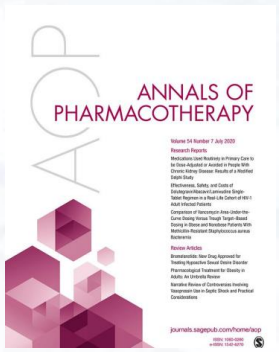
期刊報告



2022.01.06

藥物諮詢組　鄒芸軒藥師

Adjuvant atezolizumab after adjuvant chemotherapy in resected stage IB–IIIA non-small-cell lung cancer (IMpower010): a randomised, multicentre, open-label, phase 3 trial

Lancet 2021; 398: 1344–57

Stage IB-IIIA NSCLC
N=1005

Inclusion Criteria

- ≥ 18 y/o
- Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1
- Completely resected stage IB to IIIA NSCLC, and were able to receive cisplatin-based chemotherapy

Atezolizumab 1200mg IV
N=507

1:1

Best supportive care
N=498

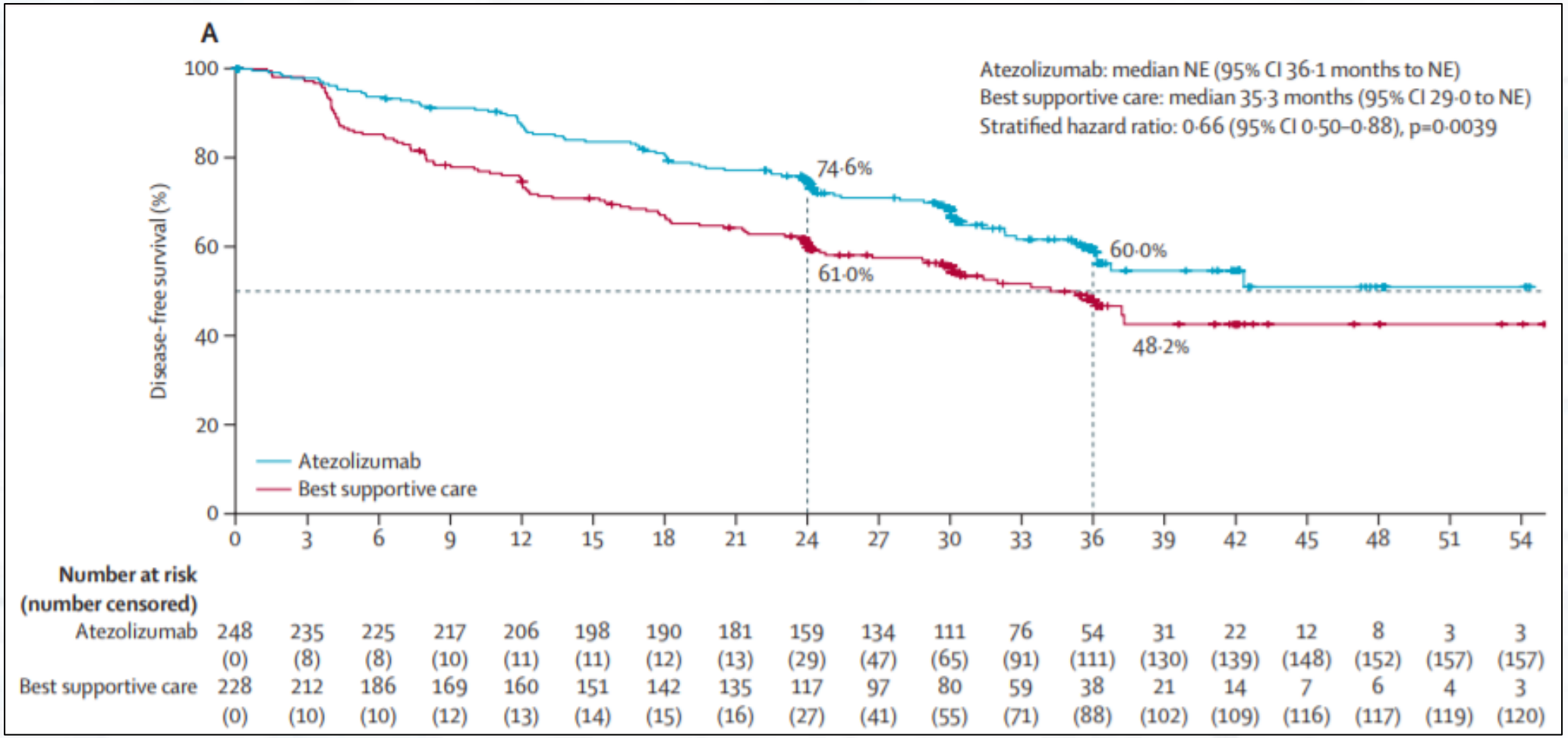
Baseline characteristics

	PD-L1 TC ≥1% stage II–IIIA group (SP263)		All stage II–IIIA group		Intention-to-treat group (stage IB–IIIA)	
	Atezolizumab (n=248)	Best supportive care (n=228)	Atezolizumab (n=442)	Best supportive care (n=440)	Atezolizumab (n=507)	Best supportive care (n=498)
Age, years	61 (56–67)	62 (56–68)	62 (56–67)	62 (55–68)	62 (57–67)	62 (56–68)
Age group						
<65 years	156 (63%)	131 (57%)	281 (64%)	263 (60%)	323 (64%)	300 (60%)
≥65 years	92 (37%)	97 (43%)	161 (36%)	177 (40%)	184 (36%)	198 (40%)
Sex						
Male	171 (69%)	147 (64%)	295 (67%)	294 (67%)	337 (66%)	335 (67%)
Female	77 (31%)	81 (36%)	147 (33%)	146 (33%)	170 (34%)	164 (33%)
Race						
White	162 (65%)	166 (73%)	307 (69%)	324 (74%)	362 (71%)	376 (76%)
Asian	78 (31%)	56 (25%)	121 (27%)	106 (24%)	130 (26%)	112 (23%)
Black or African American	2 (<1%)	0	4 (1%)	1 (<1%)	5 (1%)	1 (<1%)
Native Hawaiian or other Pacific Islander	1 (<1%)	1 (<1%)	1 (<1%)	1 (<1%)	1 (<1%)	1 (<1%)
Multiple	0	1 (<1%)	0	1 (<1%)	0	1 (<1%)
Unknown	5 (2%)	4 (2%)	9 (2%)	7 (2%)	9 (2%)	7 (1%)
ECOG performance status*						
0	140 (56%)	125 (55%)	239 (54%)	252 (57%)	273 (54%)	283 (57%)
1	107 (43%)	102 (45%)	201 (45%)	187 (43%)	232 (46%)	214 (43%)
2	1 (<1%)	1 (<1%)	2 (<1%)	1 (<1%)	2 (<1%)	1 (<1%)
Histology						
Squamous	96 (39%)	85 (37%)	150 (34%)	144 (33%)	179 (35%)	167 (34%)
Non-squamous	152 (61%)	143 (63%)	292 (66%)	296 (67%)	328 (65%)	331 (67%)
Tobacco use history						
Never	51 (21%)	41 (18%)	100 (23%)	96 (22%)	114 (23%)	108 (22%)
Previous	163 (66%)	146 (64%)	277 (63%)	270 (61%)	317 (63%)	304 (61%)
Current	34 (14%)	41 (18%)	65 (15%)	74 (17%)	76 (15%)	86 (17%)

	PD-L1 TC ≥1% stage II–IIIA group (SP263)		All stage II–IIIA group		Intention-to-treat group (stage IB–IIIA)	
	Atezolizumab (n=248)	Best supportive care (n=228)	Atezolizumab (n=442)	Best supportive care (n=440)	Atezolizumab (n=507)	Best supportive care (n=498)
(Continued from previous page)						
EGFR mutation status†						
Yes	23 (9%)	20 (9%)	49 (11%)	60 (14%)	53 (10%)	64 (13%)
No	123 (50%)	125 (55%)	229 (52%)	234 (53%)	261 (52%)	266 (53%)
Unknown	102 (41%)	83 (36%)	164 (37%)	146 (33%)	193 (38%)	168 (34%)
ALK rearrangement status†						
Yes	12 (5%)	11 (5%)	14 (3%)	17 (4%)	15 (3%)	18 (4%)
No	133 (54%)	121 (53%)	251 (57%)	256 (58%)	280 (55%)	294 (59%)
Unknown	103 (42%)	96 (42%)	177 (40%)	167 (38%)	212 (42%)	186 (37%)
PD-L1 status by SP263‡						
<1%	..	..	181 (41%)	202 (46%)	210 (41%)	234 (47%)
≥1%	248 (100%)	228 (100%)	248 (56%)	228 (52%)	283 (56%)	252 (51%)
PD-L1 status by SP142§						
TC0/1 and IC0/1	77 (31%)	66 (29%)	198 (45%)	198 (45%)	231 (46%)	231 (46%)
TC0/1 and IC2/3	66 (27%)	61 (27%)	127 (29%)	132 (30%)	146 (29%)	145 (29%)
TC2/3 and any IC	105 (42%)	101 (44%)	117 (26%)	110 (25%)	130 (26%)	122 (25%)
Stage						
IB	..	..	..	..	65 (13%)	58 (12%)
IIA	85 (34%)	76 (33%)	147 (33%)	148 (34%)	147 (29%)	148 (30%)
IIB	46 (19%)	37 (16%)	90 (20%)	84 (19%)	90 (18%)	84 (17%)
IIIA	117 (47%)	115 (50%)	205 (46%)	208 (47%)	205 (40%)	208 (42%)
Type of surgery						
Lobectomy	186 (75%)	173 (76%)	335 (76%)	340 (77%)	394 (78%)	391 (79%)
Sleeve lobectomy	3 (1%)	3 (1%)	4 (1%)	4 (<1%)	4 (<1%)	4 (<1%)
Bilobectomy	15 (6%)	9 (4%)	30 (7%)	17 (4%)	31 (6%)	19 (4%)
Pneumonectomy	43 (17%)	42 (18%)	72 (16%)	78 (18%)	77 (15%)	83 (17%)
Other	1 (<1%)	1 (<1%)	1 (<1%)	1 (<1%)	1 (<1%)	1 (<1%)

(Table 1 continues on next page)

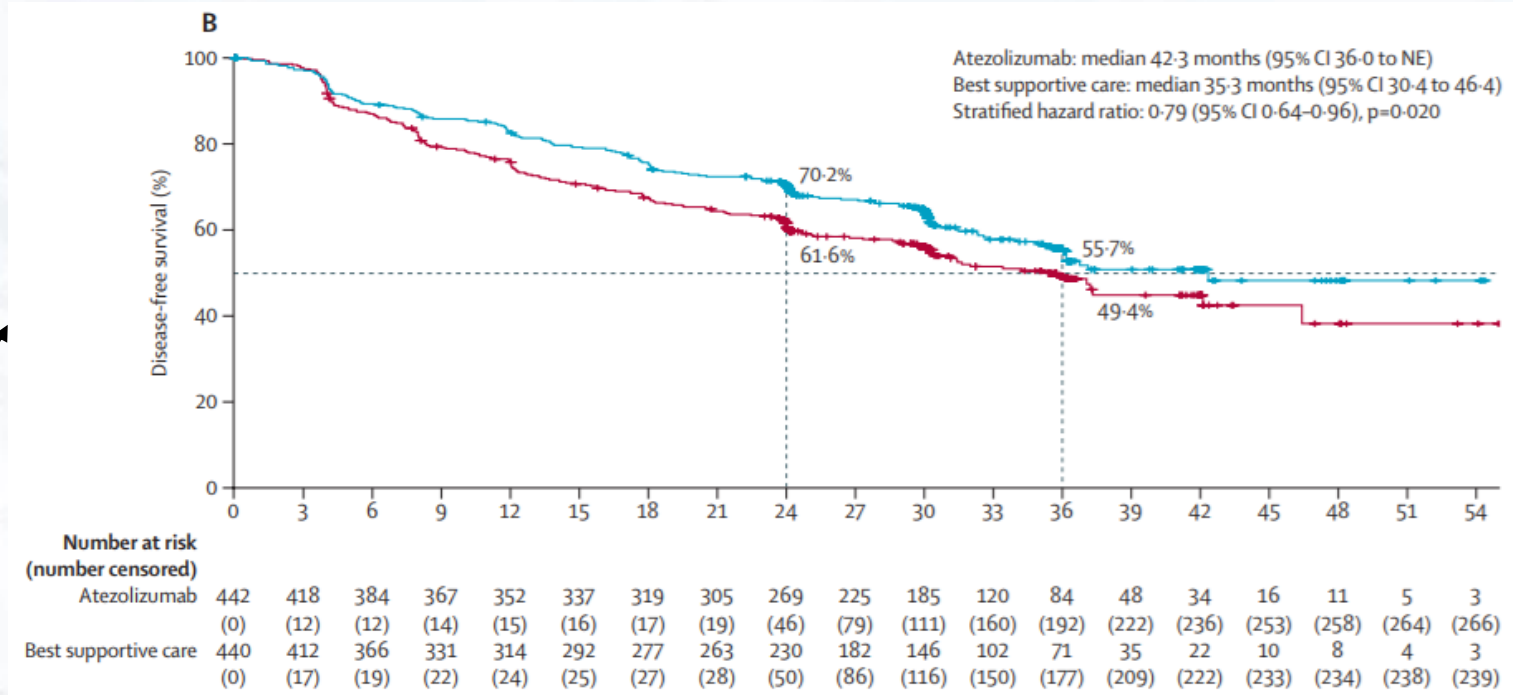
Outcomes-
PD-L1 TC ≥1% stage II–IIIA group



Outcomes

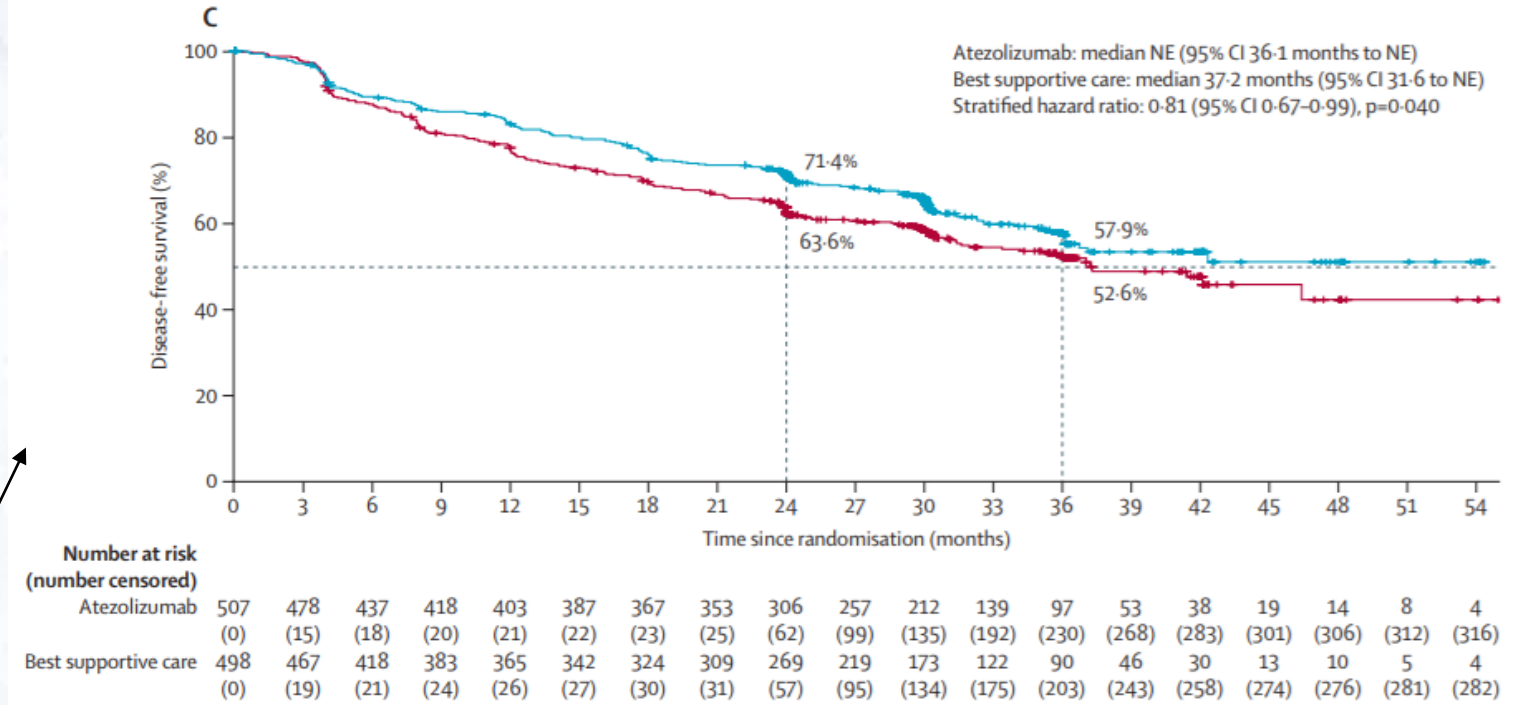
36-month disease-free survival :
Atezolizumab group: 55.7%
Placebo group: 49.4%

All stage II–IIIA group

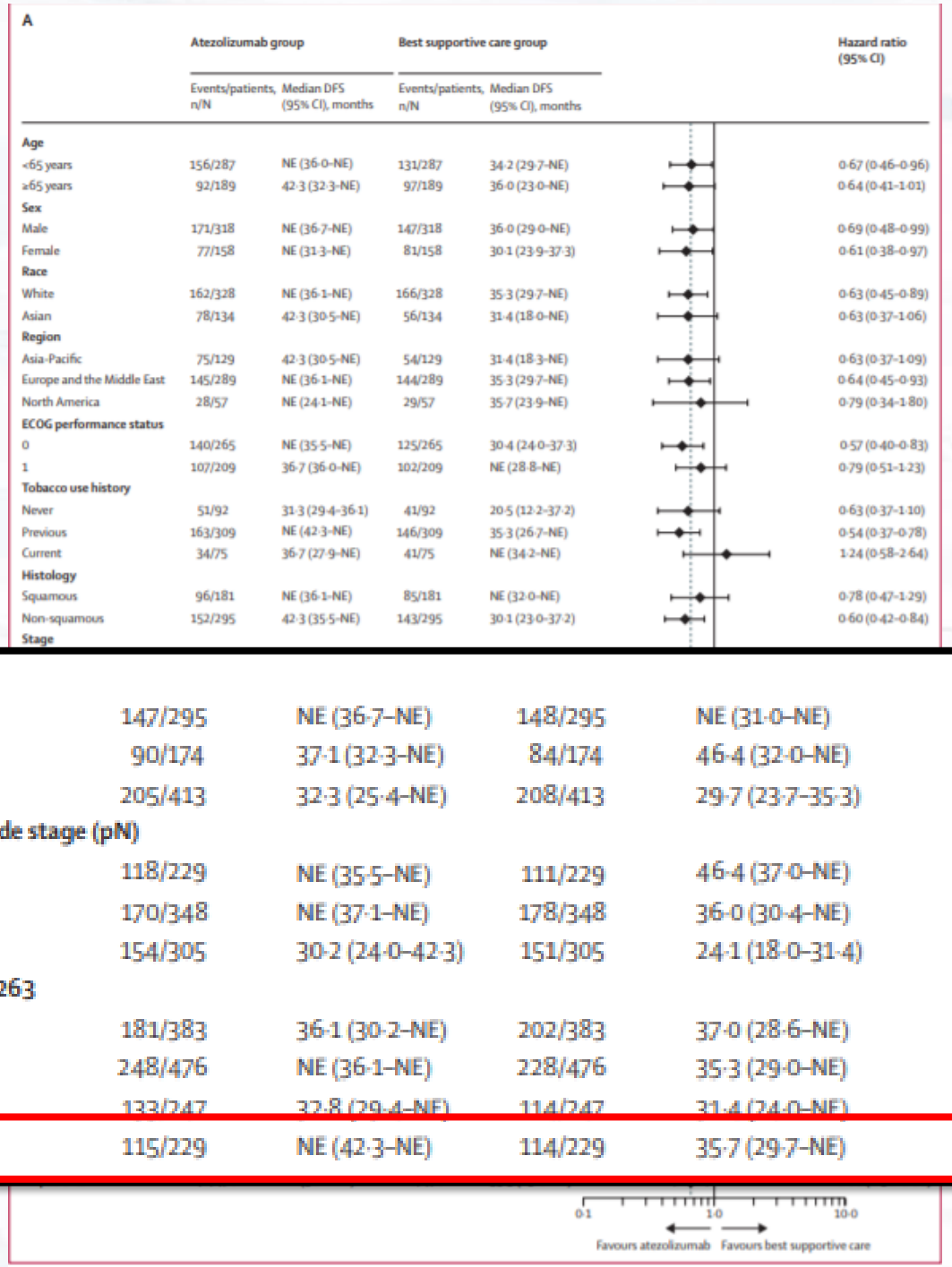


36-month disease-free survival :
Atezolizumab group: 57.9%
Placebo group: 52.6%

Intention-to-treat group



Subgroup Anaiysis



Adverse event

	Atezolizumab group (n=495)			Best supportive care group (n=495)		
	All grades	Grade 3–4	Grade 5	All grades	Grade 3–4	Grade 5
Any cause	459 (93%)	108 (22%)	8 (2%)†	350 (71%)	57 (12%)	3 (1%)‡
Cough	66 (13%)	0	0	46 (9%)	0	0
Pyrexia	65 (13%)	4 (1%)	0	11 (2%)	1 (<1%)	0
Hypothyroidism	55 (11%)	0	0	3 (1%)	0	0
Alanine aminotransferase increased	53 (11%)	8 (2%)	0	16 (3%)	1 (<1%)	0
Aspartate aminotransferase increased	53 (11%)	7 (1%)	0	16 (3%)	0	0
Arthralgia	52 (11%)	2 (<1%)	0	26 (5%)	0	0
Pruritus	51 (10%)	0	0	3 (1%)	0	0
Nasopharyngitis	33 (7%)	0	0	50 (10%)	0	0

Data are n (%). *Includes all-grade adverse events occurring in 10% or more of patients in either group, along with corresponding frequencies for grade 3–4 and grade 5 events. †Interstitial lung disease, multiple organ dysfunction syndrome, myocarditis, and acute myeloid leukaemia (all four events related to atezolizumab), and pneumothorax, cerebrovascular accident, arrhythmia, and acute cardiac failure. ‡Pneumonia; pulmonary embolism; and cardiac tamponade and septic shock in the same patient.

Table 3:* Most commonly reported adverse events in the atezolizumab or best supportive care groups

Conclusion

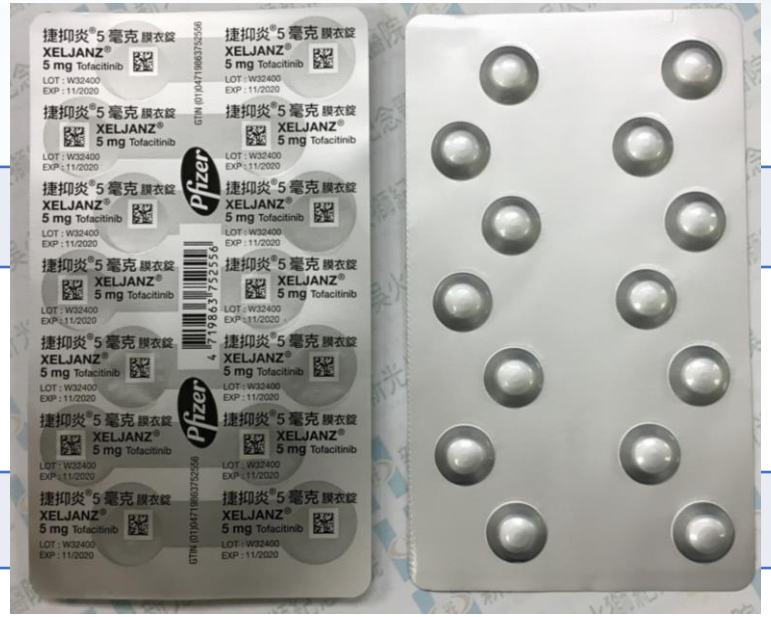
- Adjuvant atezolizumab shows a disease-free survival benefit in the stage II–IIIA population with PD-L1 TC ≥1% and in all patients in the stage II–IIIA population.

limitation

- Open-label design

Tofacitinib in juvenile idiopathic arthritis: a double-blind, placebo-controlled, withdrawal phase 3 randomised trial

Lancet 2021; 398: 1984–96



Inclusion Criteria

- aged 2-18 years
- Polyarticular course JIA

Exclusion Criteria

- systemic JIA with active systemic features other than active joints
- elevated acute-phase reactants within 6 months of enrolment
- persistent oligoarthritic
- undifferentiated JIA
- active uveitis within 3 months of enrolment

Tofacitinib in juvenile idiopathic arthritis: a double-blind, placebo-controlled, withdrawal phase 3 randomised trial

Lancet 2021; 398: 1984–96

N=225

polyarticular course JIA N=184

Tofacitinib N=72

Placebo N=70

psoriatic arthritis +enthesitis-related arthritis N=20+21

part 1 (weeks 0-18) | **part 2 (weeks 18–44)**

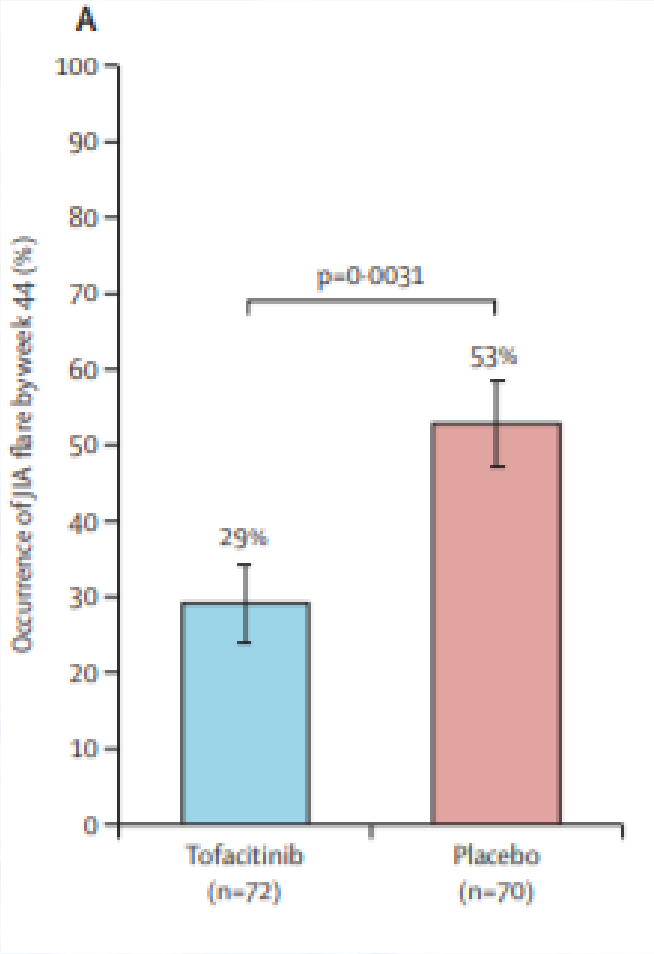
Baseline characteristics

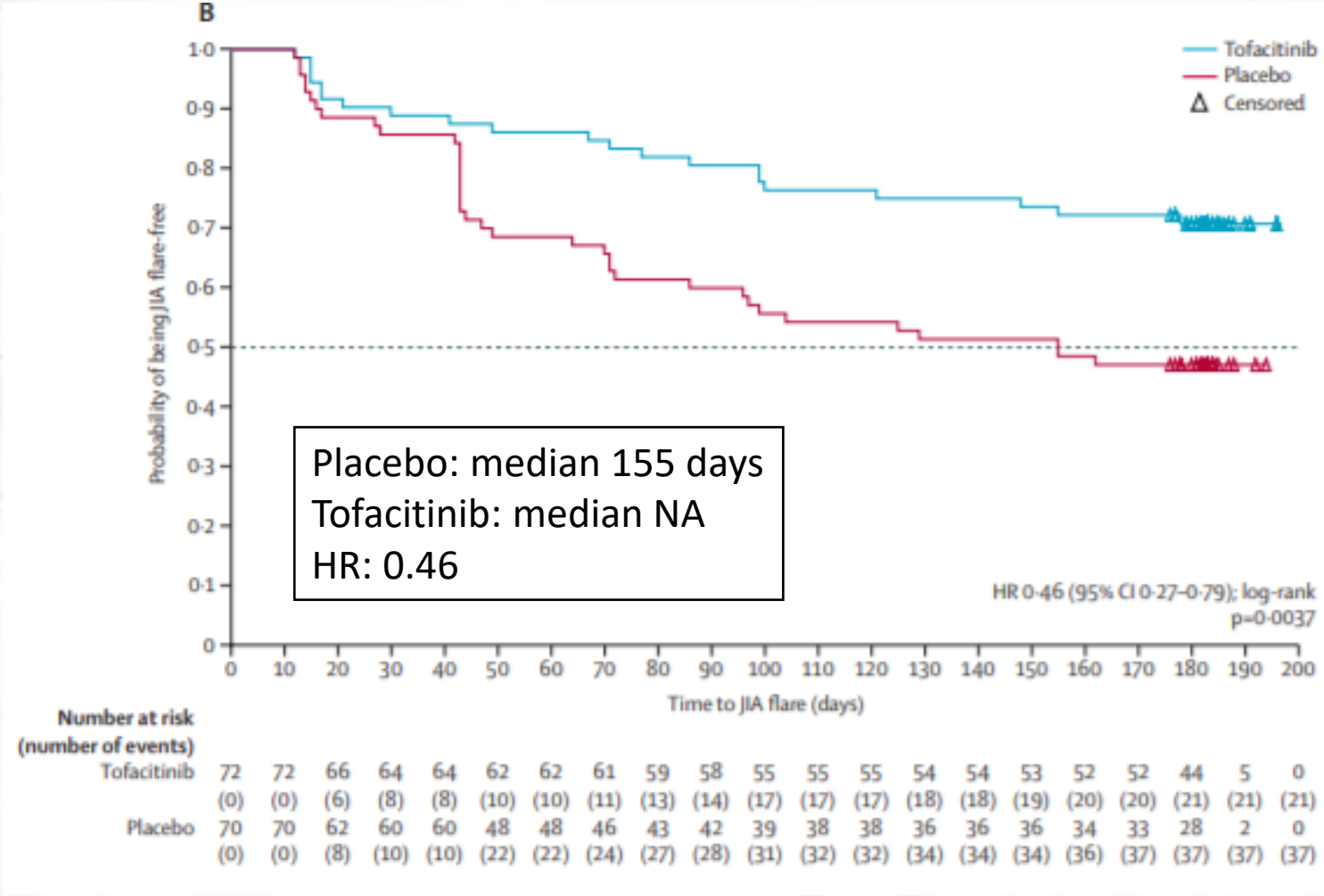
	All patients (n=225)	Patients with polyarticular course JIA enrolled for primary outcome (n=184)				Patients with psoriatic arthritis or enthesitis-related arthritis enrolled for exploratory outcomes (n=41)	
		Extended oligoarthritis (n=28)	RF-positive polyarthritis (n=39)	RF-negative polyarthritis (n=104)	Systemic JIA* (n=13)	Psoriatic arthritis (n=20)	Enthesitis-related arthritis (n=21)
Patient characteristics							
Sex							
Female	169 (75%)	19 (68%)	35 (90%)	83 (80%)	5 (38%)	15 (75%)	12 (57%)
Male	56 (25%)	9 (32%)	4 (10%)	21 (20%)	8 (62%)	5 (25%)	9 (43%)
Age, years	13·0 (9·0–15·0)	11·5 (6·5–15·0)	15·0 (12·0–16·0)	12·0 (8·0–15·0)	10·0 (8·0–14·0)	14·5 (12·0–16·0)	13·0 (11·0–16·0)
2 to <6	22 (10%)	6 (21%)	0	14 (13%)	2 (15%)	0	0
6 to <12	64 (28%)	8 (29%)	5 (13%)	34 (33%)	6 (46%)	4 (20%)	7 (33%)
12 to <18	139 (62%)	14 (50%)	34 (87%)	56 (54%)	5 (38%)	16 (80%)	14 (67%)
Age at diagnosis, years	8·0 (4·0–12·2)	3·9 (1·9–11·1)	12·8 (9·5–14·2)	6·1 (3·6–9·9)	2·5 (2·8–5·9)	12·0 (9·2–14·0)	10·1 (7·9–13·0)
Disease duration, years	2·5 (1·0–5·6)	4·0 (1·6–7·7)	1·8 (1·0–3·6)	3·5 (1·0–6·7)	5·4 (2·1–8·2)	1·5 (1·0–2·8)	1·9 (0·8–4·0)
Bodyweight, kg							
<40	84 (37%)	12 (43%)	9 (23%)	46 (44%)	9 (69%)	2 (10%)	6 (29%)
≥40	141 (63%)	16 (57%)	30 (77%)	58 (56%)	4 (31%)	18 (90%)	15 (71%)
Race							
White	196 (87%)	26 (93%)	29 (74%)	95 (91%)	11 (85%)	17 (85%)	18 (86%)
Black or African American	5 (2%)	0	3 (8%)	1 (1%)	0	0	1 (5%)
Other	24 (11%)	2 (7%)	7 (18%)	8 (8%)	2 (15%)	3 (15%)	2 (10%)
Disease activity measures							
Physician's global evaluation of overall disease activity†	6·0 (4·5–7·5)	6·8 (4·8–7·5)	6·5 (5·5–7·5)	6·5 (4·8–7·8)	7·5 (5·5–8·0)	5·0 (4·0–7·0)	6·0 (4·5–7·0)
Number of joints with active arthritis‡	10·0 (6·0–15·0)	7·0 (5·0–11·0)	11·0 (8·0–19·0)	10·0 (7·0–18·0)	9·0 (7·0–15·0)	11·0 (4·5–15·5)	7·0 (5·0–11·0)
Number of joints with limitation of motion§	6·0 (3·0–10·0)	5·0 (2·5–7·5)	4·0 (2·0–9·0)	6·0 (4·0–11·0)	9·0 (7·0–15·0)	5·0 (3·0–8·0)	5·0 (3·0–7·0)
CHAQ-DI score¶	0·9 (0·3–1·5)	1·0 (0·3–1·6)	1·3 (0·4–1·9)	0·8 (0·3–1·4)	1·6 (1·3–2·0)	0·5 (0·3–0·8)	0·6 (0·4–1·3)
Patient or parent assessment of overall wellbeing‖	5·0 (3·0–7·0)	5·8 (4·0–7·0)	5·0 (2·5–6·0)	5·0 (3·0–7·0)	5·5 (3·5–8·0)	4·0 (3·0–6·5)	5·0 (2·5–6·5)
JADAS**	20·1 (16·2–26·6)	20·6 (16·6–24·6)	22·2 (18·8–26·9)	20·7 (16·6–28·8)	23·7 (17·2–27·2)	15·5 (13·6–19·6)	16·6 (13·2–18·7)
Duration of morning stiffness, min	30·0 (15·0–60·0)	30·0 (7·5–75·0)	30·0 (20·0–60·0)	30·0 (15·5–60·0)	45·0 (30·0–60·0)	30·0 (10·0–60·0)	30·0 (15·0–60·0)
Laboratory parameters							
CRP††, mg/dL	0·3 (0·1–1·0)	0·2 (0·1–0·9)	0·6 (0·1–1·6)	0·2 (0–0·9)	0·6 (0·2–2·6)	0·2 (0·1–0·5)	0·1 (0–0·9)
ESR‡‡, mm/h	17·0 (10·0–32·0)	18·5 (10·0–32·5)	26·0 (10·0–40·0)	16·0 (10·0–26·5)	25·0 (8·0–45·0)	14·0 (10·0–28·5)	12·0 (7·0–29·0)

Data are median (IQR) or n (%). CHAQ-DI=Childhood Healthcare Questionnaire-Disability Index. CRP=C-reactive protein. ESR=erythrocyte sedimentation rate. JADAS=Juvenile Arthritis Disease Activity Score in 27 joints, based on CRP. JIA=juvenile idiopathic arthritis. RF=rheumatoid factor. *Without active systemic features at enrolment. †Scores could range from 0 to 10, with higher scores indicating more disease activity.[11] ‡71 joints were assessed.[11] §67 joints were assessed.[11] ¶Scores could range from 0 to 3, with higher scores indicating more disability.[11] ‖Scores could range from 0 to 10, with higher scores indicating worse wellbeing.[11] **Scores could range from 0 to 57, with higher scores indicating more disease activity.[11] ††Normal reference range was 0·0–2·87 mg/dL. ‡‡Normal reference range was 0–20 mm/h.

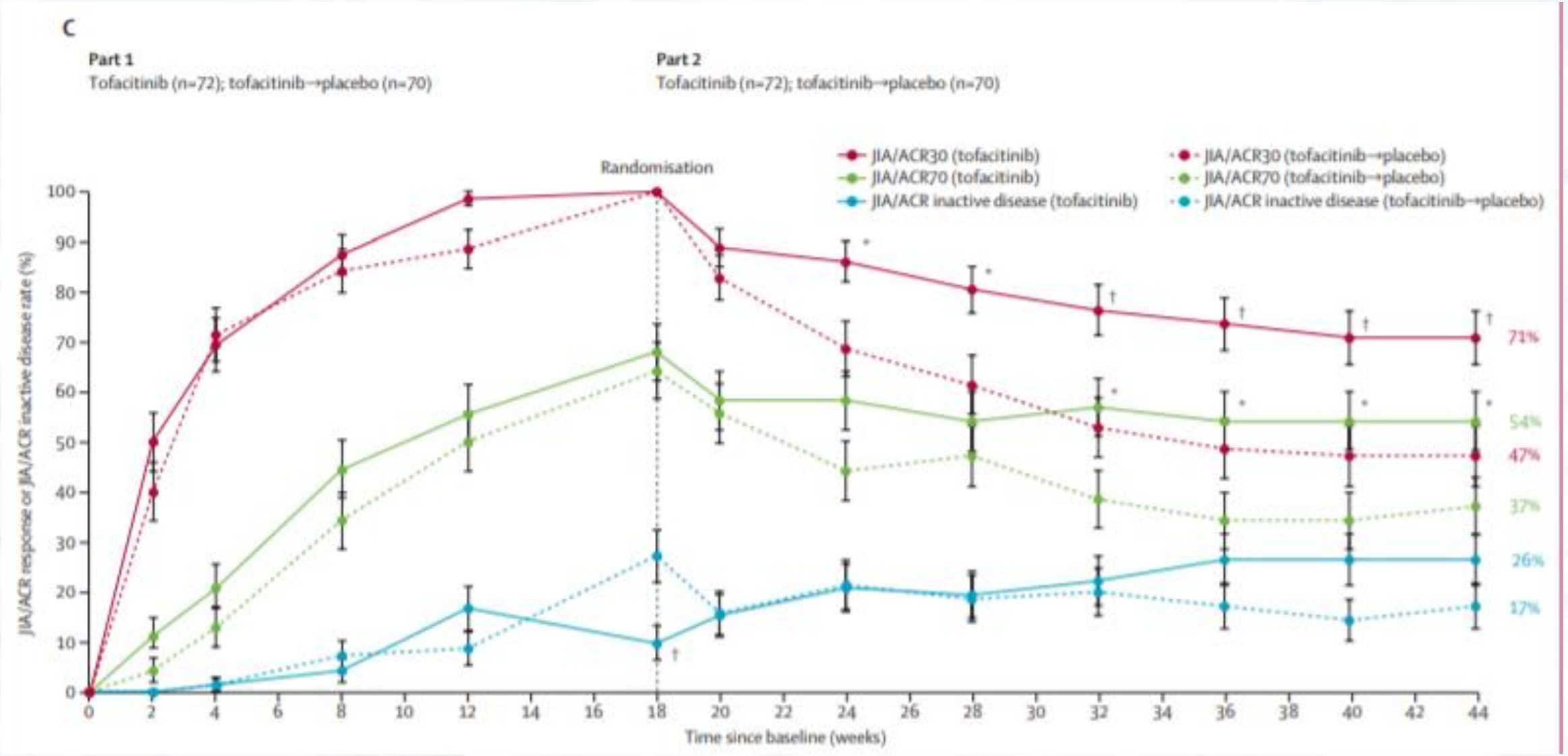
Table 1: **Demographic and baseline disease characteristics of patients receiving tofacitinib in part 1, overall, and stratified by JIA category**

Primary Outcomes

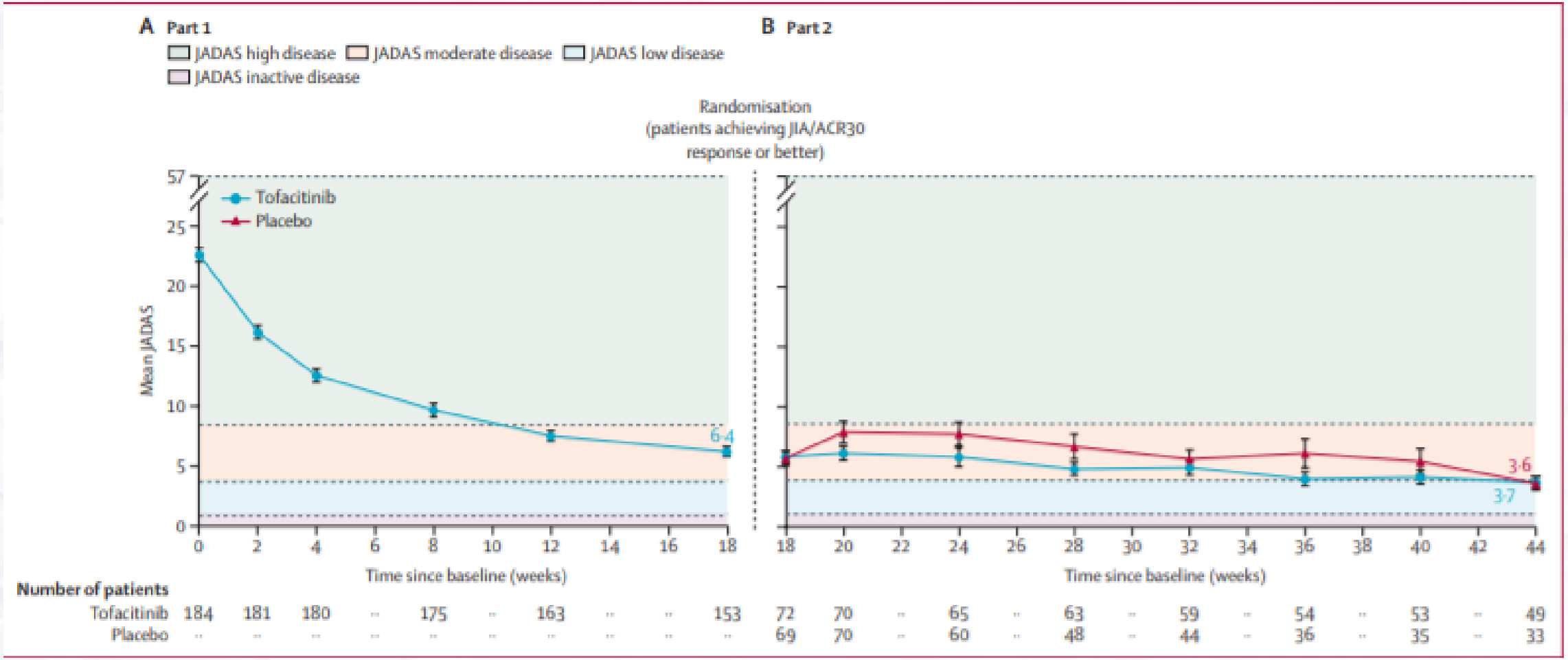




Primary Outcomes



Outcomes


A Part 1
JADAS high disease
JADAS moderate disease
JADAS low disease
JADAS inactive disease
B Part 2
Randomisation
(patients achieving JIA/ACR30
response or better)
Tofacitinib
Placebo
Mean JADAS
57
25
20
15
10
5
0
6·4
3·6
3·7
0 2 4 6 8 10 12 14 16 18
18 20 22 24 26 28 30 32 34 36 38 40 42 44
Time since baseline (weeks)
Time since baseline (weeks)
Number of patients
Tofacitinib 184 181 180 .. 175 .. 163 .. .. 153 72 70 .. 65 .. 63 .. 59 .. 54 .. 53 .. 49
Placebo .. .. 69 70 .. 60 .. 48 .. 44 .. 36 .. 35 .. 33

Adverse event

	Part 1	Part 2		Entire tofacitinib exposure period*
	Tofacitinib (n=225)	Tofacitinib (n=88)	Placebo (n=85)	Tofacitinib (n=225)
Adverse events	153 (68%)	68 (77%)	63 (74%)	189 (84%)
Incidence rate per 100 patient-years (95% CI)	..	371·7 (288·6–471·2)	417·8 (321·0–534·5)	394·0 (339·9–454·4)
Serious adverse events	7 (3%)	1 (1%)	2 (2%)	9 (4%)
Incidence rate per 100 patient-years (95% CI)	..	2·4 (0·1–13·4)	6·0 (0·7–21·8)	7·3 (3·4–13·9)
Severe adverse events	5 (2%)	0	3 (4%)	5 (2%)
Permanent discontinuation from study due to adverse events	26 (12%)	16 (18%)	29 (34%)	49 (22%)
Incidence rate per 100 patient-years (95% CI)	..	39·6 (22·6–64·3)	94·2 (63·1–135·3)	40·9 (30·3–54·1)
Temporary dose reduction or temporary hold due to adverse events	20 (9%)	9 (10%)	8 (9%)	25 (11%)
Most common adverse events by preferred term (≥10% in any treatment group)				
Upper respiratory tract infection	24 (11%)	13 (15%)	9 (11%)	34 (15%)
Disease progression	5 (2%)	8 (9%)	13 (15%)	13 (6%)
JIA exacerbation	6 (3%)	3 (3%)	12 (14%)	9 (4%)
Adverse events of special interest†				
Deaths	0	0	0	0
Hepatic events‡	3 (1%)	0	0	3 (1%)
Herpes zoster (non-serious and serious)‡§	2 (1%)	0	0	2 (1%)
Incidence rate per 100 patient-years (95% CI)	..	..	..	1·6 (0·2–5·9)
Serious infection	3 (1%)	1 (1%)¶	1 (1%)	4 (2%)¶
Incidence rate per 100 patient-years (95% CI)	..	..	3·0 (0·1–16·8)	2·4 (0·5–7·1)
Creatine kinase >2·0 × ULN	12/224 (5%)	2 (2%)	2 (2%)	13/224 (6%)
Haemoglobin <0·8 × LLN	1/224 (<0·5%)	1/87 (1%)	3 (4%)	2/224 (1%)
Lymphocytes >1·2 × ULN	2/224 (1%)	1/87 (1%)	0	3/224 (1%)
Neutrophils >1·2 × ULN	18/224 (8%)	7/87 (8%)	5 (6%)	19/224 (8%)
AST ≥1·0 × ULN	25 (11%)	12 (14%)	9 (11%)	35 (16%)
ALT ≥1·0 × ULN	33 (15%)	14 (16%)	11 (13%)	37 (16%)
HDL cholesterol <0·8 × LLN	2/223 (1%)	0‖	2/61 (3%)	2/223 (1%)
LDL cholesterol >1·2 × ULN	4/87 (5%)	0**	0††	4/87 (5%)
Cholesterol >1·3 × ULN	2/223 (1%)	0‡‡	0§§	2/223 (1%)

Adverse event

	Part 1		Part 2	
	Tofacitinib (n=225)		Tofacitinib (n=88)	Placebo (n=85)
	Baseline	Week 18	Week 44	Week 44
Creatine kinase, U/L	72·0 (45·0–96·0)	97·0 (72·0–130·0)*	104·0 (83·0–159·0)†	80·0 (56·0–109·0)‡
Haemoglobin, g/dL	12·4 (11·7–13·3)	12·8 (12·0–13·4)§	12·6 (12·2–13·2)¶	12·6 (12·3–13·5)‡
Lymphocytes, 10^3 cells per mm^3	2·1 (1·7–2·6)	2·0 (1·6–2·6)§	1·9 (1·6–2·4)¶	1·8 (1·7–2·4)‡
Neutrophils, 10^3 cells per mm^3	4·4 (3·1–5·6)	3·8 (2·9–5·1)§	3·6 (2·9–4·4)¶	3·6 (2·8–4·5)‡
AST, U/L	20·0 (17·0–24·0)	22·0 (18·0–26·0)‖	23·0 (19·0–28·0)†	19·5 (17·0–26·0)‡
ALT, U/L	13·0 (10·0–17·0)	13·0 (11·0–19·0)*	15·0 (12·0–20·0)†	13·0 (11·0–18·0)‡
HDL cholesterol, mg/dL	50·1 (42·9–57·9)**	55·6 (47·5–64·1)††	54·8 (47·5–64·1)†	48·5 (44·8–52·0)‡
Indirect LDL cholesterol, mg/dL	81·0 (64·0–94·0)**	81·9 (67·2–100·0)*	84·7 (68·0–106·9)†	79·0 (57·9–101·0)‡
Cholesterol, mg/dL	151·0 (131·0–169·5)‡‡	158·0 (139·8–179·0)††	157·9 (143·0–185·3)§§	150·0 (130·9–177·0)‡

Data are median (IQR). ALT=alanine aminotransferase. AST=aspartate aminotransferase. JIA=juvenile idiopathic arthritis. *Assessed in 186 patients. †Assessed in 58 patients. ‡Assessed in 38 patients. §Assessed in 176 patients. ¶Assessed in 57 patients. ‖Assessed in 183 patients. **Assessed in 222 patients. ††Assessed in 187 patients. ‡‡Assessed in 223 patients. §§Assessed in 59 patients.

Table 3: **Summary of laboratory values in patients with polyarticular course JIA, psoriatic arthritis, or enthesitis-related arthritis**

Conclusion

- Tofacitinib is an effective treatment in patients with polyarticular course JIA

limitation

- Population was relatively small and predominantly White
- The follow-up length of this trial in patients with JIA was too short to assess long-term safety

Safety and immunogenicity of concomitant administration of COVID-19 vaccines (ChAdOx1 or BNT162b2) with seasonal influenza vaccines in adults in the UK (ComFluCOV): a multicentre, randomised, controlled, phase 4 trial

Lancet 2021; 398: 2277

Inclusion Criteria

- ≥ 18
- Had

接種注意事項

1. **發燒或正患有急性中重度疾病者，宜待病情穩定後再接種。**
2. 本疫苗不得與其他廠牌交替使用。若不慎使用了兩劑不同COVID-19疫苗產品時，不建議再接種任何一種產品。
3. 目前尚無資料顯示與其他疫苗同時接種對免疫原性與安全性的影響。**COVID-19 疫苗與其他疫苗的接種間隔，建議間隔至少7天**。如小於上述間隔，則各該疫苗亦無需再補種。
4. 免疫功能低下者，包括接受免疫抑制劑治療的人，對疫苗的免疫反應可能減弱。(尚無免疫低下者或正在接受免疫抑制治療者的數據)
5. 目前沒有足夠數據建議孕婦可常規接種COVID-19疫苗，惟若為高感染風險可能因罹患COVID-19導致嚴重併發症的情形，可經醫師評估是否接種疫苗。
6. 若哺乳中的婦女為建議接種之風險對象(如醫事人員)，應完成接種。目前對哺乳中的婦女接種COVID-19疫苗的安全性、疫苗對母乳或受哺嬰兒之影響尚未完全得到評估，但一般認為並不會造成相關風險。接種COVID-19疫苗後，仍可持續哺乳。

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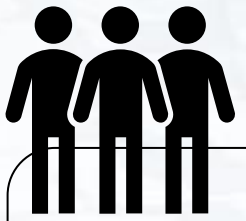
Exclus

- Had
- Had
- Hist
- Blee
- Drug or alcohol dependence, or a progressive neurological disorder

Randomised



N=679

ChAdOx1 + inactivated quadrivalent
N=129

BNT162b2 + inactivated quadrivalent
N=139

ChAdOx1 + inactivated trivalent
N=146

BNT162b2 + inactivated trivalent
N=79

ChAdOx1 + recombinant quadrivalent
N=128

BNT162b2 + recombinant quadrivalent
N=58

Baseline characteristics

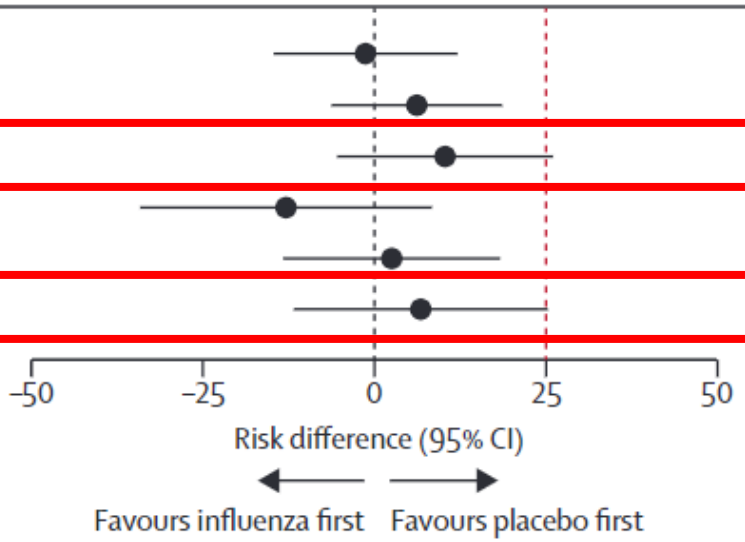
	ChAdOx1 plus cellular quadrivalent vaccine		BNT162b2 plus cellular quadrivalent vaccine		ChAdOx1 plus MF59C adjuvanted, trivalent vaccine		BNT162b2 plus MF59C adjuvanted, trivalent vaccine		ChAdOx1 plus recombinant quadrivalent vaccine		BNT162b2 plus recombinant quadrivalent vaccine	
	Placebo first (n=64)	Flu first (n=65)	Placebo first (n=71)	Flu first (n=68)	Placebo first (n=73)	Flu first (n=73)	Placebo first (n=38)	Flu first (n=41)	Placebo first (n=64)	Flu first (n=64)	Placebo first (n=29)	Flu first (n=29)
Age at screening, years	54 (43–61)	52 (40–57)	47 (34–58)	48 (35–60)	71 (69–72)	69 (67–72)	68 (67–70)	68 (67–70)	52 (44–60)	56 (51–60)	39 (33–47)	42 (31–53)
Sex												
Female	38 (59%)	43 (66%)	48 (68%)	51 (75%)	31 (42%)	44 (60%)	14 (37%)	24 (59%)	37 (58%)	34 (53%)	15 (52%)	18 (62%)
Male	26 (41%)	22 (34%)	23 (32%)	17 (25%)	42 (58%)	29 (40%)	24 (63%)	17 (41%)	27 (42%)	30 (47%)	14 (48%)	11 (38%)
Body-mass index, kg/m²	27 (24–29)	28 (25–35)	27 (23–34)	27 (24–31)	27 (24–30)	28 (26–32)	28 (25–31)	28 (26–31)	29 (24–33)	31 (26–37)	26 (23–29)	27 (25–29)
Ethnicity												
English, Welsh, Scottish, Northern Irish, or British	57 (89%)	54 (83%)	65 (92%)	60 (88%)	70 (96%)	71 (97%)	38 (100%)	39 (95%)	59 (92%)	64 (100%)	25 (86%)	25 (86%)
White Irish	2 (3%)	2 (3%)	2 (3%)	0	1 (1%)	0	0	0	0	0	0	0
Any other White background	3 (5%)	2 (3%)	2 (3%)	3 (4%)	1 (1%)	1 (1%)	0	2 (5%)	1 (2%)	0	2 (7%)	3 (10%)
White and Asian	0	1 (2%)	0	0	0	0	0	0	1 (2%)	0	0	0
Any other mixed or multiple ethnic background	0	3 (5%)	1 (1%)	2 (3%)	1 (1%)	1 (1%)	0	0	0	0	0	0
Indian	1 (2%)	3 (5%)	0	2 (3%)	0	0	0	0	0	0	1 (3%)	1 (3%)
Pakistani	1 (2%)	0	0	0	0	0	0	0	1 (2%)	0	0	0
Chinese	0	0	0	0	0	0	0	0	1 (2%)	0	0	0
Any other ethnic group	0	0	0	1 (1%)	0	0	0	0	1 (2%)	0	1 (3%)	0
Prefer not to give	0	0	1 (1%)	0	0	0	0	0	0	0	0	0
Occupation												
Employed—health-care worker	15 (23%)	18 (28%)	19 (27%)	21 (31%)	0	0	1 (3%)	0	3 (5%)	3 (5%)	5 (17%)	1 (3%)
Employed— other	30 (47%)	34 (52%)	35 (49%)	33 (49%)	4 (5%)	6 (8%)	7 (18%)	4 (10%)	39 (61%)	43 (67%)	18 (62%)	22 (76%)
Unemployed	4 (6%)	3 (5%)	3 (4%)	2 (3%)	0	0	1 (3%)	0	3 (5%)	3 (5%)	3 (10%)	2 (7%)
Student	2 (3%)	0	4 (6%)	3 (4%)	0	0	0	0	5 (8%)	0	2 (7%)	2 (7%)
Retired	13 (20%)	10 (15%)	10 (14%)	9 (13%)	69 (95%)	67 (92%)	29 (76%)	37 (90%)	14 (22%)	15 (23%)	1 (3%)	2 (7%)
Participant received influenza vaccination in winter 2020–21 programme	48 (75%)	48 (74%)	52 (73%)	55 (81%)	72 (99%)	70 (96%)	35 (92%)	40 (98%)	41 (64%)	52 (81%)	22 (76%)	13 (45%)

Data are median (IQR) or n (%). Placebo first indicates that COVID-19 vaccine alone was received at day 0. Flu first indicates that concomitant COVID-19 and influenza vaccines were received at day 0.

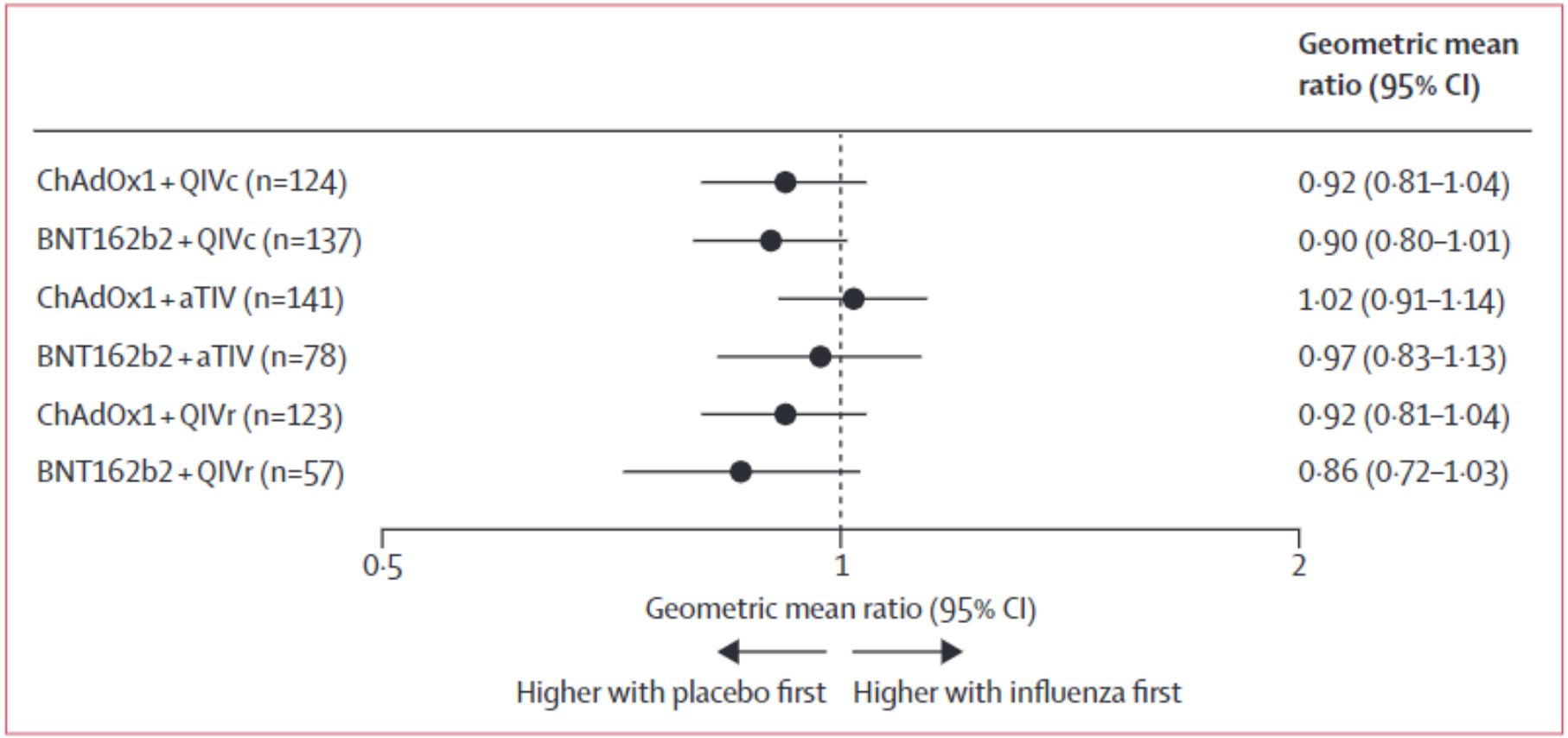
Table: **Participant demographics**

Primary Outcome- Systemic adverse reactions

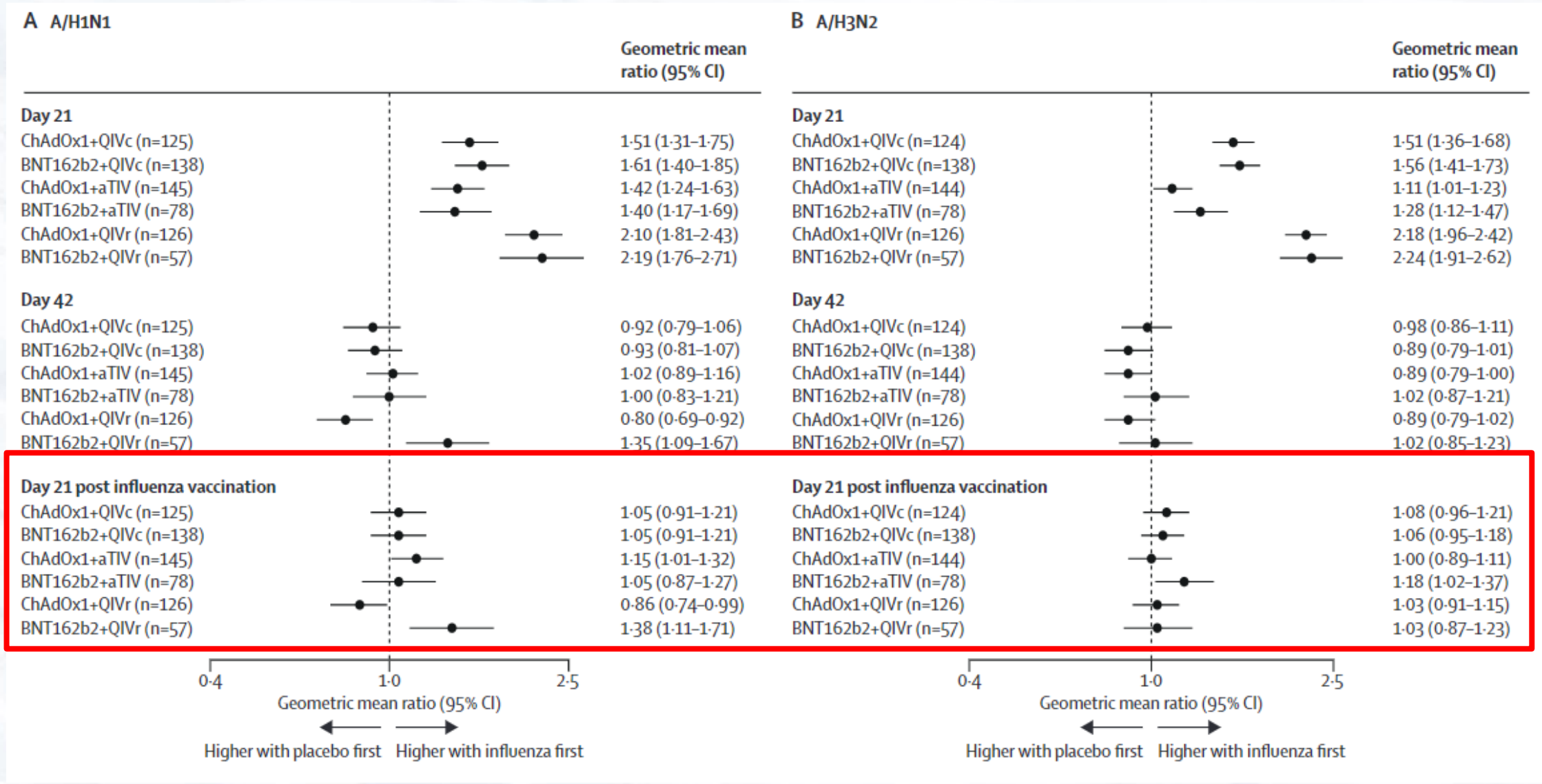
	Number of participants experiencing one or more solicited systemic events in the 7 days after second COVID-19 vaccination/ number of participants with the primary outcome in each group for each cohort		Risk difference (95% CI)
	Placebo first	Influenza first	
ChAdOx1+QIVc ITT	52/63	52/64	−1·29 (−14·69 to 12·11)
BNT162b2+QIVc ITT	54/67	59/68	6·17 (−6·27 to 18·61)
ChAdOx1+aTIV ITT	42/68	49/68	10·29 (−5·44 to 26·03)
BNT162b2+aTIV ITT	25/35	24/41	−12·89 (−34·15 to 8·37)
ChAdOx1+QIVr ITT	43/60	46/62	2·53 (−13·25 to 18·31)
BNT162b2+QIVr ITT	23/28	24/27	6·75 (−11·75 to 25·25)



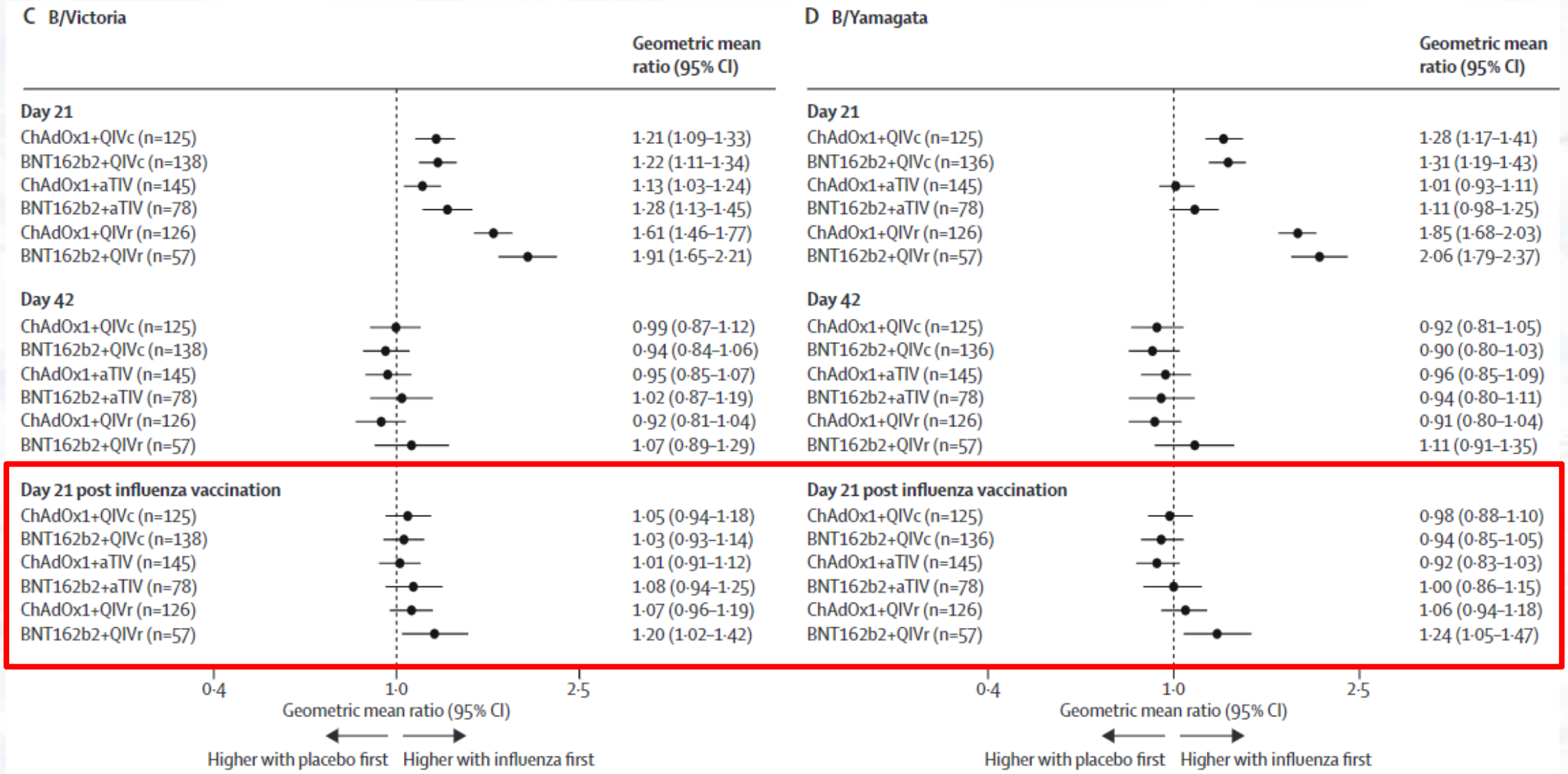
Secondary Outcome-
Anti-spike immunoglobulin (Covid-19)



Secondary Outcome- haemagglutinin antibody inhibition (Influenza)



Secondary Outcome- haemagglutinin antibody inhibition (Influenza)



Conclusion

- Concomitant vaccination with ChAdOx1 or BNT162b2 plus an age-appropriate influenza vaccine raises no safety concerns and preserves antibody responses to both vaccines

limitation

- Not known whether these findings would apply to other vaccines or not
- Influenza vaccine cause more local reactions than placebo
- Two of the cohorts had lower recruitment than planned
- T-cell responses were not evaluated

Factor VIII Inhibitor Bypassing Activity (FEIBA) Reversal for Apixaban and Rivaroxaban in Patients With Acute Intracranial and Nonintracranial Hemorrhage

Annals of Pharmacotherapy 2021, Vol. 55(12) 1455–1466

Inclusion Criteria
• patients 18 to 89 years old • ≥1 FEIBA doses in the hospital ED or inpatient setting • Apixaban or rivaroxaban presumably within 48 hours of FEIBA
Exclusion Criteria
• had a thrombosis history • prisoners, pregnant, outside the age range • received FEIBA for non-FXa inhibitor reversal (hemophilia) • had documented anticoagulant agent beyond 48 hours of presentation • had FEIBA use preoperatively for emergent procedures not specifically indicated for active bleeding reversal

	Full Cohort (N = 104)	Apixaban (n = 62)	Rivaroxaban (n = 42)	*P* value
Age, years (mean ± SD)	74.1 ± 9.9	74.9 ± 9.2	73.0 ± 10.9	0.3313
Male	59 (56.7)	37 (59.7)	22 (52.4)	0.4612
Weight, kg (mean ± SD)	92.1 ± 26.3	93.3 ± 27.3	90.1 ± 25.2	0.5191
Caucasian (non-Hispanic)	96 (92.3)	57 (91.9)	39 (92.9)	1.0000[b]
Past medical history				
Heart failure	35 (33.7)	23 (37.1)	12 (28.6)	0.3666
Hypertension	86 (82.7)	51 (82.3)	35 (83.3)	0.8869
CAD	44 (42.3)	26 (41.9)	18 (42.9)	0.9256
MI	14 (13.5)	9 (14.5)	5 (11.9)	0.7018
COPD	25 (24.0)	15 (24.2)	10 (23.8)	0.9641
Hyperlipidemia	72 (69.2)	42 (67.7)	30 (71.4)	0.6894
Diabetes mellitus	44 (42.3)	26 (41.9)	18 (42.9)	0.9256
Ischemic stroke	24 (23.1)	16 (25.8)	8 (19.0)	0.4221
Hemorrhagic stroke	11 (10.6)	9 (14.5)	2 (4.8)	0.1925
CKD	31 (29.8)	22 (35.5)	9 (21.4)	0.1242
Cirrhosis	1 (1.0)	1 (1.6)	0 (0.0)	1.0000[b]
Peripheral arterial disease	11 (10.6)	5 (8.1)	6 (14.3)	0.3447[b]
Apixaban				NA
2.5 mg bid		7 (11.3)		
5 mg bid		55 (88.7)		
Rivaroxaban				NA
15 mg daily			6 (14.3)	
20 mg daily			36 (85.7)	
Antiplatelet agents	**34 (32.7)**	**23 (37.1)**	**11 (26.2)**	0.2447
Aspirin	22 (64.7)	15 (65.2)	7 (63.6)	
Clopidogrel	2 (5.9)	1 (4.3)	1 (9.1)	
Aspirin and clopidogrel	3 (8.8)	3 (13.0)	0 (0.0)	
Nonselective NSAID	5 (14.7)	3 (13.0)	2 (18.2)	
Celecoxib	2 (5.9)	1 (4.3)	1 (9.1)	
Anticoagulant indication				
Atrial fibrillation	94 (90.4)	59 (95.2)	35 (83.3)	0.0855[b]
VTE treatment	9 (8.7)	2 (3.2)	7 (16.7)	**0.0288**[b]
VTE prophylaxis	5 (4.8)	3 (4.8)	2 (4.8)	1.0000[b]
Other indication[c]	2 (1.9)	1 (1.6)	1 (2.4)	1.0000[b]
Admitting service				0.4627[b]
Trauma	32 (30.8)	22 (35.5)	10 (23.8)	
Neurosurgery/Neurocritical care	35 (33.7)	18 (29.0)	17 (40.5)	
General surgery	4 (3.9)	3 (4.8)	1 (2.4)	
Medical intensive care	8 (7.7)	6 (9.7)	2 (4.8)	
Internal medicine	21 (20.2)	10 (16.1)	11 (26.2)	
Other admitting service (cardiac surgery, vascular surgery, cardiology, or urology)	4 (3.9)	3 (4.8)	1 (2.4)	
Baseline serum creatinine, mg/dL (mean ± SD)	1.2 ± 0.5	1.3 ± 0.5	1.0 ± 0.4	**0.0133**
Baseline hemoglobin, g/dL (mean ± SD)	11.9 ± 2.8	12.0 ± 2.6	11.7 ± 3.0	0.5889
Baseline Glasgow Coma Scale score				0.7042[b]
13-15	84 (80.8)	50 (80.6)	34 (81.0)	
9-12	10 (9.6)	5 (8.1)	5 (11.9)	
≤8	10 (9.6)	7 (11.3)	3 (7.1)	
Hemorrhage type				0.2643
Intracranial hemorrhage	55 (52.9)	30 (48.4)	25 (59.5)	
Nonintracranial hemorrhage	49 (47.1)	32 (51.6)	17 (40.5)	

	Full Cohort (N = 104)	Apixaban (n = 62)	Rivaroxaban (n = 42)	*P* value
Intracranial hemorrhage types	n = 55	n = 30	n = 25	0.4906
Spontaneous	28 (50.9)	14 (46.7)	14 (56.0)	
Traumatic	27 (49.1)	16 (53.3)	11 (44.0)	
Non-intracranial hemorrhage types	n = 49	n = 32	n = 17	0.2643
Spontaneous bleeding event	**28 (57.1)**	**17 (53.1)**	**11 (64.7)**	
Gastrointestinal	20 (71.4)	11 (64.7)	9 (81.8)	
Genitourinary	1 (3.6)	1 (5.9)	0 (0.0)	
Retroperitoneal	3 (10.7)	2 (11.8)	1 (9.1)	
Other	4 (14.3)	3 (17.7)	1 (9.1)	
Traumatic bleeding event	**21 (42.9)**	**15 (46.9)**	**6 (35.3)**	
Fall	11 (52.4)	9 (60.0)	2 (33.3)	
Motor vehicle accident	9 (42.9)	5 (33.3)	4 (66.7)	
Traumatic foley catheter removal	1 (4.8)	1 (6.7)	0 (0.0)	
Relative time between FXa inhibitor dose and FEIBA, to extent charted				0.4721[b]
<12 Hours	18 (17.3)	9 (14.5)	9 (21.4)	
12-24 Hours	12 (11.5)	8 (12.9)	4 (9.5)	
≤24 Hours	2 (1.9)	1 (1.6)	1 (2.4)	
25-48 Hours	4 (3.9)	1 (1.6)	3 (7.1)	
Active use but time not stated	68 (65.4)	43 (69.4)	25 (59.5)	
FEIBA dose, units (median [25th, 75th percentile])	4381 [3470, 4891]	4407 [3535, 4868]	4329 [3440, 4990]	0.7961
FEIBA weight-based dose, U/kg (median [25th, 75th percentile])	49.3 [46.5, 51.2]	48.7 [45.5, 51.2]	50.0 [47.9, 51.4]	0.2241
Blood product recipients within 24 hours pre-FEIBA/post-FEIBA				
PRBC before	24 (23.1)	14 (22.6)	10 (23.8)	0.8840
PRBC after	25 (24.0)	13 (21.0)	12 (28.6)	0.3733
FFP before	3 (2.9)	2 (3.2)	1 (2.4)	1.0000[b]
FFP after	5 (4.8)	1 (1.6)	4 (9.5)	0.1551[b]
Cryoprecipitate before	0 (0)	0 (0)	0 (0)	NA
Cryoprecipitate after	2 (1.9)	1 (1.6)	1 (2.4)	1.0000[b]
Platelets before	3 (2.9)	0 (0)	3 (7.1)	0.0630[b]
Platelets after	7 (6.7)	3 (4.8)	4 (9.5)	0.4363[b]
Additional product recipients				
Second FEIBA dose	2 (1.9)	1 (1.6)	1 (2.4)	1.0000[b]
Kcentra	5 (4.8)	2 (3.2)	3 (7.1)	0.3911[b]
NOVOSEVEN RT	0 (0)	0 (0)	0 (0)	NA
Profilnine	0 (0)	0 (0)	0 (0)	NA
DDAVP	8 (7.7)	4 (6.4)	4 (9.5)	0.7116[b]
Tranexamic acid	4 (3.9)	3 (4.8)	1 (2.4)	0.6459[b]
Duration of hospitalization, days (median [25th, 75th percentile])	4.7 [2.7, 8.6]	4.2 [2.8, 8.7]	4.8 [2.1, 8.6]	0.9235

Outcomes

Overall safety results: ICH + Non-ICH Cohorts				
Overall 30-day mortality	13 (12.5)	8 (12.9)	5 (11.9)	0.8799
Overall in-hospital mortality	8 (7.7)	4 (6.4)	4 (9.5)	NA
Overall discharge to 30-day mortality	5 (4.8)	4 (6.4)	1 (2.4)	NA
Overall TEE	8 (7.7)	3 (4.8)	5 (11.9)	0.2637[b]
Overall in-hospital TEE	3 (2.9)	1 (1.6)	2 (4.8)	NA
Overall discharge to 30-day TEE	5 (4.8)	2 (3.2)	3 (7.1)	NA
ICH Cohort	n = 55	n = 30	n = 25	
Overall 30-day mortality	11 (20.0)	6 (20.0)	5 (20.0)	1.0000[b]
In-hospital mortality	6 (10.9)	2 (6.7)	4 (16.0)	NA
Time from FEIBA to in-hospital death, days (median [25th, 75th percentile])	n = 6 3.3 [1.7, 3.9]	n = 2 3.4 [3.0, 3.9]	n = 4 2.7 [1.6, 6.6]	NA
Discharge to 30-day mortality	5 (9.1)	4 (13.3)	1 (4.0)	NA
Overall 30-day TEE	4 (7.3)	1 (3.3)	3 (12.0)	0.3198[b]
In-hospital TEE	**1 (1.8)**	**0 (0.0)**	**1 (4.0)**	NA
Ischemic stroke	1 (100.0)	0 (0.0)	1 (100.0)	
Discharge to 30-day TEE	**3 (5.4)**	**1 (3.3)**	**2 (8.0)**	NA
Ischemic stroke	1 (33.3)	1 (100.0)	0 (0.0)	
Cardiac thrombus	1 (33.3)	0 (0.0)	1 (50.0)	
Pulmonary embolism	1 (33.3)	0 (0.0)	1 (50.0)	
Hemostasis				0.8866[b]
Excellent	49 (89.1)	27 (90.0)	22 (88.0)	
Good	4 (7.5)	2 (6.7)	2 (8.0)	
Poor/None	1 (1.8)	0 (0)	1 (4.0)	
Unknown	1 (1.8)	1 (3.3)	0 (0.0)	
Hemostasis: effective (excellent or good)	53 (96.4)	29 (96.7)	24 (96.0)	1.0000[b]
Hemostasis – Effective				0.5024
Without antiplatelet therapy	35 (66.0)	18 (62.1)	17 (70.8)	
With ≥1 antiplatelet agents	18 (34.0)	11 (37.9)	7 (29.2)	
Non-ICH Cohort	n = 49	n = 32	n = 17	
Overall 30-day mortality	2 (4.1)	2 (6.2)	0 (0.0)	0.5374[b]
In-hospital mortality	2 (4.1)	2 (6.2)	0 (0.0)	NA
Time from FEIBA to in-hospital	n = 2	n = 2	n = 0	NA
Mortality, days (median [25th, 75th percentile])	3.3 [0.7, 5.8]	3.3 [0.7, 5.8]		
Discharge to 30-day mortality	0 (0.0)	0 (0.0)	0 (0.0)	NA
Overall 30-day TEE	4 (8.2)	2 (6.2)	2 (11.8)	0.6020[b]
In-hospital TEE	**2 (4.1)**	**1 (3.1)**	**1 (5.9)**	NA
Ischemic stroke	1 (50.0)	1 (100.0)	0 (0.0)	
Systemic embolism	1 (50.0)	0 (0.0)	1 (100.0)	
Discharge to 30-day TEE	**2 (4.1)**	**1 (3.1)**	**1 (5.9)**	NA
Peripheral arterial claudication	1 (50.0)	0 (0.0)	1 (100.0)	
Pulmonary embolism	1 (50.0)	1 (100.0)	0 (0.0)	
Hemostasis				
Excellent	26 (53.1)	18 (56.3)	8 (47.1)	0.8504b
Good	14 (28.6)	8 (25.0)	6 (35.3)	
Poor/None	9 (18.4)	6 (18.8)	3 (17.6)	
Hemostasis: effective (excellent or good)	40 (81.6)	26 (81.3)	14 (82.4)	1.0000[b]
Hemostasis – Effective				0.3920
Without antiplatelet therapy	25 (62.5)	15 (57.7)	10 (71.4)	
With ≥1 antiplatelet agents	15 (37.5)	11 (42.3)	4 (28.6)	

Conclusion

- The combined ICH and non-ICH overall rates of effective hemostasis, TEE, and mortality were comparable to preexisting studies of FEIBA for factor Xa inhibitor reversal.

limitation

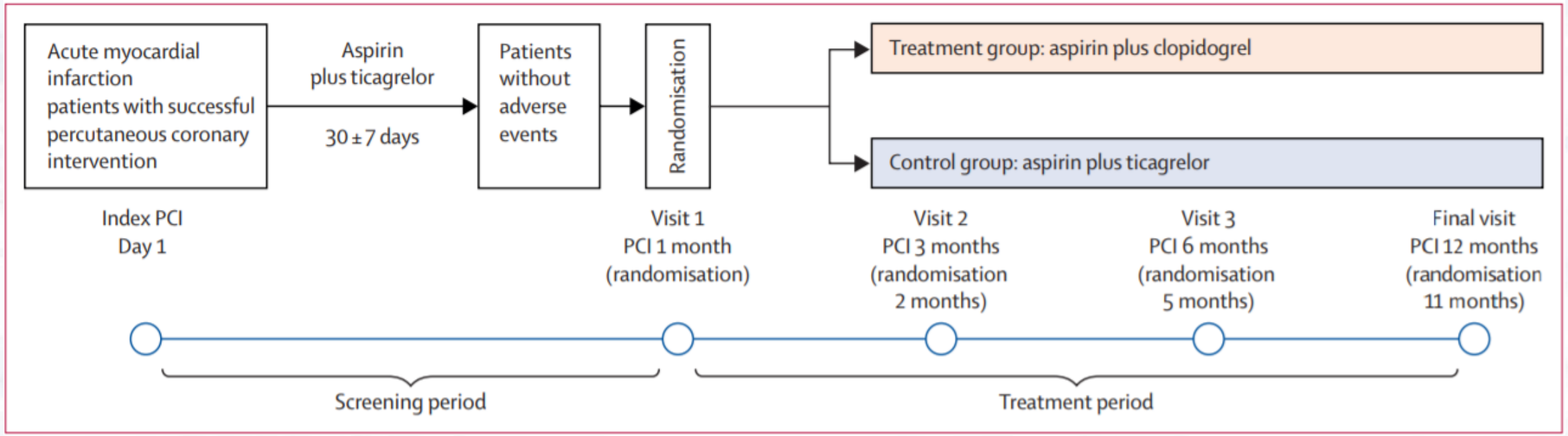
- Retrospective design
- No propensity score matching was performed between apixaban and rivaroxaban users
- No initial National Institutes of Health Stroke Scale (NIHSS) score, initial ICH score, or time from acute bleeding event onset

Unguided de-escalation from ticagrelor to clopidogrel in stabilised patients with acute myocardial infarction undergoing percutaneous coronary intervention (TALOS-AMI): an investigator-initiated, open-label, multicentre, non-inferiority, randomised trial

Lancet 2021; 398: 1305–16

Inclusion Criteria
• Biomarker-positive acute myocardial infarction who underwent successful PCI • Tolerated aspirin and ticagrelor treatment
Exclusion Criteria
• Cardiogenic shock • Active bleeding of any major organs, bleeding diathesis or coagulopathy within 2 months • Intracranial bleeding, intracranial aneurysm, arteriovenous malformation, or neoplasm

Randomised



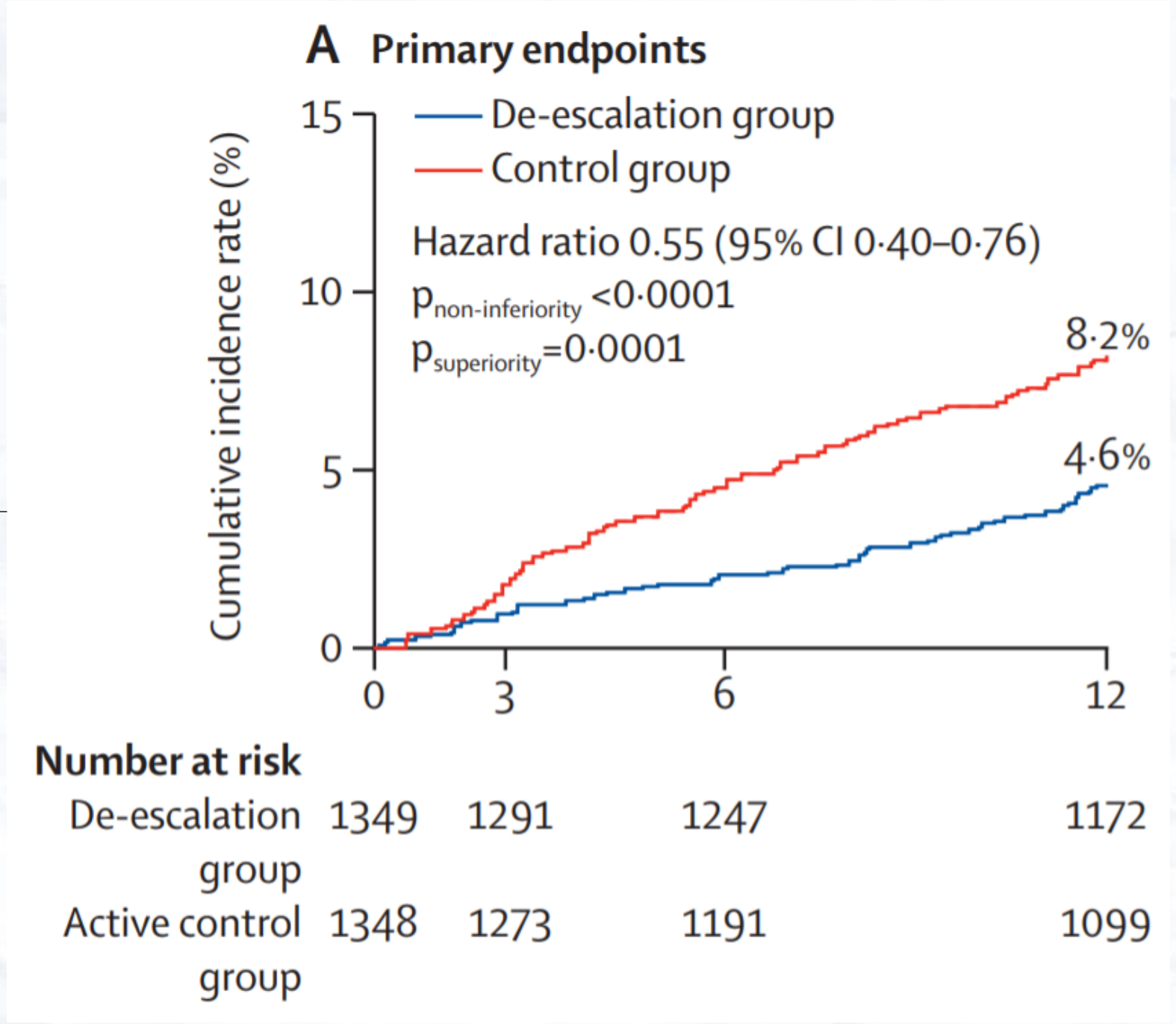
Treatment group	Control group
Aspirin 100mg QD+ Clopidogrel 75mg QD (n=1349)	Aspirin 100mg QD+ Ticagrelor 90mg BID (n=1348)

Baseline characteristics

	De-escalation group (n=1349)	Active control group (n=1348)
Age, years	60·1 (11·3)	59·9 (11·4)
≥75	157 (11·6%)	164 (12·2%)
Female sex	217 (16·1%)	237 (17·6%)
Male sex	1132 (83·9%)	1111 (82·4%)
Body-mass index*, kg/m²	24·6 (3·1)	24·5 (3·1)
Cardiovascular risk factors		
Hypertension	655 (48·6%)	663 (49·2%)
Diabetes	362 (26·8%)	369 (27·4%)
Diabetes treated with insulin	28 (2·1%)	28 (2·1%)
Dyslipidaemia	563 (41·7%)	556 (41·2%)
Current smoker	670 (49·7%)	674 (50·0%)
Impaired renal function†	160 (12·1%)	145 (10·9%)
Past medical history		
Previous percutaneous coronary intervention	61 (4·5%)	60 (4·5%)
Previous coronary artery bypass graft	3 (0·2%)	1 (0·1%)
Previous cerebrovascular accident	53 (3·9%)	50 (3·7%)
Clinical presentation		
STEMI	734 (54·4%)	721 (53·5%)
NSTEMI	615 (45·6%)	627 (46·5%)
Left ventricular ejection fraction <40%	103/1325 (7·8%)	93/1304 (7·1%)

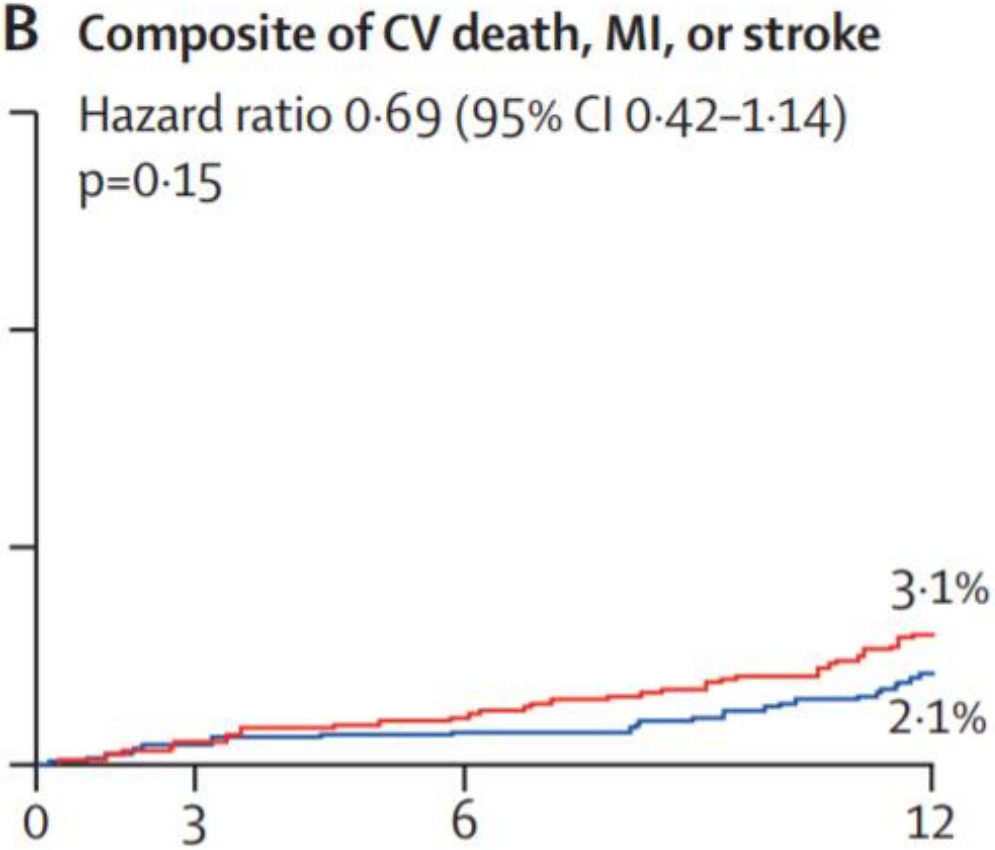
Data are n (%) or mean SD. NSTEMI=non-ST-segment elevation myocardial infarction. STEMI=ST-segment elevation myocardial infarction. *The body-mass index is the weight in kilograms divided by the square of the height in metres. †Impaired renal function was defined as an estimated glomerular filtration rate of less than 60 mL/min per 1·73 m² of body-surface area at presentation.

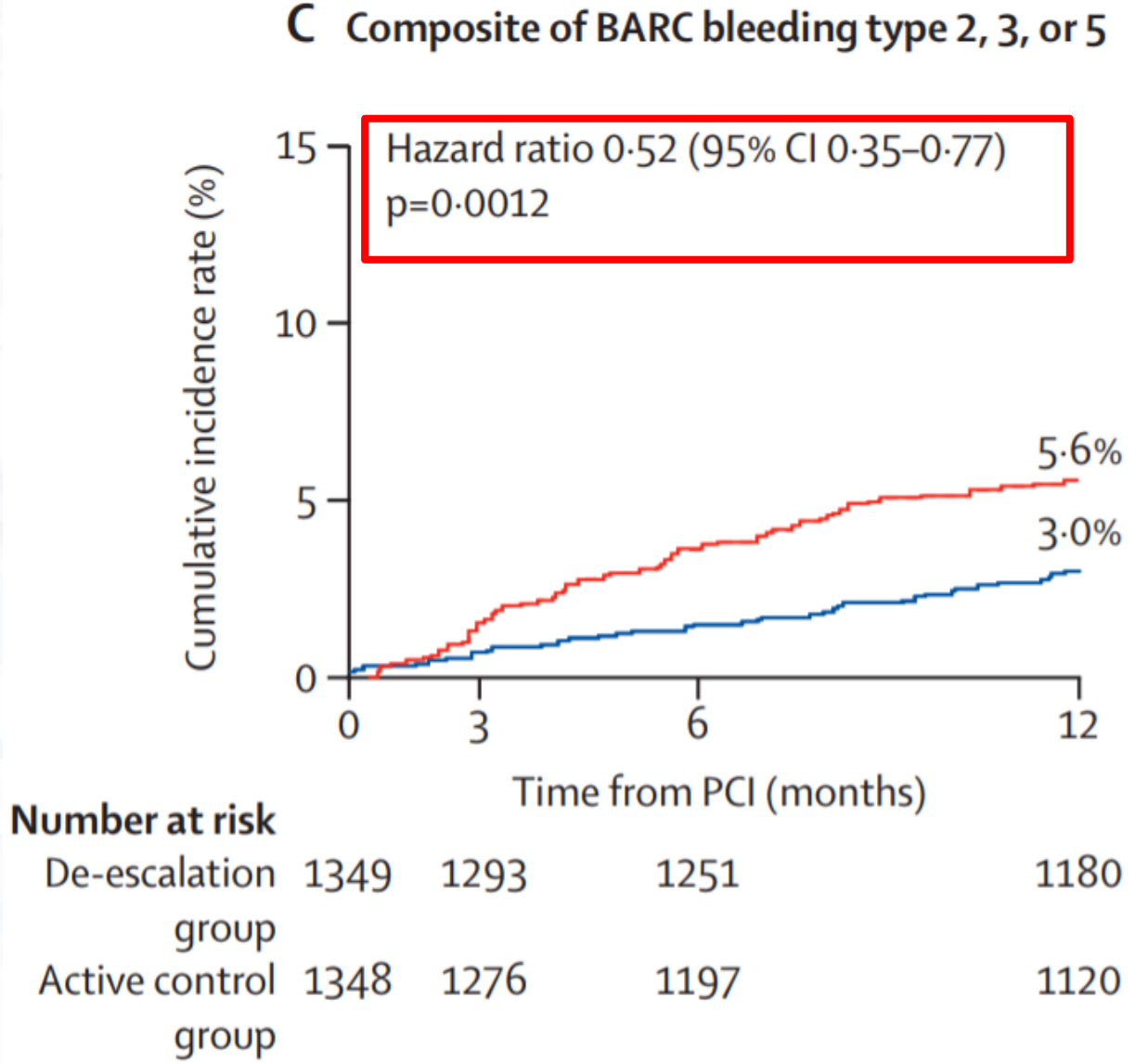
Primary Outcomes



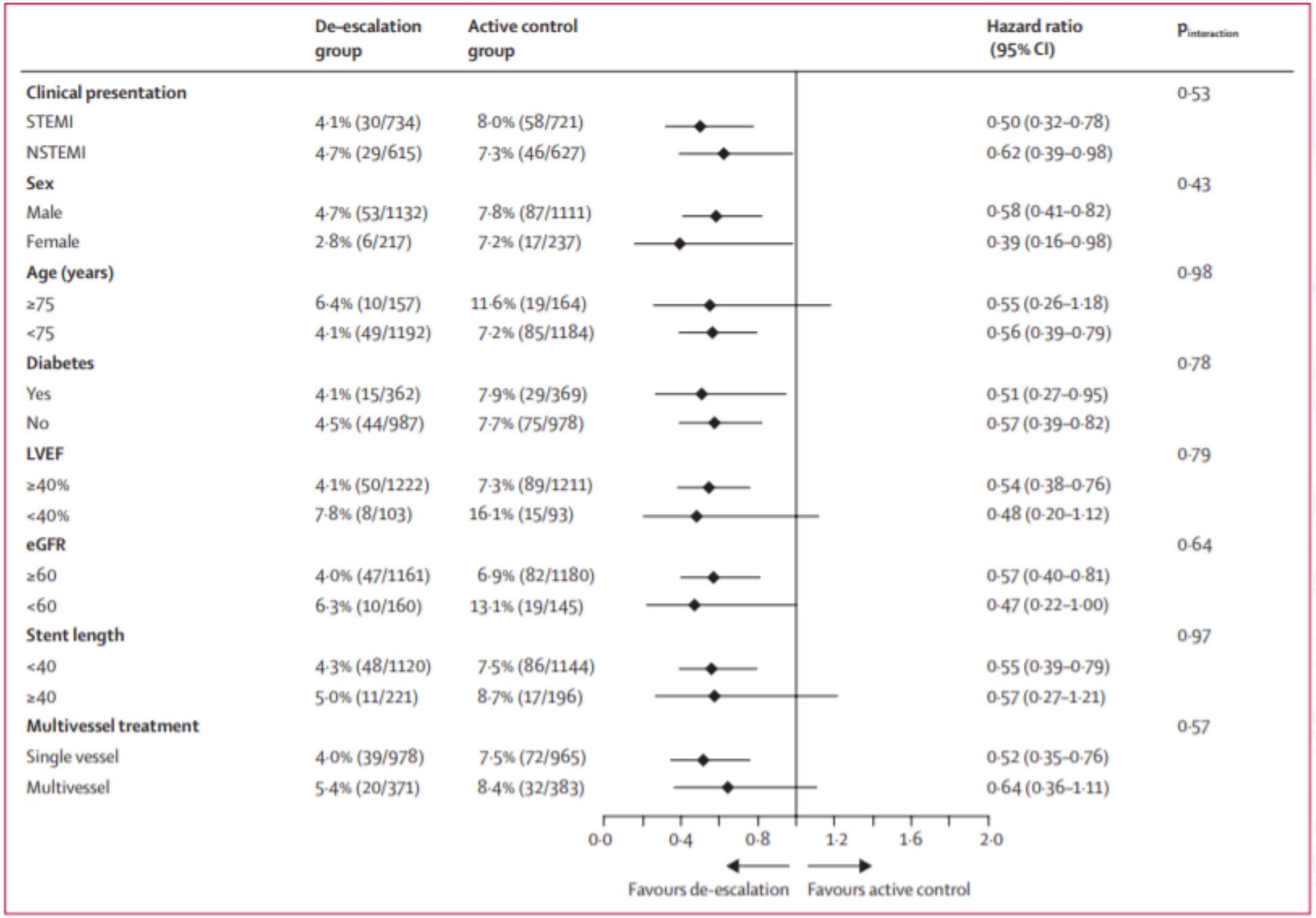
De-escalation group: 4.6%
Active control group: 8.2%
HR 0.55

Outcomes


B Composite of CV death, MI, or stroke
Hazard ratio 0·69 (95% CI 0·42–1·14)
p=0·15
3·1%
2·1%
0
3
6
12
1349 1299 1264 1201
1348 1288 1266 1147


C Composite of BARC bleeding type 2, 3, or 5
Hazard ratio 0·52 (95% CI 0·35–0·77)
p=0·0012
Cumulative incidence rate (%)
15
10
5
0
5·6%
3·0%
0
3
6
12
Time from PCI (months)
Number at risk
De-escalation group 1349 1293 1251 1180
Active control group 1348 1276 1197 1120

Subgroup Anaiysis



	De-escalation group	Active control group	Hazard ratio (95% CI)	$p_{interaction}$
Clinical presentation				0·53
STEMI	4·1% (30/734)	8·0% (58/721)	0·50 (0·32–0·78)	
NSTEMI	4·7% (29/615)	7·3% (46/627)	0·62 (0·39–0·98)	
Sex				0·43
Male	4·7% (53/1132)	7·8% (87/1111)	0·58 (0·41–0·82)	
Female	2·8% (6/217)	7·2% (17/237)	0·39 (0·16–0·98)	
Age (years)				0·98
≥75	6·4% (10/157)	11·6% (19/164)	0·55 (0·26–1·18)	
<75	4·1% (49/1192)	7·2% (85/1184)	0·56 (0·39–0·79)	
Diabetes				0·78
Yes	4·1% (15/362)	7·9% (29/369)	0·51 (0·27–0·95)	
No	4·5% (44/987)	7·7% (75/978)	0·57 (0·39–0·82)	
LVEF				0·79
≥40%	4·1% (50/1222)	7·3% (89/1211)	0·54 (0·38–0·76)	
<40%	7·8% (8/103)	16·1% (15/93)	0·48 (0·20–1·12)	
eGFR				0·64
≥60	4·0% (47/1161)	6·9% (82/1180)	0·57 (0·40–0·81)	
<60	6·3% (10/160)	13·1% (19/145)	0·47 (0·22–1·00)	
Stent length				0·97
<40	4·3% (48/1120)	7·5% (86/1144)	0·55 (0·39–0·79)	
≥40	5·0% (11/221)	8·7% (17/196)	0·57 (0·27–1·21)	
Multivessel treatment				0·57
Single vessel	4·0% (39/978)	7·5% (72/965)	0·52 (0·35–0·76)	
Multivessel	5·4% (20/371)	8·4% (32/383)	0·64 (0·36–1·11)	

Conclusion

- Switching from ticagrelor to clopidogrel reduced the risk of net clinical events up to 12 months, mainly by reducing the bleeding events

limitation

- Open-label
- The non-inferiority margin is wide
- Did not do PFT or genotyping during the study conduct.

Desloratadine Exposure and Incidence of Seizure: A Nordic Post-authorization Safety Study Using a New-User Cohort Study Design, 2001–2015

Drug Safety (2021) 44:1231–1242

Inclusion Criteria
• Denmark, Finland, Norway and Sweden • All individuals with a first-ever dispensing of desloratadine in the study period (2001–2015)
Exclusion Criteria
• Not reside in Denmark, Finland, Norway, or Sweden at the date of first prescription • Seizure, epilepsy, malignant brain tumor, or head trauma, or had redeemed a prescription of antiepileptic medicine before study entry

Baseline characteristics

	Total *N* = 1,807,347	Denmark *N* = 246,003	Finland *N* = 533,646	Norway *N* = 250,910	Sweden *N* = 776,788
Gender					
Male	890,170 (49.3)	111,376 (45.3)	301,355 (56.5)	115,731 (46.1)	361,708 (46.6)
Female	917,177 (50.7)	134,627 (54.7)	232,291 (43.5)	135,179 (53.9)	415,080 (53.4)
Age					
Mean (SD)	29.5 (22.3)	29.5 (22.4)	28.6 (22.2)	29.6 (20.6)	30.0 (22.8)
Age categories (years)					
0–5[a]	366,149 (20.3)	49,187 (20.0)	132,258 (24.8)	35,212 (14.0)	149,492 (19.2)
6–9	119,674 (6.6)	14,569 (5.9)	26,500 (5.0)	20,016 (8.0)	58,589 (7.5)
10–14	130,576 (7.2)	18,588 (7.6)	32,611 (6.1)	20,359 (8.1)	59,018 (7.6)
15–19	133,561 (7.4)	19,077 (7.8)	33,371 (6.3)	21,893 (8.7)	59,220 (7.6)
20–24	116,093 (6.4)	16,057 (6.5)	31,638 (5.9)	20,991 (8.4)	47,407 (6.1)
25–29	118,316 (6.5)	16,066 (6.5)	35,855 (6.7)	19,643 (7.8)	46,752 (6.0)
30–34	118,932 (6.6)	17,289 (7.0)	35,008 (6.6)	18,859 (7.5)	47,776 (6.2)
35–39	120,319 (6.7)	17,580 (7.1)	34,959 (6.6)	18,381 (7.3)	49,399 (6.4)
40–44	113,232 (6.3)	15,519 (6.3)	33,480 (6.3)	16,888 (6.7)	47,345 (6.1)
45–49	100,776 (5.6)	13,148 (5.3)	31,243 (5.9)	14,123 (5.6)	42,262 (5.4)
50–54	87,922 (4.9)	10,645 (4.3)	28,959 (5.4)	11,349 (4.5)	36,969 (4.8)
55–59	79,044 (4.4)	9815 (4.0)	26,176 (4.9)	9433 (3.8)	33,620 (4.3)
60–64	65,619 (3.6)	8450 (3.4)	18,177 (3.4)	7965 (3.2)	31,027 (4.0)
65–69	50,325 (2.8)	6981 (2.8)	12,106 (2.3)	6473 (2.6)	24,765 (3.2)
70–74	34,860 (1.9)	4979 (2.0)	8629 (1.6)	3871 (1.5)	17,381 (2.2)
75–79	24,518 (1.4)	3586 (1.5)	6379 (1.2)	2551 (1.0)	12,002 (1.5)
≥ 80	27,431 (1.5)	4467 (1.8)	6297 (1.2)	2903 (1.2)	13,764 (1.8)
Calendar year					
2001–2005	170,593 (9.4)	68,254 (27.7)	102,339 (19.2)	–	–
2006–2010	682,088 (37.7)	81,091 (33.0)	228,398 (42.8)	19,083 (7.6)	353,516 (45.5)
2011–2015	954,666 (52.8)	96,658 (39.3)	202,909 (38.0)	231,827 (92.4)	423,272 (54.5)
Season					
Winter	269,630 (14.9)	35,432 (14.4)	71,391 (13.4)	28,311 (11.3)	113,099 (14.6)
Spring	739,607 (40.9)	79,288 (32.2)	237,561 (44.5)	101,438 (40.4)	321,320 (41.4)
Summer	549,877 (30.4)	9,0937 (37.0)	151,408 (28.4)	87,627 (34.9)	219,905 (28.3)
Autumn	248,233 (13.7)	40,346 (16.4)	73,286 (13.7)	33,534 (13.4)	122,464 (15.8)
Diagnoses and treatments during a 5-year period prior to date of first desloratadine prescription redemption[b]					
Asthma	258,549 (14.3)	35,336 (14.4)	69,274 (13.0)	35,454 (14.1)	118,485 (15.3)
Severe rhinitis	10,096 (0.6)	4588 (1.9)	243 (0.05)	3138 (1.3)	2127 (0.3)
Chronic urticaria	37,999 (2.1)	2774 (1.1)	6093 (1.1)	1707 (0.7)	27,425 (3.5)

Outcomes

DL exposure	Number (*N*)	Follow-up time (PY)	Unadjusted			Adjusted[a]		
			IR per 100,000 PY	IRR	95% CI	IR per 100,000 PY	IRR	95% CI
Yes	745	1,166,122	63.9	1.61	(1.49–1.75)	31.6	1.46	(1.34–1.59)
No	2,627	6,634,828	39.6	1	Ref.	21.7	1	Ref.
Stratified by country								
Denmark								
Yes	129	133,806	96.4	2.38	(1.96–2.89)	42.3	1.75	(1.44–2.14)
No	503	1,242,345	40.5	1	Ref.	24.2	1	Ref.
Finland								
Yes	151	325,951	46.3	1.67	(1.40–1.98)	34.8	1.44	(1.20–1.73)
No	711	2,555,545	27.8	1	Ref.	24.1	1	Ref.
Norway								
Yes	57	173,685	32.8	1.85	(1.29–2.65)	13.0	1.98	(1.36–2.89)
No	61	343,630	17.8	1	Ref.	6.5	1	Ref.
Sweden								
Yes	408	532,679	76.6	1.41	(1.26–1.58)	47.6	1.34	(1.19–1.50)
No	1,352	2,493,308	54.2	1	Ref.	35.7	1	Ref.
Stratified by age								
0–5 years								
Yes	436	122,811	355.0	1.89	(1.69–2.11)	270.8	1.85	(1.65–2.08)
No	1,012	538,445	187.9	1	Ref.	146.5	1	Ref.
6–19 years								
Yes	143	270,274	52.9	1.36	(1.14–1.63)	36.3	1.42	(1.17–1.71)
No	655	1,685,810	38.9	1	Ref.	25.6	1	Ref.
≥ 20 years								
Yes	166	773,038	21.5	0.99	(0.84–1.16)	11.9	1.01	(0.85–1.19)
No	960	4,410,573	21.8	1	Ref.	11.8	1	Ref.

Outcomes

DL exposure	Number (*N*)	Follow-up time (PY)	Unadjusted			Adjusted		
			IR per 100,000 PY	IRR	95% CI	IR per 100,000 PY	IRR	95% CI
Non-febrile seizures in children aged 0–5 years[a]								
Yes	110	110,315	99.7	1.59	(1.28–1.97)	117.8	1.46	(1.17–1.83)
No	315	501,771	62.8	1	Ref.	80.7	1	Ref.
Febrile seizures in children aged 0–5 years[a]								
Yes	307	109,820	279.5	1.99	(1.74–2.28)	319.9	2.19	(1.90–2.51)
No	700	499,182	140.2	1	Ref.	145.5	1	Ref.
Restricting study period to years before OTC[b]								
Yes	503	732,684	68.7	1.73	(1.57–1.92)	42.0	1.47	(1.32–1.63)
No	1539	3,886,038	39.6	1	Ref.	28.6	1	Ref.
Restricting to individuals without other antihistamine prescription redemptions before inclusion								
Yes	595	654,147	91.0	1.84	(1.68–2.01)	42.8	1.51	(1.37–1.65)
No	2180	4,404,922	49.5	1	Ref.	28.4	1	Ref.
Alternative definition of DL exposure								
Following prescription redemption number[b]								
1	411	366,722	112.1	2.83	(2.55–3.14)	39.6	1.79	(1.60–1.99)
2	99	180,073	55.0	1.39	(1.14–1.70)	27.9	1.26	(1.03–1.54)
≥ 3	235	619,327	37.9	0.96	(0.84–1.10)	26.2	1.18	(1.03–1.35)
No	2627	6,634,828	39.6	1	Ref.	22.2	1	Ref.
Weeks after prescription redemption[b]								
0–4	298	399,940	74.5	1.88	(1.67–2.12)	31.2	1.57	(1.39–1.77)
5–8	224	353,666	63.3	1.60	(1.40–1.83)	26.9	1.35	(1.17–1.55)
9–16	448	595,249	75.3	1.90	(1.72–2.10)	31.2	1.57	(1.41–1.74)
17–26	402	597,738	67.3	1.70	(1.53–1.89)	25.6	1.28	(1.15–1.43)
≥ 27	2627	6,634,828	39.6	1	Ref	19.9	1	Ref

Conclusion

- The association between desloratadine exposure and incident seizure was seen in all countries, most pronounced in children aged 0–5 years.
- No difference in incidence rate of seizure was observed in adults between desloratadine exposed and unexposed.

limitation

- Lack of information on actual use of the redeemed desloratadine
- Not all drugs that could increase the risk of seizure were taken into account
- Risk of misclassification of the comorbidities included as potential confounders

Abstract

THE LANCET

Tirzepatide versus insulin glargine in type 2 diabetes and increased cardiovascular risk (SURPASS-4): a randomised, open-label, parallel-group,

24

	Tirzepatide 5 mg (n=326)	Tirzepatide 10 mg (n=321)	Tirzepatide 15 mg (n=334)	Insulin glargine (n=978)
HbA_{1c}, %				
Baseline	8·52 (0·049)	8·60 (0·049)	8·52 (0·048)	8·51 (0·028)
At week 52	6·29 (0·054)	6·09 (0·054)	5·95 (0·054)	7·09 (0·031)
Change from baseline at week 52*†	−2·24 (0·053)	−2·43 (0·053)	−2·58 (0·053)	−1·44 (0·030)
ETD vs insulin glargine	−0·80 (−0·92 to −0·68), p<0·0001‡	−0·99 (−1·11 to −0·87), p<0·0001‡	−1·14 (−1·26 to −1·02), p<0·0001‡	..
HbA_{1c}, mmol/mol				
Baseline	69·6 (0·54)	70·5 (0·54)	69·6 (0·53)	69·5 (0·31)
At week 52	45·3 (0·59)	43·1 (0·59)	41·5 (0·59)	54·0 (0·34)
Change from baseline at week 52*†	−24·5 (0·59)	−26·6 (0·59)	−28·2 (0·59)	−15·7 (0·34)
ETD vs insulin glargine	−8·8 (−10·1 to −7·4), p<0·0001‡	−10·9 (−12·3 to −9·6), p<0·0001‡	−12·5 (−13·8 to −11·2), p<0·0001‡	..
Bodyweight, kg				
Baseline	90·3 (1·03)	90·7 (1·04)	90·0 (1·02)	90·3 (0·60)
At week 52	83·4 (0·29)	81·1 (0·29)	78·9 (0·29)	92·4 (0·17)
Change from baseline at week 52†	−7·1 (0·34)	−9·5 (0·34)	−11·7 (0·33)	1·9 (0·19)
ETD vs insulin glargine	−9·0 (−9·8 to −8·3), p<0·0001	−11·4 (−12·1 to −10·6), p<0·0001	−13·5 (−14·3 to −12·8), p<0·0001	..
Participants achieving HbA_{1c} targets at week 52				
<7·0% (<53 mmol/mol)†	264 (81%)	283 (88%)	303 (91%)	496 (51%)
OR vs insulin glargine	4·78 (3·47 to 6·58), p<0·0001	9·23 (6·31 to 13·49), p<0·0001	11·87 (7·88 to 17·89), p<0·0001	..
≤6·5% (≤48 mmol/mol)	215 (66%)	244 (76%)	271 (81%)	310 (32%)
OR vs insulin glargine	4·86 (3·66 to 6·45), p<0·0001	8·93 (6·53 to 12·21), p<0·0001	11·84 (8·52 to 16·45), p<0·0001	..
<5·7% (<39 mmol/mol)	75 (23%)	105 (33%)	144 (43%)	33 (3%)
OR vs insulin glargine	9·57 (6·16 to 14·86), p<0·0001	17·11 (11·12 to 26·35), p<0·0001	26·53 (17·35 to 40·56), p<0·0001	..

THE LANCET

Tirzepatide versus insulin glargine in type 2 diabetes and increased cardiovascular risk (SURPASS-4): a randomised, open-label, parallel-group, multicentre, phase 3 trial

Lancet 2021; 398: 1811–24

	Tirzepatide 5 mg (n=329)	Tirzepatide 10 mg (n=328)	Tirzepatide 15 mg (n=338)	All tirzepatide (n=995)	Insulin glargine (n=1000)	Hazard ratio (95% CI)
MACE-4	19 (6%)	17 (5%)	11 (3%)	47 (5%), 2·97	62 (6%), 3·99	0·74 (0·51–1·08)*
Cardiovascular death	10 (3%)	1 (<1%)	5 (2%)	16 (2%), 1·01	21 (2%), 1·35	..
Myocardial infarction	7 (2%)	9 (3%)	3 (<1%)	19 (2%), 1·20	26 (3%), 1·67	..
Hospitalisation for unstable angina	0	2 (<1%)	2 (<1%)	4 (<1%), 0·25	8 (<1%), 0·51	..
Stroke	5 (2%)	5 (2%)	1 (<1%)	11 (1%), 0·70	13 (1%), 0·84	..
Other MACE						
Coronary interventions†	10 (3%)	11 (3%)	8 (2%)	29 (3%), 1·83	37 (4%), 2·38	..
Transient ischaemic attack	0	2 (<1%)	1 (<1%)	3 (<1%), 0·19	0	..
Hospitalisation for heart failure	1 (<1%)	1 (<1%)	2 (<1%)	4 (<1%), 0·25	6 (<1%), 0·39	..
Death	15 (5%)	2 (<1%)	8 (2%)	25 (3%), 1·58	35 (4%), 2·25	0·70 (0·42–1·17)*
Cardiovascular	4 (1%)	0	2 (<1%)	6 (<1%), 0·38	9 (<1%), 0·58	..
Undetermined	6 (2%)	1 (<1%)	3 (<1%)	10 (1%), 0·63	12 (1%), 0·77	..
Non-cardiovascular	5 (2%)	1 (<1%)	3 (<1%)	9 (<1%), 0·57	14 (1%), 0·90	..

THE LANCET

Once-weekly cagrilintide for weight management in people with overweight and obesity: a multicentre, randomised, double-blind, placebo-controlled and active-controlled, dose-finding phase 2 trial

Lancet 2021; 398: 2160–72

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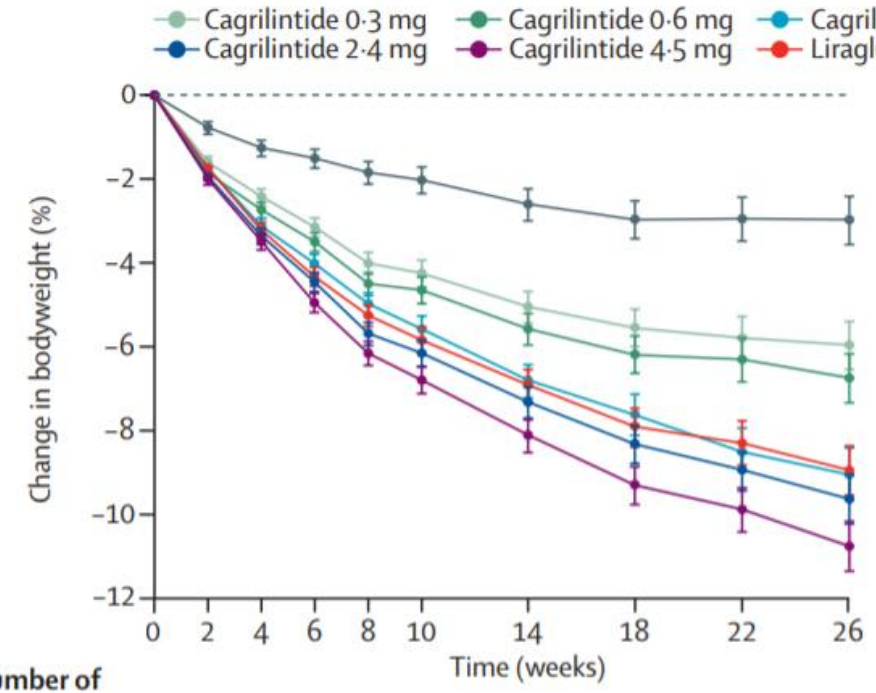
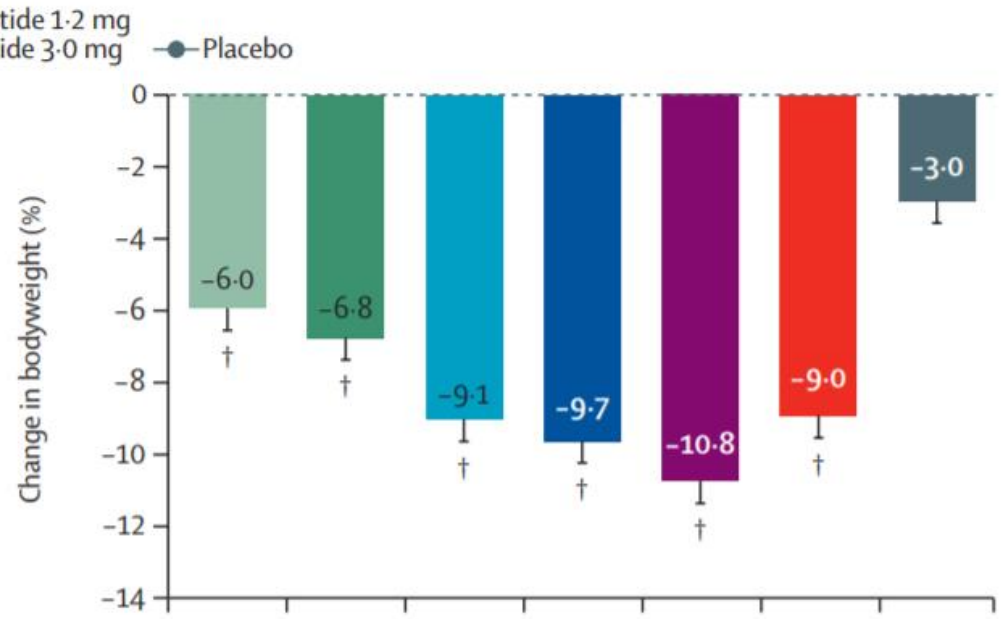
P	•
I	C
C	L
O	p

A Estimated mean change in bodyweight by treatment week



Number of participants										
Cagrilintide 0·3 mg	101	100	97	100	98	99	98	98	98	96
Cagrilintide 0·6 mg	100	99	98	96	98	97	97	94	95	97
Cagrilintide 1·2 mg	102	101	98	96	99	100	98	96	95	98
Cagrilintide 2·4 mg	102	101	100	99	100	99	99	98	97	99
Cagrilintide 4·5 mg	101	100	99	99	97	97	96	94	93	97
Liraglutide 3·0 mg	99	99	99	98	97	95	94	96	93	95
Placebo	101	101	100	95	97	94	94	91	90	95

B Estimated mean change in bodyweight from baseline to week 26



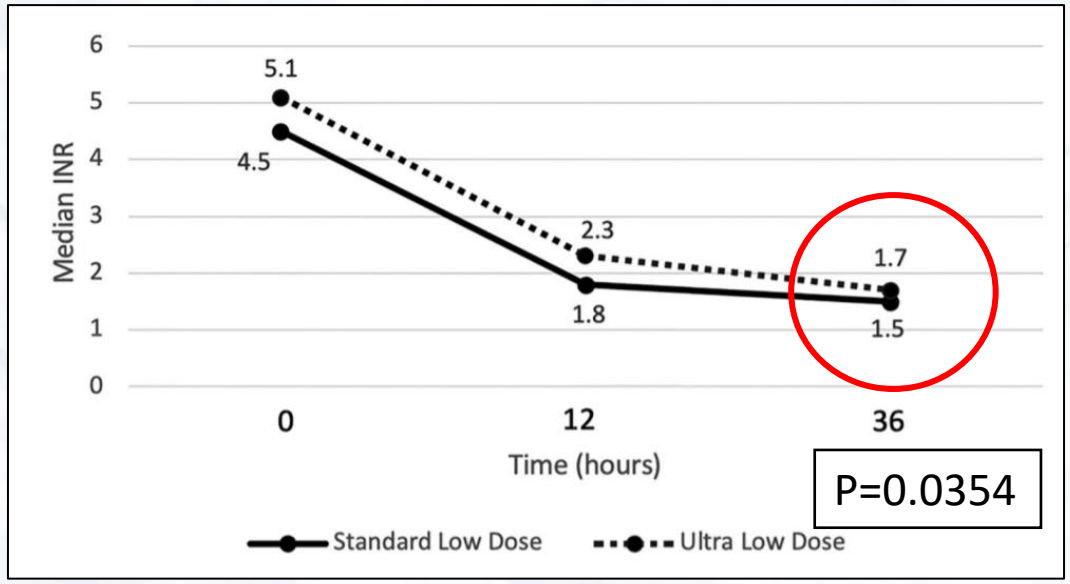
ANNALS OF PHARMACOTHERAPY

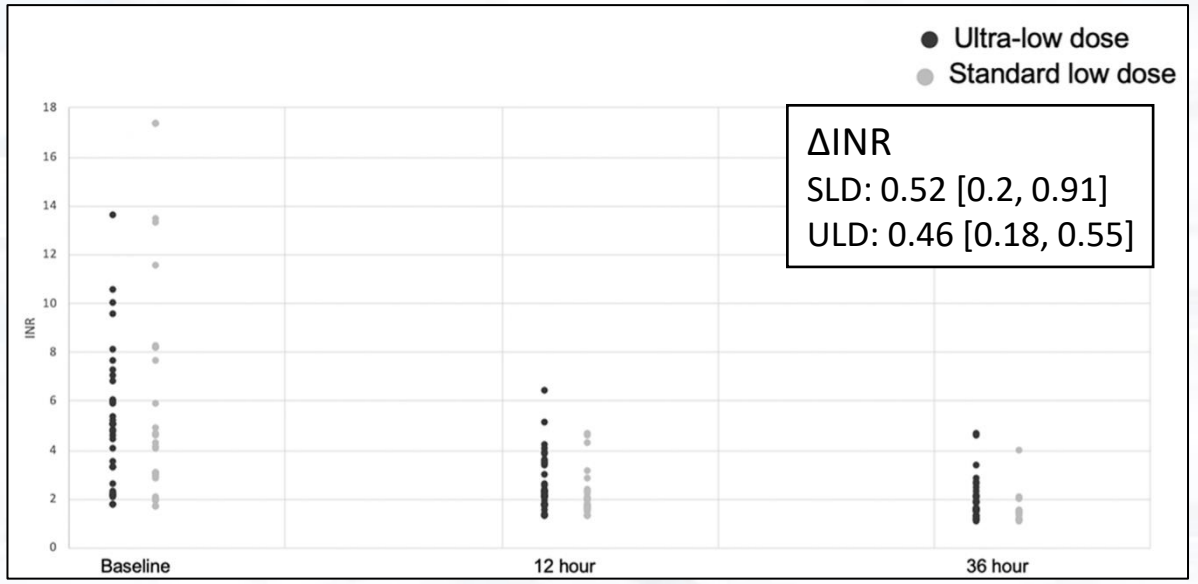
INR Response to Low-Dose Vitamin K in Warfarin Patients

Annals of Pharmacotherapy 2021, Vol. 55(12) 1455–1466

- Design: single-center, retrospective, observational cohort study

P	• ≥ 18 y/o, on warfarin therapy, and received IV vitamin K
I	Vitamin K IV 0.25-0.5 mg (ultra low-dose [ULD])
C	Vitamin K IV 1-2 mg (standard low dose [SLD])
O	ΔINR at 36 hours



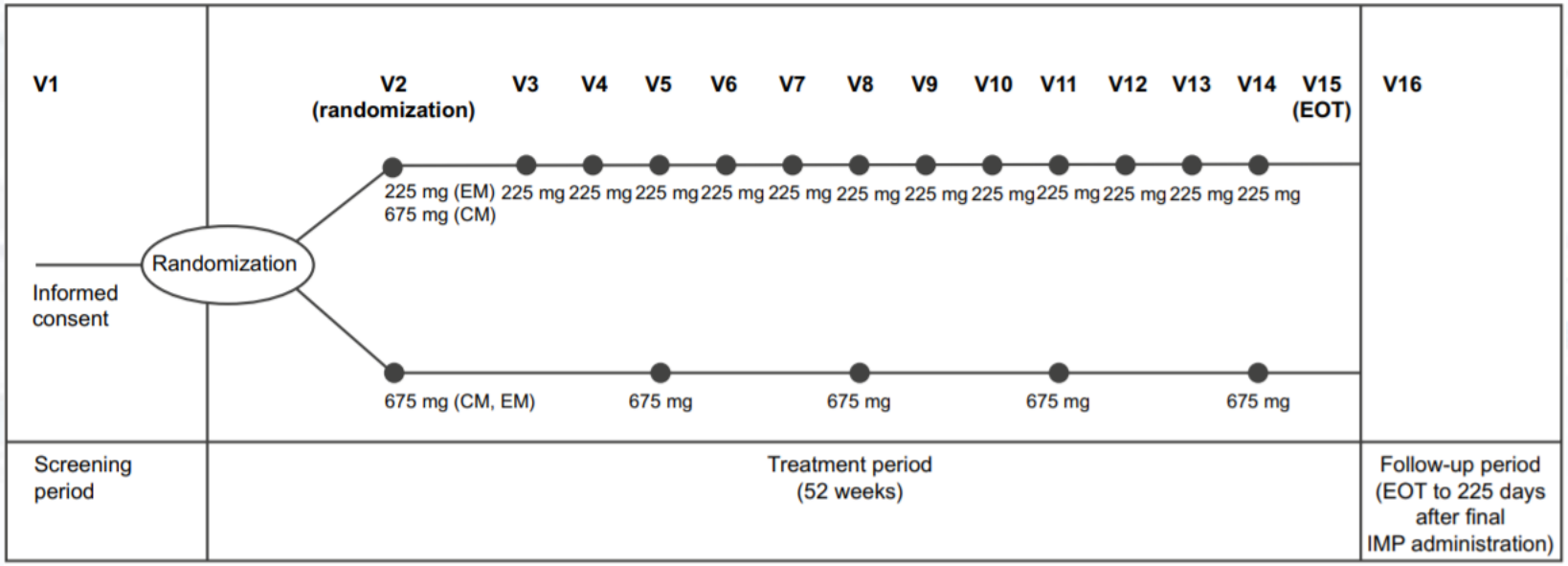


Long-Term Safety and Tolerability of Fremanezumab for Migraine Preventive Treatment in Japanese Outpatients: A Multicenter, Randomized, Open-Label Study

Drug Safety (2021) 44:1355–1364

- Design: 52-week, multicenter, randomized, open-label, parallel-group study

P	• History of migraine or clinical judgment suggests a migraine diagnosis for ≥ 12 months
I	Fremanezumab 225mg QM
C	Fremanezumab 675 mg Q3M
O	Adverse events/monthly migraine days and headache days of at least moderate severity



Long-Term Safety and Tolerability of Fremanezumab for Migraine Preventive Treatment in Japanese Outpatients: A Multicenter, Randomized, Open-Label Study

Drug Safety (2021) 44:1355–1364

Characteristics, *n* (%)	Fremanezumab		
	Monthly ($n = 25$)	Quarterly ($n = 25$)	Total ($n = 50$)
Patients with at least one TEAE	23 (92.0)	22 (88.0)	45 (90.0)
Patients with at least one TEAE related to the trial regimen	11 (44.0)	6 (24.0)	17 (34.0)
Patients with at least one serious TEAE	0	2 (8.0)	2 (4.0)
Patients with any TEAE leading to discontinuation of the trial	0	2 (8.0)	2 (4.0)
Death	0	0	0
Patients with TEAE reported in ≥ 5% of patients in any group			
Injection-site reactions			
Erythema	7 (28.0)	5 (20.0)	12 (24.0)
Induration	3 (12.0)	2 (8.0)	5 (10.0)
Pain	1 (4.0)	3 (12.0)	4 (8.0)
Pruritus	2 (8.0)	1 (4.0)	3 (6.0)
Infections and infestations			
Gastroenteritis	3 (12.0)	1 (4.0)	4 (8.0)
Influenza	1 (4.0)	2 (8.0)	3 (6.0)
Nasopharyngitis	18 (72.0)	14 (56.0)	32 (64.0)
Oral herpes	1 (4.0)	2 (8.0)	3 (6.0)
Back pain	1 (4.0)	2 (8.0)	3 (6.0)
Dysmenorrhea	2 (8.0)	1 (4.0)	3 (6.0)
Cough	1 (4.0)	2 (8.0)	3 (6.0)

TEAE treatment-emergent adverse event

Risk of Pregnancy Termination and Congenital Anomalies After Domperidone Exposure: A Study in the EFEMERIS Database

Drug Safety (2021) 44:787–796

- Design: retrospective cohort study

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	Exposed newborns (N = 13,717) n (%)	Unexposed newborns (N = 115,969)	P-value
Sex, male	N = 13,691	N = 115,802	
	6816 (49.8)	59,435 (51.3)	0.001
Prematurity	899 (6.6)	7405 (6.4)	0.44
Extreme < 28 WA	26 (2.9)	186 (2.5)	
Major (28–32 WA)	74 (8.2)	698 (9.4)	
Moderate to late (33–37 WA)	799 (88.9)	6521 (88.1)	
Low birth weight (< 2500 g)	N = 12,732	N = 106,381	
	806 (6.3)	6564 (6.2)	0.48
Small for gestational age (weight < mean – (2*SD) considering gestational age and sex)	N = 12,219	N = 102,647	
	144 (1.2)	1403 (1.4)	0.09

N total number of pregnant women, *SD* standard deviation, *WA* weeks of amenorrhoea

Outcomes

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124,161)

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THE LANCET

Stu…tia (SY…olled trial

…021; 398: 1487–97

- Design: m…

P	Alzheim…
I	Mirtaza…
C	Placebo
O	CMAI sc…

…45 or more

	Mirtazapine group (n=102)		Placebo group (n=102)		Mean difference (95% CI)	Adjusted mean difference (95% CI)*	p value
	n	Mean (SD)	n	Mean (SD)			
12-week primary outcome							
Agitation: CMAI	79	61·4 (22·6)	87	60·8 (21·8)	0·59 (−6·22 to 7·40)	−1·74 (−7·17 to 3·69)*; −0·93 (−6·42 to 4·56)†	0·530; 0·739
6-week secondary outcomes							
Agitation: CMAI	84	61·4 (23·5)	88	60·0 (19·9)	1·39 (−5·15 to 7·93)	−0·55 (−6·18 to 5·08)	0·848
Cognition: standardised MMSE	33	15·5 (7·1)	31	16·2 (7·2)	−0·68 (−4·25 to 2·89)	−0·14 (−1·17 to 1·45)	0·836
Quality of life: DEMQOL	32	95·1 (10·2)	32	96·8 (8·4)	−1·69 (−6·38 to 3·00)	1·12 (−2·74 to 4·97)	0·570
Quality of life: DEMQOL-proxy	79	96·6 (14·7)	86	94·6 (16·2)	2·03 (−2·74 to 6·79)	0·80 (−3·18 to 4·77)	0·694
Quality of life: EQ-5D, proxy report by carer	82	0·48 (0·33)	87	0·56 (0·30)	−0·08 (−0·17 to 0·02)	−0·07 (−0·13 to 0·00)	0·061
Neuropsychiatric symptoms: NPI total score	84	27·1 (20·0)	88	24·8 (20·0)	2·29 (−3·73 to 8·31)	2·03 (−2·89 to 6·95)	0·419
Neuropsychiatric symptoms: NPI agitation and aggression subscore	84	4·0 (3·6)	88	4·2 (3·5)	−0·20 (−1·28 to 0·87)	−0·34 (−1·30 to 0·62)	0·490
Neuropsychiatric symptoms: NPI depression, anxiety, and irritability subscore	84	7·9 (7·7)	88	7·2 (8·2)	0·68 (−1·72 to 3·07)	0·70 (−1·24 to 2·63)	0·482
12-week secondary outcomes							
Cognition: standardised MMSE	23	18·0 (6·0)	27	15·6 (7·5)	2·44 (−1·48 to 6·37)	1·45 (−0·20 to 3·10)	0·084
Quality of life: DEMQOL	24	94·3 (7·1)	24	97·1 (8·4)	−2·83 (−7·35 to 1·68)	−1·36 (−5·82 to 3·10)	0·549
Quality of life: DEMQOL-proxy	71	98·4 (14·5)	82	97·5 (12·4)	0·93 (−3·37 to 5·23)	0·44 (−3·09 to 3·96)	0·809
Quality of life: EQ-5D, proxy report by carer	77	0·46 (0·35)	84	0·50 (0·33)	−0·04 (−0·14 to 0·07)	−0·01 (−0·08 to 0·07)	0·822
Neuropsychiatric symptoms: NPI total score	75	23·9 (17·8)	84	25·7 (19·6)	−1·80 (−7·69 to 4·09)	−2·02 (−6·67 to 2·62)	0·393
Neuropsychiatric symptoms: NPI agitation and aggression subscore	76	4·1 (3·4)	84	4·5 (3·6)	−0·40 (−1·49 to 0·70)	−0·52 (−1·52 to 0·47)	0·305
Neuropsychiatric symptoms: NPI depression, anxiety, and irritability subscore	75	6·9 (6·7)	84	7·3 (8·0)	−0·44 (−2·77 to 1·88)	−0·58 (−2·43 to 1·27)	0·541

THE LANCET

Antibiotics for lower respiratory tract infection in children presenting in primary care in England (ARTIC PC): a double-blind, randomised, placebo-controlled trial

Lancet 2021; 398: 1417–26

- Design:

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	Placebo group (n=211)	Antibiotics group (n=221)	Adjusted* treatment estimate (95% CI)
Duration of moderately bad or worse (score ≥3) symptoms in days	6 (4 to 15)	5 (4 to 11)	Hazard ratio 1·13 (0·90 to 1·42)
Symptom severity	2·1 (1·1)	1·8 (1·1)	Difference –0·28 (–0·51 to –0·04)
Duration of symptoms until very little problem (score 1) in days	8 (5 to 19)	7 (4 to 17)	Hazard ratio 1·09 (0·86 to 1·38)
Return with new or worsening symptoms	38%	30%	Odds ratio 0·71 (0·46 to 1·09); risk ratio 0·80 (0·58 to 1·05)
Assessment or admission needed in hospital†	2%	2%	Odds ratio 1·24 (0·32 to 4·78); risk ratio 1·23 (0·32 to 4·44)
Side-effects	33%	39%	Odds ratio 1·33 (0·81 to 2·17); risk ratio 1·20 (0·87 to 1·55)

Data are median (IQR), mean (SD), or n (%). *Adjusted for previous duration of illness, baseline severity, age, and comorbidity. †Assessment or admission needed in hospital within 1 month of index consultation (appendix p 1).

Table 4: **Effectiveness of antibiotics on primary and secondary outcomes (imputed)**

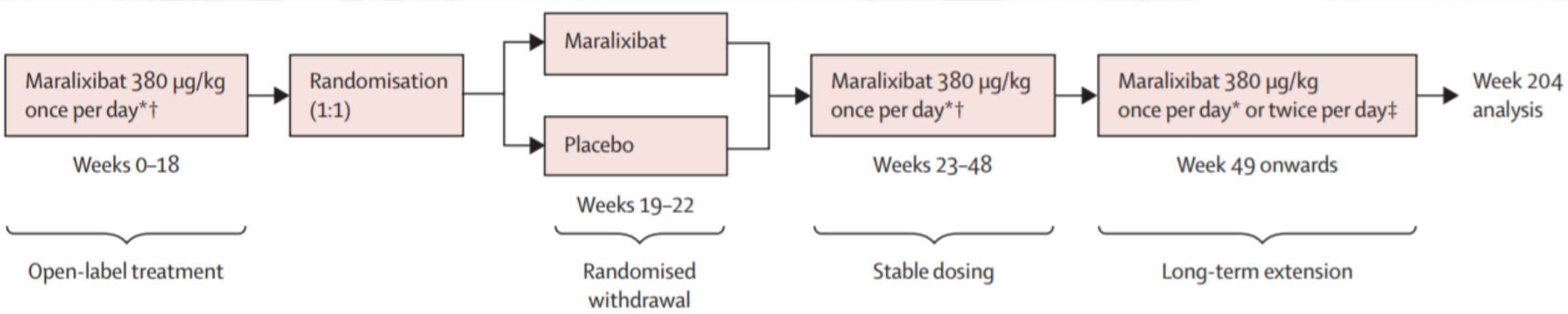
THE LANCET

Efficacy and safety of maralixibat treatment in patients with Alagille syndrome and cholestatic pruritus (ICONIC): a randomised phase 2 study

Lancet 2021; 398: 1581–92

- Design: international, multicenter, phase 2b, double-blind, placebo-controlled, drug-withdrawal study with open-label extension

P	Children aged 12 months to 18 years with a clinical diagnosis of Alagille syndrome
I	maralixibat 380 µg/kg QD
C	Placebo
O	mean sBA change during the RWD in participants with at least 50% sBA reduction by week 18



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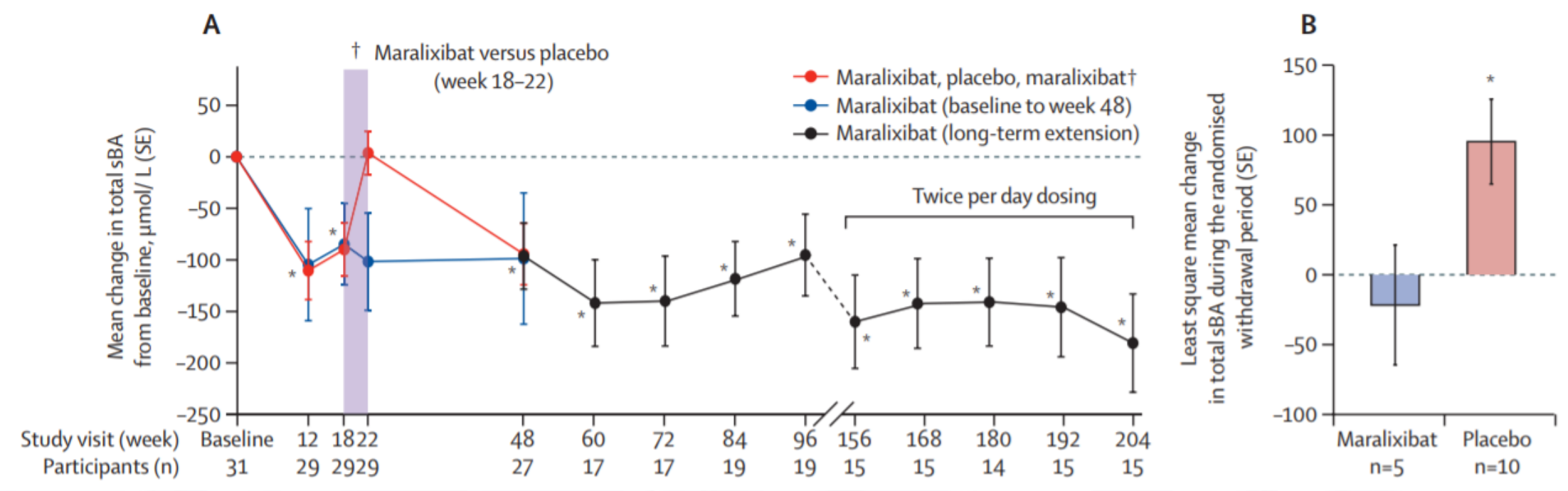
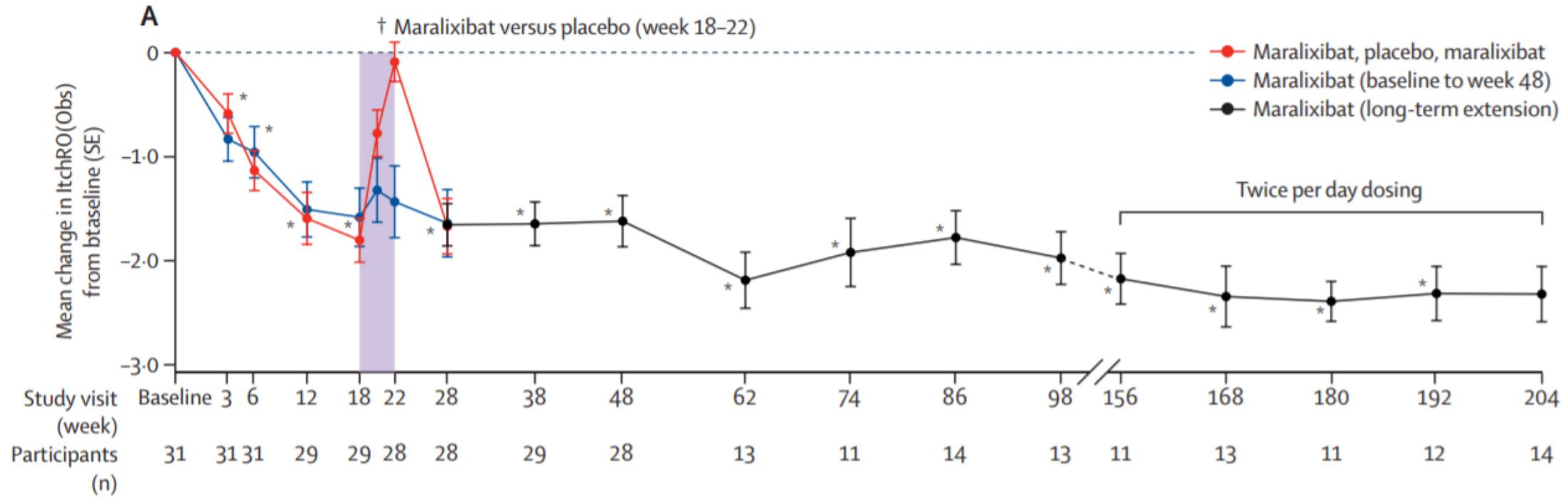


Changes in sBA



Changes in pruritus

Thank You