due to severe hip or knee OA. The association of reproductive factors and THRA or TKRA was evaluated using a multivariate-adjusted proportional hazards model. **Results:** During the mean follow-up duration of 8.2 years, 1,733 incident THRA cases and 65,108 incident TKRA cases were observed. Later age at menarche (aHR 1.12 in 13-14 years; aHR 1.24 in 15-16 years; aHR 1.32 in ≥ 17 years), longer breastfeeding (aHR 1.24 in < 6 months; aHR 1.24 in 6-12 months; aHR 1.50 in ≥ 12 months), HRT (aHR 1.06 in < 2 years; aHR 1.11 in 2-5 years; aHR 1.21 ≥ 5 years) and OC use (aHR 1.11 in < 1 year; aHR 1.17 ≥ 1 year) was associated with increased risk of TKRA for severe knee OA, while later age at menopause (aHR 0.93 in 45-49 years; aHR 0.89 in 50-54 years), longer reproductive span (aHR 0.91 in 30-34 years; aHR 0.87 in 35-39 years; aHR 0.91 in ≥ 40 years) was associated with decreased risk. With regard to THRA for severe hip OA, later menarche (aHR 1.21 ≥ 17 years), longer breastfeeding (aHR 1.39 in < 6 months; aHR 1.31 in ≥ 12 months), and HRT more than 5 years (aHR 1.49) were associated with higher risk. The association between reproductive factors and severe OA was more pronounced in underweight and younger subjects.

Conclusion: Our study found that shorter estrogen exposure was associated with higher risk of joint replacement therapy due to severe OA, and such association was more pronounced in underweight and younger subjects.

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Rheumatoid arthritis - biological DMARDs

OP0114

SHORT- AND LONGER-TERM RISKS FOR ACUTE CORONARY SYNDROME IN PATIENTS WITH RHEUMATOID ARTHRITIS STARTING TREATMENT WITH DISEASE-MODIFYING ANTI-RHEUMATIC DRUGS. A COLLABORATIVE OBSERVATIONAL HEAD-TO-HEAD STUDY ACROSS FIVE NORDIC RHEUMATOLOGY REGISTERS

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Background: Rheumatoid Arthritis (RA) is associated with increased cardiovascular co-morbidity including acute coronary syndrome (ACS), partly due to effects of systemic inflammation. Disease-modifying anti-rheumatic drugs (DMARDs) may reduce RA disease activity, but act through several pathways and may themselves have an impact on cardiovascular risks. Whether the risks of ACS associated with biologic (b) and targeted synthetic (ts) DMARDs differ is still unknown.

Objectives: To assess and compare incidences of ACS during treatment of RA with etanercept (ETA), adalimumab (ADA), infliximab (INF), certolizumab pegol (CTZ), golimumab (GOL), rituximab (RIT), abatacept (ABA), tocilizumab (TCZ), baricitinib (BAR) or tofacitinib (TOF).

Methods: We defined and pooled treatment cohorts of patients starting any of the above treatments between 2008 and 2017 from clinical rheumatology registers in Denmark (DK), Finland (FI), Norway (NO), and Sweden (SE). One patient could contribute several treatment episodes. Age, sex, co-medication (methotrexate, prednisolone), number of previous b/tsDMARDs, CRP, comorbidities (cardiovascular (including ACS (defined as ICD-10: I20.0, I21.0-4, I21.9) and cerebrovascular disease, thromboembolic events, diabetes, hospitalized infection, cancer, kidney failure, COPD) and associated drugs were extracted and used as adjustment in Cox regression analyses comparing the incidence of ACS between treatments. We used several follow-up lengths (1, 2, and up to 5 years) and two different risk windows (ACS on drug [ending follow-up on treatment discontinuation] and ACS ever since treatment start [disregarding any treatment discontinuation]). We also stratified by age and number of previous b/tsDMARDs.

Results: We included 40850 treatment courses in 24083 patients (DK 7271, FI 3732, NO 1540, and SE 11540; around 75% women). ETA was the most common treatment (27%) whereas BAR and TOF comprised $< 1\%$, and the other DMARDs 6-14% each. The proportions with a history of ACS at treatment start ranged from 1.2% (NO) to 1.8% (DK).

We found 780 incident ACS events during 141 326 person-years (pyrs) in the 5-year follow-up time and "ACS ever since treatment start" risk window, resulting in a crude incidence rate of 5.5 events per 1000 pyrs. No event was recorded for BAR nor TOF, which also had the shortest follow-up. Adjusted hazard ratios (HR) increased slightly with longer follow-up times, but the two risk windows provided similar HRs. For the 5-year follow-up, RIT was associated with an increased risk of ACS compared to ETA (Table), while no association was observed for shorter follow-up times. Stratifying on age did not modify the associations. Separate analyses by number of previous b/tsDMARDs suggested that ABA (HR=1.8, 95% CI 1.0-3.3), INF (HR=2.2, 95% CI 1.0-4.6) and RIT (HR=1.9, 95% CI 1.1-3.4) were associated with increased risks of ACS compared to ETA in the subgroup of patients with two or more previous bDMARDs (Figure), whereas no differences were found among patients starting either drug as 1st/2nd bDMARD.

Table 1. Comparisons of risks for ACS during a 5-year follow-up since start of bDMARD treatment.

Drug	N events	pyrs	Crude incidence rate/ 1000 pyrs	HR (95% CI) ¹
ETA	175	35917	4.9	ref.
ADA	115	24093	4.8	1.0 (0.8-1.3)
CTZ	54	14158	3.8	0.9 (0.6-1.2)
GOL	40	9006	4.4	1.1 (0.8-1.5)
INF	106	17803	6.0	1.2 (0.9-1.5)
ABA	70	10795	6.5	1.1 (0.8-1.4)
RIT	158	16622	9.5	1.3 (1.0-1.6)
TCZ	62	12866	4.8	0.9 (0.5-1.2)
BAR	0	36		
TOF	0	30		

Pyrs: person-years; HR: hazards ratio¹ adjustment: see text.

Conclusion: In this cohort including $\geq 24,000$ patients followed for up to 5 years, the ACS incidence rate was 5.5/1000 pyrs, with RIT showing an increased risk compared to ETA. In clinical practice, the choice of bDMARD does not seem to influence ACS risk in the short term. In the longer term, differences in ACS risk between bDMARDs may reflect channeling to these, or truly differential effects in subpopulations of patients.

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Figure: Comparisons of risks for ACS during a 5-year follow-up since start of bDMARD treatment, stratified on number of previous b/tsDMARDs: Hazards ratio and 95% confidence intervals (with etanercept as reference)

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agreements with Karolinska Institutet with JA as principal investigator, mainly in the context of safety monitoring of biologics via the ARTIS national safety monitoring system.

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OP0115

EFFICACY AND SAFETY OF ABBV-3373, A NOVEL ANTI-TNF GLUCOCORTICOID RECEPTOR MODULATOR ANTIBODY DRUG CONJUGATE, IN PATIENTS WITH MODERATE TO SEVERE RHEUMATOID ARTHRITIS DESPITE METHOTREXATE THERAPY: A PHASE 2A PROOF OF CONCEPT STUDY

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Background: ABBV-3373 is a novel antibody drug conjugate composed of adalimumab (ADA) linked to a proprietary and highly potent glucocorticoid receptor modulator (the anti-inflammatory payload) currently evaluated for the treatment of rheumatoid arthritis (RA).

Objectives: To assess the efficacy and safety of ABBV-3373 vs ADA in RA patients (pts).

Methods: This was a 24-week (wk) randomized, double-blind, double-dummy, active-controlled Phase 2a study of intravenously (IV)-administered ABBV-3373 100 mg (for 12 wks followed by placebo [PBO] for 12 wks) vs subcutaneous injections of ADA 80 mg every other wk (for 24 wks) in pts on background methotrexate. The primary endpoint was the change from baseline (BL) in DAS28(CRP) at Wk 12. Pre-planned statistical methods incorporating pre-specified historical ADA data both alone (pre-specified success criterion, 2-sided $P \leq 0.1$) and supplemented with in-trial ADA data (pre-specified success criterion, probability >95%) were used to achieve adequate statistical power with a reduced trial size. Assay sensitivity was evaluated through construction of a synthetic PBO arm by propensity score matching, using individual pt-level PBO data from 3 recent sponsor-run trials of similar populations and trial settings. Secondary endpoints at Wk 12 included 1) mean change from BL in CDAI, SDAI, DAS28(ESR), HAQ-DI; 2) proportion of pts achieving DAS28(CRP) ≤ 3.2 , ACR20/50/70 responses, HAQ-DI ≤ 0.22 . Continuous and categorical efficacy variables were analyzed using mixed effect model repeated measurements and Cochran-Mantel-Haenszel test, respectively; non-responder imputation was applied to missing categorical data. Treatment-emergent adverse events were summarized through Wk 12.

Results: A total of 48 pts were randomized and treated (ABBV-3373: 31; ADA: 17); 46 pts (96%) completed 12 wks of study treatment. BL demographics and disease characteristics were indicative of established RA and similar among the 2 treatment arms and the synthetic PBO arm. ABBV-3373 demonstrated significant improvement in mean DAS28(CRP) at Wk 12 vs the pre-specified historical ADA (-2.65 vs -2.13; $P=0.022$) and numerically greater improvement vs the combined in-trial and historical ADA arm (-2.65 vs -2.29; probability 90%; Figure). Comparable improvements in disease activity and targets were observed for ABBV-3373 and in-trial ADA. Assay sensitivity was supported by the fact that both ABBV-3373 and ADA arms were superior to synthetic PBO ($P<0.001$). For secondary endpoints, greater efficacy was observed with ABBV-3373 vs historical

ADA; ABBV-3373 was predicted with 79-99% probability to be better than ADA based on the combined in-trial and historical ADA data. 2 serious infections were reported with ABBV-3373 (pneumonia, upper respiratory tract infection) and none with ADA through Wk 12 (Table). 1 event of anaphylactic shock reaction was reported with ABBV-3373. After increasing the duration of IV administration from 3 min to 15-30 min, no similar events were observed.

Conclusion: These data demonstrate the clinical efficacy of ABBV-3373 and its potential to provide improved outcomes for RA pts compared to ADA. The safety profile of ABBV-3373 was generally similar to ADA.

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Figure. Analysis of Primary, Secondary, and Additional Efficacy Endpoints at Week 12

* $P < 0.05$ for ABBV-3373 vs historical ADA, in-trial ADA, and synthetic placebo, respectively. [†] ABBV-3373 better than ADA based on the historical/in-trial ADA; the success criterion was probability >95%. ADA, adalimumab; ACR20/50/70, ≥20%/50%/70% improvement in American College of Rheumatology response criteria; BL, baseline; CDAI, clinical disease activity index; DAS28(CRP), 28-point disease activity score based on C-reactive protein; DAS28(ESR), 28-point disease activity score based on erythrocyte sedimentation rate; HAQ-DI, health assessment questionnaire disability index; LRA, low disease activity; MCID, minimal clinically important difference (change from baseline in HAQ-DI < 0.22); SDAI, simplified disease activity index. [‡] Efficacy endpoints based on non-responder imputation. ABBV-3373 vs in-trial ADA comparison was not adequately powered due to small sample sizes. For ADA vs combined ADA the probability of ABBV-3373 being better than ADA is presented. Historical ADA cohort includes patients receiving ADA 80 mg every other week from prior studies. [§] Analysis only included patients with baseline HAQ-DI < 0.22. Forty-seven patients met the criterion.

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OP0116

ELDERLY PATIENTS ARE NOT AT INCREASED RISK OF SERIOUS INFECTIONS WHEN RECEIVING bDMARDs OR JAK INHIBITORS COMPARED TO csDMARD TREATMENT

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Background: Elderly rheumatoid arthritis (RA) patients are generally at increased risk of serious infections (SI). At the same time, treatment with bDMARDs has been associated with a higher SI risk than treatment with csDMARDs (1). However, long-term use of bDMARDs did not increase the risk of SI in a small group of elderly patients over 65 (2). The extent to which elderly patients are exposed to a higher SI risk when treated with JAK inhibitors (JAKi) is an open question.

Objectives: To assess the effects of bDMARDs and specifically JAKi on the risk of SI in elderly patients with RA.

Methods: The German register RABBIT is a prospective, longitudinally followed cohort of RA patients enrolled with a new start of a DMARD after at least one csDMARD failure. This analysis comprises patients over 70 years of age who were enrolled between 01/2007 and 04/2020 and had at least one follow-up.

Table 1. Treatment Emergent Adverse Events up to Week 12

Event, n (%)	ADA (N = 17)	ABBV-3373 (N = 31)
Adverse event (AE)	12 (70.6)	11 (35.5)
AE with reasonable possibility of being drug related [§]	3 (17.6)	2 (6.5)
Severe AE	0	1 (3.2)
Serious AE	0	4 (12.9) [#]
AE leading to Discontinuation of Study Drug	1 (5.9)	1 (3.2)
Serious infections	0	2 (6.5)
Opportunistic infection excluding Tuberculosis	0	0
Allergic Reactions Including Hypersensitivity, Angioedema, and Anaphylaxis	2 (11.8) ^{&}	1 (3.2) [^]
Systemic glucocorticoid events	0	0
All deaths	0	0

[§]As assessed by investigator. [#]Serious AEs: 1 non-cardiac chest pain, 1 pneumonia, 1 upper respiratory tract disease and 1 anaphylactic shock. [&]1 Type I hypersensitivity, 1 Pruritus [^]1 Anaphylactic shock