ABSTRACT

World Congress on Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (WCO-IOF-ESCEO 2021): Oral Communication Abstracts

OC1
RECENT SENTINEL FRACTURES AND SUBSEQUENT FRACTURE PROBABILITIES OVER TWO, FIVE AND 10-YEAR TIMEFRAMES

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Objective: Increasing evidence that the recency of prior fractures affects subsequent fracture risk has led to calls for fracture risk to be expressed over short timeframes. This analysis quantified the effect of a recent sentinel fracture, by skeletal site, on the 2-, 5-, and 10-year probability of fracture.

Methods: The study used data from the Reykjavik Study fracture register. Fracture probabilities were determined after a sentinel fracture (humeral, clinical vertebral, forearm and hip fracture) occurring within the previous 2 years, and probabilities for a prior osteoporotic fracture irrespective of recency. The probability ratios (recent/any prior) were used to adjust fracture probabilities over 2-, 5-, and 10-year time horizons.

Results: As expected, probabilities decreased with shorter time horizons. Probability ratios varied according to age and the site of sentinel fracture. The ratios were higher for shorter the time horizons, but the absolute increases in fracture probabilities were much reduced reflecting lower absolute probability with shorter time horizons. The relationship between time horizon and fracture risk was not linear; for example, at the age of 50 years, the 10-year probability in the presence of a recent clinical vertebral fracture was 3.6 times the 2-year probability, whereas at the age of 90, the ratio was only 1.7. The lower ratios at older ages reflect the incorporation of death risk into probability calculations, so that the 10-year probability approaches the 2-year and 5-year probabilities.

Conclusion: Probability ratios provide adjustments for fracture recency which can readily inform clinical decision-making. At advanced ages, FRAX 10-year probability calculates a 'remaining life-time' risk of fracture with values approaching those over shorter time frames. The 10-year probability of fractures is an appropriate metric to capture the impact of the recency of sentinel fractures.

OC2
ASSOCIATIONS BETWEEN BONE AND VASCULAR HEALTH IN THE UK BIOBANK

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Background: Osteoporosis and ischaemic heart disease (IHD) are important public health problems, particularly in aging populations. Multiple studies suggest associations between the two conditions beyond shared risk factors. However, existing work is limited by small sample sizes and limited assessment of possible biological mechanisms. Furthermore, although differential disease pattens by sex and menopause status have been reported for both IHD and osteoporosis, the modifying effect of such factors on the relationship between the two conditions has not been adequately studied.

Objective: We used the UK Biobank resource to investigate associations between bone health as assessed by speed of sound (SOS) from quantitative heel ultrasound and 1) arterial compliance measures: arterial stiffness index (ASI) from finger plethysmography and aortic distensibility (AoD) from cardiovascular magnetic resonance and 2) Incident IHD outcomes: IHD mortality and incident myocardial infarction (MI)

Methods: We estimated associations between SOS and ASI (n=159,542) and AoD (n=18,229) in multivariable linear regression models adjusting for age, exercise, smoking, deprivation, alcohol intake, hypercholesterolaemia, diabetes, and hypertension. We considered differential relationships by sex or menopause and tested mediating effect of a wide range of blood biomarkers and cardiometabolic morbidities. We considered associations of SOS with IHD mortality and incident MI (n=477,683) using competing risk regression models, adjusting for covariates as before.

Results: In fully adjusted models, better bone health (higher SOS) was associated with better vascular health (lower ASI, higher AoD). These relationships were consistent for men and women and with menopause status. The mediating variables considered provided only partial explanation of observed associations, with different directions of effect in men and women across several mediators. Better bone health (higher SOS) was associated with significantly lower risk of IHD mortality in men and women, although less robustly in the latter.

Conclusions: In this large, standardised cohort, we demonstrate association of better bone health with better vascular health for both men and women. Underlying mechanisms are complex and there is evidence of variation by sex.

OC3

A MULTICENTER, OBSERVATIONAL, EXTENSION STUDY EVALUATING THE SAFETY, TOLERABILITY, AND EFFICACY OF A SINGLE LORECIVIVINT INJECTION IN KNEE OA SUBJECTS

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Objective: Lorecivivint [LOR] is a novel intra-articular [IA] CLK/DYRK inhibitor in development to treat knee osteoarthritis [OA]. This study evaluated safety and exploratory efficacy of a single IA LOR injection in subjects from two consecutive Phase 2 trials with moderate to severe knee OA.

Methods: This was a 5-year, Phase 3, multicenter, observational extension study (NCT02951026) of completer subjects from consecutive 12- and 6-month Phase 2 LOR trials (NCT02536833, NCT03122860). Subjects received one LOR or placebo [PBO] injection at their parent trial baseline visit (Month 0). Pooled data from clinic visits at 6, 12, 24, and 36 months were used to analyze serious adverse events [SAEs], knee-related AEs, and AEs of newly diagnosed conditions needing treatment for all LOR doses.

Post hoc baseline-adjusted ANCOVA of time points to 18 months (across current/parent trials) was used to compare changes from baseline in a subject subgroup (unilateral symptoms, no widespread pain, 18-month post-injection radiograph at study termination) in WOMAC Pain and Function scores and medial joint space width (mJSW) between the pivotal 0.07 mg LOR dose and PBO groups.

Results: 119/703 (17%) subjects discontinued prior to study termination; no remaining subjects (n=495 LOR-treated; 208 PBO) withdrew due to treatment-related AEs. Baseline subject characteristics and incidences of AEs were similar between LOR and PBO groups. Four AEs in 3 (0.6%) subjects across all LOR doses were considered study-drug related; 68 serious AEs in 38 (5.4%) subjects were reported (none considered treatment-related). One death (control group) occurred. The 0.07 mg LOR group (n=59) showed greater mean improvements from baseline vs. the control group (n=70) in WOMAC Pain and Function at 6 (Pain: -8.16, 95% CI [-15.60, -0.71], $P=0.032$; Function: -9.47 [-17.09, -1.84], $P=0.015$) and 12 (Pain: -8.51 [-15.17, -1.85], $P=0.013$; Function: -9.62 [-16.83, -2.42], $P=0.009$) months. No mJSW progression was observed in any group.

Conclusions: LOR appeared safe and well tolerated. Post hoc efficacy analyses demonstrated durable symptom improvements in WOMAC Pain and Function for up to 12 months vs. controls.

Table 1. Key safety results (adverse events [AEs]) for all injected doses of lorecivivint and all controls (extension study reports only)

AEs Reported ≥1%	0.03 mg n=131	0.07 mg n=135	0.15 mg n=65	0.23 mg n=135	Other n=29	Control n=208^	All N=703
Total AEs/Unique subjects (%)	50 / 24 (18.3)	28 / 21 (15.6)	25 / 11 (16.9)	64 / 33 (24.4)	10/4 (13.8)	60/44 (21.2)	237 / 137 (19.5)
Osteoarthritis	13 / 9 (6.9)	6 / 6 (4.4)	1 / 1 (1.5)	6 / 5 (3.7)	1 / 1 (3.4)	6/6 (2.9)	33 / 28 (4.0)
Arthralgia	6 / 5 (3.8)	5 / 5 (3.7)	1 / 1 (1.5)	6 / 6 (4.4)	1 / 1 (3.4)	8/7 (3.4)	27 / 25 (3.6)
Meniscus Injury	3 / 3 (2.3)	2 / 2 (1.5)	1 / 1 (1.5)	1 / 1 (0.7)	0 / 0 (0.0)	2/2 (1.0)	9 / 9 (1.3)
Hypertension	2 / 2 (1.5)	0 / 0 (0.0)	2 / 2 (3.1)	2 / 2 (1.5)	0 / 0 (0.0)	6/6 (2.9)	12 / 12 (1.7)
Target Knee AEs (Total)	22 / 15 (11.5)	8 / 7 (5.2)	6 / 3 (4.6)	11 / 9 (6.7)	4 / 1 (3.4)	12/11 (5.3)	63 / 46 (6.5)
Osteoarthritis	8 / 8 (6.1)	2 / 2 (1.5)	1 / 1 (1.5)	2 / 2 (1.5)	1 / 1 (3.4)	4/4 (1.9)	18 / 18 (2.6)
Arthralgia	4 / 4 (3.1)	2 / 2 (1.5)	1 / 1 (1.5)	4 / 4 (3.0)	1 / 1 (3.4)	4/4 (1.9)	16 / 16 (2.3)
Meniscus Injury	2 / 2 (1.5)	2 / 2 (1.5)	1 / 1 (1.5)	1 / 1 (0.7)	0 / 0 (0.0)	1/1 (0.5)	7 / 7 (1.0)
Serious AEs							
Subjects Reporting SAEs	14 / 8 (6.1)	8 / 6 (4.4)	8 / 4 (6.2)	32 / 14 (10.4)	1 / 1 (3.4)	5/5 (2.4)	68 / 38 (5.4)

#AE / #subjects (%) reported.
Other: All subjects treated with anything other than the protocol-specified dose of LOR
^Control= Placebo, Sham, and 2 PBO subjects with dose of PBO not specified by protocol

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OC4

FRACTURE RISK IN PARKINSON'S DISEASE: DRIVEN BY LOW BONE STRENGTH, MUSCLE WEAKNESS OR FALLS?

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Objective: The relative contributions of factors such as muscle strength, falls risk and low BMD to fracture risk in Parkinson's Disease (PD) remains unclear. We addressed this issue in an analysis of community-dwelling women age 75 years or more recruited to a prospective, single centre study.

Material and Methods: 5212 women were recruited to an MRC-funded prospective, randomised, double-blind, placebo-controlled study of the oral bisphosphonate, clodronate. The women were unselected for osteoporosis or fracture risk. Participants completed a self-reported questionnaire capturing medical history, previous fractures, family history of fractures, recent falls, and current medications. A diagnosis of PD was made if it was self-reported and appropriate medication recorded. Each participant had measurements of hip and forearm BMD, and muscle strength (hand grip strength and maximum isometric quadriceps strength). Incident radiographic or surgically verified fractures, and deaths, were recorded over an average follow-up of 3.8 years.

Results: 47 of the women (0.9%) had a diagnosis of PD at study entry. They were of similar age to those without PD, but reported higher disability scores, lower quality of life, and a higher prevalence of falls within the month prior to entry (17% vs 5.1%, p=0.003). While BMD at the forearm and hip regions was lower in PD, this only reached statistical significance at the femoral neck (0.61 ± 0.12 vs 0.65 ± 0.12 g/cm2, p=0.037). Right hand grip strength was lower, but not statistically significant, in PD but right quadriceps strength was much reduced (96.9 ± 49.3 vs 126.3 ± 59.3 N, p=0.003). During follow-up, 620 women (11.9%) sustained one or more osteoporotic fractures. PD was associated with 2.2-fold increase in the risk of osteoporotic fracture (Table). Adjustment for falls or quadriceps strength markedly reduced the hazard ratio, while femoral neck BMD adjustment had only a small impact.

Conclusion: These data suggest that knowledge of prior falls and/or quadriceps strength are likely to capture the impact of PD in future iterations of fracture risk models such as FRAX.

Model (adj. for age, BMI and treatment)	HR	95%CI	P-value
Parkinson's Disease	2.22	1.22–4.04	0.009
+FN-BMD	2.03	1.12–3.70	0.02
+Maximum R Quads Strength	1.62	0.77–3.42	0.21
+Falls	1.71	0.94–3.12	0.079
+All 3 of above	1.38	0.65–2.92	0.399

OC5

PREVALENCE AND AGREEMENT BETWEEN RECENT SARCOPENIA DEFINITIONS: FINDINGS FROM FOUR POPULATION-BASED COHORTS

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Objectives: The study aim was to assess, within each of four different population-based cohorts, prevalence of, and agreement between, two recent sarcopenia definitions, among older white men and women.

Material and Methods: Participants in the Health, Aging and Body Composition Study (Health ABC) (n = 1734, 52% men), Hertfordshire Cohort Study (HCS) (n = 304, 52% men), Osteoporotic Fractures in Men Sweden Study (MrOS Sweden) (n = 2852, 100% men) and the Osteoporotic Fractures in Men US Study (MrOS US) (n = 5189, 100% men) were analysed. Appendicular lean mass was ascertained using DXA; muscle strength by grip dynamometry; and usual gait speed was measured as a marker of mobility.

The sarcopenia definitions of interest were proposed by the Sarcopenia Definitions and Outcomes Consortium (SDOC) and the 2018 European Working Group on Sarcopenia in Older People (EWGSOP2). SDOC defines sarcopenia as having weak grip strength (<35.5 kg [men], <20 kg [women]) and slow gait speed (<0.8 m/s). EWGSOP2 defines sarcopenia as having weak grip strength (<27 kg [men], <16 kg [women]) and low appendicular lean mass index (<7.0 kg/m^2 [men], <5.5 kg/m^2 [women]). Cohen's kappa (κ) statistic was used to assess agreement between the definitions.

Results: Mean (SD) ages of participants were: Health ABC [74.3 (2.8) years]; HCS [75.4 (2.5)]; MrOS Sweden [74.9 (3.1)]; and MrOS US [73.8 (5.9)]. Prevalence of sarcopenia according to SDOC vs EWGSOP2 was as follows: Health ABC (men: 0.3% vs 1.5%, women: 1.0% vs 2.1%); HCS (men: 15.3% vs 0.0%, women: 19.0% vs 0.7%); MrOS Sweden (men: 1.0% vs 0.5%); and MrOS US (men: 1.5% vs 1.3%). Agreement was low between SDOC and EWGSOP2 ($\kappa < 0.2$ within each cohort).

Conclusions: Sarcopenia prevalence varied and agreement was low between SDOC and EWGSOP2. SDOC sarcopenia was more common in HCS than in Health ABC, perhaps due to the latter cohort's requirement for participants to have no mobility disability at enrolment. A consensus definition for sarcopenia is required.

OC6

GLUCOSAMINE SULPHATE: AN UMBRELLA REVIEW OF HEALTH OUTCOMES

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Objectives: Glucosamine sulphate (GS) can be used as background therapy in people affected by knee osteoarthritis (OA). Knowledge regarding the efficacy and safety of GS is of importance since its use worldwide is increasing. Therefore, the present study aimed to map and grade the diverse health outcomes associated with GS using an umbrella review approach.

Methods: Medline, Cinahl and Embase databases were searched until 1 April 2020. An umbrella review of systematic reviews and meta-analyses of randomized controlled trials (RCTs) was carried out. The evidence from the RCTs was graded using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool.

Results: From 140 articles returned, 11 systematic reviews, for a total of 21 outcomes (37 RCTs; 3949 participants; almost all using 1500 mg/day), were included. No systematic reviews/meta-analyses of observational studies were included. Regarding the findings of the meta-analyses, 9/17 outcomes were statistically significant, indicating that GS is more effective than placebo. A high certainty of evidence, as assessed by GRADE, supported the use of GS (*versus* placebo) in improving the Lequesne Index, joint space width change, joint space width change after 3 years of follow up, joint space narrowing and OA progression. No difference in terms of adverse effects was found between GS and placebo. In systematic reviews, GS was associated with a better glucose profile and a better physical function performance than placebo.

Conclusion: GS, when used as a prescription drug (i.e. crystalline glucosamine sulphate) at 1500 mg daily dosage, can positively affect the cartilage structure, reduce pain, improve function and glucose metabolism in people with knee OA, without having a greater incidence of adverse effects than placebo.

OC7

THE ASSOCIATIONS BETWEEN DISEASE MODIFYING ANTIRHEUMATIC DRUGS AND INCIDENT AS WELL A PROGRESSION OF RADIOGRAPHIC HAND OSTEOARTHRITIS IN RHEUMATOID ARTHRITIS PATIENTS

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Objectives: To assess the associations between disease modifying antirheumatic drugs (DMARDs) and incident as well as progression of radiographic distal interphalangeal (DIP) osteoarthritis (OA) in rheumatoid arthritis (RA) patients.

Methods: We performed two observational cohort studies in the Swiss Clinical Quality Management registry (SCQM) [1997–2014]. RA patients who had ≥ 2 eligible hand radiographs were included at their first eligible radiograph (i.e. if all 8 DIP joints could be scored). Modified Kellgren-Lawrence scores (KLS) were used to define incident/existing DIP OA (i.e. KLS ≥ 2 in ≥ 1 DIP joint), and progression of existing DIP OA (i.e. increase of ≥ 1 in KLS in ≥ 1 DIP joint). We divided the study population into two cohorts based on whether DIP OA was present or absent at cohort entry (cohorts 1 and 2, respectively). Cox time-varying regression were performed to estimate hazard ratios (HR) with 95% confidence intervals (CI) of DIP OA progression (cohort 1) or incidence (cohort 2) in the mutually exclusive exposure groups biologic (b) DMARD monotherapy, bDMARD/ conventional synthetic (cs) DMARD combination therapy, past DMARD use, or no DMARD use, when compared to csDMARD use.

Results: Among 2234 RA patients with 5928 eligible radiographs followed for an average of 3 years, 1340 patients had radiographic DIP OA at cohort entry (cohort 1). bDMARD monotherapy had an increased risk of radiographic DIP OA progression compared to csDMARD monotherapy (adjusted HR 1.36, 95% CI 1.08–1.71). The risk was not significant in csDMARD/bDMARD combination users (HR 1.13, 95% CI 0.97–1.32), absent in past DMARD users (HR 0.99, 95% CI 0.68–1.43), and significantly lower among non-DMARD users (HR 0.56, 95% CI 0.34–0.93). In 894 patients without initial DIP OA (cohort 2), the risk of incident OA did not differ between treatment groups.

Conclusions: Our results suggest that monotherapy with bDMARDs is not associated with incident DIP OA but may increase the risk of radiographic progression of existing DIP OA when compared to csDMARDs.

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OC8

MEANINGFUL IMPROVEMENTS IN WOMAC PAIN AND PHYSICAL FUNCTION IN THREE PHASE 3 TRIALS OF TANEZUMAB IN PATIENTS WITH MODERATE-TO-SEVERE OSTEOARTHRITIS: A RESPONDER ANALYSIS

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Objective: To evaluate differences between treatment groups in the proportion of patients (pts) with osteoarthritis (OA) meeting meaningful within patient change thresholds for improvements in Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)* Pain and Physical Function in three phase 3 trials of subcutaneous (SC) tanezumab (tnz), an antibody against nerve growth factor. While 30% improvement is widely accepted as moderately clinically meaningful, improvements of 1 point or 15% have recently been suggested as minimally clinically meaningful[1].

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Methods: All 3 studies enrolled pts with radiographically confirmed OA of the hip or knee who had inadequate response or could not tolerate standard of care analgesics. Pts in study 1 (NCT02697773) and study 2 (NCT02709486) received SC placebo, tnz 2.5 mg, 2.5 mg then 5 mg (2.5/5 mg) or 5 mg. Pts in study 3 (NCT02528188) received oral nonsteroidal anti-inflammatory drugs (NSAIDs), SC tnz 2.5 mg or 5 mg. Responder analyses based on at least 1 point and 15% improvement from baseline were performed at wks 16, 24 and 16 in studies 1, 2 and 3, respectively.

Results:

Pts, %	Study 1			Study 2			Study 3		
	Tnz 2.5mg (n=231)	Tnz 2.5/5mg (n=233)	Placebo (n=232)	Tnz 2.5mg (n=283)	Tnz 5mg (n=284)	Placebo (n=282)	Tnz 2.5mg (n=1002)	Tnz 5mg (n=998)	NSAID (n=996)
WOMAC Pain									
≥1-point improvement	81.0	83.7	75.0	79.4	79.9	68.3	83.2	81.3	80.4
p-value[a]	0.1523	0.0326		0.0020	0.0010		0.1224	0.6684	
≥15% improvement	80.5	81.1	70.7	79.8	79.9	68.7	81.4	80.4	78.8
p-value[a]	0.0244	0.0141		0.0019	0.0014		0.1534	0.3908	
WOMAC Physical Function									
≥1-point improvement	77.1	80.3	72.0	79.1	80.3	66.9	82.2	81.1	77.6
p-value[a]	0.2638	0.0469		0.0010	0.0004		0.0139	0.0661	
≥15% improvement	76.6	80.7	69.8	80.1	81.7	67.6	80.8	80.8	77.2
p-value[a]	0.1569	0.0090		0.0005	0.0001		0.0516	0.0511	

[a]Chi-square test. Studies 1 and 2 vs placebo; study 3 vs NSAID.

Conclusions: A significantly greater proportion of pts had ≥ 1-point or ≥ 15% improvement in WOMAC Pain and Physical Function in the 2.5/5 mg group in study 1 and both tnz groups in study 2 vs placebo. Across the 3 studies, approximately 80% of pts in tnz groups experienced meaningful improvements in WOMAC Pain and Function.

References:

[1]Conaghan PG et al., ACR/ARHP 2020 Annual Scientific Meeting.

OC9

MAINTENANCE OF EFFECT OF BUROSUMAB TREATMENT AND THE IMPACT OF TREATMENT INTERRUPTION ACROSS A 96-WEEK PHASE 3 STUDY AND 48 WEEKS OF A PHASE 3B STUDY IN ADULTS WITH X-LINKED HYPOPHOSPHATEMIA (XLH)

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Objective: To evaluate the effects of continued burosumab treatment and treatment interruption on patient-reported outcomes (PROs; Western Ontario McMaster Universities Osteoarthritis® Index [WOMAC], Brief Pain Inventory Short Form [BPI-SF], Brief Fatigue Inventory), functional tests (6-Minute Walk Test [6MWT], Timed Up and Go test) and maintenance of serum phosphate in adults with XLH.

Methods: European subjects (n = 47) who received up to 96 weeks' burosumab treatment in the phase 3 studies (UX023-CL303/304; NCT02526160/NCT02537431) were invited to enrol in the phase 3b BUR02 study (NCT03920072); 35 enrolled into BUR02 of whom 31 had previously been enrolled in CL303 and had received up to 48 weeks' further burosumab treatment at the data cut (January 2021). Between the studies (6–26 months), 23 subjects received interim burosumab (continuous or partial); 8 received none.

Results: Mean age at CL303 baseline was 42.9 years (18.5–59.9), 67.7% were female; 30 had documented *PHEX* mutations. Mean (SE) BPI-SF average Worst Pain was 6.74 (0.21), least squares mean change from baseline for all subjects was significant (p < 0.05) at all time-points from CL303 week 12 to BUR02 week 48, except for CL303 week 24. For all subjects, BPI-SF Worst Pain meaningful change from CL303 baseline ($\geq$ 1.72 point decrease) was seen at CL303 week 96 and BUR02 weeks 36 and 48. Improvements in BPI-SF Worst Pain scores were maintained through BUR02 in subjects who received interim burosumab. In those who did not receive interim burosumab, scores at BUR02 baseline had returned to CL303 pre-treatment levels, and did not recover to CL303 week 96 levels by BUR02 week 48. Similar profiles were seen for all PROs, functional tests, and trough serum phosphate: benefits were maintained at the start of BUR02 in those who received interim burosumab whereas deterioration towards CL303 baseline levels was seen in those who did not (e.g. 6MWT mean (SE) change from CL303 baseline + 49.18 (10.83) vs − 8.13 (47.40) m). Benefits were seen with the restart of burosumab treatment but recovery often took 36 weeks or longer.

Conclusion: Continued, uninterrupted treatment with burosumab is warranted to sustain the clinical and biological benefits of treatment.

OC10

ROMOSOZUMAB EFFICACY AND SAFETY IN EUROPEAN PATIENTS: A SUBANALYSIS OF THE PHASE 3, RANDOMISED FRAME STUDY

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Objective(s): Results from the FRAME and extension study (NCT01575834) of romosozumab (Romo) for the treatment of postmenopausal (PM) osteoporosis (OP) showed significant reductions in vertebral (V) and clinical fracture (fx).[1] This post hoc analysis assessed efficacy and safety of Romo vs placebo (PBO) in women enrolled in Europe (EU).

Materials and Methods: PM women with OP at the hip were randomised 1:1 to Romo 210 mg or PBO monthly to Month (M) 12, followed by denosumab (Dmab) 60 mg every 6 months to M36 in both groups. We assessed least squares mean % change from baseline (CfB) in bone mineral density (BMD) at lumbar spine (LS), total hip (TH) and femoral neck (FN); fx outcomes and adverse events (AEs). Vfxs were assessed by baseline and yearly X-rays and analysed by logistic regression; other fx types were captured at time of event and analysed by Cox proportional hazards model.

Results: 3013/7180 patients (pts) (42%) were enrolled in EU (1494 Romo; 1519 PBO). Incidence of all fx types was lower for Romo vs PBO at M12 and Romo → Dmab vs PBO → Dmab at M36 (Table). Similar reductions were observed at M24. BMD CfB were greater for Romo vs PBO pts at M12 and Romo → Dmab vs PBO → Dmab at M36 for LS (M12/M36 differences: 12.3%/10.1%), TH (5.2%/4.6%) and FN (5.0%/4.5%) (all p < 0.001). Incidence of AEs and serious cardiovascular events were balanced between groups throughout.

Conclusion(s): In EU pts, Romo treatment resulted in early and sustained risk reduction for all major fx types.

Table: Fracture outcomes

	PBO→Dmab (N=1519) n (%)	Romo→Dmab (N=1494) n (%)	Odds ratio / Hazard ratio[a] (95% CI)
New vertebral fx			
M12	29/1368 (2.1)	6/1338 (0.4)	0.21 (0.09–0.52)
M36	44/1371 (3.2)	13/1341 (1.0)	0.30 (0.16–0.57)
Clinical fx			
M12	54 (3.6)	21 (1.4)	0.39 (0.24–0.65)
M36	107 (7.0)	64 (4.3)	0.61 (0.45–0.83)
Nonvertebral fx			
M12	45 (3.0)	21 (1.4)	0.47 (0.28–0.79)
M36	97 (6.4)	63 (4.2)	0.66 (0.48–0.91)
Hip fx			
M12	9 (0.6)	3 (0.2)	0.34 (0.09–1.27)
M36	18 (1.2)	8 (0.5)	0.47 (0.20–1.07)
MOF			
M12	42 (2.8)	14 (0.9)	0.34 (0.19–0.62)
M36	85 (5.6)	46 (3.1)	0.55 (0.39–0.79)

[a]Incidence of Vfx presented as odds ratios; all other fx types presented as hazard ratios. CI: confidence interval; fx: fracture; MOF: major OP fx; Vfx: vertebral fracture.

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Janssen, Lilly, MSD, Mundipharma, Novo Nordisk, Sanofi, Shire, Technopharma, UCB Pharma and Viatris; JT: Employee of UCB Pharma; MO: Employee of Amgen; PL: Grants and/or advisor from Amgen, UCB Pharma, Richter and Teva; ZW: Employee of Amgen and owns stock in Amgen.

OC11

MULTIDIMENSIONAL PROGNOSTIC INDEX AND THE RISK OF FRACTURES: AN 8-YEAR LONGITUDINAL COHORT STUDY IN THE OSTEOARTHRITIS INITIATIVE

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Background: Fractures increase risk for disability and poor quality of life in older people. Frailty may be associated with higher fracture risk, but limited research has been carried out using a multidimensional approach to frailty assessment and diagnosis. The present research aimed to investigate whether the multidimensional prognostic index (MPI), based on comprehensive geriatric assessment (CGA), is associated with the risk of fractures in the Osteoarthritis Initiative (OAI) study.

Methods: Community-dwellers affected by knee OA or at high risk for this condition were followed-up for 8 years. A standardized CGA including information on functional, nutritional, mood, comorbidities, medications, quality of life and co-habitation status was used to calculate the MPI. Fractures were diagnosed using self-reported information. Cox's regression analysis was carried out and results are reported as hazard ratios (HRs), with their 95% confidence intervals (CIs), adjusted for potential confounders.

Results: The sample consisted of 4,024 individuals (mean age 61.0 years, females = 59.0%). People with incident fractures had a significant higher MPI baseline value than those without (0.42 ± 0.18 vs. 0.40 ± 0.17). After adjusting for eight potential confounders, people with an MPI over 0.66 (HR = 1.71; 95%CI: 1.29–2.28) experienced a higher risk of fractures. An increase in 0.10 point in MPI score corresponded to an increase in fracture risk of 6% (HR = 1.06; 95%CI: 1.01–1.11). Higher MPI values were also associated with a higher risk of non-vertebral clinical fractures.

Conclusion: Higher MPI values at baseline were associated with an increased risk of fractures, reinforcing the importance of CGA in predicting fractures in older people.

OC12

THE PREVALENCE OF COMMUNITY-DWELLING OLDER ADULTS AT HIGH FRACTURE RISK WHO ARE NOT TAKING OSTEOPOROSIS MEDICATIONS: RESULTS FROM THE CANADIAN LONGITUDINAL STUDY ON AGING (CLSA)

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Objective: There is an established osteoporosis care gap, where individuals who have had a fracture do not receive subsequent treatment. Care gap studies have focused on the post-fracture context, and we know very little about whether individuals with other fracture risk factors are receiving treatment. The purpose of our study was to estimate the prevalence of community dwelling older adults at high fracture risk who are not taking osteoporosis medication using the Canadian Longitudinal Study on Aging (CLSA).[1]

Material and methods: We included CLSA participants who completed the baseline (2015) comprehensive interview and had dual-energy X-ray absorptiometry (DXA) (N = 28,781). We describe the age- and sex- stratified proportion and prevalence of people at high fracture risk (FRAX® major osteoporotic fracture probability > 20%) and not taking an osteoporosis medication. Osteoporosis medications were defined using the Public Health Agency of Canada standards for osteoporosis surveillance and identified via drug identification numbers.[2] Sampling weights, as defined by the CLSA, were applied.[1]

Results: The mean age of participants was 70.0 (SD 10.3). Overall, 6.2% were at high fracture risk. Of people who were at high risk, 96.6% of men and 79.8% of women were not taking an osteoporosis medication. This proportion decreased with age, for both men (45–54 years: 100%; 55–64 years: 98.9%; 65–74 years: 96.7%; 75 + years: 91.2%) and women (45–54 years: 96.4%; 55–64 years: 86.2%; 65–74 years: 82.7%; 75 + years: 74.0%) but was higher for men at all ages. The prevalence of people at high fracture risk and not taking an osteoporosis medication per 1000 persons increased with age for both men (45–54 years: 10.1; 55–64 years: 19.8; 65–74 years: 20.8; 75 + years: 17.8) and women (45–54 years: 13.2; 55–64 years: 34.9; 65–74 years: 64.7; 75 + years: 153.2) and was highest for women aged 75 years or older.

Conclusions: Our study demonstrates that most community-dwelling older adults at high fracture risk are not receiving osteoporosis medication, particularly men. This presents an opportunity for improved primary fracture prevention in the community.

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Disclosures

OC13

PATIENT'S PREFERENCES FOR LIFESTYLE CHANGES IN OSTEOPOROTIC FRACTURE PREVENTION: A CROSS-EUROPEAN DISCRETE-CHOICE EXPERIMENT

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Objective: Healthy lifestyle habits are recommended for preventing osteoporotic fracture, alongside drug therapy. In this study, we aimed to

assess patients' preference to adopt lifestyle changes to prevent osteoporotic fractures.

Methods: A discrete-choice experiment was conducted in seven European countries: Belgium, France, Ireland, Spain, Switzerland, the Netherlands and United Kingdom. Patients were repetitively asked if they would closely follow different regimens of lifestyle recommendations that varied with respect to 6 attributes and different levels (options): physical activity (levels: not included, moderate or high), calcium and vitamin D status (levels: not included, taking supplements or improve nutrition and assure a minimal daily sunlight exposure), smoking (levels: not included or quit smoking), alcohol (levels: not included or moderate consumption), weight reduction (levels: not included or ensure a healthy body weight) and fall prevention (levels: not included, receive general advice or following a one-day prevention program). A conditional logit model was used to estimate patient's preferences for all participants (global model) and per country.

Results: In total, 1042 patients completed the questionnaire, with samples varying between 91 and 244 per country. Overall, patients were favourable to lifestyle changes for preventing osteoporotic fractures (positive and significant coefficients in the global model as well as in all countries separately). However, among the lifestyle factors proposed, consensually across all countries, patients were not prone to engage in high physical activity (i.e. walking for 30-40 minutes, 3-4 times per week or equivalent). In Ireland, Belgium, the Netherlands and Switzerland, patients were not favourable neither to follow a one-day falls prevention program. Belgian, Swiss and Dutch patients were not prone neither to modify their nutrition (i.e. diet rich in calcium and consumption of fish at least twice a week) and ensure a 10-15 minutes daily sunlight exposure. In the global model as well as for Belgian and Dutch patients separately, we observed favourable intention from patients to reduce their alcohol consumption, engage in moderate physical activity, taking calcium and vitamin D supplements and ensure a normal body weight for preventing fractures.

Conclusions: Patient's healthy lifestyle behaviours are essential for an optimal osteoporosis management. This is the first study that explicit patients' preferences for lifestyle factors in preventing osteoporotic fracture. In an ideal patient-centred approach, fracture prevention should take these considerations and preferences into account.

OC14

PARATHYROIDECTOMY IS ASSOCIATED WITH REDUCED RISK OF FRACTURE AND CARDIOVASCULAR EVENTS IN PATIENTS DIAGNOSED WITH PRIMARY HYPERPARATHYROIDISM – A NATIONAL, RETROSPECTIVE COHORT STUDY

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Background: Previous studies have shown that patients with primary hyperparathyroidism (PHPT) have an increased risk of fractures and other comorbidities such as cardiovascular events, but the effect of parathyroidectomy (PTX) on these outcomes, has been insufficiently studied. Most previous studies have been limited in size and results have not been consistent.

Method: In this retrospective cohort study of all patients diagnosed with PHPT (ICD-10 E210) at hospitals in Sweden between July 1st 2006 and Dec 31st 2017, we investigated the association between PHPT diagnosis, parathyroidectomy, and outcomes. In total, we identified 16 652 patients with PHPT who were assigned 166 520 age and sex-matched controls from the general population. The primary aim of this study was to investigate whether the diagnosis of PHPT was associated with an increased risk of fractures and cardiovascular events (CVE). The secondary aim was to determine if PTX in patients with PHPT diagnosis was associated with a reduced risk of these outcomes.

Results: The majority of the patients were female (78.2 %), the mean (standard deviation) age 67.4 (12.8) years, and the follow-up time for the entire patient group was 35 423 patient-years. In a Cox proportional hazards model, adjusted for age, sex, and calendar year, patients with PHPT had a higher risk of any fracture (adjusted HR 95% CI: 1.30 (1.22-1.38)), hip fracture (1.25 (1.11-1.40)), and major osteoporotic fracture (1.28 (1.19-1.38)) compared to controls. Furthermore, patients with PHPT had a higher risk of cardiovascular events (1.46 (1.35-1.57)) and death (1.44 (1.37-1.52)). In a Poisson regression model with PTX as a time-dependent variable, PTX was associated with reduced risk of hip fracture (HR 0.77 (0.61-0.97), any fracture (HR 0.83 (0.74, 0.92)) and CVE (HR 0.77 (0.68-0.88) in patients with PHPT.

Conclusions: Patients with primary hyperparathyroidism have an increased risk for fractures, cardiovascular events, and death. Parathyroidectomy was associated with a reduced risk of fractures and cardiovascular events, indicating that surgery could have beneficial effects in patients with PHPT.

OC15

FRAILTY IS ASSOCIATED WITH INFLAMMATION AND REDUCED BONE MINERAL DENSITY INDEPENDENT OF FAT MASS: FINDINGS FROM UK BIOBANK

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Objective: Frailty represents a huge public health burden. Fundamental aging processes (e.g. chronic inflammation) are associated with frailty, but the independence of these relationships from age, sex, lifestyle and adiposity is unclear. Using UK Biobank, we investigated associations between frailty, blood biomarkers and bone health, independent of these characteristics.

Material and Methods: 502,640 participants aged 40-69 years were recruited to UK Biobank 2006-10. Venous blood samples were obtained. From 2014 onwards, a subset attended an imaging follow-up, including whole-body DXA (GE Lunar iDXA), grip strength (Jamar dynamometer), and a questionnaire. Frailty was defined using a modification of Fried's classification (at least 3 of weight loss, mental exhaustion, low physical activity, slow gait speed and low grip strength). The presence of 1-2 criteria designated pre-frailty. Linear regression was used to discern associations between frailty status, biochemical markers (CRP, 25(OH)-vitamin D, HbA1c) and bone outcomes, adjusting for age, sex, smoking, alcohol, educational level and total fat mass assessed by DXA. Non-frail was the reference category and blood biomarkers were standardised (β: mean difference in SD).

Results: 22,332 participants (11,484 women, 10,848 men) with frailty assessment and DXA bone measures or blood biochemistry were included in the analysis; 547(2.4%) were frail and 9359(41.9%) pre-frail. Frail participants were more likely to be female [59.6% vs. 50.9%], older [mean(SD) 63.2(7.9) vs. 62.6(7.3)years], of higher BMI [mean(SD) 30.7(6.4) vs. 25.9(4.0)kg/m^2]. After full adjustment, frail

participants had higher CRP [+0.34 SD(95% CI 0.18, 0.51], lower 25(OH)-vitamin D [-0.36 SD(-0.54,-0.19)] and higher HbA1c [+0.27 SD(0.10, 0.43)], all p<0.001. Frail participants had lower femoral neck [-0.03 g/cm^2(-0.05, -0.01),p=0.02] and lumbar spine bone mineral density (BMD) [-0.03 g/cm^2(-0.05, -0.002),p=0.002]. BMD associations were only apparent after fat adjustment. Similar associations were observed for pre-frail vs. non-frail participants.

Conclusion: In UK Biobank, frailty is associated with high levels of systemic inflammation, low 25(OH)-vitamin D, poorer glucose handling and lower BMD, independent of age, sex, lifestyle and fat mass. These findings suggest that frailty associations with age-associated inflammation (inflammaging) are only partly mediated via adiposity and warrant further mechanistic investigation.

OC16

EPIGENETIC AGE ACCELERATION ASSOCIATIONS WITH SKELETAL OUTCOMES: DIFFERENTIAL IMPACTS IN MEN AND WOMEN

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Objectives: Epigenetic clocks are composed of a selection of CpG sites which have the potential to capture 'biological age' and provide a measure of age acceleration (calculated as the difference between biological and chronological age). Here we investigate the associations between age acceleration (according to three different clocks: Horvath pan-tissue, GrimAge and PhenoAge) and hip DXA parameters.

Materials and methods: Participants were recruited across three generations of the Hertfordshire Intergenerational Study; original cohort members, their children, and grandchildren. Hip DXA was performed (Lunar iDXA, GE Healthcare) and whole blood DNA methylation was analysed using the Illumina 850k array (Infinium MethylationEPIC BeadChip) following which GrimAge, PhenoAge and Horvath pan-tissue age acceleration were calculated. Associations with DXA hip measures (including Bone Mineral Density (BMD), Bone Mineral Content (BMC) and bone area) were analysed using linear regression in sex-stratified unadjusted models and those adjusted for age and BMI. Results are presented as β coefficients with 95% confidence intervals.

Results: A total of 114 participants (39 males and 75 females) were recruited, mean age of 56 years (range 18 to 88). Relationships varied in different clocks; Horvath pan-tissue age acceleration was not associated with DXA measures in any models. However, greater GrimAge acceleration was associated with significantly lower hip BMC (β=-0.94 (-1.50,-0.38), p<0.01 and lower bone area (β= -0.28 (-0.55,-0.01), p<0.05) in males in fully-adjusted models, and with lower hip BMD in males in unadjusted models (β= -0.02 (-0.04,-0.01), p<0.05). Greater PhenoAge acceleration was associated with lower hip BMC in males in models adjusted for age and BMI (β= -0.34 (-0.65,-0.03), p<0.05) and lower hip BMD in males in unadjusted models only (β= -0.01 (-0.02,-0.00), p<0.05). No significant associations were observed in females.

Conclusions: Our results demonstrate that the newer iterations of epigenetic clocks (GrimAge and PhenoAge) which were designed to measure age-related phenotypic changes are associated with bone measures at the hip, whereas the first-generation clocks (Horvath pan-tissue) were not. These sex-specific associations require further investigation.

OC17

COMPARISON OF FRACTURE RATES AND ECONOMIC OUTCOMES BETWEEN WOMEN WITH OSTEOPOROSIS RECEIVING RISEDRONATE GASTRO-RESISTANT (GR) AND ALENDRONATE

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Objective: This study aimed at comparing the risk of fractures and economic outcomes between women with osteoporosis receiving risedronate GR vs alendronate immediate-release. Risedronate GR offers a more convenient dosing option by eliminating the need for fasting and has a higher oral bioavailability[‡] than alendronate.

Material and Methods: Women with osteoporosis from a US claims database (2009-2019) were analyzed. They were observed for ≥2 years following the date of their first observed dispensing for an oral bisphosphonate and classified into the GR or alendronate cohort based on the treatment initiated on that date (index date). Women from the two cohorts were then matched 1:1 based on demographic and clinical characteristics evaluated during a six-month period prior to the index date. Incidence rates (IRs) of fractures and healthcare resource utilization per 1,000 patient-years were compared between the two cohorts using IR ratios (IRRs).

Results: 1,807 patients were selected in each cohort (median age: 60.0 years; average observation period [years]: GR: 4.3, alendronate: 4.6). The IR of fractures was statistically significantly lower in the GR vs the alendronate cohort for any fracture sites (IRR: 0.81, p<0.05) and spine fractures (IRR: 0.69, p<0.05) (table). Numerical trends of lower incidence of fractures among women in the GR cohort were observed for the other examined skeletal sites (table). Compared to the alendronate cohort, the GR cohort incurred fewer hospitalizations (IR, GR: 112.03; alendronate: 134.69; IRR: 0.85, p<0.05) translating into numerically lower hospitalization costs (average per-patient-per-year; GR: $3,605; alendronate: $4,572, p=0.0681).

Conclusion: This study indicates that women treated with risedronate GR have a lower incidence of fractures compared to those treated with alendronate, consistent with the hypothesis that the gastro-resistant formulation of risedronate improves medication absorption, thus enabling a greater effectiveness.

	IR GR (N = 1,807)	IR Alendronate (N = 1,807)	IRR (95% CI)
Any site	33.97	42.53	0.81 (0.66—0.98) *
Hip	9.21	9.61	0.99 (0.65—1.51)
Pelvis	2.07	3.12	0.68 (0.35—1.33)
Spine	10.76	15.86	0.69 (0.49—0.97) *
Wrist/arm	14.52	15.86	0.91 (0.70—1.20)

[‡]Risedronate GR SmPC

*Significant at the 5% level

OC18

LOCAL OSTEO-ENHANCEMENT PROCEDURE SIGNIFI-CANTLY INCREASES BONE MINERAL DENSITY IN THE PROXIMAL FEMUR OF POSTMENOPAUSAL WOMEN WITH OSTEOPOROSIS AT HIGH RISK FOR HIP FRACTURE

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Objective: Assess the improvement of proximal femur bone mineral density (BMD) in two prospective clinical studies two years after treatment with a AGN1 hip Local Osteo-enhancement Procedure (LOEP).
Materials and Methods: LOEP was evaluated in prospective, single-armed, cohort clinical studies in USA (Copley) and Europe (Confirm). Studies received ethics committee and IRB approvals; all subjects provided written consent. Criteria for both studies included post-menopausal women at high risk of hip fracture with femoral neck T-score ≤ -2.5. LOEP was performed by injecting the femoral neck and intertrochanteric areas of the proximal femur with a triphasic, resorbable calcium-based implant (AGN1). 72 osteoporotic subjects/85 hips were treated with LOEP as unilateral or bilateral cases. To date, a sub-set of 26 operated hips in 25 subjects was evaluated with baseline and 2-year BMD data (Copley, 12; Confirm, 14). Copley evaluated the AGN1 implant resorption and replacement with bone utilizing sequential radiographs and computerized tomography (CT) scans at 12 wks, 24 wks and 5–7 years. The Confirm study is ongoing and will collect follow-up data to 5 years.
Results: Subjects were aged 70 ± 10 with a baseline mean femoral neck T-Score of -3.0 ± 0.5 (N = 26). The mean pre-operative FRAX score for 10-year probability of hip fracture was $11 \pm 10\%$ (N = 26). Skin-to-skin surgical time was 16 ± 4 min (N = 14). The mean volume of injection was 17.6 ± 2.6 cc (N = 26). CT and radiographs demonstrated complete AGN1 resorption and replacement with bone (N = 26). Baseline femoral neck BMD was not statistically different between studies (p = 0.085). After 2.1 ± 0.4 years, the mean percent difference in BMD increased by $61\% \pm 37\%$ (p < 0.001) from baseline (N = 26). All patients were weight bearing as tolerated after surgery and returned to activities of daily living in less than one week.
Conclusion: This data supports the use of AGN1 LOEP for high-risk patients with osteoporosis-related bone loss and demonstrates that the treatment significantly improves BMD from baseline which is expected to reduce hip fracture risk. The overall impact of LOEP on hip fracture reduction is currently being evaluated in an ongoing multi-national randomized, controlled, prospective, single-blinded clinical study.
Disclosures: J.D.-consultant, research support; J.H.-stock, employee and board AgNovos Healthcare; J.S.-stock, employee AgNovos Healthcare; J.C.-consultant; B.H.-stock, employee AgNovos Healthcare

OC19

A PROSPECTIVE OPEN-LABEL OBSERVATIONAL STUDY OF A BUFFERED SOLUBLE 70 MG ALENDRONATE EFFER-VESCENT TABLET ON UPPER GASTROINTESTINAL SAFETY AND MEDICATION ERRORS: THE GASTROPASS STUDY

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Objectives: To investigate the incidence of upper Gastrointestinal (GI) AEs (oesophageal toxicity, gastritis, gastric ulcers and duodenitis) and medication errors (MEs) associated with a buffered soluble alendronate 70 mg effervescent (ALN-EFF) tablet.
Material and Methods: In this multicenter prospective observational post-authorisation safety study conducted in Italy and Spain, post-menopausal women (PMW) with osteoporosis (naïve to bisphosphonates (BP)) were treated weekly with ALN-EFF and followed for 12 ± 3 months. Information was collected on AEs, MEs (error in following administration instructions), persistence and compliance.
Results: Patients (N = 1,028) aged 67 ± 9 years (mean ± SD) received ALN-EFF weekly. The cumulative incidence of upper GI AEs related to ALN-EFF (primary endpoint) was 9.6%, vast majority being of mild intensity. The most frequently occurring upper GI AEs related to ALN-EFF were dyspepsia (2.7%), gastroesophageal reflux disease (2.4%), and nausea (2.2%). None of the relevant upper GI AEs listed in the primary endpoint and no serious AEs were reported. At least one ME occurred in 29.9% of patients. However, the majority of MEs were associated with administration instructions applicable to any oral BP and only 7 MEs were associated with ALN-EFF. ALN-EFF was discontinued in 209/1,028 (20.3%) patients. Compliance with ALN-EFF was high with a mean Morisky-Green score of 92.8 ± 18.6.
Conclusions: PMW with osteoporosis treated with ALN-EFF in a real-world setting, experienced few upper GI AEs. They also had a low discontinuation and high compliance compared to other formulations, suggesting that ALN-EFF may increase patient satisfaction and therefore long-term adherence and efficacy.
Disclosures: Adami personal fees Amgen, Theramex. Black personal fees Merck, Amgen, Asahi-Kasei, Eli Lilly, EffRx, University of Pittsburg. Blanch-Rubió grants/consulting fees Amgen, Laboratorio Stada, Gedeon-Rhicter Ibérica, Lilly España, Pfizer, Gebro Pharma, UCB Pharma. Minisola speaker Abiogen, Amgen, Bruno Farmaceutici, Diasorin, Eli Lilly, Shire, Sandoz, Takeda. Advisory boards Abiogen, Kyowa Kirin, Pfizer, UCB. Ponce Vargas research fees Laboratories Lacer. Qizilbash owner OXON Epidemiology. Study sponsored by EffRx Pharmaceuticals

OC20

OSTEOCALCIN, MUSCLE FUNCTION AND 15-YEAR FALLS-RELATED HOSPITALISATIONS IN OLDER WOMEN: THE PERTH LONGITUDINAL STUDY OF AGEING WOMEN

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Objective: We tested the hypothesis that undercarboxylated osteocalcin (ucOC) and the ucOC to total (t)OC ratio are associated with muscle function and 15-year falls-related hospitalisations in older women.
Material and Methods: Serum OC and ucOC was assessed in 1261 older women (mean age 75.2 ± 2.7 years) at year-1 of the Calcium Intake Fracture Outcome Study trial, forming the Perth Longitudinal Study of Ageing Women (PLSAW, 1998 to 2013). Timed-up-and-go (TUG) and grip strength was assessed at baseline (1998) and at 5 years. Falls-related hospitalisations over a 14.5-year follow-up was captured by the Hospital Morbidity Data Collection, via the Western Australian Data Linkage System.
Results: At baseline, women with higher ucOC/tOC ratio (quartile 4) had slower TUG performance compared to quartile 1 by 0.68 secs (~0.68 secs, p < 0.01); grip strength and 5-year change in TUG and grip was not significantly different (p > 0.05). Higher ucOC/tOC ratio was significantly associated with poorer TUG performance at baseline and 5-year change in performance (all p < 0.05). Those with the highest

ucOC/tOC had greater falls-related hospitalisations (unadjusted log rank p = 0.004) that remained significant after adjusting for key variables (HR 1.31, 95% CI 1.09–1.57, p = 0.004).

Conclusions: We identified many older women with high ucOC/tOC ratio that also have poorer physical function, including a long-term decline and increased risk of falls-related hospitalisation. This data supports the concept that quantifying ucOC/tOC ratio could be used as a predictor of these adverse outcomes, possibly enabling early intervention and minimising future fall risk. This should be explored in future.

OC21

RELATIONSHIPS BETWEEN MALNUTRITION, SARCOPENIA, AND FRAILTY AND THE INCIDENCE OF COVID-19 IN OLDER ADULTS: DATA FROM THE SARCOPHAGE COHORT

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Objectives: The identification of risk factors for COVID-19 is requested to implement targeted prevention strategies. Therefore, this study aimed to evaluate the associations between the incidence of COVID-19 and malnutrition, sarcopenia, and frailty, identified as potential risk factors in previous cross-sectional studies.

Materials and methods: Community-dwelling older adults aged over 65 years from the Sarcopenia and Physical Impairments with Advancing Age (SarcoPhAge) cohort were included in the present study. Malnutrition, sarcopenia, and frailty were assessed at the last available follow-up from the SarcoPhAge cohort (i.e., the fifth year that ended in June 2019) according to the Mini-Nutritional Assessment short-form, the European Working Group on Sarcopenia in Older People (EWGSOP2), and the Fried criteria, respectively. Information regarding the COVID-19 was gathered by phone calls interviews to measure its self-declared incidence between March 2020 and April 2021. Cox-regressions adjusted for age, sex, body mass index, number of drugs and comorbidities per participants, Mini-Mental State Evaluation score, and physical activity level in analyses on malnutrition and sarcopenia, and Kaplan–Meier curves were performed.

Results: The total study sample comprises 241 participants (median age 75.6 (73.0 – 80.6) years, 63.1% women) who were assessed for the three diseases and for which we have obtained information regarding the COVID-19. Among them, 27 participants (11.2%) developed the non-fatal Covid-19. No significant increased risks of Covid-19 were observed in patients with malnutrition (adjusted HR: 1.14 [0.26 – 5.07]) and sarcopenia (adjusted HR: 1.25 [0.35 – 4.42]). Nevertheless, the incidence of COVID-19 was significantly higher in frail (32.0%) than in robust participants (8.8%) (adjusted HR: 3.97 [1.56 – 10.10]), which was confirmed by the Kaplan–Meier curves ($p < 0.001$). Among the frailty syndrome components, a low physical activity level was the only one significantly associated with an increased risk of COVID-19 (adjusted HR: 5.18 [1.37 – 19.54]).

Conclusion: A fourfold increased risk to develop COVID-19 was observed in the presence of the frailty syndrome. As we are the first to evaluate prospectively these associations, further investigations are needed to elaborate on our findings.

OC22

FUNCTIONAL BRAIN PROCESSES IN SARCOPENIA – EVIDENCE FOR DIFFERENTIAL CENTRAL NEURAL MECHANISMS IN DYNAPENIC OLDER ADULTS

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Objectives: Recently, the European Working Group on Sarcopenia in Older People revised its definition and diagnostic criteria for sarcopenia (EWGSOP2), placing muscle strength at the forefront instead of muscle mass. The etiology and pathogenesis of dynapenia (or low muscle strength) is still not fully understood, but there is emerging evidence that central neural factors constitute critical determinants. Some studies have highlighted the relationships between muscle health and structural changes in brain, while the relationships with functional changes in brain has never been fully explored. In this study, we aimed thus to investigate functional brain processes in dynapenia.

Methods: This single-centre, cross-sectional study included 62 community-dwelling older adults (mean age 73.1 years; 59 females) in Geneva (Switzerland). Participants underwent i) detailed skeletal muscle assessments as well as ii) functional magnetic resonance imaging (fMRI) acquired on a 3 Tesla MRI scanner (Siemens® Trio, Germany) during the performance of a dual-task paradigm, consisting of a visual baseline, two single-tasks (motor joystick and arithmetic task) and a dual-task (motor and arithmetic task combined). Low muscle strength was defined according to handgrip strength (JAMAR® dynamometer) and/or chair rise time measurements using the EWGSOP2 cut-off points.

Results: 47% (29/62) of participants were classified as dynapenic according to EWGSOP2. No differences were found between dynapenic and non dynapenic groups in regard to cognitive (MMSE) and frontal executive functioning (FAB), and gait speed.

fMRI results reveal a differential recruitment of motor circuits in the brain during the dual-task condition in dynapenic as compared with non dynapenic participants. In particular, while the brain activity during the single-tasks did not differ between the two groups, only during the dual-task condition non dynapenic participants showed significant increased activation in the premotor cortex as compared to dynapenic participants. This could be interpreted such that in dynapenia there is an insufficient recruitment of activity in the brain's motor areas, when a task gets more complex.

Conclusions: Our results point to a dysfunctional involvement of brain activity in dynapenia in a multi-tasking paradigm. A better knowledge of the link between dynapenia and brain functions could provide new impulses in the diagnosis and development of effective early-targeted interventions for sarcopenia.

OC23

QUALITY OF LIFE, RESOURCE USE AND COSTS RELATED TO FRAGILITY FRACTURES: DEVELOPMENT AND EVALUATION OF MULTIDISCIPLINARY POST-FRACTURE CARE PATHWAYS

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Objectives: To identify multidisciplinary care pathways for individual fracture sites (hip, vertebrae, wrist, humerus); and to determine the costs and impact of these care pathways on health-related quality of life (HRQoL) recovery.

Methods and Materials: The study included 4126 adults aged ≥ 50 years with a fragility fracture (1657 hip, 681 vertebrae, 1354 wrist, 434 humerus) from the International Cost & Utility Related to Osteoporotic Fractures Study (ICUROS) – an observational study in Austria, Australia, Estonia, France, Italy, Lithuania, Mexico, Russia, Spain & the UK. There were three main study components: 1) latent class analyses (LCA) to identify distinct care pathways ("classes") that were statistically and clinically meaningful, representing common patterns of health service use in patients over 12-months; 2) multivariable logistic regression to analyze associations between each class and HRQoL recovery; and 3) a micro-costing analysis to determine direct health care costs per participant in each class (2020 Australian Dollars) and post-hoc Bonferroni tests to determine significant differences.

Results: The LCA determined 20 classes across the four fracture sites. Different classes were associated with HRQoL recovery at 12-months, although theses classes generally included the combination of primary care; allied healthcare; osteoporosis medication use; vitamin D/calcium supplementation; and non-opioid analgesic use. The total direct cost of fractures was estimated at $89,564, $38,926, $18,333, and $39,461 per patient for hip, vertebral, wrist and humeral participants, respectively. The cost analysis identified that classes associated with HRQoL recovery were also less costly.

Conclusions: By using LCA on health service use, we were able to identify several multidisciplinary care pathways for individual fracture sites and determine the cost and impact of each care pathway on HRQoL recovery. These care pathways may assist health care providers worldwide in allocating resources for fractures in more cost-effective ways.

OC24

UC-II® COLLAGEN HELPS SUPPORT KNEE JOINT MOBILITY IN HEALTHY SUBJECTS: A RANDOMIZED, DOUBLE BLIND, PLACEBO-CONTROLLED STUDY

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Objective: Joint discomfort is a common issue seen in athletes and in normal active people. UC-II® undenatured type II collagen is a dietary ingredient derived from chicken sternum and has been shown in clinical studies to support knee joint comfort and flexibility. Herein, we report results from a 24 week randomized, placebo-controlled, double-blind study evaluating the efficacy and tolerability of UC-II® collagen in managing knee joint discomfort and mobility in healthy subjects who experience activity-related joint pain.

Material and Methods: Healthy subjects, (n = 96), who reported knee joint pain of 5 on an 11-point Likert scale while performing a single-leg-step-down (SLSD) test were randomized to receive placebo (PLA, n = 48), or 40 mg/day of UC-II® providing ≥ 3% undenatured type II collagen (n = 48) for 24 weeks. Joint mobility was measured from the daily number of steps using a step counter (without sporting activity). While joint discomfort was evaluated using subjective questionnaire including the Knee Injury and Outcome Score (KOOS).

Results: At the end of the study, subjects in collagen group reported taking higher number of daily steps than baseline value. A sub group-analysis based on gender showed significantly higher number of daily steps in males from the collagen group versus the PLA group (+ 669 steps vs. -526 steps, p = 0.0374). Similarly, a subgroup analysis based on age showed that collagen supplemented subjects between 20 and 35 years old took higher numbers of steps on SLSD test before reporting the pain score of 5 on the Likert scale, and this change was significant versus the pre-supplementation value (p = 0.0409). In terms of joint discomfort measures, collagen group reported a significant decrease in the duration of knee pain during regular sporting activities versus the PLA group (p < 0.05). Furthermore, the analysis of KOOS subscale data demonstrated a significant reduction in joint discomfort during sports or recreational activities in collagen group versus the baseline value (p = 0.0009) and no significance observed between the treatments. Collagen supplemented group also showed improved quality of life over the study period (p < 0.05). No significant change was observed in the PLA group. As for the KOOS individual questions, collagen group experienced significant reduction in knee pain versus the PLA group during knee twisting/pivoting (p = 0.0346), while walking descending stairs (p = 0.0215) and walking on a flat surface (p = 0.0241) after 24 weeks of supplementation.

Conclusion: In conclusion, these results suggest that UC-II® undenatured type II collagen supplementation supports joint mobility and may reduce joint discomfort during the activities of daily living.

Disclosures: Vijaya Juturu, Shane Durkee and Zainulabedin Saiyed are Lonza CHI Inc. Employers.

OC25

10-YEAR TRENDS IN PREVALENCE OF RADIOGRAPHIC HIP OSTEOARTHRITIS IN JAPANESE MEN AND WOMEN: COMPARISON OF BASELINE AND 4TH RESEARCH ON OSTEOARTHRITIS/OSTEOPOROSIS AGAINST DISABILITY STUDY SURVEYS

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Objective: We investigated 10-year trends in the prevalence of radiographic hip osteoarthritis (OA) in Japanese men and women based on data obtained from a large-scale nationwide cohort study (The Research on Osteoarthritis/osteoporosis Against Disability study).

Methods: We analyzed the data of 2,924 participants (1,026 men, 1,898 women) aged 40–89 years (mean 70.7 years) residing in urban, mountainous, and coastal communities, using information from a baseline survey performed in 2005–2007. We also analyzed the data of 2,347 participants (726 men, 1,621 women) aged 40–89 years (mean 69.2 years) obtained from the 4th survey in 2015–2016. Radiographs were scored using the Kellgren/Lawrence (KL) grading system; radiographic hip OA was defined as a KL score ≥ 2.

Results: The prevalence of radiographic hip OA was 18.4% and 14.4% in men and women, respectively in the baseline survey and 16.0% and 10.7%, respectively in the 4th survey. The prevalence of radiographic hip OA in men and women aged 40–60 years was significantly lower in the 4th survey than in the baseline survey and was significantly lower only in men in their 70 s in the baseline than in the 4th survey. Logistic regression analysis performed after adjustment for age, sex, body mass index, and communities showed that the prevalence of radiographic hip OA in the 4th survey was significantly lower than that in the baseline survey (odds ratio 0.55, 95% confidence interval 0.46–0.65).

Conclusion: In the population-based survey with a 10-year interval, the prevalence of radiographic hip OA tended to decrease. This preferable change in radiographic hip OA circumstances could contribute to the decrease in the occurrence of osteoporotic fracture in the future.

OC26

SAFETY, TOLERABILITY, AND PHARMACOKINETICS OF AN INTRA-ARTICULAR CORTICOSTEROID INJECTION ADMINISTERED 7 DAYS BEFORE OR AFTER INTRA-ARTICULAR LORECIVIVINT INJECTION INTO THE SAME KNEE OF HEALTHY VOLUNTEERS: AN OPEN-LABEL, PARALLEL-ARM STUDY

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Background: Knee osteoarthritis (OA) is a painful condition frequently treated by intra-articular (IA) corticosteroid injections. Lorecivivint (LOR), a novel IA CLK/DYRK inhibitor that modulates Wnt and inflammatory pathways, is in development as a potential knee OA treatment. While LOR is proposed for stand-alone use, in clinical practice, providers might administer LOR in close time proximity to IA corticosteroid. This open-label, parallel-arm, healthy volunteer study was conducted to assess safety, tolerability, and pharmacokinetic interactions between LOR and triamcinolone acetonide (TCA) when the two medications were administered 7 days apart.

Methods: Healthy volunteers were randomized 1:1 to Treatment Arm 1 (IA 40 mg TCA on Day 1 followed by IA 0.07 mg LOR on Day 8) or Treatment Arm 2 (IA 0.07 mg LOR on Day 1 followed by IA 40 mg TCA on Day 8). All injections were performed on the right knee. For each treatment arm, treatment-emergent adverse events (TEAEs) were categorized by "epoch", with Epoch 1 spanning from first until second injection, and Epoch 2 spanning from second injection until end of study. In Treatment Arm 1, plasma TCA levels were assessed on Days 1 (before TCA dosing and up to 12 h after), 2 (24 h after), 3, 5, 8 (before LOR dosing and up to 8 h after), 11, and 15. Plasma LOR concentrations were assessed on Day 8 (before LOR dosing and up to 8 h after). In Treatment Arm 2, plasma LOR levels were assessed on Days 1 (before LOR dosing and up to 8 h after), 8 (up to 8 h after TCA dosing), 9 (24 h after), 10, and 12. Plasma TCA levels were assessed on Days 8 (before TCA dosing and up to 12 h after), 9 (24 h after), 10, 12, 15, 18, and 22.

Results: Forty subjects (age 41.3 ± 7.2 years; BMI 27.8 ± 2.98 kg/m^2; female 40.0%) were evaluated. A total of 18 TEAEs were reported by 11 (27.5%) subjects (Table 1). LOR injection-related TEAEs were similar between arms and there were no serious adverse events. In all subjects and at all time points, plasma LOR concentrations were below the limit of quantification (0.1 ng/ml). Geometric mean concentrations and PK parameters for TCA were similar between treatment arms (Fig. 1).

Conclusion: There were no quantifiable plasma concentrations of LOR in either treatment arm, and the PK of TCA was not changed when administered after LOR injection compared to when administered alone. No safety signals were observed. These results suggested

administering LOR and TCA within a 7-day period of each other should not pose a safety concern.

Table 1. TEAEs by Preferred Term (SAS)

Preferred Term	Treatment Arm 1				Treatment Arm 2			
	TA (Epoch 1) (N=20)		TA + LOR (Epoch 2) (N=20)		LOR (Epoch 1) (N=20)		LOR + TA (Epoch 2) (N=20)	
	n (%)	Total Number of Events	n (%)	Total Number of Events	n (%)	Total Number of Events	n (%)	Total Number of Events
TEAEs	4 (20.0)	5	3 (15.0)	8	2 (10.0)	2	3 (15.0)	3
Injection site bruising	4 (20.0)	4	0	0	1 (5.0)	1	2 (10.0)	2
Injection site pain	0	0	1 (5.0)	2	0	0	0	0
Back pain	1 (5.0)	1	0	0	0	0	0	0
Flank pain	0	0	1 (5.0)	1	0	0	0	0
Musculoskeletal discomfort	0	0	1 (5.0)	1	0	0	0	0
Pain in extremity	0	0	1 (5.0)	1	0	0	0	0
Headache	0	0	1 (5.0)	1	1 (5.0)	1	0	0
Hypersensitivity	0	0	0	0	0	0	1 (5.0)	1
Skin abrasion	0	0	1 (5.0)	1	0	0	0	0
Adnexa uteri pain	0	0	1 (5.0)	1	0	0	0	0

All subjects received both study injections, TA and LOR, in a randomized manner in either Treatment Arm 1 (TA then LOR) or Treatment Arm 2 (LOR then TA). Epoch 1 spans the duration from the first injection until just prior to the second injection. Epoch 2 spans the duration from the second injection until the end of study phone visit or early termination. TEAEs were coded using MedDRA v23.1 and are presented in descending order of frequency.
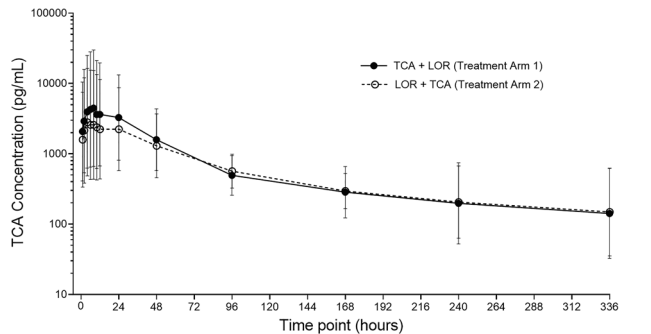TA = triamcinolone acetonide; LOR = lorecivivint

Figure 1. Plasma concentration of triamcinolone acetonide (TCA) following intra-articular (IA) knee injection (40 mg) 7 days before (Treatment Arm 1) and after (Treatment Arm 2) IA lorecivivint (LOR) (0.07 mg). Values shown are geometric means (geometric SD) for all post-injection time points; those reported below the lower limit of quantification (LLOQ, <20.0 pg/ml) were set to ½ × LLOQ.

OC27

EFFECT OF 2 FORMS OF VITAMIN D ON SKELETAL MUSCLE FIBER SIZE AND VITAMIN D RECEPTOR (VDR) CONCENTRATION IN YOUNGER POSTMENOPAUSAL WOMEN

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Objective: To examine the effect of 25(OH)D$_3$ (HyD), vitamin D$_3$ (VD$_3$) or placebo on intramyonuclear VDR expression, muscle fiber cross-sectional area (FCSA), and muscle satellite cell activation.

Methods: The study was conducted in a subset of the HyD ($n=11$), VD$_3$ ($n=12$), and placebo ($n=13$) groups of the HyD Osteopenia Study, a randomized controlled trial in postmenopausal women aged 50–70 years with osteopenia. Women were randomized to HyD 20 mcg/d, VD$_3$ 3200 IU/d, or matching placebo for 6 months. Baseline and 6-month FCSA and intramyonuclear VDR concentration were measured from vastus lateralis muscle cross-sections probed for fiber type I, VDR, and PAX-7 (satellite cell marker) using immunofluorescence.

Results: Baseline mean (SD) age was 61 ± 4 years and 25OHD was 21.6 ± 9.5 ng/mL. Baseline characteristics were similar except body mass index (BMI) which was slightly lower in the VD$_3$ group compared to the HyD and placebo groups. At 6 months, serum 25(OH)

D levels were 82.7 ± 27.5 ng/mL (HyD), 55.4 ± 8.5 ng/mL (VD$_3$), 33.1 ± 14.4 ng/mL (placebo), ANOVA $P < 0.001$. After adjustments for baseline 25OHD and BMI, the mean (SE) percent change in total (type I/II) FCSA was $-4.3 \pm 9.2\%$ (HyD), $25.1 \pm 9.1\%$ (VD$_3$), $4.7 \pm 8.4\%$ (placebo), with $P = 0.033$ between HyD and VD$_3$. More pronounced differences between HyD and VD$_3$ were noted in type I compared to the type II fibers. Percent changes in VDR and PAX-7 concentrations did not differ significantly by group (all $P > 0.223$).

Conclusion: Although HyD vs. VD$_3$ resulted in higher final 25OHD levels, muscle fiber size significantly increased with VD$_3$ and did not change with HyD in 6 months in younger postmenopausal women. This result supports concerns that higher 25OHD levels may not benefit skeletal muscle outcomes.

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OC28

NEUROFILAMENT-LIGHT CHAINS (NF-L), A BIOMARKER OF NEURONAL DAMAGE, IS INCREASED IN SARCOPENIC PATIENTS: RESULTS OF THE SARCOPHAGE STUDY

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Backgrounds: Recently, several papers have made the hypothesis that sarcopenia might partially due to a nervous system failure. Indeed, part of the diagnosis is based on volitional tasks that require the integrity of the nervous system to be properly realized. In the recent years, neurofilament light chains (NF-L) have emerged as a new highly specific blood-biomarker of neuronal damage. Its expression has been reported to be modified in both central and peripheral neuropathies as well as traumatic brain injuries.

Objectives: In this study, we measured NF-L in a large cohort of older individuals to define its expression in presence of sarcopenia.

Methods: The SarcoPhAge cohort is a Belgien cohort of community-dwelling older adults. A diagnosis of sarcopenia was established according to the European Working Group on Sarcopenia in older People 2 (EWGSOP2) criteria. Muscle strength was evaluated with a hydraulic hand-dynamometer, appendicular lean mass by Dual-Energy X-Ray Absorptiometry and physical performance by the Short Physical Performance Battery test (SPPB). NF-L, was measured on all the available sera collected at time of inclusion (n = 409) using the SiMoA technology (Quanterix°).

Results: NF-L was increased in sarcopenic patients (median NF-L: 43.0 pg/mL) compared to controls (median NF-L: 21.1 pg/mL) (p-value: < 0.0001). We also observed a significant difference between subjects with high SPPB score (score: 10 – 12) (median NF-L: 19.5 pg/mL), intermediate SPPB score (score: 7 – 9) (median NF-L: 24.5 pg/mL) and low SPPB score (score: 0—6) (median NF-L: 27.7 pg/mL) (p-value: < 0.0001). The rank correlation gave a Spearman's rho of -0.267 (p-value < 0.0001). A significant correlation was also observed between appendicular lean mass/height^2 (ALM/h^2) and NF-L (rho: -0.200; p-value < 0.0001) but also between handgrip strength and NF-L (rho: -0.196; p-value = 0.0001). In a multiple regression after adjustment for potential confounding variables, NF-L was independently associated with SPPB score (p-value: < 0.0001) but not with ALM/h^2 or handgrip strength.

Conclusions: In this study, we showed that NF-L is increased in sarcopenic patients and is more particularly associated with SPPB score. Our results suggest that sarcopenia may share common features with neurodegeneration.

OC29

CORTICAL PORE SIZE DISTRIBUTION AND VISCOELASTIC HUMAN TIBIA PROPERTIES DISCRIMINATE FRAGILITY FRACTURES INDEPENDENT OF BONE MINERAL DENSITY

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Objectives: Osteoporosis is a disorder of bone remodeling leading to reduced bone mass, structural deterioration, and increased bone fragility. The established diagnosis is based on the measurement of areal bone mineral density by dual energy x-ray absorptiometry (DXA), which poorly captures individual bone loss and structural decay. Enlarged cortical pores in the tibia have been proposed to indicate structural deterioration and reduced bone strength in the hip.

Material and Methods: In this cross-sectional study, we have assessed for the first time the cortical pore diameter distribution Ct.Po.Dm.D together with viscoelastic bone properties (i.e. slope and intercept of the frequency-dependent attenuation Ct.α_f and Ct.α_o) at the anteromedial tibia midshaft by means of a novel ultrasonic cortical backscatter (CortBS) technology. We hypothesized that the CortBS biomarkers are associated with the occurrence of fragility fractures in postmenopausal women (N = 55). The discrimination performance was assessed by means of multivariate PLS discrimination analyses with Leave-One-Out Cross-Validation (PLS-LOOCV) and benchmarked with models obtained from DXA and site-matched second-generation high-resolution peripheral computed tomography (HR-pQCT).

Results: The short-term precision of the individual CortBS parameter estimations was in the range between 1.7 and 13.9%. Ct.Po.Dm values were in the range between 20 and 62.8 μm. CortBS parameters were associated with subject's age (R^2 = 0.45), height (R^2 = 0.36), and marginally with weight (R^2 = 0.25) and *BMI* (R^2 = 0.22). We found a superior discrimination performance of CortBS (area under the receiver operating characteristic curve: $0.69 \leq AUC \leq 0.75$) compared to DXA ($0.53 \leq AUC \leq 0.55$) and a similar performance compared to HR-pQCT ($0.68 \leq AUC \leq 0.73$).

Conclusions: CortBS is the first quantitative bone imaging modality that can quantify viscoelastic and microstructural tissue deteriorations in cortical bone, which occur during normal aging and the development of osteoporosis. A widespread application of the method is anticipated to enable an early identification of people at increased risk, a timely initiation of preventive therapies, and subsequently to a reduction of the prevalence of fragility fractures in people with metabolic bone diseases.

Disclosures: JM is employee of poroUS GmbH, a startup developing the CortBS technology. KR is inventor on the patent applications (EP3641657A1, US 2020/0129140, CN110769754A and JP 2019–570,514) describing the CortBS technology.

OC30

IN HEALTHY MEN, EARLY DECLINE IN TRABECULAR BONE MINERAL DENSITY IS, IN PART, RELATED TO DECREASES IN SEX STEROIDS

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Introduction: Bone mass is known to decline in aging men and this decline is in part affected by sex steroid exposure. However, it is unclear how early after achieving peak bone mass bone loss begins and whether this decline is associated with sex steroid levels in young adulthood.

Objective: Investigating longitudinal changes in trabecular and cortical vBMD in relation to sex steroid levels, body composition and lifestyle factors in young adult men.

Methods: Longitudinal observational study. 999 healthy men aged 24–46 years of whom 691 were re-evaluated after a mean period of 12 years. Serum sex hormone binding globulin (SHBG) levels were measured using immuno-assay. Testosterone (T), estradiol (E2), were measured using LC–MS/MS, free T calculated (cFT). Volumetric BMD was determined at the non-dominant arm (radius, at 4% and 66% of bone length from distal) using pQCT (Stratec XCT-2000, Stratec Medizintechnik, Germany, version 6.0). Linear mixed models were used for statistical analyses. All models comprised lifestyle factors and were adjusted for age and body mass index (BMI).

Results: Baseline age was 34 ± 6 years. Mean BMI increased by 1.19 kg/m^2. Trabecular vBMD decreased by 1.7% (228.9 mg/mm^3 vs 225.0 mg/mm^3), no changes over time in cortical vBMD were observed. Mean T levels decreased by 14.2% (20.8 nmol/l vs. 17.8 nmol/l), cFT by 19.1% (392 pmol/l vs. 317 pmol/l). Mean E2 levels did not change over time. SHBG increased by 3.0% (39.8 nmol/l vs. 41.0 nmol/l). Larger decreases in T, cFT and E2 (all $p < 0.03$) but not SHBG ($p > 0.05$) were associated with more pronounced decreases of trabecular vBMD over time.

Conclusion: Shortly after achieving peak bone mass, a modest trabecular decline was appreciated. This decline was in part associated with declining sex steroid levels. Moreover this decline persisted after correction for changes in body composition and lifestyle factors.

OC31

MULTICENTER PROSPECTIVE STUDY TO ASSESS EFFICACY AND SAFETY GLYCOSAMINOGLYCAN PEPTIDE COMPLEX IN PATIENTS WITH KNEE OSTEOARTHRITIS AND COMORBIDITY

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Objective/Introduction: We have conducted an open prospective observational multicenter study «Osteoarthritis: evaluation of progression in real clinical practice», aiming to assess the efficacy and safety of glycosaminoglycan peptide complex therapy in pts with knee (KOA) and comorbidity.

Materials and Methods: 179 outpatients (predominantly females – 86,6%) from 10 Russian constituent territories were enrolled in the study after signing the informed consent. The inclusion criteria were primary tibiofemoral Kellgren-Lawrence score grade II or III knee OA and comorbidity (type 2 diabetes mellitus and/or arterial hypertension), ≤ 40 mm pain intensity during walking on visual analogue scale (VAS), requiring NSAID intake (for at least 30 days during 3 months prior to enrollment). Mean age was $62,1 \pm 7,4$ years, mean BMI – $31 \pm 5,3$ kg/m2, disease duration – 8 (5—12) years. Grade II OA was documented in 70,9% of patients, Grade III—in 29,1%. Speaking of comorbidity, 92,2% of pts had hypertension, 14,5% had CAD, 19,6% had well controlled type 2 diabetes mellitus and 50,8% had obesity. Patients received two 8-week courses of trial medication,

each consisting of intramuscular injections of 3×2 ml ampoules per week. The study duration was 10 months. Efficacy and safety evaluations were made based on VAS pain assessment, Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)—(WOMAC pain (0–500), WOMAC function (0–1700), WOMAC stiffness (0–200)), VAS patients' health status, EQ-5D-based assessment of patients' quality of life, global physician's and patient's efficacy assessment, and daily NSAIDs requirements. Lab parameters of uric acid, fasting glucose and CRP were assessed on each visit. Statistica10.0 was used for statistical analysis.

Results: Statistically significant pain mitigation (VAS) while walking was documented in two months after start of treatment (60 (50–69) vs 40 (27–54) mm, $p < 0,0001$), with subsequent further improvement during all 8 months (Fig. 1). This picture corresponds with synovitis decline throughout the trial (55,6% pts initially vs 39,2% after 8 mo of treatment, OR = 1,94, 95%CI 1,13–3,34, p = 0,02). There was no aggravation of pain after discontinuation of the drug (during 2-4mo FUP), indicating strong aftereffect of glycosaminoglycan peptide complex. Similar trends were observed with total WOMAC score (1130 (829–1436) – at baseline, and 596 (364–948) mm – by the end of the study, $p < 0,0001$), and all WOMAC sub-scores (229 (159–308) – baseline WOMAC pain, 114 (65–184) mm – by the end of the study $p < 0,0001$; stiffness–98 (60–124) and 50 (25–81) mm, $p < 0,0001$; function–801 (541–1035) and 480 (289–687) mm, $p < 0,0001$, respectively). Statistically significant improvement of patients' quality of life by EQ-5D and general health status was observed during the follow up period (respectively, 0,52 (-0,02–0,59) and 0,69 (0,59–0,80), $p < 0,0001$; 50 (40–60) and 60 (44–70) mm, $p < 0,0001$). By the end of treatment 82,7% were categorized as responders by OMERACT-OARSI criteria, 60,3% pts did not take any NSAIDs. Glycosaminoglycan peptide complex therapy did not have any effect on comorbid disease course, did not impair protein or glucose metabolism (uric acid: $316,5 \pm 74,9$ vs $306,3 \pm 67,5$ μmol/l, $p > 0,05$ and glucose $5,7 \pm 1,2$ vs $5,7 \pm 1,2$ mmol/l, $p > 0,05$). Minor adverse reactions were documented in 5 pts (2,8%).

Conclusion: Obtained results show glycosaminoglycan peptide complex as rather safe disease modifying therapy in OA pts with comorbidity. Glycosaminoglycan peptide complex therapy reduces pain, stiffness, and use of NSAIDs, improves quality of life and joint function, and does not have any effect on protein and glucose metabolism. The drug demonstrated a favorable safety profile and sustainable aftereffect, lasting for at least 4 mo post-treatment.

OC32

IDENTIFICATION OF PATIENTS AT LOW, HIGH AND VERY HIGH RISK OF OSTEOPOROTIC FRACTURES IN THE UK USING FRAX

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A major use of FRAX has been its incorporation into treatment and assessment guidelines. The setting of intervention thresholds (the fracture probability above which to recommend treatment) has varied in different countries. Guidelines variously use an age-dependent fracture probability, or a fixed probability threshold applied to all relevant ages. In the UK, the National Osteoporosis Guideline Group (NOGG) have adopted a hybrid threshold. For men and women, the intervention threshold up to age 70 years is set at a risk equivalent to that associated with a prior fracture and therefore rises with age. At age 70 years and above, fixed thresholds are applied. The proportion of women potentially eligible for treatment rises from approximately 30% to 50% with age, largely driven by the prevalence of prior fracture.

The development of new anabolic interventions for osteoporosis has widened the strategies for its management, in particular, the need to identify patients at very high risk. Such patients might be preferentially targeted with an anabolic agent in the first instance, followed by an inhibitor of bone resorption to maintain a long-term response. NOGG has developed thresholds that characterise men and women with high and very high fracture risk; very high risk is classified as a fracture probability that exceeds the original (and current) intervention threshold by 60%. The proportion of women at very high risk rises from approximately 7% to 36% with age. Clinical scenarios that determine very high risk commonly arise through a combination of clinical risk factors. Additionally, a recent fracture within the past two years has been shown to increase the risk of refracture over and above that calculated by FRAX. Adjustments to FRAX probabilities have been made available to account for the recency of fracture. Such adjustments identify very high risk patients, particularly those with a recent vertebral fracture.

OC33
CIRCULATING MICRORNA AS BIOMARKERS OF OSTEO-POROSIS AND FRACTURE RISK

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Objectives: MicroRNAs (miRNAs) demonstrated to be key regulators of bone modelling and remodelling, through epigenetic post-transcriptional control of gene expression in bone cells. Deregulation of expression and/or activity of specific miRNAs may concur to osteoporosis development and fragility fracture risk. Serum dosage of specific circulating microRNAs (c-miRNA) has recently become subject of investigation by the scientific community as possible early-stage and non-invasive diagnostic biomarkers for osteoporosis and/or prognostic marker for the individual risk of osteoporosis-associated fragility fractures.

Material and methods: The expression of human miRNAs was measured, by next generation sequencing (NGS), in serum samples of 50 osteoporotic patients (18 without fracture, 18 with lumbar spine fracture and 14 with femoral neck fracture) vs 30 individuals with normal bone mass (T-score at lumbar spine, femoral neck and total femur ≥ 1), who have not received any anti-fracture medical therapy at the time of serum collection. c-miRNAs, identified as significantly differentially expressed between the two groups, were validated by Droplet-Digital-PCR (ddPCR) technology in a larger number of serum samples, from untreated patients, presenting different bone phenotypes [105 with osteoporosis (54 without fracture, 32 with lumbar spine fracture, 16 with femoral neck fracture and 3 with both spine and femur fracture), 62 with osteopenia and 46 with healthy BMD.

Results: NGS identified 5 miRNAs (miR-8085, miR-320a-3p, miR-23a-3p, miR-4497, miR-145-5p) as differentially expressed between

non-fractured osteoporosis cases and normal bone samples. ddPCR confirmed miR-23a-3p as less expressed in osteoporosis, with or without fracture, than osteopenia and normal bone, miR-320a-3p as more expressed in osteoporosis with fracture and less expressed in osteoporosis without fracture, both with respect to the other two groups of bone phenotypes, and identified miR21-5p as more expressed in osteoporosis, with or without fracture, than osteopenia and normal bone.

Conclusions: Our data suggested these three c-miRNAs as possible serum diagnostic biomarkers of osteoporosis. Circulating miR-320a-3p appeared to be a promising prognostic indicator of fracture risk in osteoporotic patients. Further studies, in larger and different populations, are needed to confirm these data, to translate the use of c-miRNAs as diagnostic and prognostic biomarkers of osteoporosis and fracture into the clinical practice.

OC34
PALOVAROTENE FOR THE TREATMENT OF FIBRODYS-PLASIA OSSIFICANS PROGRESSIVA IN FEMALES AGED ≥ 8 YEARS AND MALES AGED ≥ 10 YEARS: DATA FROM THE PHASE III MOVE TRIAL

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Objective(s): Assess the safety and efficacy of palovarotene (PVO), a selective retinoic acid receptor-γ, in preventing new heterotopic ossification (HO) in young patients with fibrodysplasia ossificans progressiva (FOP).

Material and Methods: The phase III MOVE trial (NCT03312634) compared efficacy data from PVO-treated patients with FOP aged ≥ 4 years with untreated participants aged ≤ 65 years from an FOP natural history study (NHS; NCT02322255). Annualized change in new HO volume was assessed by low-dose whole-body computed tomography. Adverse events (AEs) were assessed; given the known class effect of retinoids on the skeleton, bone safety assessments were included. Month 18 interim safety and post hoc efficacy data from MOVE are reported, focusing on females/males aged $\geq 8/10$ years at enrollment (ages at which healthy controls reach ~80% of adult height).[1]

Results: Efficacy analyses included individuals aged $\geq 8/10$ years with ≥ 1 post-Baseline HO volume measurement (MOVE: N = 77;

NHS: N = 76). Mean [SE] new HO was 57.0% lower with PVO (10.65 [3.64] × 10^3 mm^3) versus no treatment (24.78 [6.19] × 10^3 mm^3) as analyzed without square-root transformation of HO volume. Safety data included 86 patients from MOVE aged ≥ 8/10 years. The most common treatment-emergent AEs were mucocutaneous: dry skin (67.4%), lip dryness (44.2%), alopecia (34.9%). Premature physeal closure (PPC) serious AEs occurred in 11/21 (52.4%) patients aged < 8/10 years and 9/36 (25.0%) ≥ 8/10– < 14 years at enrollment.

Conclusion(s): PVO may be an important therapeutic option in FOP. As HO is cumulative and functional disability begins in childhood, most benefit would accrue to young individuals, although the risk of PPC must be considered in growing children.

References: 1. Greulich W. Radiographic Atlas of Skeletal Development of the Hand and Wrist: Stanford Univ. Press, 1959.

OC35

MIGHT NSAID USE INTERACT WITH BISPHOSPHONATE EFFICACY? EXPLORATORY ANALYSIS FROM THE CLODRONATE HIP STUDY

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Objectives: NSAIDs are commonly used in the setting of musculoskeletal disorders. It has been hypothesized that NSAIDs might have weak but beneficial effects on bone health, including fracture risk, but most studies have been unable to adjust for potential confounders. We explored the relationship between NSAIDs and fracture risk within the setting of a well-documented, randomised, placebo-controlled study of the bisphosphonate, clodronate.

Material and Methods: 5212 community-dwelling, women age 75 years and older, unselected for osteoporosis were included in this single centre trial. Clodronate 1600 mg daily was compared to placebo over a 3 year treatment period, and reduced osteoporotic fracture risk by 23%. Concurrent medication use at baseline was used to identify those prescribed oral NSAIDs. Only verified, incident fractures were included in the analysis. Using Cox regression, the impact of NSAIDs on fracture risk was examined as well as the anti-fracture efficacy of clodronate in those using or not using NSAIDs.

Results: 1082 (20.8%) women reported use of NSAIDs at baseline. They were slightly, but significantly, younger (mean 79 vs 80 years, p = 0.004) and heavier (mean 66.7 vs 64.7 kg, p < 0.001) than non-users, with slightly higher femoral neck BMD (FN-BMD, 0.66 vs 0.64 g/cm2, p < 0.001). When adjusted for age, FN-BMD and weight, NSAID use was associated with a significant increase in osteoporotic fracture risk (HR 1.29, 95%CI 1.03–1.62, p = 0.025). However, this increase in risk was not statistically significant in the placebo group (HR 1.14, 0.84–1.55). In women receiving clodronate, the effect of the bisphosphonate to reduce osteoporotic fracture risk was not observed in those receiving NSAIDS (HR 0.95, 0.65–1.41, p = 0.81) in contrast to those not using NSAIDs (HR 0.71, 95%CI 0.58–0.89, p = 0.002).

Conclusion: The analysis suggests that the efficacy of the bisphosphonate, clodronate, to reduce fracture risk was negated in those receiving NSAIDs. The mechanism, if real, is unclear, but this observation may be of significant clinical importance. Further exploration in other studies with commonly used oral bisphosphonates is required.