment for age, clinic, race, BMI, alcohol use, calcium use, smoking, and other medications
Any PPIs	Targownik 2008 (33) Canada 1996 – 2004 Case-control	15,792 cases with fractures; 47,289 matched controls Continuous exposure: > 70 % of their person-time before the fracture date classified as PPI exposure time (> 0.70 standard doses per day).	Risk of hip, wrist, spine fractures & PPI use ≥ 7 years aOR = 1.92 (95% CI, 1.16–3.18) Risk of hip fractures &PPI use PPI use ≥ 5 years, aOR = 1.62 (95% CI, 1.02–2.58) PPI use ≥ 6 years, aOR = 2.49 (95% CI, 1.33-4.67) PPI use ≥ 7 years, aOR = 4.55 (95% CI, 1.68–12.29) Adjustment for income, region of residence, diagnoses, home care use and multiple medications. No adjustment for alcohol consumption, smoking or the use of calcium / vitamin D supplements.
Any PPIs	Kaye 2008 (34) UK 1995 – 2005 Nested case-control	1,098 cases with fractures; 10,923 matched controls Men and women aged 50 – 79 years Age, sex, index date and Duration of history recorded match. Analysis restricted to cases with no major medical risk factors for hip fracture.	Risk of hip fracture & PPI use Hip fracture RR= 0.9 (95% CI, 0.7–1.11) Among men, for each additional 10 PPI prescriptions, RR = 1.0 (95% CI, 0.9–1.1), among women, 0.9 (95% CI, 0.8–1.0). Among aged 50–59 years, RR = 0.7 (95% CI, 0.4–1.4), 60–69 years RR =1.0 (95% CI, 0.8–1.1), 70–79 years RR = 0.9 (95% CI, 0.8–1.0)
Any PPIs	de Vries 2009 (35) UK	234,144 PPI only users	Risk of hip fracture & PPI use

	1988-2007 Retrospective cohort	Men and women aged > 40 years	Compared to past use, aRR = 1.22 (95% CI, 1.10-1.37) high dose (>1.75 DDD), aRR 1.45 (95% CI, 1.06-1.99) short duration, 1.31 (95% CI, 1.09-1.58) >3 years, aRR 1.17 (95% CI, 0.98-1.41) Adjustment for age, comorbidities, smoking, BMI, history of fracture, calcium and vitamin D supplements, and other medications.
Omeprazole	Roux 2009 (36) EU Prospective cohort	1211 postmenopausal women aged 55 – 79 years	Vertebral fractures assessed by X-Ray at baseline and end of 6yr F/u & PPI use At baseline 5% were using omeprazole. Age-adjusted rates for vertebral fractures were 1.89 (omeprazole users) and 0.60 per 100 person/yrs for nonusers (RR=3.41)(p=0.009) Multivariate analysis risk factors include omeprazole use (RR=3.10, p=0.027l), age>65 (RR=2.34, p=0.44), low lumber spine BMD (RR=2.38, p=0.04) Adjustment for BMI, history of fracture / falls, other medications, and bone mineral density.
Omeprazole	Kirkpantur 2009 (24) Turkey Cross sectional	68 maintenance hemodialysis pts (Group 1–36 PPI users Group 2 (32, PPI nonusers)	Radius, hip, and spine BMD assessment and correlated with PPI use and other variables Mean duration of PPI use was 27 ± 5 mos. PPI users had lower BMD at all sites (p=0.019–0.04) Serum Ca, PTH, phosphate similar in two groups
Any PPIs	Corley 2010 (37) US 1995-2007 Case-control	33,752 cases with Fractures;130,471 matched controls	Risk of fracture 7 PPI use ≥ 2 years of and 1 other risk factor OR = 1.30 (95% CI, 1.21–1.39) Risk of fracture increased with higher PPI dose OR = 1.41 (95% CI, 1.21-1.64) and in longer duration of PPl exposure OR=1.85 (1.41–2.43) Statistical adjustment. The increased fracture for PPI use was confined to persons with at least one other risk factor.
Omeprazole Esomeprazole Lansoprazole Pantoprazole Rabeprazole	Gray 2010 (38) US Enrollment 1993-2005 Prospective cohort 130,487 postmenopausal women 50-79yo	2,831 PPIs users 127,756 non-PPIs Users	Risk of total fractures & PPI use Current PPI users Risk of total fractures, aHR = 1.25 (95% CI, 1.15-1.36) Risk of hip fracture, aHR = 1.00 (95% CI, 0.71-1.40) Risk of spine fracture, aHR = 1.47 (95% CI, 1.18-1.82) Risk of wrist fracture, aHR = 1.26 (95% CI, 1.05-1.51) Multivariate adjustment for age, race, BMI, smoking, physical activity, history of fracture, comorbidities, and other medications
Omeprazole Esomeprazole Lansoprazole Pantoprazole Rabeprazole	Chiu 2010 (39) Taiwan 2005-2006 Case-control	1241 hip fracture cases (522 men) 1241 controls	Risk of hip fracture & PPI use Dose-response, compared to no use: Cummulative DDDs with PPI last use ≤4 yr preceding hip fracture: ≤18.7 DDD, aOR = 0.78 (95% CI, 0.47-1.29) 18.8-91 DDD, aOR = 2.00 (95% CI, 1.28-3.14); >91 DDD, aOR = 2.12 (95% CI, 1.39-3.25)
Omeprazole Esomeprazole Rabeprazole Lansoprazole Pantoprazole	Targownik 2010 (21) Canada 1984-2004 2001-2006 2 databases Case-control, cross-sectional, longitudinal	Cross-sectional 2193 cases with osteoporosis at the hip; 5527 controls with normal hip measurements 3596 cases with osteoporosis at the lumbar spine 10,257 normal controls. Longitudinal 2549subjects underwent 2 separate BMD assessments The main interval between assessments of BMD - 2.31+/- 0.5 years.	Osteoporosis & PPIs use Hip osteoporosis, OR= 0.84 (95% CI, 0.55–1.34) The lumbar spine osteoporosois, OR=0.79 (95% CI, 0.59 –1.06) for PPI use >1500 doses over the previous 5 years. In the longitudinal study no significant decrease was observed in BMD at either site attributable to PPI use.

Omeprazole Esomeprazole Pantoprazole Lansoprazole Rabeprazole	Pouwels 2011 (40) Netherland 1991-2002 Case-control	6,763 hip/femur fracture 26,341 controls Current users defined as patients who had received at least one PPI dispensing within 30 days before the index date.	Risk of hip/femur fracture & PPI use Distant past use: aOR = 1.24 (95% CI, 1.08-1.43) Past use: aOR = 0.97 (95% CI, 0.74-1.26) Recent use: aOR = 0.96 (95% CI, 0.83-1.12) Current use: aOR = 1.20 (95% CI, 1.04-1.40) Low dose use: aOR=1.21 (95% CI, 0.93-1.57) High dose: aOR=1.35 (95% CI, 1.02-1.78) Short exposure: aOR=1.31 (95% CI, 0.98-1.76) Longer exposure: aOR= 1.09 (95% CI, 0.81-1.47) No adjustment for body mass index, alcohol consumption, smoking or the use of calcium / vitamin D supplements.
Any PPIs	Abrahamsen 2011 (41) Denmark 1996-2005 Cohort	38,088 incident Alendronate users: 6,431 men, 31,657 women	HR hip fracture & PPI use Alendronate, highly refill compliant, HR=1.28 (95% CI, 1.05-1.56) Alendronate, moderately refill compliant, HR=1.53 (95% CI, 1.02-2.29)
Prilosec Nexium Prevacid Protonix Aciphex	Khalili 2012 (25) US 1976-2008 Prospective cohort	79,899 eligible women 5,341 regular PPI users 74,558 non-users	Risk of hip fracture & PPI use PPI use incr. from 6.7% in 2000 to 18.9% in 2008; Abs. risk of hip fracture for regular PPI users 2.02 per 1000 person years vs 1.51 per 1000 PY for non-users; PPI use of 2 years, aHR=1.36 (95% CI, 1.12-1.65) 4 years, aHR=1.42 (95% CI, 1.05-1.93) 6-8 years, aHR=1.54 (95% CI, 1.03-2.31)
Any PPIs	Targownik 2012 (22) Canada 1995-1997 10yrs follow-up Retrospective cohort	8,340 subjects PPI users (N=228) Non-PPI users (N=8,112)	BMD & PPI use PPI users had lower BMD at baseline than PPI non-users, but PPI use over 10 years did not appear to be associated with accelerated BMD loss.
Any PPIs	Fraser 2013 (28) Canada 1995-1997enrollment 10 year F/U Cohort	9,423 6,539 females 2,884 males	Risk of fracture & PPI use PPI exposure, time-dependent: HR=2.24 (95% CI, 1.27-3.96), aHR=1.75 (95% CI, 0.94-3.26) PPI ever used: HR=1.76 (95% CI, 1.15-2.71); aHR=1.52 (95% CI, 0.99-2.35)
Any PPIs	Abrahamsen 2013 (27) Denmark 2000 Case-control	10,530 hip fracture cases	Risk of hip fracture & PPI use Hip fracture with PPI use: aOR=1.13 (95% CI, 1.05-1.21) Age >70 years: PPI: aOR=1.14 (95% CI, 1.06-1.22)
Omeprazole Esomeprazole Pantoprazole Rabeprazole Lansoprazole	Lee 2013 (42) Korea 2005-2006 Case-control	24,710 cases 98,642 controls ≥65 years old	Risk of incident hip fracture & PPI use Pantoprazole, aOR=1.71 (95 % CI, 1.39–2.11) Rabeprazole, aOR=1.35 (95 % CI, 1.10–1.67), Omeprazole, aOR=1.22 (95 % CI, 1.08–1.38) Esomeprazole and Lansoprazole did not show increased risk of fracture
Omeprazole Esomeprazole Rabeprazole Pantoprazole Lansoprazole	Reyes 2013 (43) Spain 2007-2010 Case-control	358 cases 698 controls	Risk of hip fracture & PPI use OR=1.44 (95% CI, 1.09-1.89) aOR=1.24 (95% CI, 0.93-1.65)
Any PPIs	Maggio 2013 (23) Italy Retrospective cohort	1038 participants 36 PPI users 1002 non-users 65 years or older	BMD &PPI use PPI users showed age- and sex-adjusted lower vBMDt than nonusers (180.5±54.8 vs. 207.9±59.4, p=0.001) Adjustment for caloric intake, PTH, Vitamin D, calcium intake, levels of E2, IL-6, IGF-1 and Bio-T.
Esomeprazole Rabeprazole Lansoprazole	Sharara 2013 (19) Lebanon Short-term-12wks Prospective matched controlled	58 participants (29 per group) Healthy adult males (age 18–50 years)	Calcium/Bone metabolism &PPI use No difference between the groups in levels of Albumin, Phosphate, Calcium, Ionized Calcium PTH, 25-OH-vitamin D, Osteocalcin, C-terminal cross-linked telopeptides of type I collagen before and after PPI treatment.
Esomeprazole Lansoprazole Pantoprazole	Ozdil 2013 (20) Turkey 2009-2011	114 GERD patients (18–56 years) 110 healthy controls	Bone density & PPIs use BMD by using dual-energy X-ray absorptiometry at lumbar spine and femur neck.

	Prospective case-control study	The mean duration of treatment with PPIs - 8.5 ± 2.3 months. F/u 6 months	Significant reduction in BMD in PPIs users. The mean reduction in total vertebra T score compared to pre-treatment values 00.23 ± 0.42 units (95 % CI 0.15–0.30) ($p<0.01$); the mean reduction in the femur T score 0.10 ± 0.40 units (95 % CI 0.03–0.18) ($p = 0.03$). Reduction following treatment in L4 and total vertebra T scores of lansoprazole group - significantly higher than of pantoprazole group ($p = 0.04$). Reduction in femur T score of esomeprazole group - higher than of lansoprazole group and pantroprazole group. No statistically significant differences.
Any PPIs	Ding 2014 (44) US 1999-2002 Retrospective cohort	1,604 PPI users 23,672 nonusers	Any fracture & PPI use, aHR=1.27 (95% CI, 1.12-1.43) Hip fracture: aHR=1.32 (95% CI, 1.01-1.71) Vertebral fracture: aHR = 1.69 (95% CI, 1.26–2.27) Adjustment for gender, race, age, BMI, comorbidity, smoking status and medication usage
Omeprazole Pantoprazole	Adams 2014 (45) US Cases: 1997-2006 Pharm. data 1991-2006 Case-control	6774 pairs of men aged 45 years or older w matched on age, race, and medical center. Cases with incident hip fracture	Risk of hip fracture &PPI use Omeprazole use Ever, OR=1.31 (95% CI, 1.18-1.46) aOR=1.13 (95% CI, 1.01-1.27) Greatest adherence (medication possession ratio > 80%) aOR=1.33 (95% CI, 1.09-1.62) Highest tertile of duration, aOR=1.23 (95% CI, 1.02-1.48) Recent use, aOR=1.22 (95% CI, 1.02-1.47) Pantoprazole use Ever, OR=1.25 (95% CI, 1.11-1.41) aOR=1.10 (95% CI, 0.97-1.24) Longest duration aOR=1.25 (95% CI, 1.02-1.53) Most recent use aOR=1.38 (95% CI, 1.12-1.71) Adjustment for comorbidities.
Omeprazole	Ceo Soriano 2014 (26) UK 2000-2008 Cohort, Nested case-control	1,538,855 contributed p/time 10,958 cases of hip fracture; 10,000 controls	Risk of hip fracture & PPIs use Overall incidence of hip fracture per 1000 person-years – 1.31 (95% CI, 1.28–1.33). Risk of hip fracture &current PPI use, aOR=1.07 (95% CI, 1.30–1.48) Recent use, aOR=1.29 (95% CI, 1.52–2.15) Medium single use PPI dose: aOR=1.11 (95% CI, 1.01-1.22) High single use PPI dose: aOR=1.31 (95% CI, 1.06-1.16) Omeprazole: aOR=1.14 (95% CI, 1.03-1.27) Multivariate adjustment.
Any PPIs	Moberg 2014 (46) Sweden 1995-2012 Restrospective cohort	6917 postmenopausal women	Risk of fracture & current PPI users, OR=2.53 (95% CI, 1.28–4.99) Women having had a fracture after the age of 40, but before inclusion in the study, OR=1.70 (95% CI1.24–2.32) Use of PPI and HT, OR=3.37 (95% CI, 1.96–5.80) On PPIs only, without HT use, OR=1.13 (95%, CI 0.57–2.24) Multivariate adjustment for age, BMI and current smoking status
Omeprazole Esomeprazole Pantoprazole Lansoprazole Rabeprazole	Lewis 2014 (29) Australia 2003-2008 Prospective cohort	1025 with bone fracture Elderly postmenopausal women	Risk of falls and fracture & long-term PPI therapy Risk of fall, aOR=2.17 (95% CI, 1.25-3.77) Risk of fractures, aOR=1.95 (95% CI, 1.20-3.16) Adjustment for age, low BMI, physical activity, smoked ever, diabetes, and CNS medication use.
Any PPIs	Prieto-Alhambra 2014 (47) Spain 2006-2011 Retrospective cohort	7,449 out of 21,385 oral bisphosphonate new users >6 months of therapy	Fracture risk & PPI use Incidence of fracture while on treatment - 3.4/100 person-years (95%CI, 3.1-3.7). PPI use, SHR=1.22 (95% CI, 1.02-1.46)
Any PPIs	Freedberg 2015 (48) UK 1994-2013 Nested case-control	124,799 cases and 605,643 controls 4-29 years old	Risk of fracture & PPI use Among children<18yo, aOR=1.13 (95% CI, 0.92-1.39) Among young adults 18–29 yo, aOR=1.39 (95 % CI, 1.26-1.53)

			Adjustment for prior use of histamine-2 receptor antagonists, anti-epileptic drugs, opiates, and oral glucocorticoids.
Any PPIs	Solomon 2015 (49) US Enrollment 1996-98 A median 9.9 yrs f/u Community-based longitudinal cohort	207 new users of PPIs, 185 new users of H2RAs, and 1,676 non-users. Mean age - 50 years	Bone mineral density & PPIs or H2 Receptor Antagonists use No difference in the annualized BMD change at the lumbar spine, femoral neck, or total hip in PPI users compared with H2RA users or non-users.