Achievement and Maintenance of Disease Targets with Upadacitinib in Rheumatoid Arthritis: 2-Year Outcomes from the UPHOLD Real-World Study

Authors: Andrew Östör · Eugen Feist · Prodromos Sidiropoulos · Jérôme Avouac · Martin Rebella · Rajaie Namas · Frank Buttgereit · Philip G. Conaghan · Ana B. Romero · Erin L. McDearmon-Blondell · Ivan Lagunes-Galindo · Tianming Gao · Aditi Kadakia · Tim Shaw · Suzan Attar

A. Östör

Monash University & Emeritus Research, Melbourne, Victoria, Australia

Australian National University, Canberra, Australia

Cabrini Medical Centre, Malvern, Victoria, Australia

E. Feist

Helios Department of Rheumatology and Clinical Immunology, Vogelsang-Gommern, Experimental Rheumatology of the Otto-von-Guericke University, Magdeburg, Germany

P. Sidiropoulos

Faculty of Medicine, University of Crete, Heraklion, Greece

J. Avouac

Service de Rhumatologie, Hôpital Cochin, AP-HP.Centre – Université Paris Cité, Paris, France

M. Rebella

Departamento de Medicina, Facultad de Medicina, Universidad de la República, Montevideo, Uruguay

Unidad de Enfermedades Autoinmunes Sistémicas, MUCAM, Montevideo, Uruguay

R. Namas

Medical Subspecialties Institute, Division of Rheumatology, Cleveland Clinic Abu Dhabi, Abu Dhabi, UAE

F. Buttgereit

Department of Rheumatology and Clinical Immunology, Charité – Universitätsmedizin Berlin, Berlin, Germany

Deutsches Rheumaforschungszentrum, ein Institut der Leibniz Gemeinschaft, Berlin, Germany

P. G. Conaghan

Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds & NIHR Leeds Biomedical Research Centre, Leeds, UK

A. B. Romero

AbbVie S.L.U., Madrid, Spain

E. L. McDearmon-Blondell · I. Lagunes-Galindo · T. Gao · A. Kadakia

AbbVie Inc., North Chicago, IL, USA

T. Shaw

AbbVie Ltd, Maidenhead, UK

S. Attar

King Abdulaziz University, Jeddah, Saudi Arabia

Corresponding author: Andrew Östör

Email: andrewostor@gmail.com

Address: Suite 43, Cabrini Medical Centre, 183 Wattletree Rd, Malvern, VIC 3144, Australia

Supplementary tables and figures

Table S1 Participating countries and study sites

Countries (*N* = 19)	**No. of study sites (*N* = 263)**
Argentina	9
Australia	5
Austria	6
Belgium	14
France	73
Germany	19
Greece	13
Ireland	4
Israel	9
Italy	29
Kuwait	3
Mexico	9
Russian Federation	18
Saudi Arabia	5
Spain	28
Switzerland	7
Taiwan	6
United Arab Emirates	4
Uruguay	2

Table S2 Baseline patient demographics and disease characteristics

Variables	**FAS (*N* = 1699)**
Age, years, mean (SD)	56.9 (12.4)
Female, *n* (%)	1358 (79.9)
Race, *n* (%)	
White	1180 (69.5)
Asian	85 (5.0)
Arabic	75 (4.4)
Other[a]	40 (2.4)
Body mass index, kg/m^2, mean (SD)[b]	27.0 (5.5)
RA duration from diagnosis, years, mean (SD)	10.1 (9.1)
Erosions on X-ray, *n* (%)	710 (41.8)
Smoking status, *n* (%) (*N* = 1696)	
Current	318 (18.8)
Former	355 (20.9)
Never	1023 (60.3)
Vaccination status[c]	
SARS-CoV-2	842 (49.6)
Varicella zoster[d]	101 (5.9)
Seasonal influenza	350 (20.6)
Streptococcus pneumoniae	352 (20.7)
Rheumatoid factor and/or ACPA positive, *n* (%)[e]	546 (77.8)

Disease activity, mean (SD)	
DAS28(CRP)	4.6 (1.2)
CDAI	26.6 (12.6)
SDAI	28.2 (14.0)
Swollen joint count	5.7 (5.2)
Tender joint count	8.2 (6.4)
Presence of ≥ 1 cardiovascular risk factor, *n* (%)[f]	1059 (62.3)
Initiated upadacitinib as monotherapy, *n* (%)	821 (48.3)
Initiated upadacitinib with csDMARDs, *n* (%)	878 (51.7)
Concomitant corticosteroids, *n* (%)[g]	735 (43.3)
Concomitant NSAIDs, *n* (%)[g]	355 (20.9)
Any prior therapies, *n* (%)[h]	
≥ 1 csDMARD[i]	1209 (79.3)
≥ 1 bDMARD[i]	980 (64.3)
≥ 1 tsDMARD[i]	279 (18.3)

[a]Includes Black or African American, Indian, American Indian or Alaska Native, and multiple; unknown, *n* = 17; not applicable (for French patients only), *n* = 302. [b]Of 1646 patients with available data, 43 (2.6%) were underweight (BMI < 18.5), 617 (37.5%) were normoweight (BMI 18.5–24.9), 576 (35.0%) were overweight (BMI 25.0–29.9), and 410 (24.9%) were obese (BMI ≥ 30). [c]The decision to offer the option of vaccination to patients before initiating upadacitinib was at the discretion of the treating physician. Analysis of vaccination rates per region and the possible association with observed adverse event rates was not conducted in this study. [d]Shingrix, 49 (2.9%); Zostavax, 42 (2.5%); unknown, 10 (0.6%). [e]Patients with ≥ 1 positive result for either rheumatoid factor or ACPA; *n* = 702. [f]History of hypertension, diabetes mellitus, high-density lipoprotein cholesterol ≤ 40 mg/dL in ≥ 1 measurement before enrollment, low-density lipoprotein cholesterol ≥ 130 mg/dL in ≥ 1 measurement

before enrollment and current/former tobacco/nicotine use. Information on statin use at baseline was not collected. [g]*N* = 1312. [h]Not ongoing; [i]*N* = 1524. Patients may be counted multiple times between types of therapy

ACPA anti-citrullinated peptide antibody, *bDMARD* biologic disease-modifying antirheumatic drug, *BMI* body mass index, *CDAI* clinical disease activity index, *csDMARD* conventional synthetic disease-modifying antirheumatic drug, *DAS28(CRP)* disease activity score in 28 joints using C-reactive protein, *FAS* full analysis set, *NSAID* nonsteroidal anti-inflammatory drug, *RA* rheumatoid arthritis, *SARS-CoV-2* severe acute respiratory syndrome coronavirus 2, *SD* standard deviation, *SDAI* simplified disease activity index, *tsDMARD* targeted synthetic disease-modifying antirheumatic drug.

Table S3 Treatment-emergent events leading to death

TEAEs	System Organ Class/Preferred Term	Possibility of being related to study drug
Chest infection[a]	Infections and infestations/Lower respiratory tract infection	No reasonable possibility
Respiratory distress[a]	Respiratory, thoracic and mediastinal disorders/Respiratory distress	No reasonable possibility
Septic shock[a]	Infections and infestations/Septic shock	No reasonable possibility
Acute myocardial infarction	Cardiac disorders/Acute myocardial infarction	No reasonable possibility
Cardio-respiratory arrest	Cardiac disorders/Cardio-respiratory arrest	No reasonable possibility
Multiple organ failure	General disorders and administration site conditions/Multiple organ dysfunction syndrome	No reasonable possibility
Pneumonia	Infections and infestations/Pneumonia	Reasonable possibility
Multiple organ failure	General disorders and administration site conditions/Multiple organ dysfunction syndrome	Reasonable possibility
Domestic accident	Injury, poisoning and procedural complications/Accident at home	No reasonable possibility
Metastatic renal carcinoma	Neoplasms benign, malignant and unspecified (incl cysts and polyps)/Renal cancer metastatic	No reasonable possibility
Gastrointestinal bleeding	Gastrointestinal disorders/Gastrointestinal hemorrhage	No reasonable possibility

SARS-CoV-2 infection	Infections and infestations/COVID-19	No reasonable possibility
Transmural myocardial infarction	Cardiac disorders/Myocardial infarction	No reasonable possibility
Unknown cause of death[b]	General disorders and administration site conditions/Death	No reasonable possibility
COVID-19[b]	Infections and infestations/COVID-19	No reasonable possibility
COVID-19	Infections and infestations/COVID-19	No reasonable possibility
COVID-19	Infections and infestations/COVID-19	No reasonable possibility

Adverse events coded using MedDRA version 26.0

[a]Three events in the same patient. [b]Two events in the same patient

COVID-19 coronavirus disease 2019, *SARS-CoV-2* severe acute respiratory syndrome coronavirus 2, *TEAE* treatment-emergent adverse event.

Table S4 Malignancy events through 24 months

SOC Preferred term	FAS (*N* = 1699) *n* (%)
Breast cancer[a]	4 (0.2)
Colorectal cancer[b]	4 (0.2)
Renal cancer	3 (0.2)
Hematological malignancies[c]	3 (0.2)
Ovarian cancer	2 (0.1)
Adenocarcinoma	1 (0.1)
Oropharyngeal cancer	1 (0.1)
Pancreatic carcinoma (metastatic)	1 (0.1)
Cervix carcinoma stage 0	1 (0.1)
Thyroid cancer	1 (0.1)
Malignant melanoma	1 (0.1)
Nonmelanoma skin cancer[d]	12 (0.7)

[a]Includes breast cancer (*n* = 3) and invasive breast carcinoma (*n* = 1). [b]Includes adenocarcinoma of colon (*n* = 1), colon cancer (*n* = 1), colorectal adenocarcinoma (*n* = 1), and colorectal cancer (*n* = 1). [c]Includes acute myeloid leukemia (*n* = 1), Hodgkin's disease (*n* = 1), and non-Hodgkin's lymphoma (*n* = 1). [d]Includes basal cell carcinoma (*n* = 6), skin cancer (*n* = 2), squamous cell carcinoma (*n* = 2), and squamous cell carcinoma of skin (*n* = 2).

FAS full analysis set, *SOC* System Organ Class.

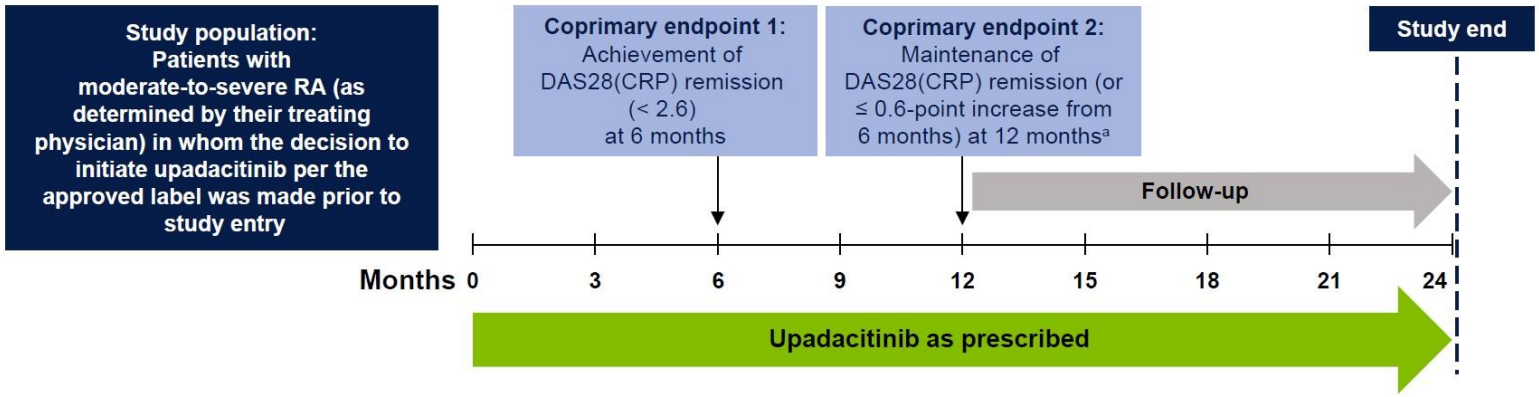


Fig. S1 Study design. [a]In patients who achieved DAS28(CRP) remission at 6 months. *DAS28(CRP)* disease activity score in 28 joints using C-reactive protein, *RA* rheumatoid arthritis.

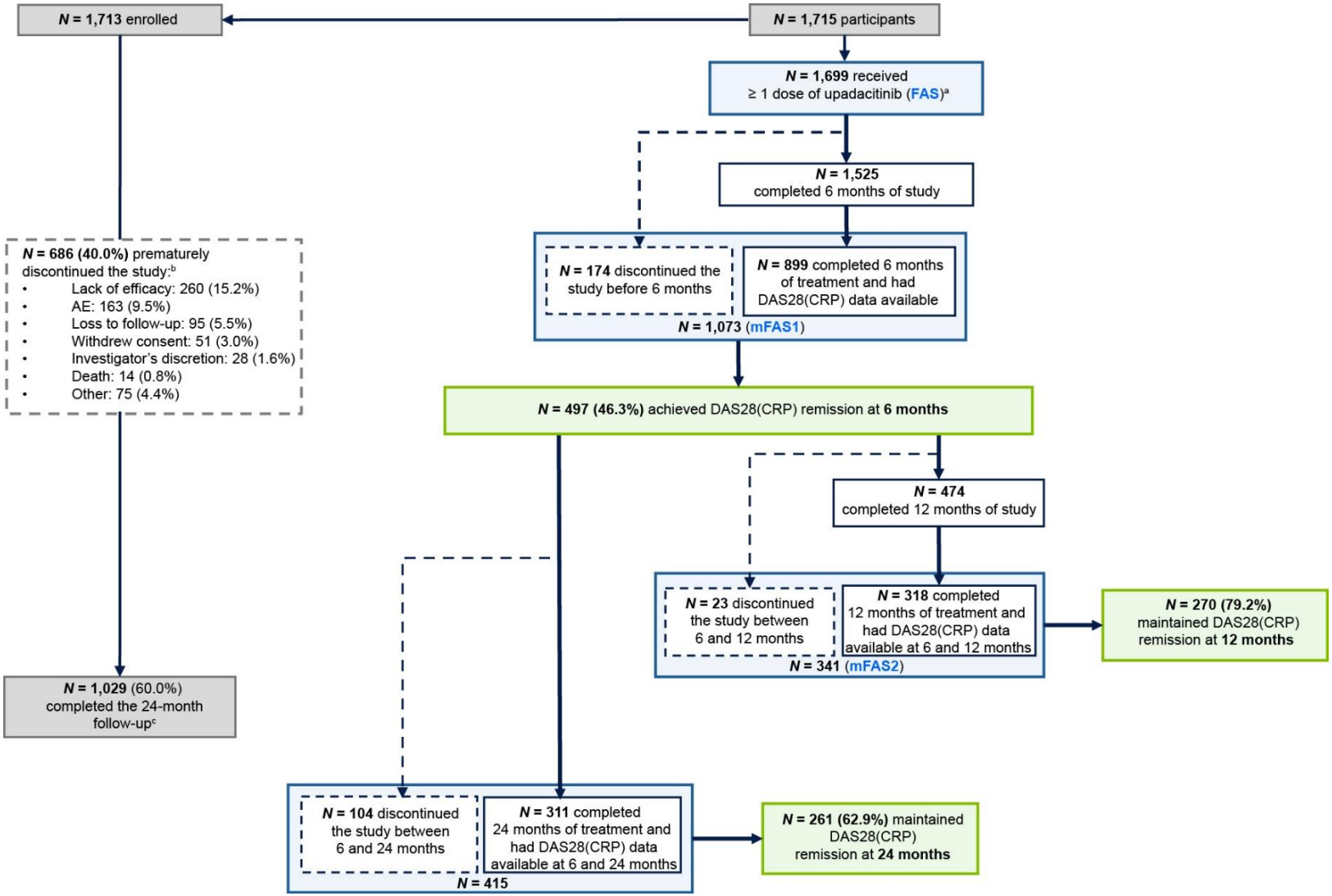


Fig. S2 Patient disposition and key datasets. [a]Includes two patients not meeting eligibility criteria who were treated with upadacitinib. [b]Includes patients for each primary reason for premature discontinuation from baseline to the 24-month visit (some patients may have discontinued treatment but remained in the study and completed the 24-month follow-up for baseline and safety assessments; "premature" refers to patients who discontinued the study before the specified timepoint). [c]Includes patients with study status "Completed" and patients with available data for the 24-month visit. *AE* adverse event, *DAS28(CRP)* disease activity score in 28 joints using C-reactive protein, *f/u* follow-up, *FAS* full analysis set, *mFAS* modified FAS.

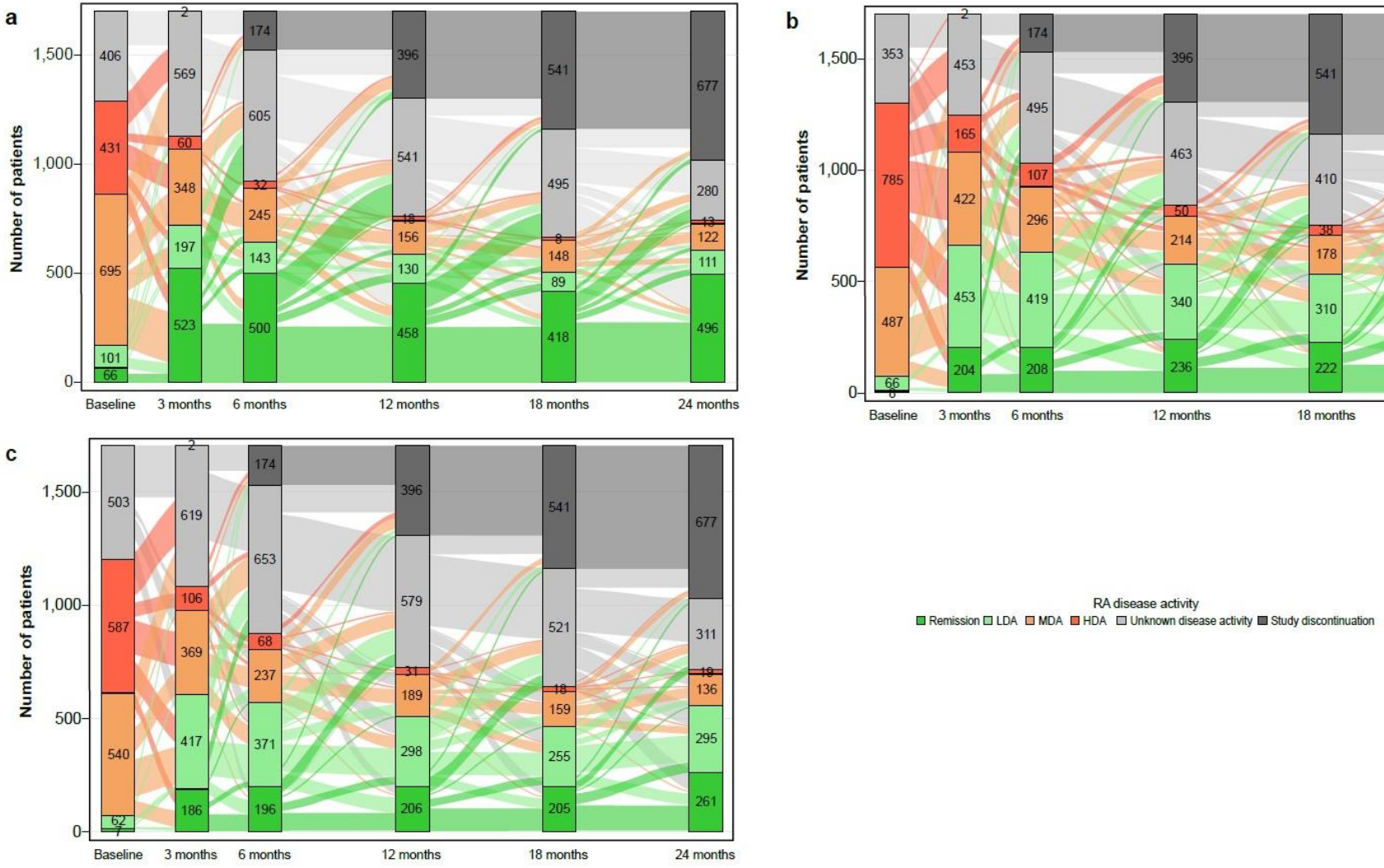


Fig. S3 Sankey diagrams of remission, LDA, MDA, and HDA using **a** DAS28(CRP), **b** CDAI, and **c** SDAI scores. DAS28(CRP) remission: < 2.6; LDA: 2.6 ≤ DAS28(CRP) ≤ 3.2; MDA: 3.2 < DAS28(CRP) ≤ 5.1; HDA: > 5.1. CDAI remission: ≤ 2.8; LDA: 2.8 < CDAI ≤ 10.0; MDA: 10.0 < CDAI ≤ 22.0; HDA: > 22.0. SDAI remission: ≤ 3.3; LDA: 3.3 < SDAI ≤ 11.0; MDA: 11.0 < SDAI ≤ 26.0; HDA: > 26.0. *CDAI* clinical disease activity index, *DAS28(CRP)* disease activity score in 28 joints using C-reactive protein, *HDA* high disease activity, *LDA* low disease activity, *MDA* moderate disease activity, *RA* rheumatoid arthritis, *SDAI* simplified disease activity index.

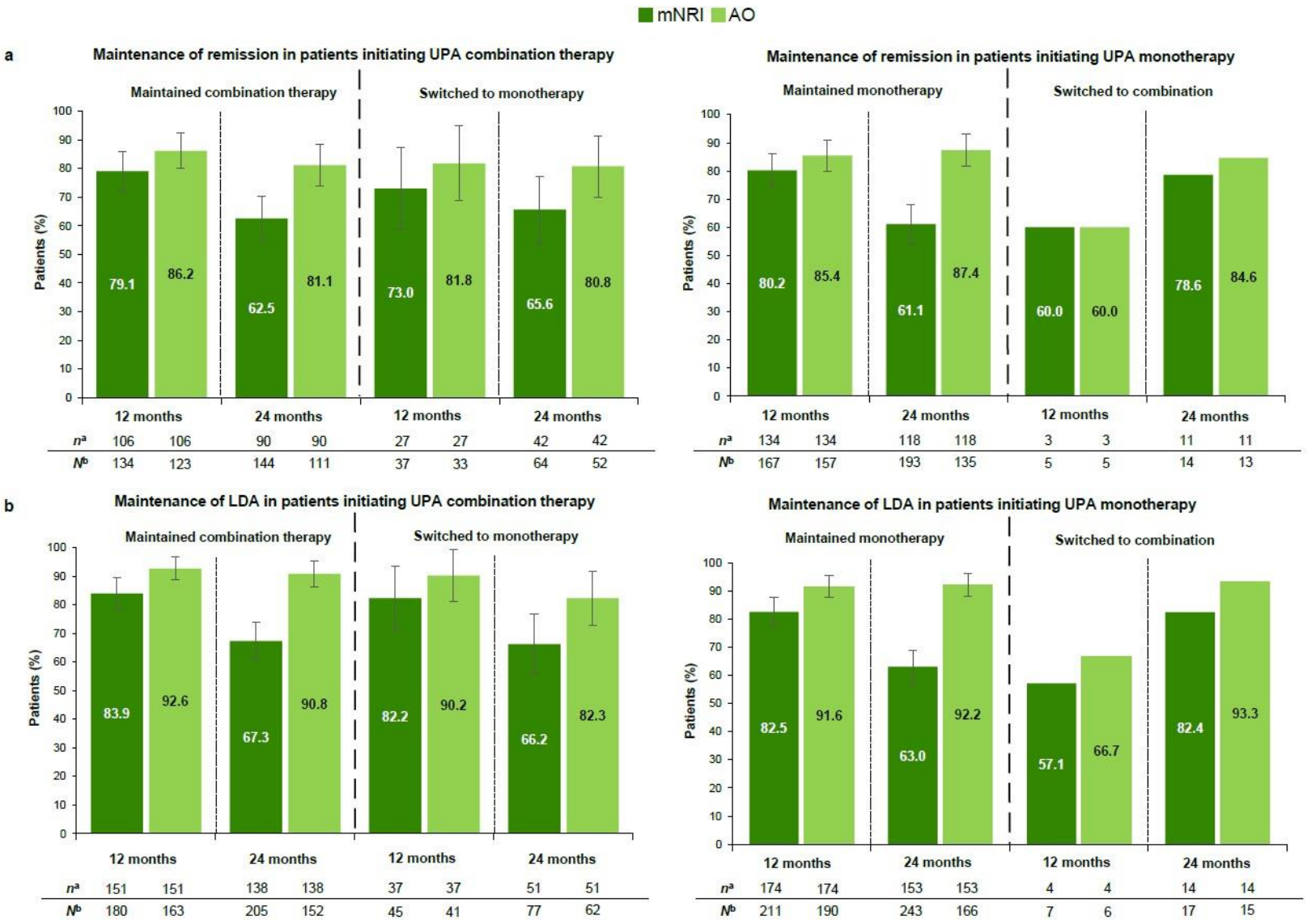


Fig. S4 Maintenance of **a** DAS28(CRP) remission (< 2.6) or **b** DAS28(CRP) LDA (≤ 3.2) through 24 months by baseline therapy strategy. [a]Patients who maintained remission/LDA or had a ≤ 0.6-point increase in DAS28(CRP) at the respective 12- and 24-month timepoints. [b]Patients initiating UPA at baseline as monotherapy (± glucocorticoids) or combination therapy (with conventional synthetic DMARDs ± glucocorticoids), who achieved DAS28(CRP) remission/LDA at 6 months, had DAS28(CRP) data available at 6 and 12 or at 6 and 24 months, and continued receiving UPA at 12 or 24 months (AO) (or who discontinued between 6 and 12, or between 6 and 24 months; mNRI). Error bars represent 95% confidence intervals. *AO* as observed, *DAS28(CRP)* disease activity score in 28 joints using C-reactive protein, *DMARD* disease-modifying antirheumatic drug, *LDA* low disease activity, *mNRI* modified nonresponder imputation, *UPA* upadacitinib.

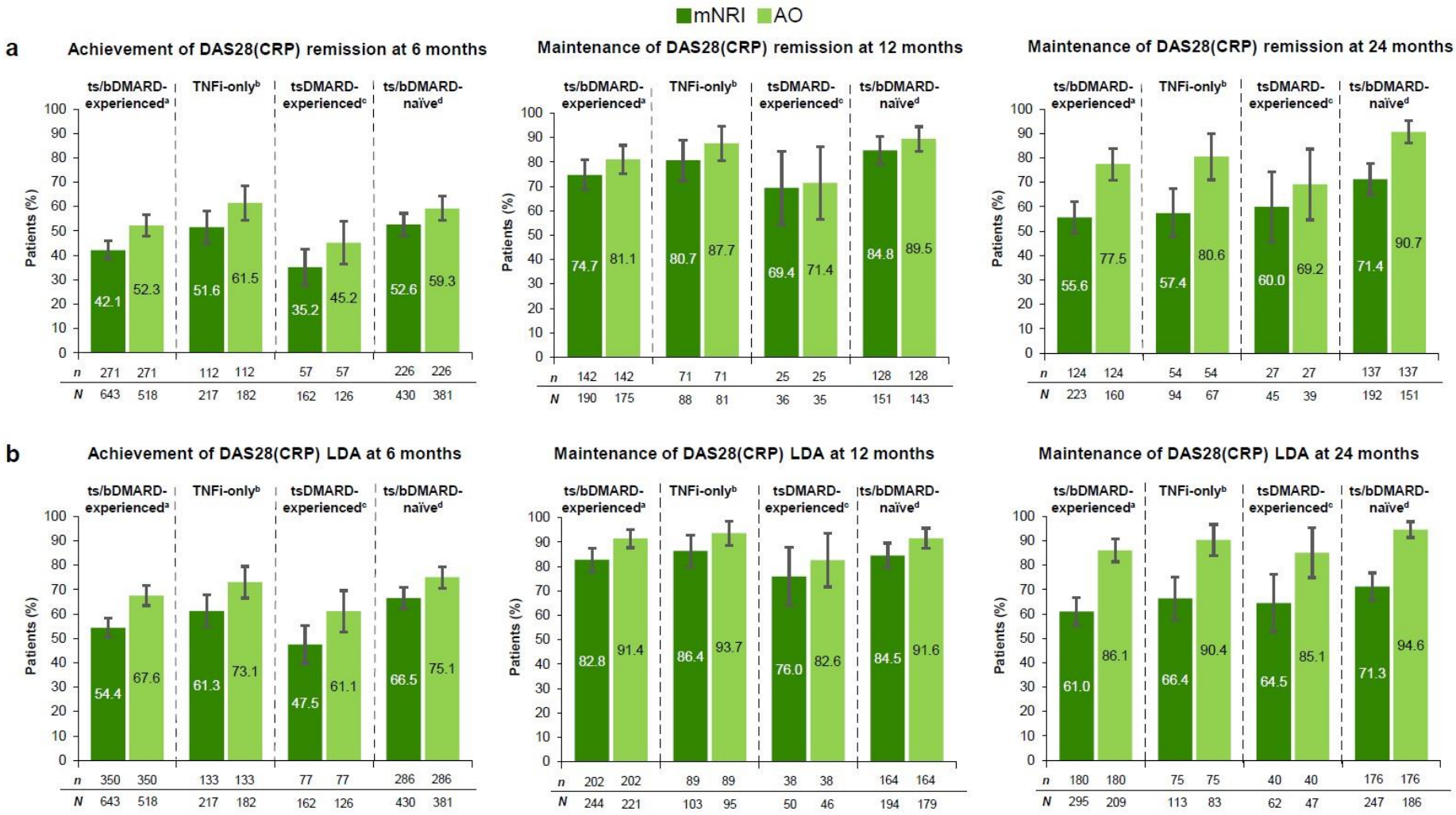


Fig. S5 Subgroup analysis of achievement and maintenance of **a** DAS28(CRP) remission (< 2.6) and **b** LDA (≤ 3.2) through 24 months per prior therapy (mNRI and AO). [a]Prior use of any tsDMARD or bDMARD; *N* = 1029. [b]Prior use of only a TNFi; *N* = 332. [c]Prior use of a tsDMARD; *N* = 279. [d]No prior use of any TNFi, bDMARD, or tsDMARD at baseline; *N* = 670. Error bars represent 95% confidence intervals. *AO* as observed, *bDMARD* biologic DMARD, *DAS28(CRP)* disease activity score in 28 joints using C-reactive protein, *DMARD* disease-modifying antirheumatic drug, *LDA* low disease activity, *mNRI* modified nonresponder imputation, *TNFi* tumor necrosis factor inhibitor, *tsDMARD* targeted synthetic DMARD.

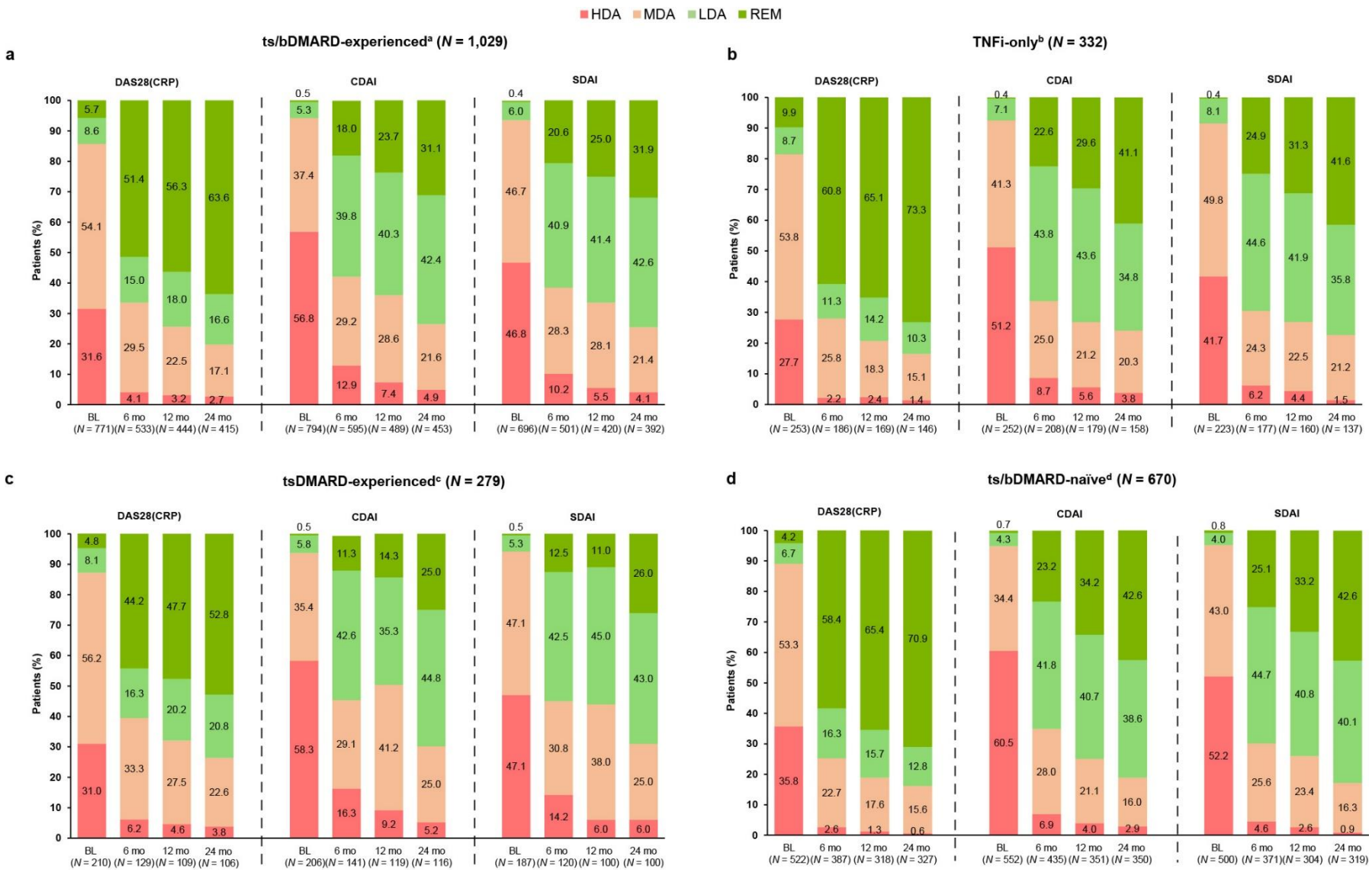
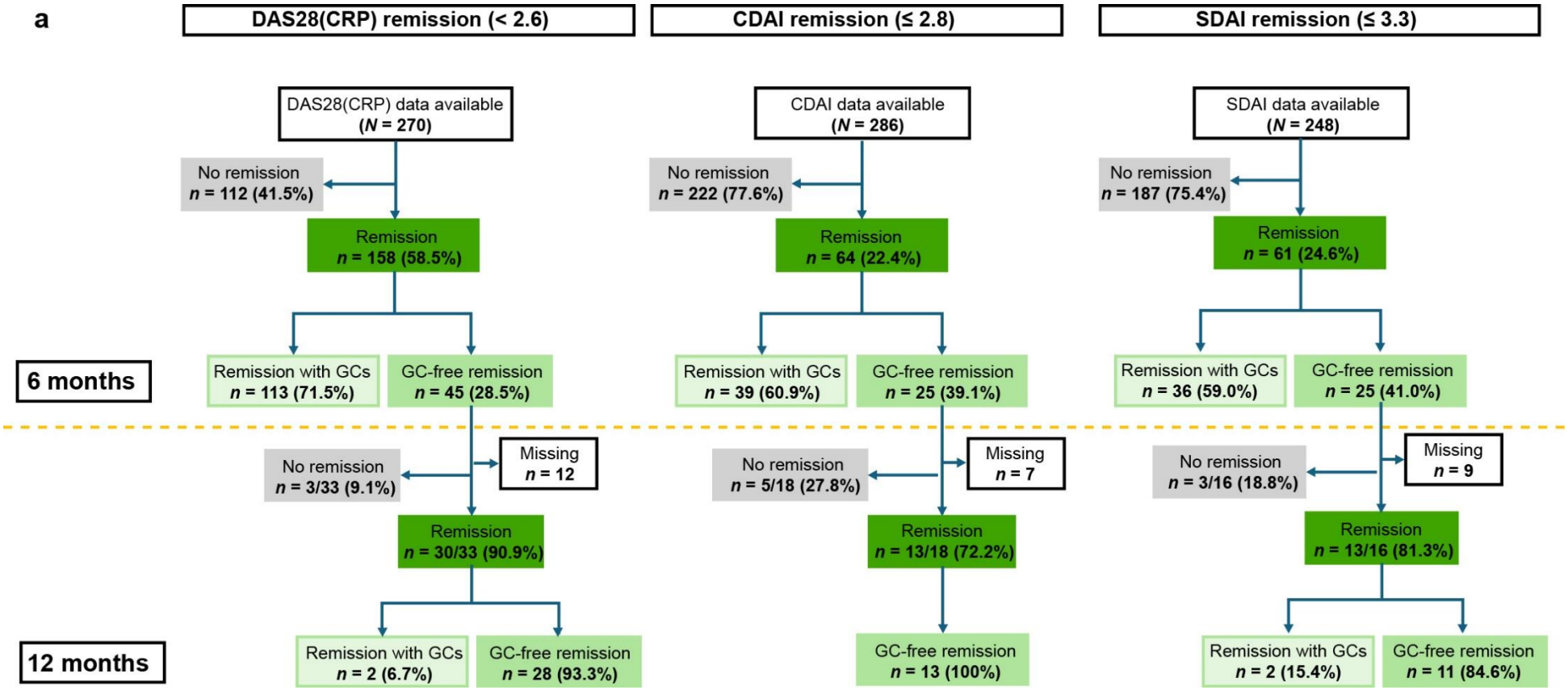


Fig. S6 Subgroup analysis of disease activity by DAS28(CRP), CDAI, and SDAI cutoffs in **a** ts/bDMARD-experienced, **b** TNFi-only, **c** tsDMARD-experienced, and **d** ts/bDMARD-naïve patients per visit (AO)**.** [a]Prior use of any tsDMARD or bDMARD. [b]Prior use of only a TNFi. [c]Prior use of a tsDMARD. [d]No prior use of any TNFi, bDMARD, or tsDMARD at baseline. Data presented are AO. The proportion of patients who achieved each level of disease activity was calculated using the number of patients with nonmissing data for the disease activity score as the denominator. The sum of the proportions may not total 100% due to rounding. DAS28(CRP) remission: < 2.6; LDA: 2.6 ≤ DAS28(CRP) ≤ 3.2; MDA: 3.2 < DAS28(CRP) ≤ 5.1; HDA: > 5.1. CDAI remission: ≤ 2.8; LDA: 2.8 < CDAI ≤ 10.0; MDA: 10.0 < CDAI ≤ 22.0; HDA: > 22.0. SDAI remission: ≤ 3.3; LDA: 3.3 < SDAI ≤ 11.0; MDA: 11.0 < SDAI ≤ 26.0; HDA: > 26.0. *AO* as observed, *bDMARD* biologic DMARD, *BL* baseline, *CDAI* clinical disease activity index, *DAS28(CRP)* disease activity score in 28 joints using C-reactive protein, *DMARD* disease-modifying antirheumatic drug, *HDA* high disease activity, *LDA* low disease activity, *MDA* moderate disease activity, *mo* month, *REM* remission, *SDAI* simplified disease activity index, *TNFi*, tumor necrosis factor inhibitor, *tsDMARD* targeted synthetic DMARD.



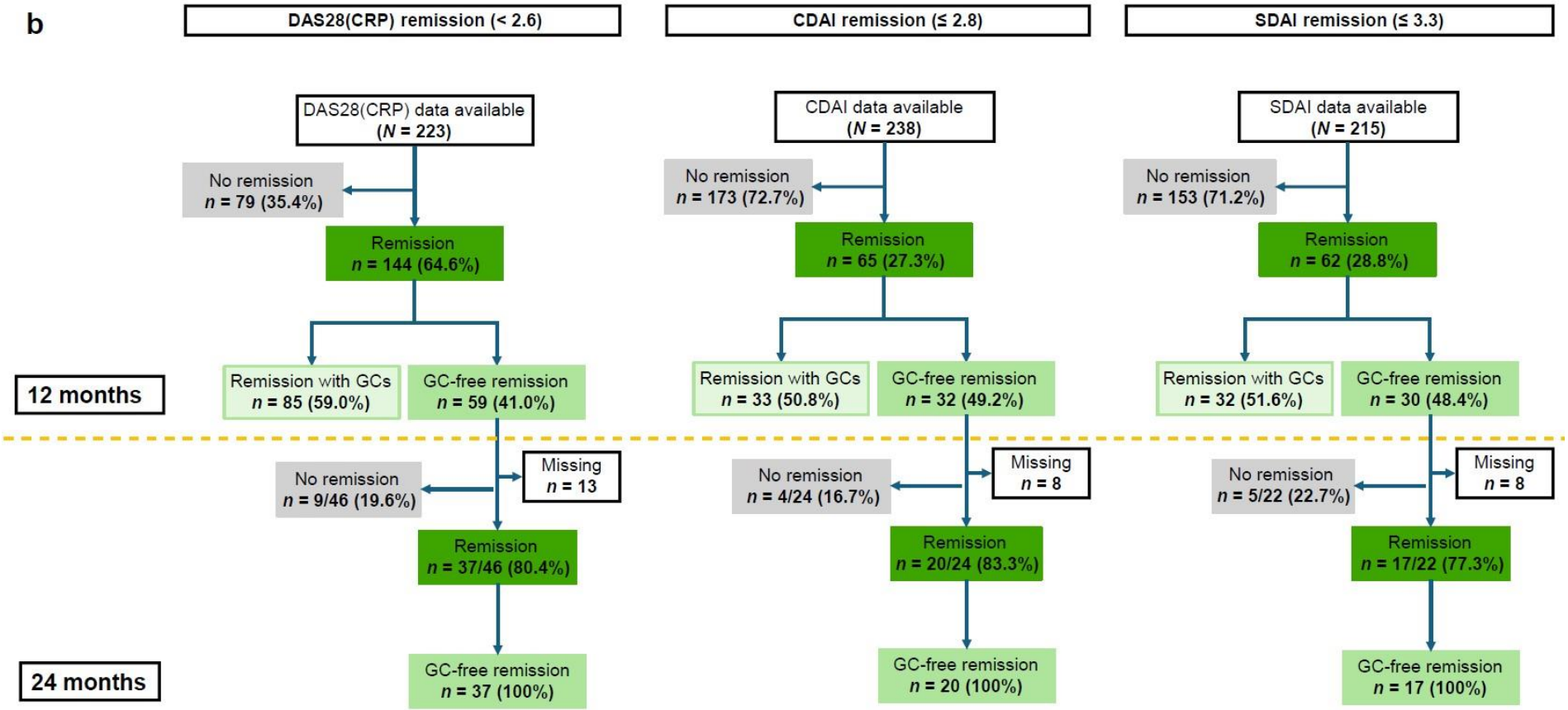


Fig. S7 GC-free remission in patients with RA treated with upadacitinib who **a** achieved clinical remission at 6 months and maintained remission at 12 months and **b** achieved clinical remission at 12 months and maintained remission at 24 months per DAS28(CRP) (< 2.6), CDAI (≤ 2.8), and SDAI (≤ 3.3) cutoffs among patients taking GCs at baseline (AO). *AO* as observed, *CDAI* clinical disease activity index, *DAS28(CRP)* disease activity score in 28 joints using C-reactive protein, *GC* glucocorticoid, *SDAI* simplified disease activity index.

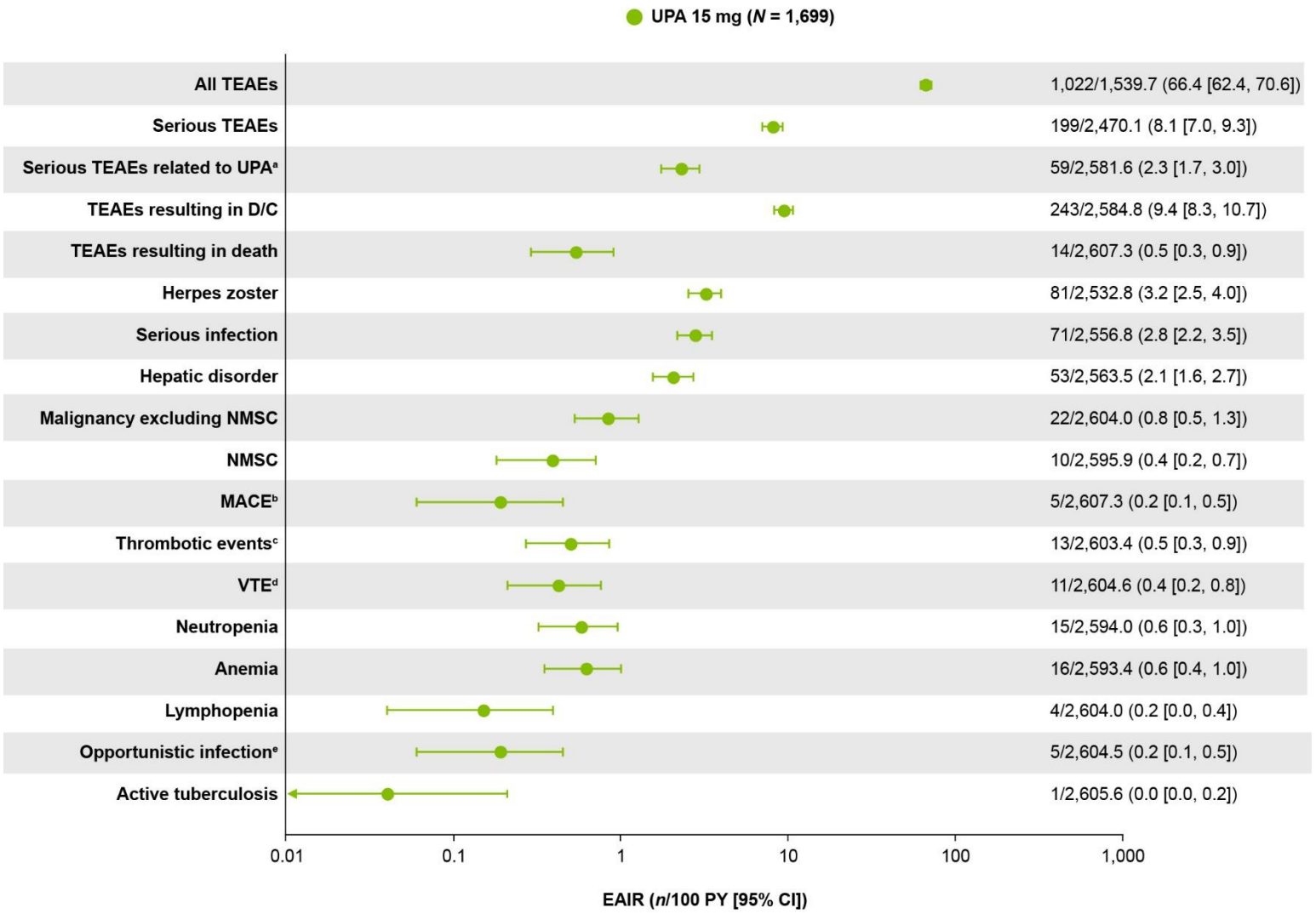


Fig. S8 EAIRs of TEAEs in patients with moderate-to-severe RA treated with upadacitinib 15 mg. [a]Reasonable possibility. [b]Includes cardiovascular death, nonfatal myocardial infarction and nonfatal stroke. [c]Includes VTE, other venous thrombosis and arterial thromboembolic events. [d]Includes deep vein thrombosis, venous thromboembolism, and pulmonary embolism. [e]Excluding herpes zoster and active tuberculosis. Safety was evaluated by assessing all TEAEs (adverse events occurring after the first dose of study drug and up to 30 days after the last dose of study drug) occurring in the FAS up to the data cutoff date of 15 May 2024. There were no reported events of gastrointestinal perforation. *CI* confidence interval, *D/C* discontinuation, *EAIR* exposure-adjusted incidence rate, *FAS* full analysis set, *MACE* major adverse cardiovascular events, *NMSC* nonmelanoma skin cancer, *PY* patient-years, *RA* rheumatoid arthritis, *TEAE* treatment-emergent adverse event, *UPA* upadacitinib, *VTE* venous thromboembolic events.