期刊報告

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THE LANCET

Lancet 2019; 394: 1335–43

Edoxaban-based versus vitamin K antagonist-based antithrombotic regimen after successful coronary stenting in patients with atrial fibrillation (ENTRUST-AF PCI): a randomised, open-label, phase 3b trial

Background: However, the effects of Edoxaban in combination with a P2Y12 inhibitor in the setting of PCI are unexplored.

Atrial Fibrillation

CAD require PCI

Treatment

Warfarin/ NOACs

+

DAPT

Method

- Trial design:
  randomised, multicentre, open-label, non-inferiority phase 3b trial

- **AF requiring oral anticoagulation.**
- **Age > 18.**
- **Had a successful PCI for stable CAD or ACS.**

(N=1506)

Edoxaban 60mg QD + P2Y12 inhibitors (N=751)

Endoxaban adjust dose:
- CrCl: 15-50 ml/min
- BW < 60kg
- Concomitant use specified potent p-gp inhibitors

Warfarin + P2Y12 inhibitors + Aspirin (N=755)

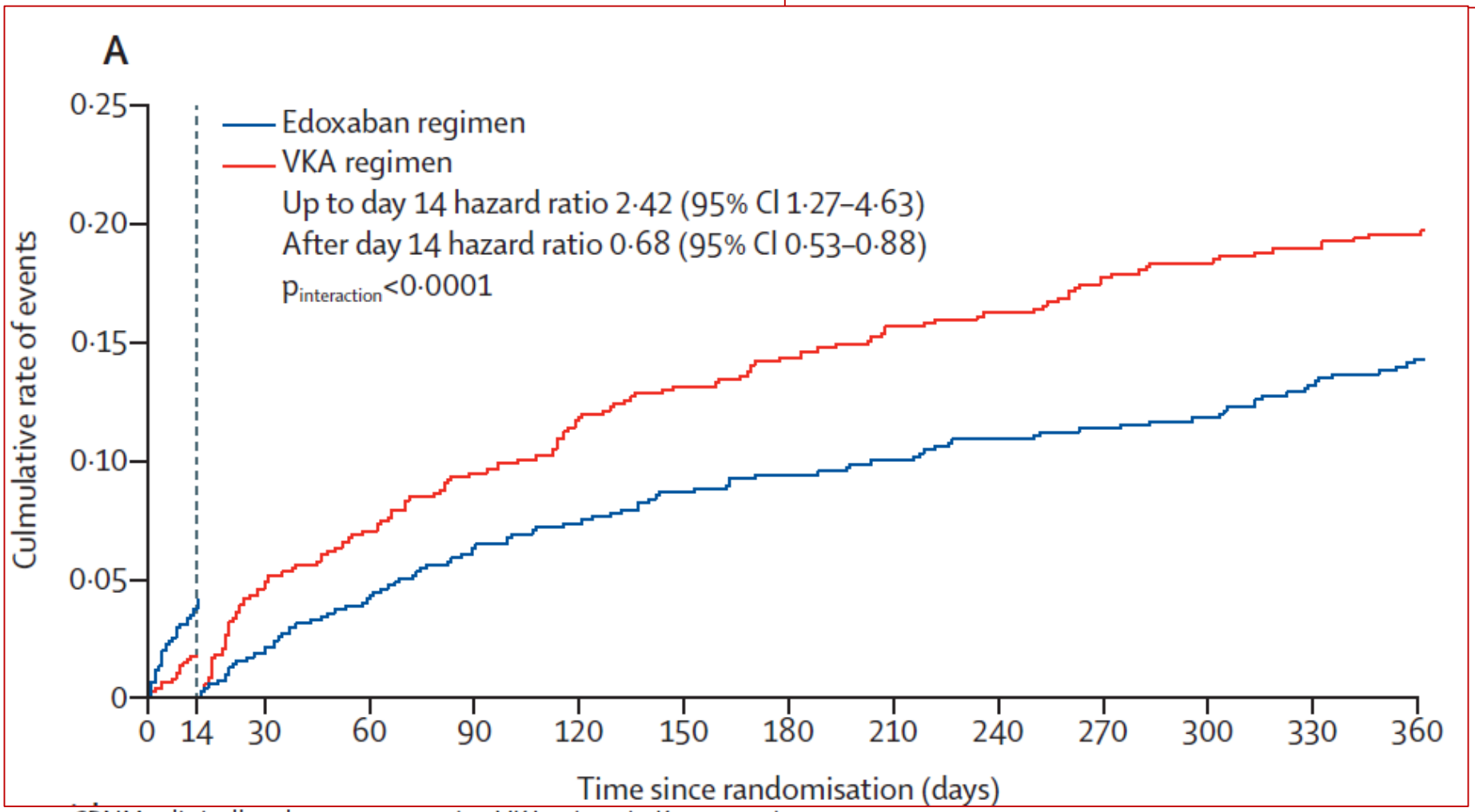
- **Primary outcome:**
  Composite of major or clinically relevant non-major (CRNM) bleeding within 12 months.

Baseline characteristics

- Age: 70
- Type of P2Y12 inhibitors:
  - Clopidogrel (93%)
  - Ticagrelor (7%)
  - Prasugrel 5 mg (<1%)
  - Prasugrel 10 mg (<1%)
- Clinical presentation
  - ACS (52%)
  - SCAD (48%)
- No significant difference between groups.

Primary Outcome

	Edoxaban regimen	VKA regimen	Hazard ratio (two-sided 95% CI)
Primary outcome of major or CRNM bleeding (ISTH)			
Intention-to-treat analysis			
Number of patients	751	755	..
Number of patients with event	128 (17%)	152 (20%)	..
Annualised event rate	20·7	25·6	0·83 (0·65–1·05)



CRNM=clinically relevant non-major. VKA=vitamin K antagonist.

Outcome

Major bleeding (ISTH)				
Intention-to-treat analysis				
Number of patients	751	755	..	
Number of patients with event	45 (6%)	48 (6%)	..	
Annualised event rate	6·7	7·2	0·95 (0·63–1·42)	

Main efficacy outcome (composite of cardiovascular death, stroke, systemic embolic event, myocardial infarction, or definite stent thrombosis)				
Intention-to-treat analysis				
Number of patients	751	755	..	..
Number of patients with event	49 (7%)	46 (6%)	..	..
Annualised event rate	7·3	6·9	1·06 (0·71–1·69)	..

Conclusion

- In patients with AF who had PCI, the edoxaban-based regimen was non-inferior for bleeding compared with the VKA-based regimen, without significant differences in ischaemic events.

NOACs + P2Y12 inhibitors VS. Triple therapy

- **Efficacy outcome in ischemic events are similar between two groups.**

ISTH Major or Clinically Relevant Non-Major Bleeding

Drugs	Trial	NOAC		VKA		Risk Ratio, 95% CI
		Events	Total	Events	Total	Risk Ratio 95%CI
Edoxaban	ENTRUST-AF PCI	128	751	152	755	0.85 (0.68, 1.05)
Dabigatran	RE-DUAL PCI	305	1744	264	981	0.65 (0.56, 0.75)
Apixaban	AUGUSTUS	84	1143	210	1123	0.39 (0.31, 0.50)
Rivaroxaban	PIONEER-AF PCI	117	696	178	697	0.66 (0.53, 0.81)

Drugs	Dose
Edoxaban	60 mg QD (30mg in specific population)
Dabigatran	110 mg/ 150 mg BID (110 mg in U.S)
Apixaban	5 mg BID (2.5 mg in specific population)
Rivaroxaban	15 mg QD

★ NOACs + Clopidogrel for 12 months

Thrombotic	Bleeding	Recommondation
Low	Low	Others add aspirin for one month in patients at the lowest end of the bleeding risk spectrum.
Low	High	In patients at the highest bleeding risk, we consider stopping the P2Y12 inhibitor at six months.
High	Low	Some of our experts continue aspirin after the procedure for a period of one to six months.
High	High	Individualized patient decision making is essential. Some of our experts add aspirin for one month after the procedure in this high thrombotic risk group.

Ref: https://www.uptodate.com/contents/coronary-artery-disease-patients-requiring-combined-anticoagulant-and-antiplatelet-therapy?search=af%20CAD&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1#H24

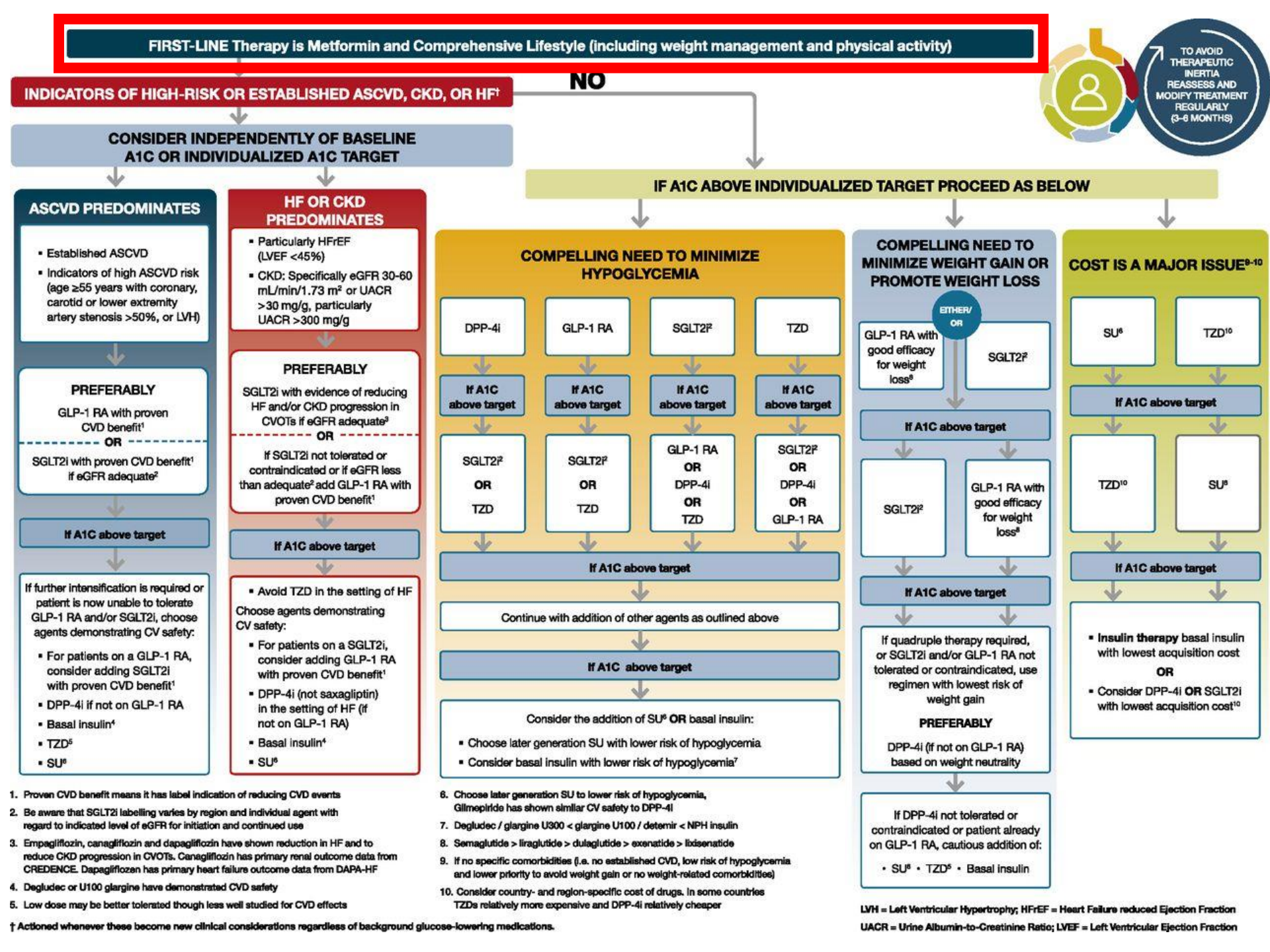
THE LANCET

Lancet 2019; 394: 1519–29

Glycaemic durability of an early combination therapy with vildagliptin and metformin versus sequential metformin monotherapy in newly diagnosed type 2 diabetes (VERIFY): a 5-year, multicentre, randomised, double-blind trial

Background: Although initial combination therapy has been suggested to offer more opportunities than a traditional stepwise approach, its validity remains to be determined.

Does early intensive treatment have better outcome?



1. Proven CVD benefit means it has label indication of reducing CVD events
2. Be aware that SGLT2i labelling varies by region and individual agent with regard to indicated level of eGFR for initiation and continued use
3. Empagliflozin, canagliflozin and dapagliflozin have shown reduction in HF and to reduce CKD progression in CVOTs. Canagliflozin has primary renal outcome data from CREDENCE. Dapagliflozen has primary heart failure outcome data from DAPA-HF
4. Degludec or U100 glargine have demonstrated CVD safety
5. Low dose may be better tolerated though less well studied for CVD effects
6. Choose later generation SU to lower risk of hypoglycemia, Glimepiride has shown similar CV safety to DPP-4i
7. Degludec / glargine U300 < glargine U100 / detemir < NPH insulin
8. Semaglutide > liraglutide > dulaglutide > exenatide > lixisenatide
9. If no specific comorbidities (i.e. no established CVD, low risk of hypoglycemia and lower priority to avoid weight gain or no weight-related comorbidities)
10. Consider country- and region-specific cost of drugs. In some countries TZDs relatively more expensive and DPP-4i relatively cheaper

† Actioned whenever these become new clinical considerations regardless of background glucose-lowering medications.

LVH = Left Ventricular Hypertrophy; HFrEF = Heart Failure reduced Ejection Fraction
UACR = Urine Albumin-to-Creatinine Ratio; LVEF = Left Ventricular Ejection Fraction

GLYCEMIC CONTROL ALGORITHM

INDIVIDUALIZE GOALS

A1C ≤6.5% For patients without concurrent serious illness and at low hypoglycemic risk

A1C >6.5% For patients with concurrent serious illness and at risk for hypoglycemia

LIFESTYLE THERAPY (Including Medically Assisted Weight Loss)

Entry A1C <7.5%

MONOTHERAPY [1]

- ✓ Metformin
- ✓ GLP1-RA [2,3]
- ✓ SGLT2i [2,3]
- ✓ DPP4i
- ⚠ TZD
- ✓ AGi
- ⚠ SU/GLN

If not at goal in 3 months proceed to Dual Therapy

Entry A1C ≥7.5%

DUAL THERAPY [1]

MET or other 1st-line agent +

- ✓ GLP1-RA [2,3]
- ✓ SGLT2i [2,3]
- ✓ DPP4i
- ⚠ TZD
- ⚠ Basal Insulin
- ✓ Colesevelam
- ✓ Bromocriptine QR
- ✓ AGi
- ⚠ SU/GLN

If not at goal in 3 months proceed to Triple Therapy

TRIPLE THERAPY [1]

MET or other 1st-line agent + 2nd-line agent +

- ✓ GLP1-RA [2,3]
- ✓ SGLT2i [2,3]
- ⚠ TZD
- ⚠ Basal Insulin
- ✓ DPP4i
- ✓ Colesevelam
- ✓ Bromocriptine QR
- ✓ AGi
- ⚠ SU/GLN

If not at goal in 3 months proceed to or intensify insulin therapy

Entry A1C >9.0%

SYMPTOMS

NO	YES
DUAL Therapy OR TRIPLE Therapy	INSULIN ± Other Agents

ADD OR INTENSIFY INSULIN

Refer to Insulin Algorithm

LEGEND

- ✓ Few adverse events and/or possible benefits
- ⚠ Use with caution

1 Order of medications represents a suggested hierarchy of usage; length of line reflects strength of recommendation

2 Certain GLP1-RAs and SGLT2is have shown CVD and CKD benefits—preferred in patients with those complications

3 Include one of these medications if CHD present

PROGRESSION OF DISEASE

 DOI 10.4158/CS-2018-0535

Cohort study

The Legacy Effect in Type 2 Diabetes: Impact of Early Glycemic Control on Future Complications (The Diabetes & Aging Study)

Diabetes Care 2019;42:416–426 | https://doi.org/10.2337/dc17-1144

Table 2—Associations among various early HbA_{1c} exposure periods and subsequent outcomes

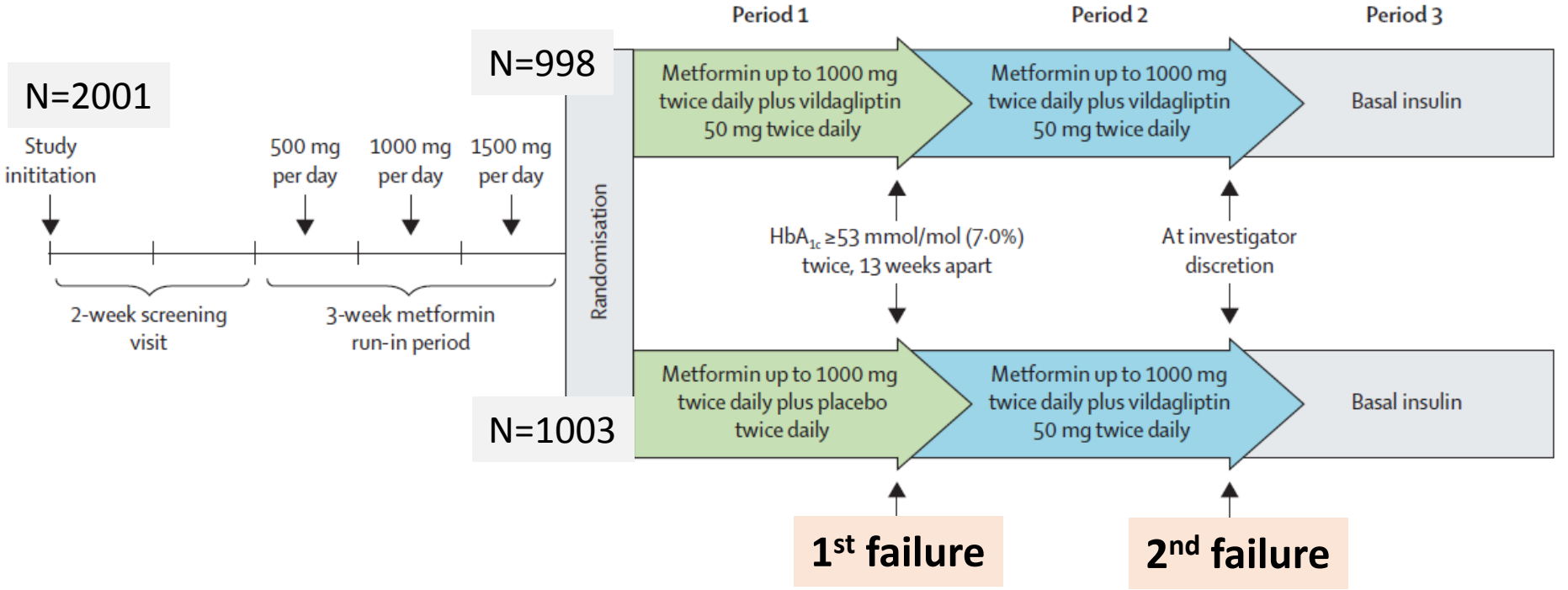
	Microvascular events			Macrovascular events			Death		
Early period and mean glycemic control	*n*/total *n*	Adjusted HR (95% CI)	*P* value	*n*/total *n*	Adjusted HR (95% CI)	*P* value	*n*/total *n*	Adjusted HR (95% CI)	*P* value
0–1 year									
HbA_{1c}									
<6.5% (<48 mmol/mol)	864/14,080	Reference		3,668/13,455	Reference		744/14,286	Reference	
6.5% to <7.0% (48 to <53 mmol/mol)	372/5,774	1.204 (1.063–1.365)	0.004	1,497/5,552	1.188 (1.116–1.264)	<0.0001	268/5,877	1.137 (0.985–1.313)	0.079
7.0% to <8.0% (53 to <64 mmol/mol)	385/4,656	1.391 (1.226–1.578)	<0.0001	1,244/4,501	1.287 (1.203–1.377)	<0.0001	224/4,730	1.290 (1.104–1.507)	0.001
8.0% to <9.0% (64 to <75 mmol/mol)	154/1,390	1.603 (1.340–1.917)	<0.0001	383/1,351	1.369 (1.227–1.527)	<0.0001	68/1,418	1.262 (0.978–1.628)	0.073
≥9.0% (≥75 mmol/mol)	232/1,259	2.213 (1.892–2.590)	<0.0001	382/1,220	1.485 (1.329–1.659)	<0.0001	66/1,290	1.320 (1.017–1.713)	0.037
Missing	647/7,047	1.354 (1.218–1.505)	<0.0001	1,899/6,867	1.112 (1.050–1.177)	0.0003	437/7,136	1.235 (1.094–1.394)	0.001

CONCLUSIONS

Among patients with newly diagnosed diabetes and 10 years of survival, HbA_{1c} levels ≥6.5% (≥48 mmol/mol) for the 1st year after diagnosis were associated with worse outcomes. Immediate, intensive treatment for newly diagnosed patients may be necessary to avoid irremediable long-term risk for diabetic complications and mortality.

Method

Open-label RCT



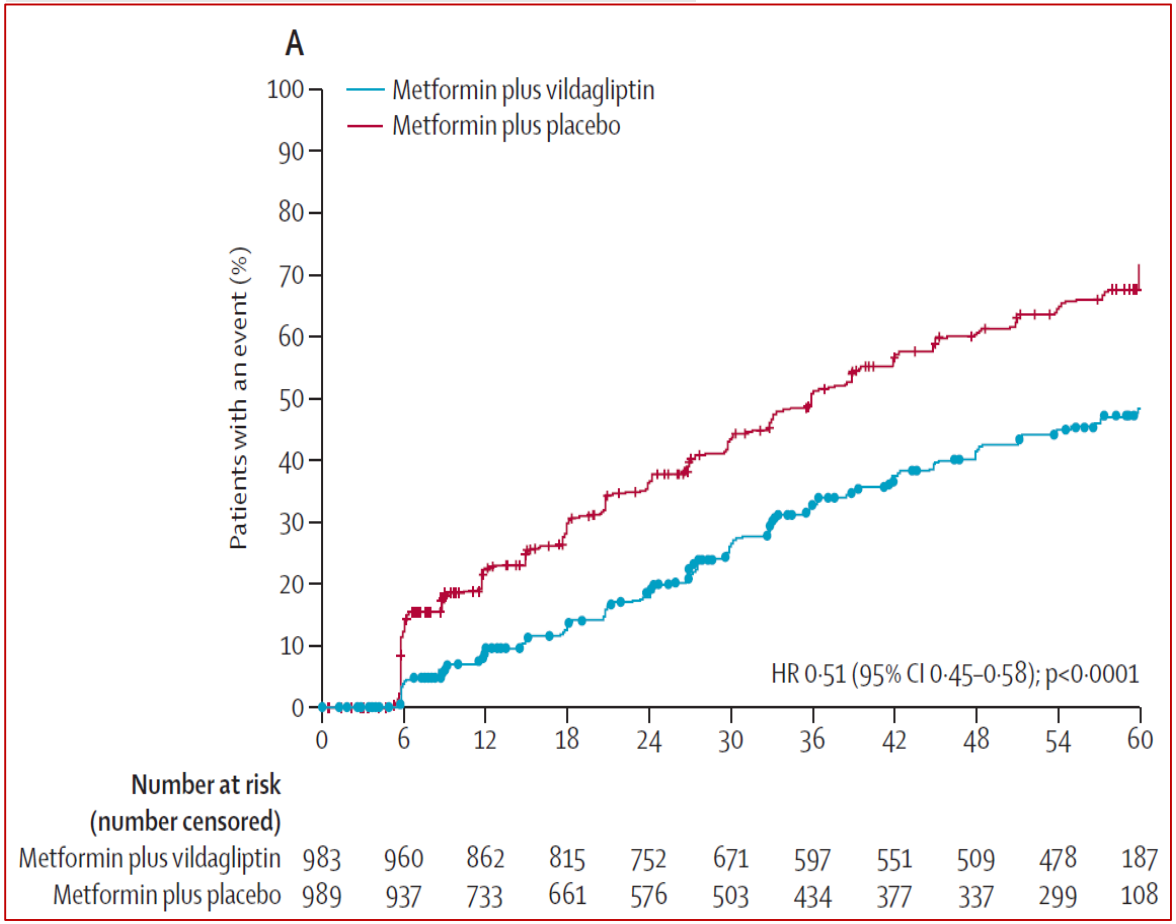
- **Primary outcome:**
  The time from randomisation to initial treatment failure. (HbA1c >7·0% at two consecutive scheduled visits, 13 weeks apart from randomisation through period 1.)

Baseline characteristics

- Age: 54
- HbA1c:
  - Mean: 6.7%
  - HbA1c < 7%: 72.3%
  - HbA1c > 7%: 27.5%
- BMI: 31.2
- Baseline eGFR:
  - Normal (>90): 43.3%
  - Mild (60-90): 53.3%
  - Moderate (30-60): 3.5%
- No significant difference between groups.

Primary outcome

Time to initial treatment failure.



Incidence rate

Combination group: 43.6%

Monotherapy group: 62.1%

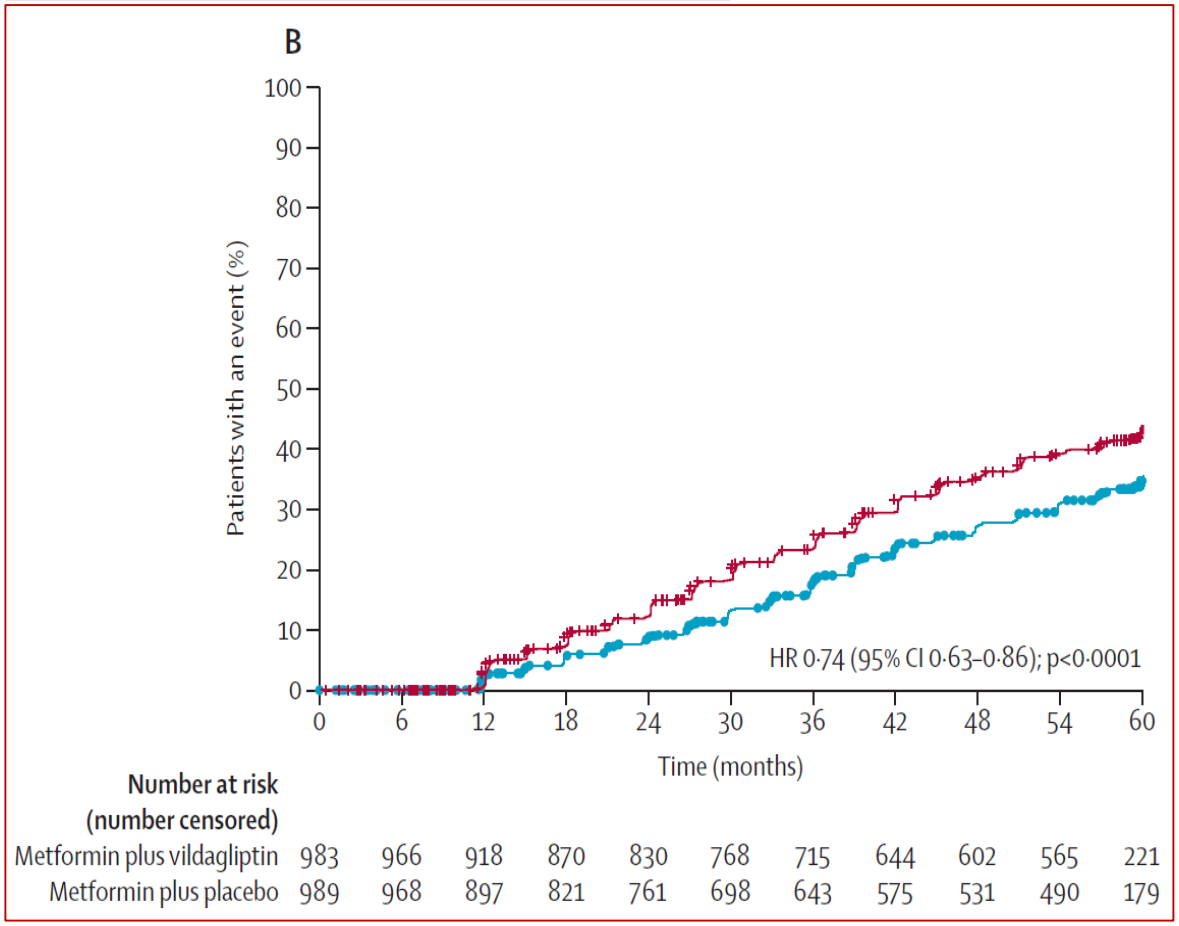
Time to treatment failure

Combination group: 61.9 months

Monotherapy group: 36.1 months

Outcome

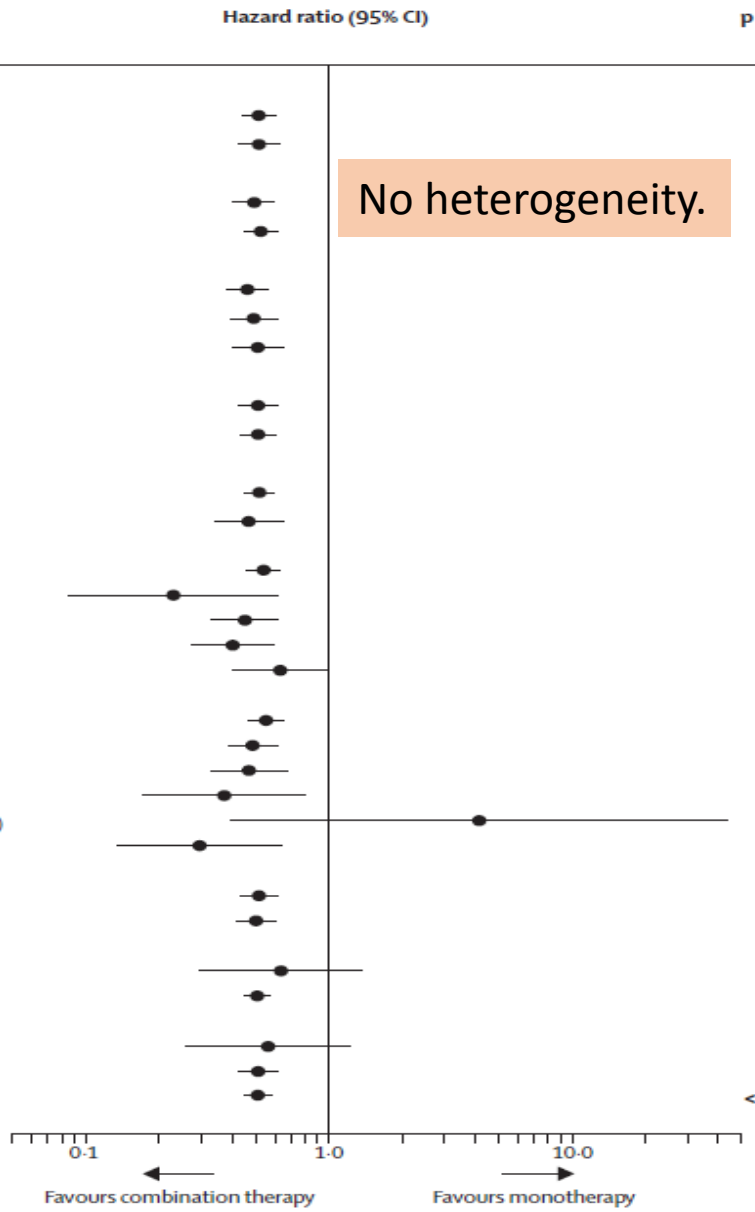
Time to second treatment failure.



Number at risk (number censored)											
Metformin plus vildagliptin	983	966	918	870	830	768	715	644	602	565	221
Metformin plus placebo	989	968	897	821	761	698	643	575	531	490	179

Sub-group analysis

	Metformin plus vildagliptin	Metformin plus placebo	Hazard ratio (95% CI)	p value
HbA_{1c} (mmol/mol; %)				0·48
<53 mmol/mol (7·0%)	260 (36·4%)	376 (54·0%)	0·51 (0·44–0·60)	
≥53 mmol/mol (7·0%)	169 (62·8%)	238 (81·2%)	0·52 (0·42–0·63)	
BMI (kg/m²)				0·70
<30	168 (40·2%)	267 (60·8%)	0·49 (0·41–0·60)	
≥30	261 (46·2%)	347 (63·1%)	0·52 (0·45–0·62)	
Age (years)				0·91
≤51	190 (52·2%)	239 (72·4%)	0·46 (0·38–0·56)	
51–59	133 (45·2%)	205 (62·7%)	0·49 (0·39–0·61)	
>59	106 (32·6%)	170 (51·2%)	0·51 (0·40–0·65)	
Gender				0·88
Male	201 (45·4%)	311 (64·5%)	0·51 (0·43–0·61)	
Female	228 (42·2%)	303 (59·8%)	0·51 (0·43–0·61)	
Current smoker				0·69
No	363 (43·5%)	524 (61·4%)	0·52 (0·45–0·59)	
Yes	66 (44·3%)	90 (66·7%)	0·47 (0·34–0·65)	
Race				0·22
White	273 (45·9%)	374 (61·7%)	0·54 (0·46–0·63)	
Black	8 (30·8%)	17 (77·3%)	0·23 (0·08–0·62)	
Asian	67 (36·6%)	106 (57·9%)	0·45 (0·33–0·62)	
Native American	44 (42·7%)	69 (65·7%)	0·40 (0·27–0·59)	
Other	37 (48·7%)	48 (65·7%)	0·63 (0·40–0·99)	
Geographical region				0·13
Europe	234 (45·3%)	317 (61·2%)	0·55 (0·47–0·65)	
Latin America	121 (46·4%)	177 (66·3%)	0·49 (0·38–0·61)	
Southeast Asia	51 (41·5%)	78 (60·9%)	0·47 (0·33–0·67)	
East Asia	10 (21·7%)	20 (48·8%)	0·37 (0·17–0·80)	
Australia	3 (60·0%)	1 (20·0%)	4·16 (0·40–43·59)	
Africa	10 (31·2%)	21 (70·0%)	0·29 (0·13–0·64)	
eGFR (mL/min per 1·73 m²)				0·77
<90	225 (40·2%)	320 (58·1%)	0·52 (0·43–0·61)	
≥90	204 (48·2%)	294 (67·1%)	0·50 (0·42–0·60)	
eGFR (mL/min per 1·73 m²)				0·59
<60	13 (39·4%)	21 (55·3%)	0·64 (0·29–1·38)	
≥60	416 (43·8%)	593 (62·4%)	0·51 (0·45–0·58)	
eGFR (mL/min per 1·73 m²)				0·77
30 to <60	13 (39·4%)	21 (56·8%)	0·56 (0·26–1·22)	
60 to <90	212 (40·2%)	299 (58·3%)	0·51 (0·43–0·61)	
Overall	**429 (43·6%)**	**614 (62·1%)**	**0·51 (0·45–0·58)**	**<0·0001**



No heterogeneity.

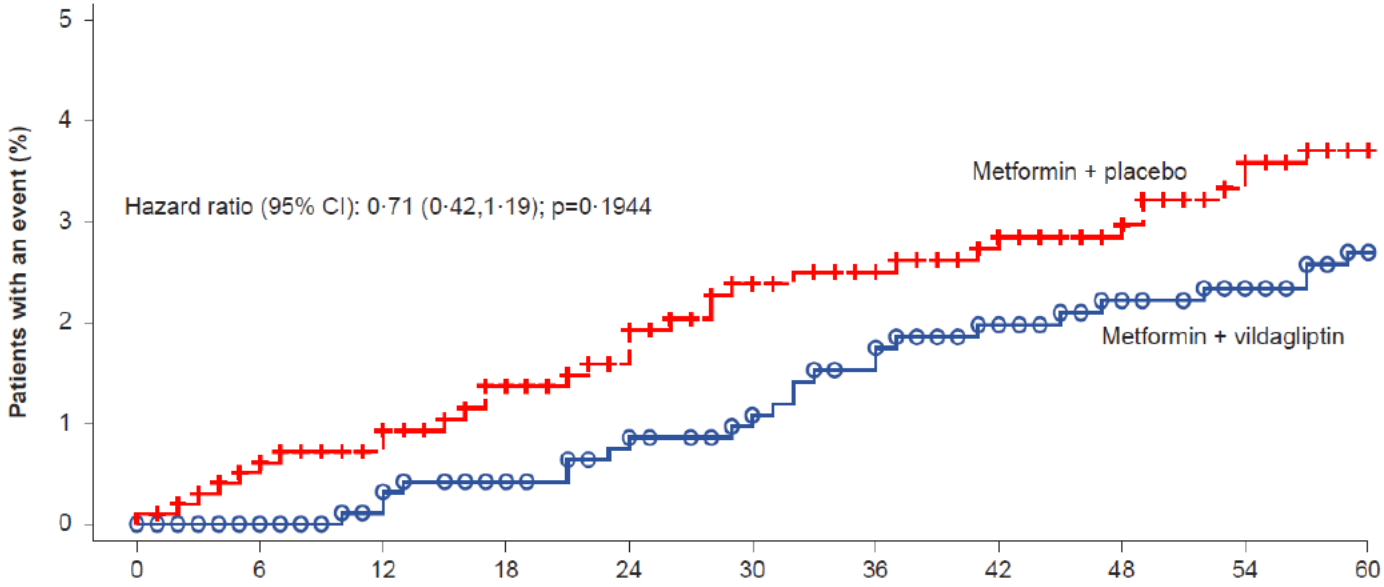
Figure 4: Subgroup analysis of time to initial treatment failure

Safety outcome

- The overall safety and tolerability profile was similar between treatment approaches.
- Hypoglycaemic events are low. (1.3% v.s 0.9%)
- 4% annualised rate of discontinuation was low, and similar between the groups (4.1% in the combination treatment group, 5.3% in the monotherapy group).

Other outcomes

Time to first adjudicated macrovascular events



Patients at risk											
Metformin + vildagliptin	996	970	947	924	912	890	874	846	822	809	731
Metformin + placebo	1003	967	923	895	875	852	842	824	806	783	710
Number of events											
Metformin + vildagliptin	0	0	3	4	8	10	16	18	20	21	24
Metformin + placebo	1	6	9	13	18	22	23	26	27	32	33

Conclusion

- Early intervention with a combination therapy provides greater and durable long-term benefits compared with the current standard-of-care initial metformin monotherapy for patients with newly diagnosed type 2 diabetes.

9.6 Early combination therapy can be considered in some patients at treatment initiation to extend the time to treatment failure. **A**

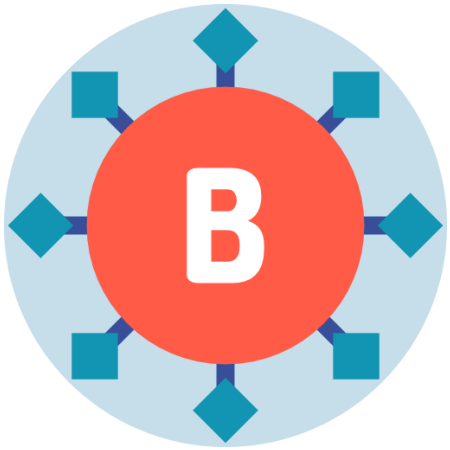
(1)原則上第二型糖尿病治療應優先使用 metformin，或考慮早期開始使用胰島素。除有過敏、禁忌症、不能耐受或仍無法理想控制血糖的情形下，可使用其他類口服降血糖藥物。

(2)TZD 製劑、DPP-4抑制劑、SGLT-2抑制劑、以及含該3類成分之複方製劑，限用於已接受過最大耐受劑量的 metformin 仍無法理想控制血糖之第二型糖尿病病人，且 SGLT-2抑制劑與 DPP-4抑制劑及其複方製劑宜二種擇一種使用。

THE LANCET

Lancet 2019; 394: 2271–81

Four versus six cycles of CHOP chemotherapy in combination with six applications of rituximab in patients with aggressive B-cell lymphoma with favourable prognosis (FLYER): a randomised, phase 3, non-inferiority trial



B cell
non-Hodgkin lymphoma

6 cycles (every 21 days)

R	Rituximab	375 mg/m²
C	Cyclophosphamide	750 mg/m²
H	Doxorubicin	50 mg/m²
O	Vincristine	50 mg/m²
P	Prednisolone (Oral)	100 mg

International Prognostic Index

- Age >60
- Serum lactate dehydrogenase concentration above normal
- ECOG performance status ≥2
- Ann Arbor stage III or IV
- Number of extranodal disease sites >1

Method

- Trial design: open-label, international, multicentre, prospective, randomised phase 3 non-inferiority trial.

- **Age: 18-60** **(N=592)**
- **Stage I or II, normal LDH, ECOG: 0-1**
- **Without bulky disease (maximal tumour diameter <7·5 cm).**

6 cycle R-CHOP (N=295)

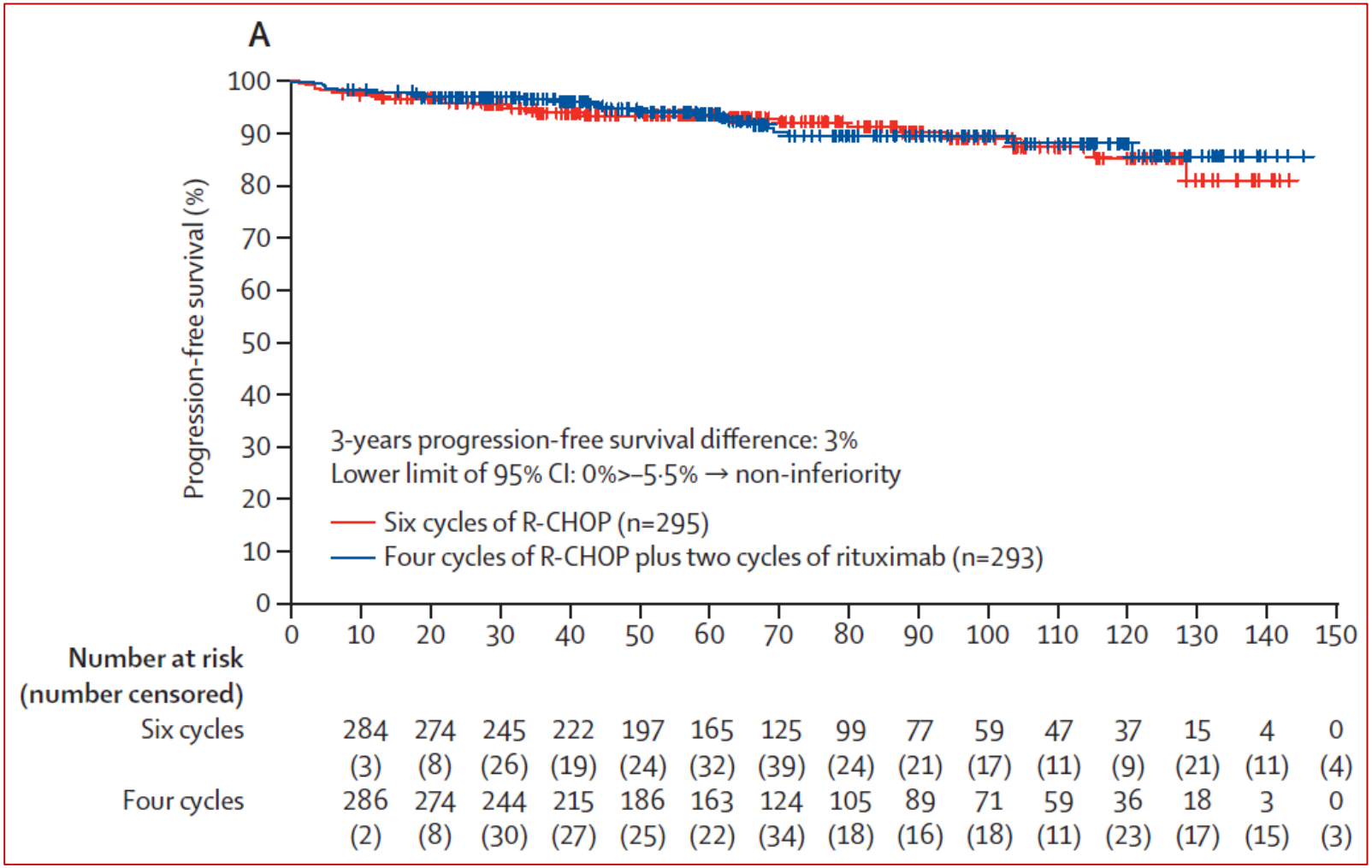
4 cycle R-CHOP + 2 dose Rituximab (N=297)

- **Primary outcome: Progression-free survival after 3 years**

Primary outcome

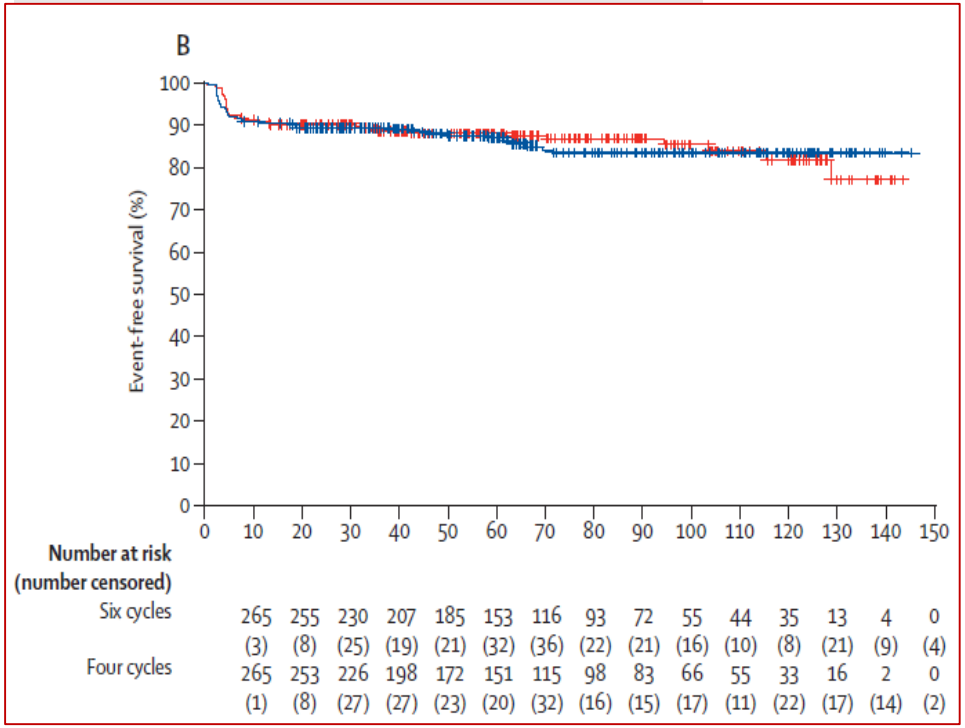
Progression-free survival

Median follow-up: 66 months

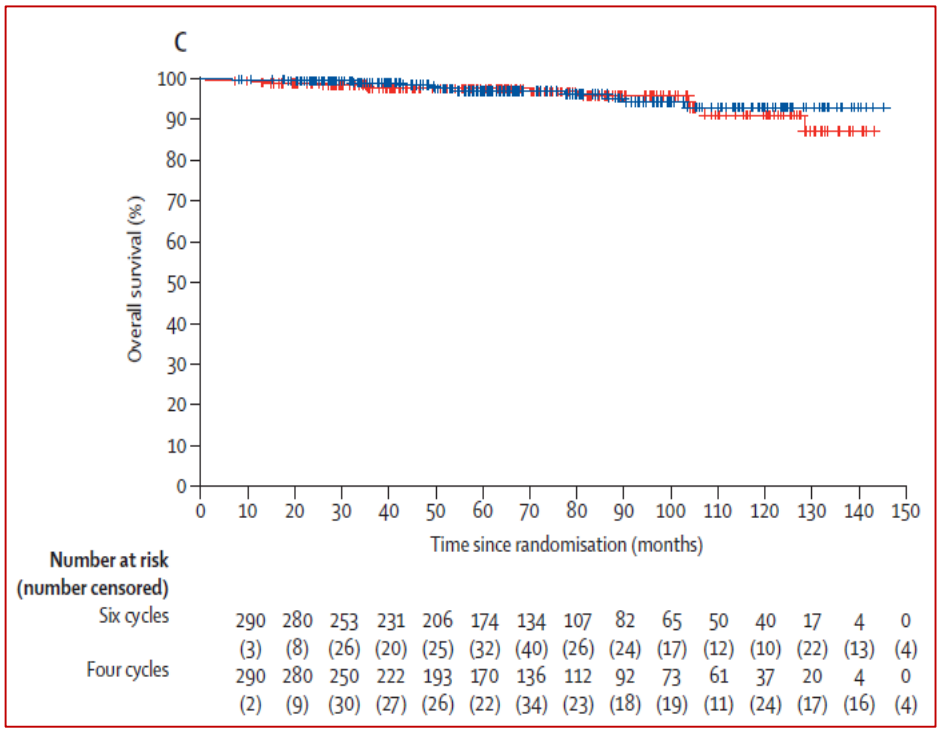


Outcome

Event-free survival



Overall survival



Outcome

	Four cycles of R-CHOP plus two cycles of rituximab group (n=293)	Six cycles of R-CHOP group (n=295)
Complete response or unconfirmed complete response	267 (91%; 87–94)	271 (92%; 88–95)
Partial response*	8 (3%)	11 (4%)
No change	0	1 (<1%)
Progressive disease	3 (1%)	3 (1%)
Not evaluated or missing data†	15 (5%)	9 (3%)
Relapse after complete response or unconfirmed complete response	11/267 (4%; 2–7)	13/271 (5%; 3–8)
Relapse after partial response	2/8 (25%)	2/11 (18%)
Relapse after no change	0	1/1 (100%)
Relapse after not evaluated or missing data	3/15 (20%)	2/9 (22%)

Adverse events

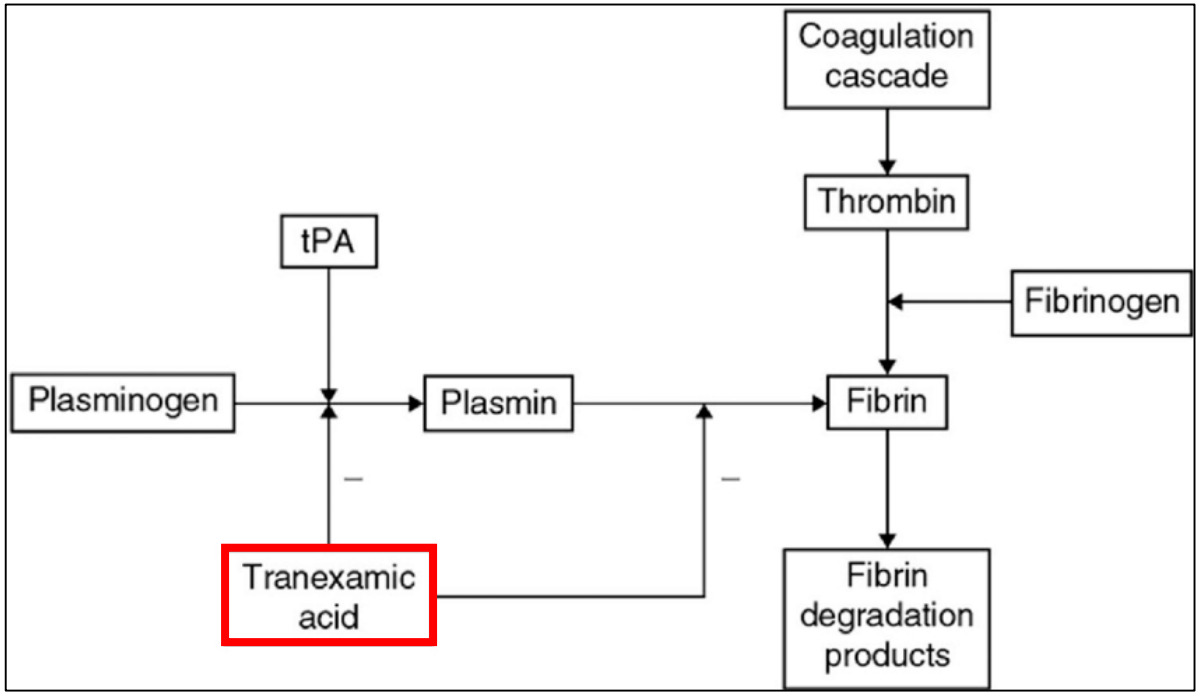
	Four cycles of R-CHOP plus two cycles of rituximab group (n=293)		Six cycles of R-CHOP group (n=295)	
	Any grade	Grades 3–4	Any grade	Grades 3–4
Leucocytopenia*	171	80	237	110
Anaemia†	107	2	172	8
Thrombocytopenia‡	16	5	17	7
Non-haematological adverse event	1036	52	1280	71
Infection	116	22	156	23
Paresthesia	342	16	370	14
Nausea	221	6	319	12
Vomiting	61	1	117	7
Mucositis	80	1	105	3
Constipation	100	4	69	2
Mood alteration	59	1	60	0
Diarrhoea	33	0	40	6
Arrhythmia	8	1	24	0
Allergy	16	0	19	3
Paraplegia	..	..	1§	1
Therapy-associated deaths	..	..	2¶	..

THE LANCET

Lancet 2019; 394: 1713–23

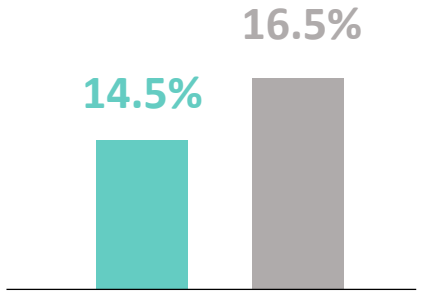
Effects of tranexamic acid on death, disability, vascular occlusive events and other morbidities in patients with acute traumatic brain injury (CRASH-3): a randomised, placebo-controlled trial

Background: Intracranial bleeding is common after traumatic brain injury (TBI) and can cause brain herniation and death. We aimed to assess the effects of tranexamic acid in patients with TBI.



CRASH-2

Mortality: RR: 0.91; p=0.0035



Traumatic extracranial bleeding

Ref: Crash-2: *Lancet* 2010; 376: 23–32.

Method

- Trial design: international, multi-centre, randomised, placebo-controlled trial

(N=12737)

- **Adults with TBI who were within 3 h of injury***
- **GCS score of 12 or lower or any intracranial bleeding on CT scan.**
- **No major extracranial bleeding.**

Tranexamic acid (N=6406)

Dose: loading dose 1 g over 10 min then infusion of 1 g over 8 h

Placebo (N=6331)

N=4613 within 3h

N=4514 within 3h

- **Primary outcome:**
  Head injury-related death in hospital within 28 days of injury in patients treated within 3 h of injury.

Baseline characteristics

	Tranexamic acid (n=4649)	Placebo (n=4553)
Sex*		
Men	3742 (80%)	3660 (80)
Women	906 (19%)	893 (20)
Age, years		
Mean (SD)	41·7 (19·0)	41·9 (19·0)
<25	1042 (22%)	996 (22%)
25–44	1716 (37%)	1672 (37%)
45–64	1169 (25%)	1184 (26%)
≥65	722 (16%)	701 (15%)
Time since injury, h		
Mean (SD)	1·9 (0·7)	1·9 (0·7)
≤1	877 (19%)	869 (19%)
>1–2	2003 (43%)	1889 (41%)
>2–3	1769 (38%)	1795 (39%)
Systolic blood pressure, mm Hg		
<90	89 (2%)	85 (2%)
90–119	1508 (32%)	1490 (33%)
120–139	1461 (31%)	1504 (33%)
≥140	1576 (34%)	1466 (32%)
Unknown	15 (<1%)	8 (<1%)

	Tranexamic acid (n=4649)	Placebo (n=4553)
Glasgow Coma Scale score		
3	495 (11%)	506 (11%)
4	213 (5%)	213 (5%)
5	163 (4%)	172 (4%)
6	221 (5%)	232 (5%)
7	311 (7%)	294 (6%)
8	354 (8%)	315 (7%)
9	335 (7%)	292 (6%)
10	371 (8%)	364 (8%)
11	375 (8%)	390 (9%)
12	476 (10%)	478 (10%)
13	297 (6%)	312 (7%)
14	526 (11%)	458 (10%)
15	484 (10%)	492 (11%)
Unknown	28 (1%)	35 (1%)
Pupil reaction		
None reacted	425 (9%)	440 (10%)
One reacted	374 (8%)	353 (8%)
Both reacted	3706 (80%)	3636 (80%)
Unable to assess or unknown	144 (3%)	124 (3%)

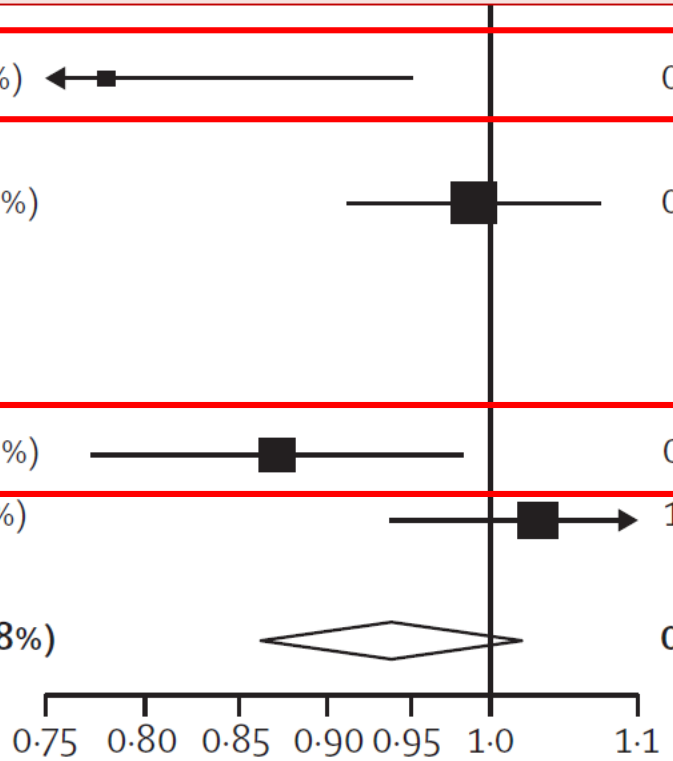
Severe: 40%

Moderate: 33%

Mild: 27%

Primary Outcome

	Tranexamic acid	Placebo	Risk ratio (95% CI)
All	855/4613 (18·5%)	892/4514 (19·8%)	0·94 (0·86–1·02)
Excluding patients with GCS score of 3 or bilateral unreactive pupils*	485/3880 (12·5%)	525/3757 (14·0%)	0·89 (0·80–1·00)
GCS			
Mild to moderate (9–15)	166/2846 (5·8%)	207/2769 (7·5%)	0·78 (0·64–0·95)
Severe (3–8)	689/1739 (39·6%)	685/1710 (40·1%)	0·99 (0·91–1·07)
p=0·030			
Pupil reactivity			
Both react	440/3820 (11·5%)	493/3728 (13·2%)	0·87 (0·77–0·98)
Any non-reactive	415/793 (52·3%)	399/786 (50·8%)	1·03 (0·94–1·13)
p=0·032			
Overall	**855/4613 (18·5%)**	**892/4514 (19·8%)**	**0·94 (0·86–1·02)**



Effect of tranexamic acid on head injury-related death by severity and time to treatment in all patients

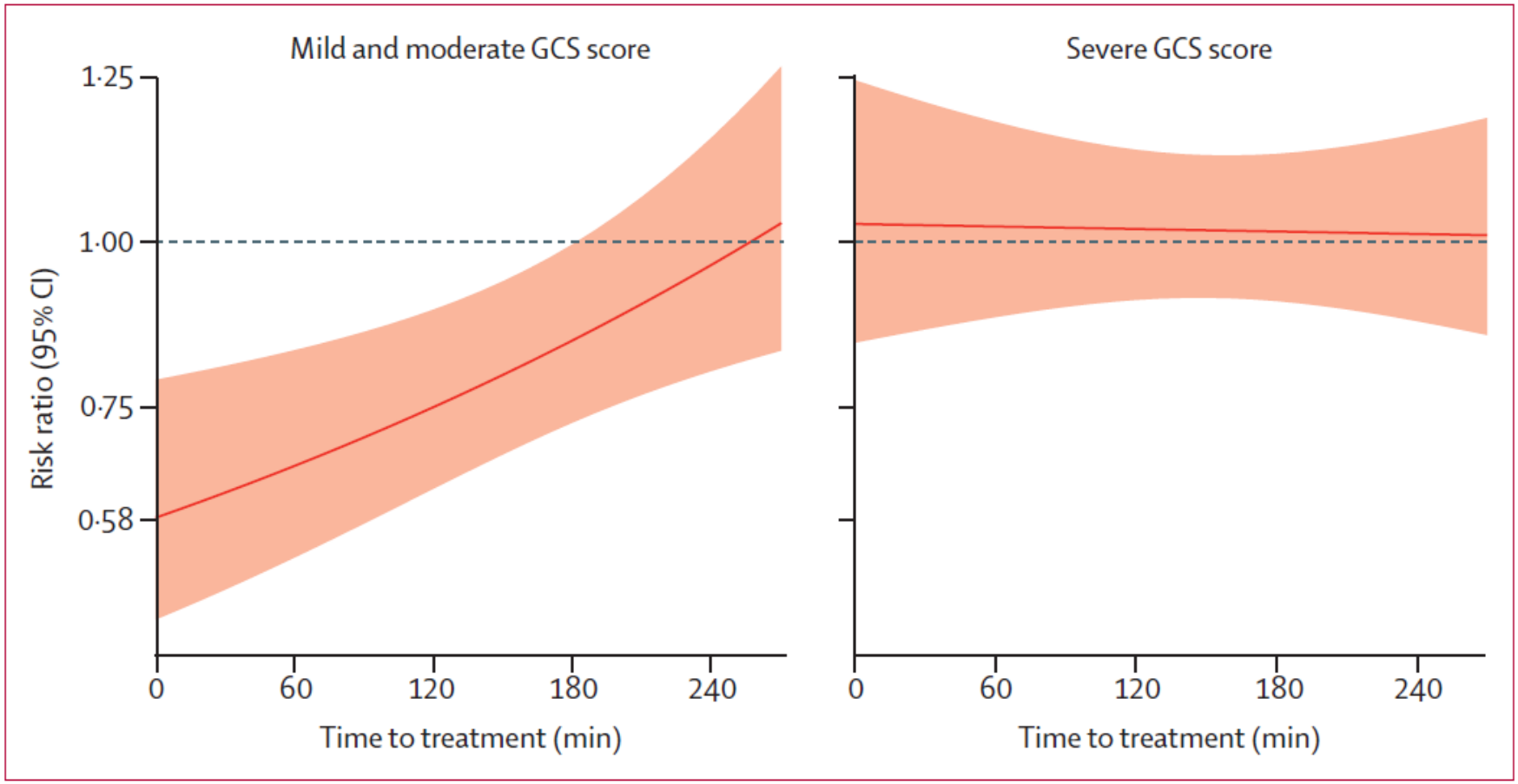


Figure 4: Effect of tranexamic acid on head injury-related death by severity and time to treatment in all patients

Other outcomes

- No effects of disability, vascular occlusive events, and other complications.
- No evidence of any increased risk of adverse events.

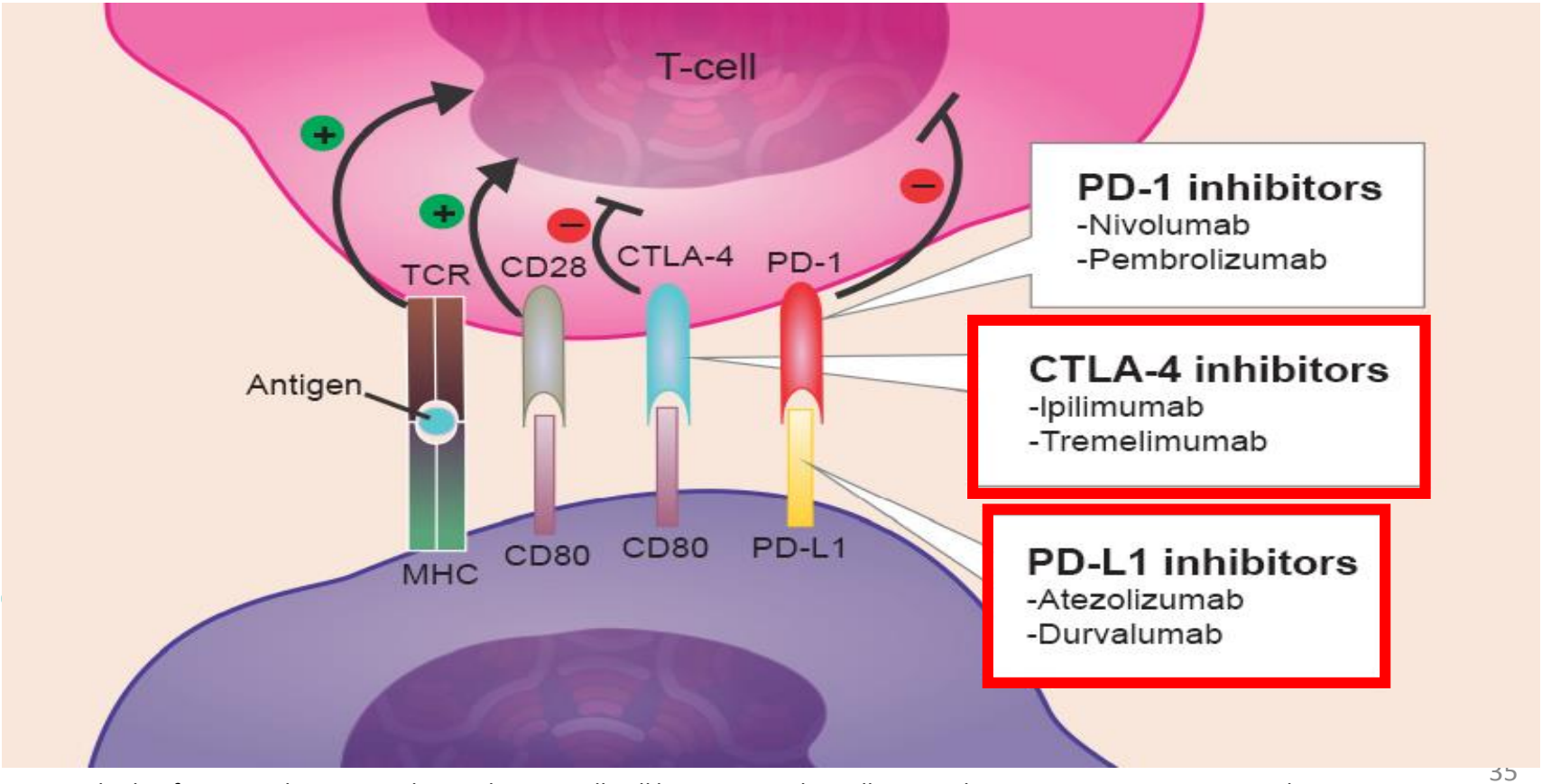
Conclusion

- Tranexamic acid is safe in patients with TBI and that treatment within 3 h of injury reduces head injury-related deaths.

THE LANCET

Lancet 2019; 394: 1713–23

Durvalumab (Imfinzi) plus platinum–etoposide versus platinum–etoposide in first-line treatment of extensive-stage small-cell lung cancer (CASPIAN): a randomised, controlled, open-label, phase 3 trial

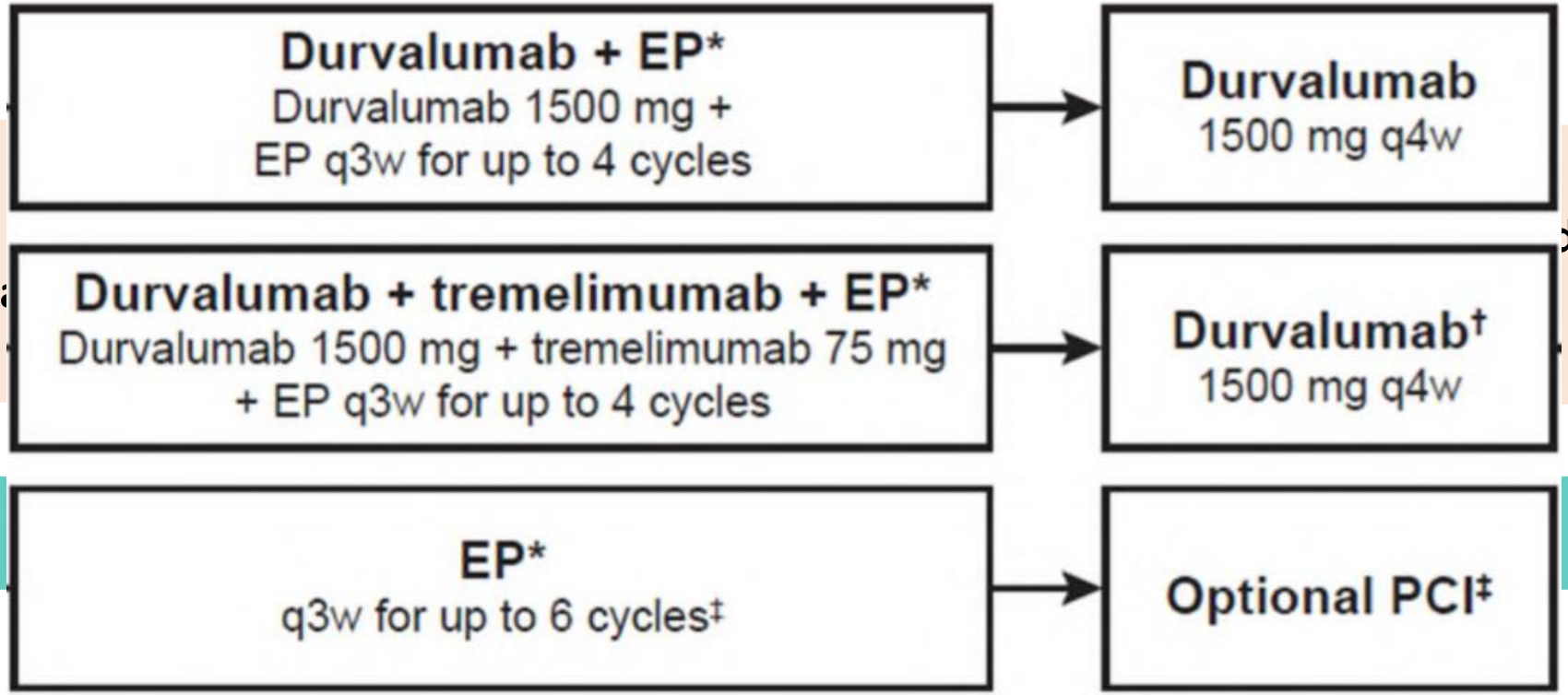


Ref: Potential role of immunotherapy in advanced non-small-cell lung cancer, de Mello RA, Veloso AF, Esrom Catarina P, Nadine S, Antoniou G

Method

- Trial design: randomised, open-label, phase 3 trial

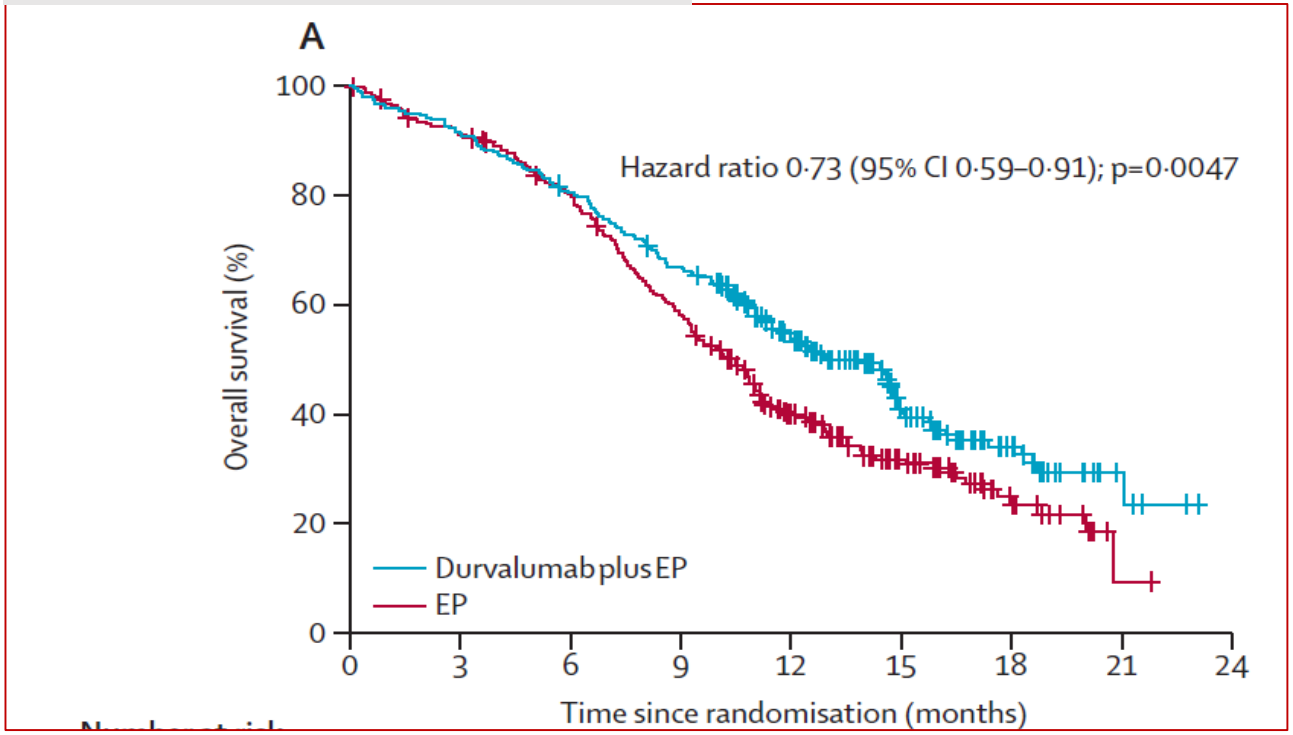
- **Adults with untreated ES-SCLC**
- **ECOG status 0 or 1.** **(N=805)**
- **Life expectancy of at least 12 weeks.**
- **Suitability for first-line platinum-based chemotherapy**
- **Adequate organ and marrow function**



Outcome

- Medium follow up: 14.2 months.

Overall survival



	Durvalumab	Platinum–etoposide
Overall survival (months)	13	10.3
12 month survival rate	54%	40%
18 month survial rate	34%	25%

Safety

- **More** AEs in leukopenia, cough, hyponatremia, hypertension, lipase increased, amylase increased.
- **Less** AEs in neutropenia, anemia, thrombocytopenia.
- Others AEs are similar.

台灣部核適應症 (免疫療法)

- Tecentriq (Atezolizumab)
  - 小細胞肺癌-與carboplatin和etoposide併用，適用於第一線治療成人擴散期小細胞肺癌(extensive stage small cell lung cancer)。
- Keytruda (Pembrolizumab)
  - 小細胞肺癌-治療先前至少已接受兩種治療的局部晚期或轉移性小細胞肺癌 (SCLC) 病人。本項適應症係依據腫瘤整體反應率及治療反應持續時間加速核准，此適應症仍須執行確認性試驗以證明其臨床效益。
- Imfinzi (Durvalumab)
  - 台灣未核准用於小細胞肺癌。

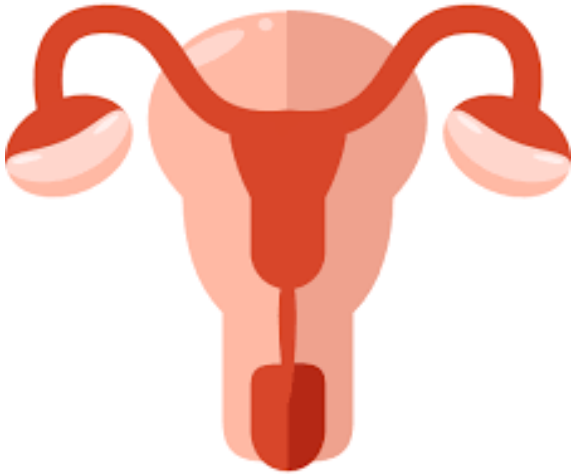
Immunotherapy (SLC)

	Imfinzi	Tecentriq	Keytruda
Drugs	Durvalumab	Atezolizumab	Pembrolizumab
Dosage	500 mg/vial	1200 mg/vial	100 mg/vial
Dose	1500 mg Q3W (4 cycle) ,1500 mg Q4W	1200 mg Q3W	200 mg Q3W
Cost/vial	$92983	$145695	$71523
Cost/year	$3905286	$2525380	$2479464
Efficacy	Overall survival: 13 v.s 10.3 months	Over survival: 12.3 v.s 10.3 months	ORR: 19% Complete response:2% Durable response >6 mon: 94% >12 mon: 63% >18 mon: 56%

THE LANCET

Lancet 2019; 394: 2084–95

Weekly dose-dense chemotherapy in first-line epithelial ovarian, fallopian tube, or primary peritoneal carcinoma treatment (ICON8): primary progression free survival analysis results from a GCIG phase 3 randomised controlled trial



Epithelial Ovarian Cancer (EOC)

FIGO Stage	
I	Tumor limited to 1 ovary or both ovaries.
II	Pelvic extension (below the pelvic brim) or primary peritoneal cancer.
III	Confirmed spread to the peritoneum outside the pelvis and/or metastasis to the retroperitoneal lymph nodes
IV	Distant metastasis.

Treatment

1. Primary surgical cytoreduction → Systemic chemotherapy.
2. Neoadjuvant chemotherapy → Surgery

First-line:

Carboplatin [AUC] 5 or 6 + Paclitaxel 180 mg/m^2 **Q3W** (6 cycles)

Lancet Oncol 2013; 14: 1020–26

Long-term results of dose-dense paclitaxel and carboplatin versus conventional paclitaxel and carboplatin for treatment of advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer (JGOG 3016): a randomised, controlled, open-label trial

P	Stage II–IV ovarian cancer	C	Carboplatin [AUC] 6 Q3W + Paclitaxel 180 mg/m^2 Q3W
I	Carboplatin [AUC] 6 Q3W + Paclitaxel 80 mg/m^2 QW	O	Progression-free survival: 28·2 vs 17·5 months (HR: 0·76, 95% CI 0·62–0·91; p=0·0037)

Interpretation Dose-dense treatment offers better survival than conventional treatment and is a potential new standard of care for first-line chemotherapy for patients with advanced epithelial ovarian cancer.

Method

- Trial design: international, open-label, randomized phase 3, three-arm trial

- **Stage IC–IV epithelial ovarian cancer.**
- **ECOG: 0-2**
- **Life expectancy longer than 12 weeks**
- **Adequate haematological, renal, and hepatic functions.**

(N=1566)

(1) Carboplatin [AUC] 5or6 Q3W + Paclitaxel 175 mg/m^2 Q3W (N=522)

(2) Carboplatin [AUC] 5or6 Q3W + Paclitaxel 80mg/m2 QW (N=523)

(3) Carboplatin [AUC] 2 QW + Paclitaxel 80mg/m^2 QW (N=521)

- **Primary outcome: Progression-free survival.**

Baseline characteristics

- Age: 62
- **Region: UK (89%)**

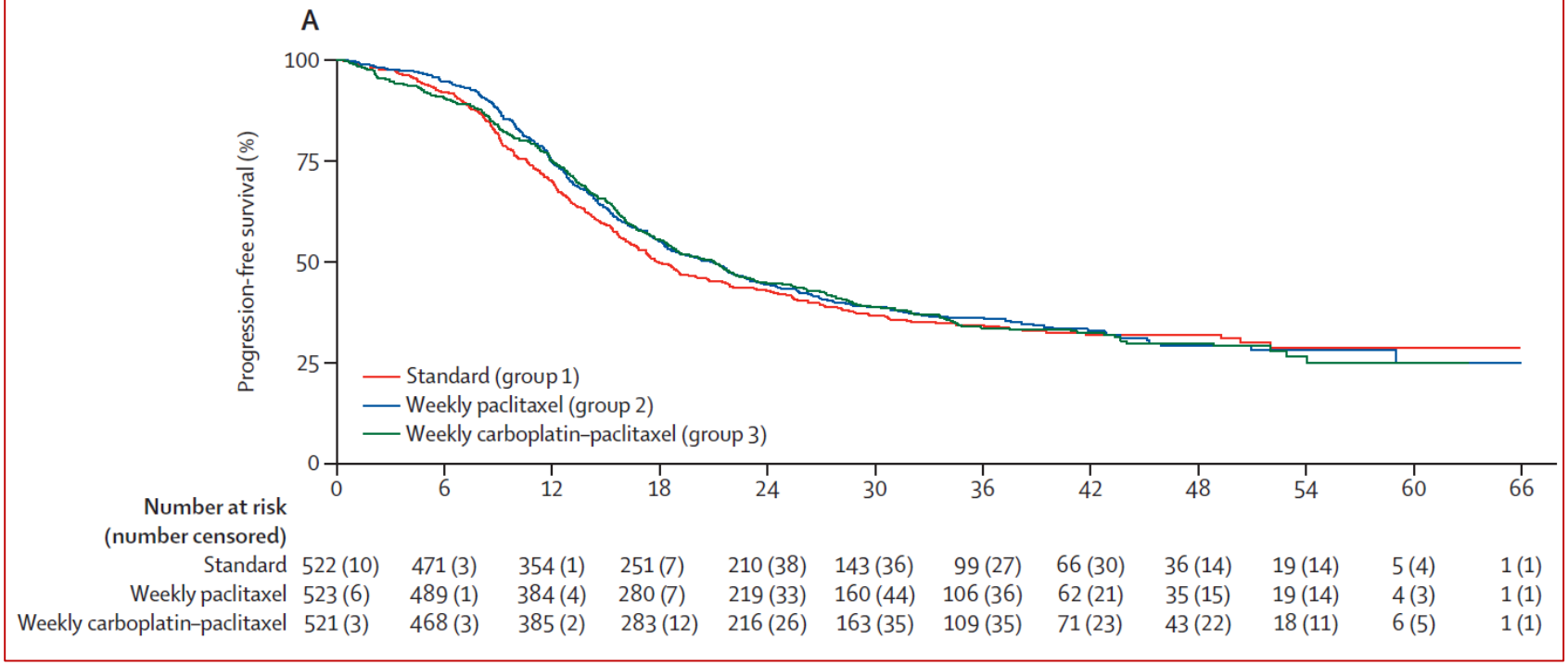
Origin	
Ovary (epithelial)	420 (81%)
Fallopian tube	24 (5%)
Primary peritoneal	77 (15%)
Missing data	1 (<1%)

FIGO stage	
IC or IIA	56 (11%)
IIB or IIC	47 (9%)
IIIA or IIIB	43 (8%)
IIIC	273 (52%)
IV	103 (20%)

Timing of surgery	
Immediate	251 (48%)
Delayed	257 (49%)
Inoperable	14 (3%)

Primary outcome

Progression-free survival



Number at risk (number censored)												
Standard	522 (10)	471 (3)	354 (1)	251 (7)	210 (38)	143 (36)	99 (27)	66 (30)	36 (14)	19 (14)	5 (4)	1 (1)
Weekly paclitaxel	523 (6)	489 (1)	384 (4)	280 (7)	219 (33)	160 (44)	106 (36)	62 (21)	35 (15)	19 (14)	4 (3)	1 (1)
Weekly carboplatin–paclitaxel	521 (3)	468 (3)	385 (2)	283 (12)	216 (26)	163 (35)	109 (35)	71 (23)	43 (22)	18 (11)	6 (5)	1 (1)

Restricted mean survival time

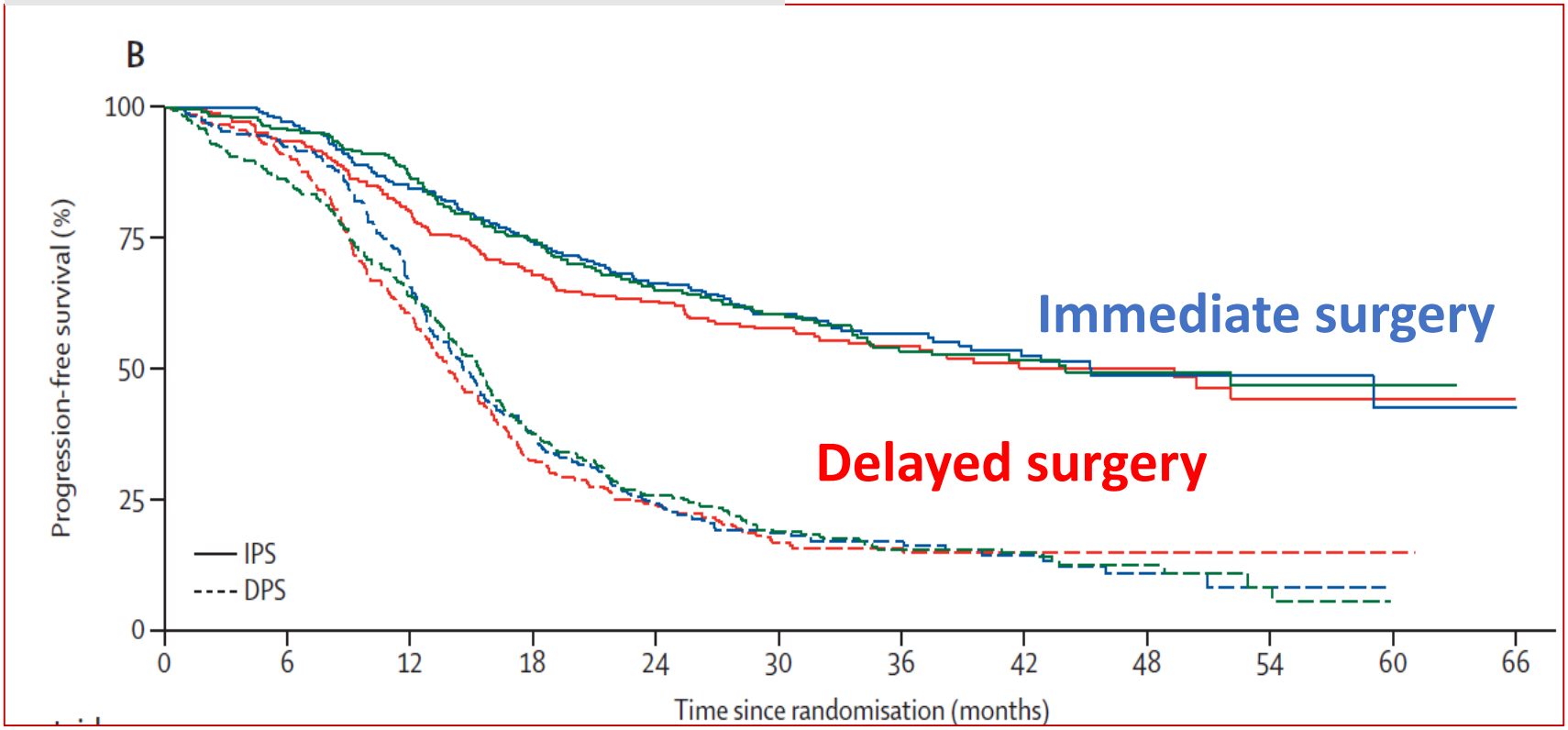
24·4 months [97·5% CI 23·0–26·0] in group 1.

24·9 months [24·0–25·9] in group 2.

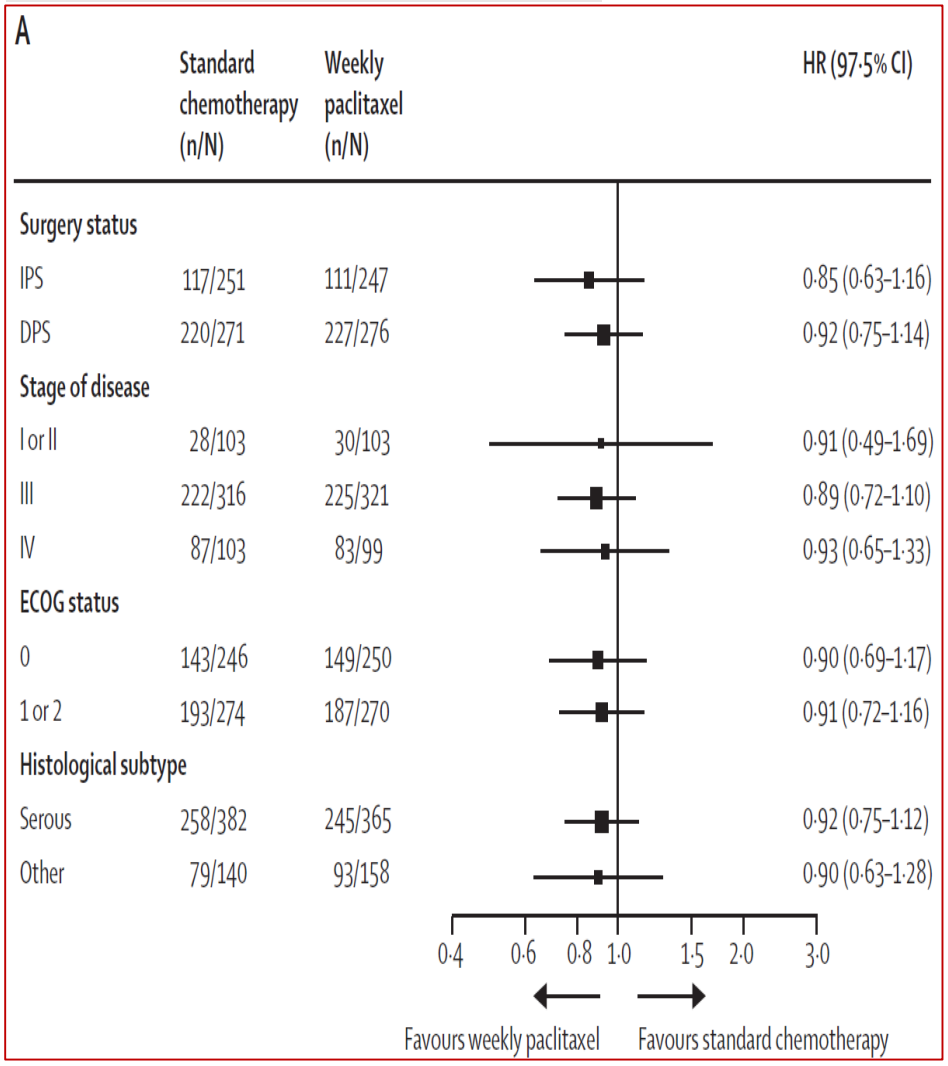
25·3 months [23·9–26·9] in group 3.

Primary outcome

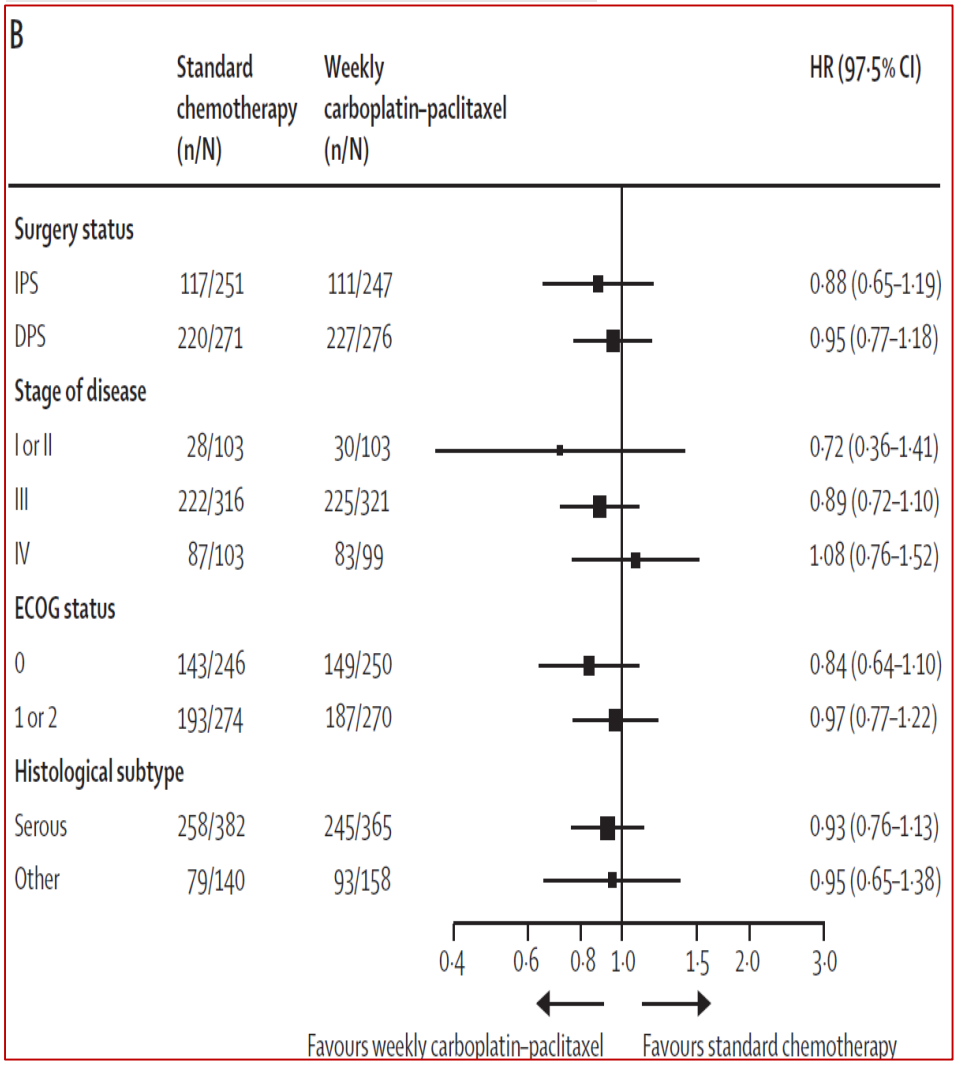
Progression-free survival



PFS (Group 1 vs. 2)



PFS (Group 1 vs. 3)



Safety outcome

- Both weekly treatments were associated with more treatment modifications and a higher incidence of grade 3 or higher toxic effects.

Conclusion

- Weekly dose-dense paclitaxel should no longer be recommended as a component of first-line epithelial ovarian cancer treatment for women of non-Japanese ethnic origin.

Conventional vs. Dose-dense

	ICON-8	JGOG 3016	MITO-7
Comparison	C Q3W + P Q3W C Q3W + P QW C QW + P QW	C Q3W + P Q3W C Q3W + P QW	C Q3W + P Q3W C (AUC 2) QW+ P (**60**) QW
Efficacy (PFS)	No difference	Dose dense	No difference
Safety	Conventional	Conventional	Dose dense (AE, QOL)
Population	European (UK)	Asian (Japan)	European (Italy, France)

Drugs (2019) 79:1947–1962

Once-Daily versus Twice-Daily Tacrolimus in Kidney Transplantation: A Systematic Review and Meta-analysis of Observational Studies

Tacrolimus Once Daily (ADVAGRAF) Versus Twice Daily(PROGRAF) in *De Novo* Renal Transplantation: A Randomized Phase III Study

	Overall population		Per-protocol set	
	Tacrolimus BID (n = 336)	Tacrolimus QD (n = 331)	Tacrolimus BID (n = 291)	Tacrolimus QD (n = 280)
Primary endpoint				
Local BPAR over 24 weeks				
Event rate for BPAR	14.9%	18.6%	15.8%	20.4%
p-Value†	0.245		0.182	
Treatment difference (Tacrolimus QD minus Tacrolimus BID)	3.8%		4.5%	

Method: Systematically reviewed all observational studies that compared clinical outcomes between ER-Tac and IR-Tac in KTRs.

Outcome

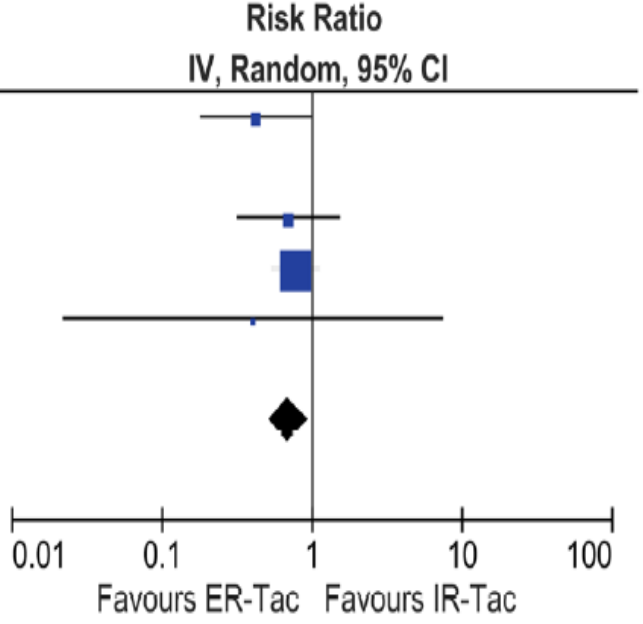
- Recruited 10 studies (1176 adults).

12-month biopsy-proven acute rejection

Study or Subgroup	ER-Tac Events	ER-Tac Total	IR-Tac Events	IR-Tac Total	Weight	Risk Ratio IV, Random, 95% CI	Year
Fanous 2013	7	106	15	95	13.3%	0.42 [0.18, 0.98]	2013
Ishida 2013	0	10	0	35		Not estimable	2013
Masutani 2014	15	90	7	29	15.3%	0.69 [0.31, 1.53]	2014
Niioka 2017	26	80	59	140	70.3%	0.77 [0.53, 1.12]	2017
Ho 2019	0	19	3	55	1.1%	0.40 [0.02, 7.41]	2019
Total (95% CI)		**305**		**354**	**100.0%**	**0.69 [0.51, 0.95]**	
Total events	48		84				

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.80$, df = 3 (P = 0.61); $I^2 = 0\%$

Test for overall effect: Z = 2.30 (P = 0.02)



- No difference in other outcomes.

ADVERSE DRUG REACTION BULLETIN

Adverse Drug Reaction Bulletin. 318(1):1231-1234, October 2019.

Drug causes of intracerebral haemorrhage

Drug cause HTN

- Oral contraceptives
- Sympathomimetic drugs (e.g. ephedrine, phenylephrine)
- NSAIDs
- Corticosteroids
- Immunomodulators (e.g. ciclosporin, leflunamide, and infliximab)
- Antipsychotics/ Antidepressants
- EPO
- Ergot alkaloids

Drugs cause bleeding

- Anticoagulants/ Thrombolytic drugs

Drugs of abuse

- Amphetamines, cocaine.

Statins*

Abstract

THE LANCET

Lancet 2019; 394: 2263–70

Irbesartan in Marfan syndrome (AIMS): a double-blind, placebo-controlled randomised trial

P	Marfan syndrome	**C**	Placebo
I	Irbesartan 150 mg (300 mg as tolerated)	**O**	Change in aortic root systolic diameter (mm): 0.53 vs. 0.74 Difference: -0.22 (-0.41 to -0.02)

THE LANCET

Lancet 2019; 394: 1325–34

Percutaneous coronary intervention versus coronary artery bypass grafting in patients with three-vessel or left main coronary artery disease: 10-year follow-up of the multicenter randomised controlled SYNTAX trial

P	De-novo three-vessel or left main CAD	**C**	CABG
I	PCI (first-generation paclitaxel-eluting stents)	**O**	10-years all-cause mortality: HR: 1.17; p=0.092 10-years ACM in three vessel disease: HR: 1.41; (95% CI 1.1-1.8)

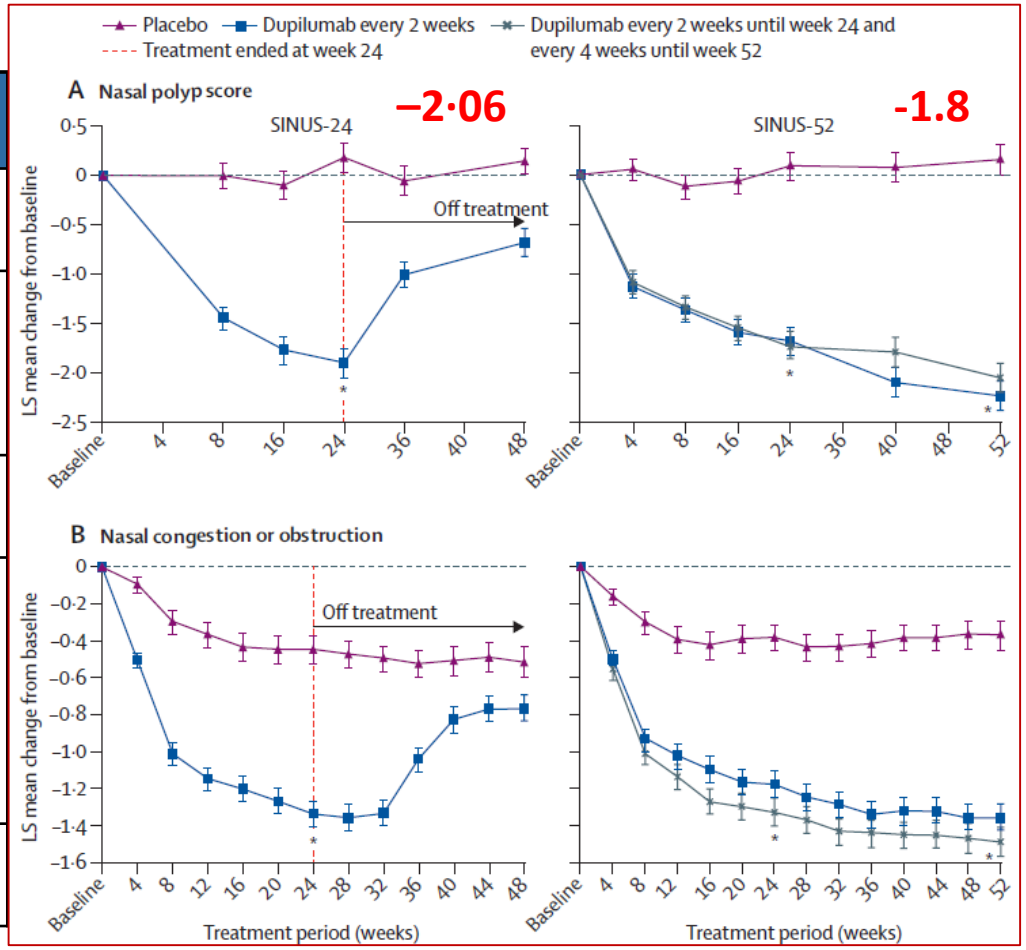
THE LANCET

Lancet 2019; 394: 1638–50

Efficacy and safety of dupilumab in patients with severe chronic rhinosinusitis with nasal polyps (LIBERTY NP SINUS-24 and LIBERTY NP SINUS-52): results from two multicentre, randomised, double-blind, placebo-controlled, parallel-group phase 3 trials

LIBERTY NP SINUS– 24

NPS	
0	Absence of polyps
1	Small polys in middle meatus/ edema
2	Middle meatus obstruction
3	Polyps extend beyond middle meatus without complete nasal obstruction
4	Massive nasal polyposis



THE LANCET

Lancet 2019; 394: 1807–15

Recurrence of breast cancer after regional or general anaesthesia: a randomised controlled trial

P	Women having potentially curative primary breast cancer resections	**C**	General anaesthesia (sevoflurane/opioid analgesia)
I	Regional anaesthesia analgesia (paravertebral block/ propofol)	**O**	No difference in recurrence rate: 10% vs. 10% (HR: 0·97, 95% CI 0·74–1·28) No difference in incisional pain.

	Pembrolizumab alone vs. CT	Pembrolizumab+CT vs. CT
PD L1 CPS >1	12·3 *vs.* 10·3 months (HR: 0·78 [0·64–0·96], p=0·0086)	13·6 *vs.* 10·4 months (HR: 0·65 [0·53–0·80], p<0·0001)
PD L1 CPS>20	14·9 *vs.* 10·7 months (HR: 0·61 [0·45–0·83], p=0·0007)	14·7 *vs.* 11·0 months (HR: 0·60 [0·45–0·82], p=0·0004)
All population	11·6 *vs.* 10·7 months (HR: 0·85 [0·71–1·03], non-inferior)	13·0 *vs.* 10·7 months (HR: 0·77 [0·63–0·93], p=0·0034)

Lancet 2019; 394: 2108–17

- JAK1 selective inhibitor

citinib in patients with active
CT-AXIS 1): a multicentre,
lacebo-controlled, phase 2/3 trial

ASAS response
1. Patient global assessment of disease activity.
2. Patient assessment of back pain.
3. Bath Ankylosing Spondylitis Functional Index (BASFI).
4. Inflammation defined as the mean of the BASDAI questions on severity and duration of morning stiffness.

C	**Placebo**
O	**ASAS 40 response at week 14:** **48 [52%] of 93 patients vs. 24 [26%] of 94 patients; p=0·0003**

Lancet 2019; 394: 2096–107

Isatuximab plus pomalidomide and low-dose dexamethasone versus pomalidomide and low-dose dexamethasone in patients with relapsed and refractory multiple myeloma (ICARIA-MM): a randomised, multicentre, open-label, phase 3 study

P	**Relapsed and refractory multiple myeloma had received at least two previous treatment.**	**C**	**Pomalidomide 4 mg +** **Dexamethasone 40 mg.**
I	**Isatuximab 10 mg/kg +** **Pomalidomide 4 mg +** **Dexamethasone 40 mg**	**O**	**Progression-free survival** **11.5 vs. 6.5 months (HR: 0.6; p=0.001)** **No difference in overall survival.**

THE LANCET

Lancet 2019; 394: 1993-2001

Results of a 6-week treatment with 10 mg prednisolone in patients with hand osteoarthritis (HOPE): a double-blind, randomised, placebo-controlled trial

P	Symptomatic hand osteoarthritis and signs of inflammation in their distal /proximal interphalangeal joints	**C**	Placebo
I	10 mg prednisolone QD for 6weeks	**O**	VAS-reported finger pain: –21·5 (SD 21·7) vs.–5·2 (24·3) Mean difference: –16·5 (95% CI –26·1 to –6·9; p=0·0007).

THE LANCET

Lancet 2019 1540-1550

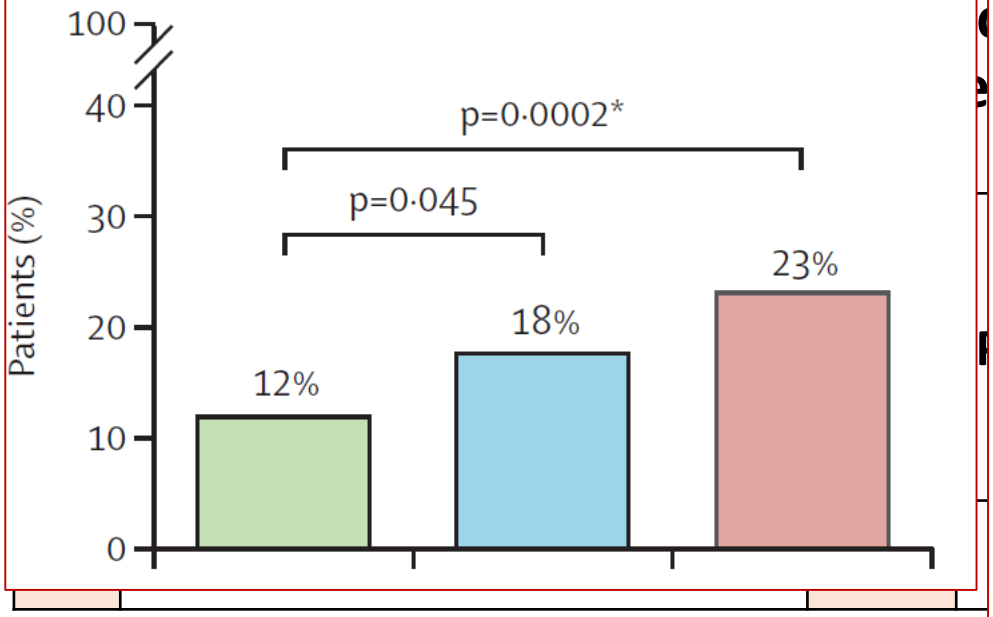
Patiromer versus placebo to enable spironolactone use in patients with resistant hypertension and chronic kidney disease (AMBER): a phase 2, randomised, double-blind, placebo-controlled trial

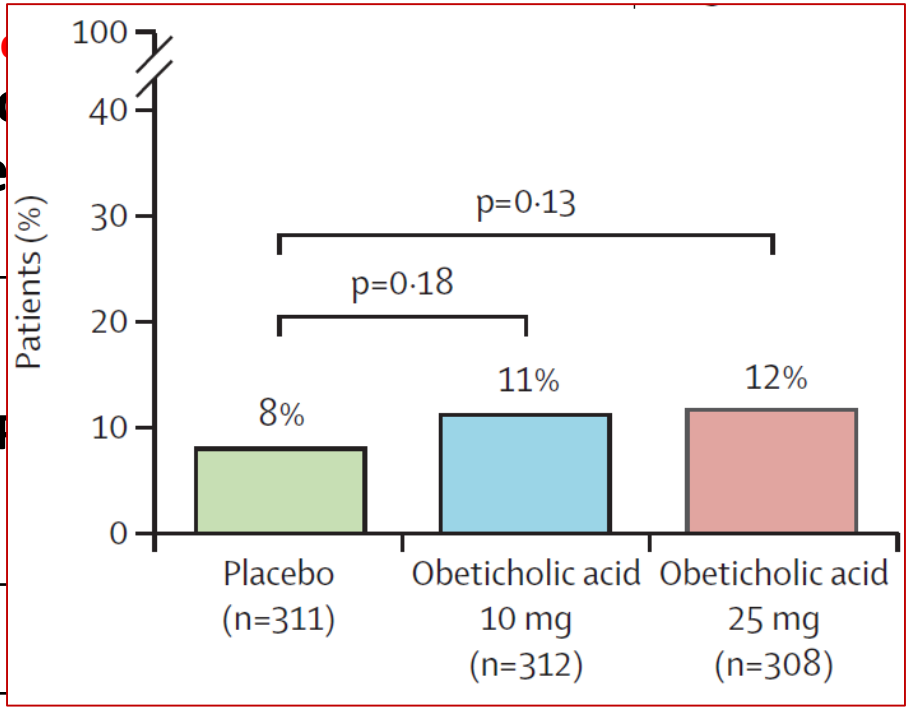
P	CKD and uncontrolled HTN.	**C**	Placebo + Spironolactone
I	Patiromer 8.4 g QD + Spironolactone	**O**	Remained on spironolactone at week 12: 86% vs. 66% (p<0.0001). Change in SBP: -11.7 vs. -10.8 (p=0.58). Less hyperkalemia in patiromer group.

Resmetirom (MGL-3196) for the treatment of non-alcoholic steatohepatitis: a multicentre, randomised, double-blind, placebo-controlled, phase 2 trial

P	Non-alcoholic steatohepatitis/ hepatic fat fraction of at least 10%	**C**	Placebo
I	Resmetirom 80mg QD	**O**	Reduction of hepatic fat Week 12: -32.9% vs. -10.4% (p<0.0001) NASH resolution with no worsening of fibrosis

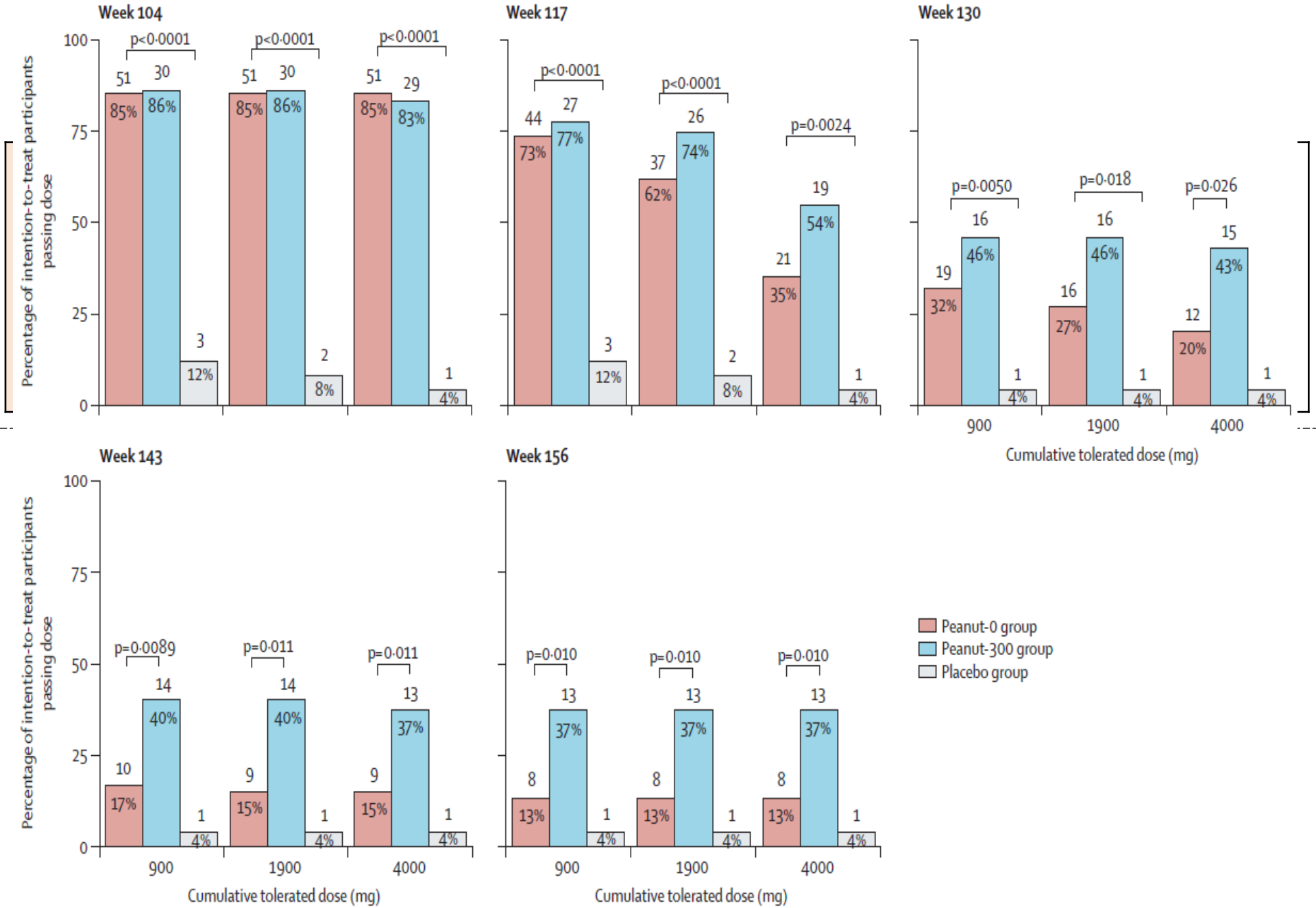
Improvement in fibrosis with no worsening of NASH





THE LANCET

Lancet 2019; 394: 2073–83



Lasmiditan (Reyvow®)

Indication: Acute treatment of migraine with or without aura in adults.
Mechanism: 5-HT1F receptor agonist

Brolucizumab (Beovu®)

Indication: Exudative (wet) age-related macular degeneration (AMD)
Mechanism: VEGF inhibitor.

Elexacaftor/Ivacaftor/Tezacaftor (Trikafta®)

Indication: Cystic fibrosis in patients aged ≥ 12 years who have ≥ 1 F508del mutation in the CFTR gene.
Mechanism: CFTR correctors (Elexacaftor and Tezacaftor)/ CFTR potentiator (Ivacaftor).

Tenapanor (Ibsrela®®)

Indication: Constipation-predominant irritable bowel syndrome (IBS-C).
Mechanism: Sodium/hydrogen exchanger 3 (NHE3) inhibitors.

Trifarotene (Aklief®)

Indication: Acne vulgaris in patients 9 years of age and older
Mechanism: Selective retinoic acid receptor (RAR)-γ agonist. (fourth-generation retinoid)

Upadacitinib (Rinvoq®)

Indication: Moderately to severely active RA who have had an inadequate response or intolerance to methotrexate.
Mechanism: JAK 1 inhibitor.

Others

- Safety and efficacy of a self-expanding versus a balloon-expandable bioprosthesis for transcatheter aortic valve replacement in patients with symptomatic severe aortic stenosis: a randomised non-inferiority trial
- Safety and efficacy of a self-expanding versus a balloon-expandable bioprosthesis for transcatheter aortic valve replacement in patients with symptomatic severe aortic stenosis: a randomised non-inferiority trial
- Public-access defibrillation and neurological outcomes in patients with out-of-hospital cardiac arrest in Japan: a population-based cohort study
- External beam accelerated partial breast irradiation versus whole breast irradiation after breast conserving surgery in women with ductal carcinoma in situ and node-negative breast cancer (RAPID): a randomised controlled trial
- Laparoscopic supracervical hysterectomy versus endometrial ablation for women with heavy menstrual bleeding (HEALTH): a parallel-group, open-label, randomised controlled trial

Thank you