APPLE COPD Trial Supplementary materials

Supplementary Table S1: Dosing schedule of those starting treatment

	Dosing received	Placebo	Aspirin	Ticagrelor	DAPT	Total
Number completed treatment intervals†	**1-2**	26 (83.9%)	26 (83.9%)	19 (65.5%)	12 (41.4%)	83 (69.2%)
	1-#	3 (9.7%)	4 (12.9%)	6 (20.7%)	2 (6.9%)	15 (12.5%)
	#-#	2 (6.5%)	1 (3.2%)	4 (13.8%)	15 (51.7%)	22 (18.3%)
Total starting treatment n(%)		31 (100%)	31 (100%)	29 (100%)	29 (100%)	120 (100%)
Time of treatment from randomisation (days): Min Median (IQR) Max N		 0 0.0 (0.0, 0.0) 1‡ 31	 0 0.0 (0.0, 0.0) 6‡ 31	 0 0.0 (0.0, 0.0) 0 29	 0 0.0 (0.0, 0.0) 0 29	 0 0.0 (0.0,0.0) 6 120
Time on treatment from randomisation (days): Min Median (IQR) Max n		 89 183.0 (181.0, 189.0) 269 31	 114 186.0 (182.0, 191.0) 281 31	 22 182.0 (143.5, 185.0) 250 28*	 2 162.0 (37.5, 184.0) 222 28*	 2 182 (175,189) 281 118*

1= BL to 3 months, 2=3 months- 6 months # did not complete interval.

**There are two patients that did not return after their baseline visit and being dispensed the first set of drugs so there time on treatment is unknown and set to missing.*

† Defined as being on treatment until the end of that interval based on a non-missing visit date.

‡ Only 2 participants did not start treatment on the day of randomisation.

Supplementary Table S2 (a): Dosage summary for aspirin or aspirin placebo

	Placebo n=31			Aspirin n=31			Ticagrelor n=29			DAPT n=29			Total (n=120)		
	BL-3M	**3M-6M**	**Total**	**BL-3M**	**3M-6M**	**Total**	**BL-3M**	**3M-6M**	**Total**	**BL-3M**	**3M-6M**	**Total**	**BL-3M**	**3M-6M**	**Total**
Number of patients observed at later visit	**29**	**28**		**30**	**28**		**25**	**23**		**17**	**23**		**101**	**102**	
Number with % protocol dose ≥80%, n (%)	21 (84%)	23 (88.5)	21 (87.5)	22 (88)	24 (92.3)	21 (91.3)	21 (87.5)	17 (100)	17 (100)	10 (76.9)	11 (84.6)	9 (81.8)	74 (85.1)	75 (91.5)	68 (90.7)

Supplementary Table S2 (b): Dosage summary for Ticagrelor or placebo Ticagrelor

	Placebo n=31			Aspirin n=31			Ticagrelor n=29			DAPT n=29			Total (n=120)		
	BL-3M	**3M-6M**	**Total**	**BL-3M**	**3M-6M**	**Total**	**BL-3M**	**3M-6M**	**Total**	**BL-3M**	**3M-6M**	**Total**	**BL-3M**	**3M-6M**	**Total**
Number of patients observed at later visit	**29**	**28**		**30**	**28**		**25**	**23**		**17**	**23**		**101**	**102**	
Number with % protocol dose ≥80%, n(%)	21 (84)	22 (84.6)	21 (87.5)	22 (88)	24 (92.3)	20 (87)	20 (87)	17 (100)	17 (100)	10 (76.9)	10 (76.9)	8 (72.7)	73 (84.9)	73 (89)	66 (88)

Supplementary Table S3: A tabulation of bleeding safety information.

		Total				Placebo				Aspirin				Ticagrelor				DAPT			
Variable		**1M**	**3M**	**6M**	**Total**	**1M**	**3M**	**6M**	**Total**	**1M**	**3M**	**6M**	**Total**	**1M**	**3M**	**6M**	**Total**	**1M**	**3M**	**6M**	**Total**
BARC [2]	**No bleeding**	110 (97)	94 (98)	102 (100)	306 (98)	28 (93)	26 (100)	28 (100)	82 (98)	30 (97)	27 (96)	28 (100)	85 (98)	27 (100)	24 (96)	23 (100)	74 (99)	25 (100)	17 (100)	23 (100)	65 (100)
	Type 1	3 (3)	2 (2)	0 (0)	5 (2)	2 (7)	0 (0)	0 (0)	2 (2)	1 (3)	1 (4)	0 (0)	2 (2)	0 (0)	1 (4)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
	Type 2-5b	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

Supplementary Table S4: Summary statistics for breathlessness measures (repeated by treatment group).

	Total		Placebo		Aspirin		Ticagrelor		DAPT	
Variable	**Baseline**	**6M**	**Baseline**	**6M**	**Baseline**	**6M**	**Baseline**	**6M**	**Baseline**	**6M**
MRC dyspnoea Mean (SD) n	3.5 (1.1) 120	3.6 (1.1) 102	3.6 (1.0) 31	3.8 (1.0) 28	3.7 (1.1) 31	3.7 (1.0) 28	3.4 (1.3) 29	3.4 (1.3) 23	3.3 (1.2) 29	3.3 (1.2) 23
FEV1 (L) Mean (SD) n	1.22 (0.59) 119	1.14 (0.56) 101	1.21 (0.49) 30	1.16 (0.47) 27	1.19 (0.72) 31	1.10 (0.69) 28	1.22 (0.62) 29	1.07 (0.58) 23	1.27 (0.53) 29	1.22 (0.48) 23
FEV1 % Mean (SD) n	46.5 (17.6) 119	42.7 (16.8) 101	45.4 (18.8) 30	42.9 (18.0) 27	46.5 (17.8) 31	41.7 (16.9) 28	46.1 (18.7) 29	40.3 (18.4) 23	47.9 (15.5) 29	46.3 (14.0) 23
FVC Mean (SD) n	2.51 (0.92) 118	2.45 (0.92) 101	2.65 (0.81) 30	2.61 (0.79) 27	2.35 (1.04) 30	2.35 (1.12) 28	2.51 (0.99) 29	2.31 (0.83) 23	2.54 (0.86) 29	2.51 (0.88) 23

Supplementary Table S5 (a): Reported AEs on ITT population

Related to treatment	Severity	Placebo n(%)	Aspirin n(%)	Ticagrelor n(%)	DAPT n(%)	Total
Definitely	**Mild**	0	0	0	2 (6.25)	2 (1.82)
	Moderate	0	0	0	0	0
	Severe	0	0	0	1 (3.13)	1 (0.91)
Probable	**Mild**	0	0	1 (2.86)	3 (9.38)	4 (3.64)
	Moderate	0	0	2 (5.71)	5 (15.6)	7 (6.36)
	Severe	0	0	0	0	0
Possible	**Mild**	1 (4.76)	0	4 (11.4)	2 (6.25)	7 (6.4)
	Moderate	1 (4.76)	0	3 (8.57)	6 (18.75)	10 (9.09)
	Severe	0	0	0	0	0
Unlikely	**Mild**	0	1 (4.55)	1 (2.86)	0	2 (1.82)
	Moderate	0	0	0	1 (3.13)	1 (0.91)
	Severe	0	0	0	0	0
Unrelated	**Mild**	13 (61.9)	16 (72.7)	20 (57.1)	10 (31.25)	59 (53.6)
	Moderate	6 (28.57)	5 (22.7)	4 (11.4)	1 (3.1)	16 (14.6)
	Severe	0	0	0	1 (3.1)	1 (0.9)
Total Related (Possible, Probable, Definitely)	**Mild**	1 (4.76)	0	5 (14.3)	7 (21.88)	13 (11.8)
	Moderate	1 (4.76)	0	5 (14.29)	11 (34.38)	17 (15.45)
	Severe	0	0	0	1 (3.13)	1 (0.91)
Total unlikely or unrelated	**Mild**	13 (61.9)	17 (77.27)	21 (60)	10 (31.25)	61 (55.45)
	Moderate	6 (28.57)	5 (22.7)	4 (11.4)	2 (6.25)	17 (15.5)
	Severe	0	0	0	1 (3.1)	1 (0.9)
Total (Related & Unrelated)	**Mild**	14 (61.9)	17 (77.3)	26 (74.29)	17 (53.1)	74 (67.27)
	Moderate	7 (33.67)	5 (22.7)	9 (25.7)	13 (40.6)	34 (30.9)
	Severe	0	0	0	2 (6.25)	2 (1.82)

Supplementary Table S5(b): Tabulation of AEs according to predefined categories. % are by column.

Predefined Category	Severity	Placebo n(%)	Aspirin n(%)	Ticagrelor n(%)	DAPT n(%)	Total
Exacerbation of COPD	**Total**	16	19	24	11	70
	Mild	12 (75)	15 (78.95)	20 (83.3)	9 (81.8)	56 (80)
	Moderate	4 (25)	4 (21.05)	4 (16.7)	1 (9.09)	13 (18.57)
	Severe	0	0	0	1 (9.09)	1 (1.43)
Worsening Breathlessness	**Total**	1	0	5	7	13
	Mild	0	0	1 (20)	0	1 (7.69)
	Moderate	1 (100)	0	4 (80)	7 (100)	12 (92.3)
	Severe	0	0	0	0	0
Other	**Total**	4	3	6	14	27
	Mild	2 (50)	2 (66.67)	5 (83.3)	8 (57.1)	17 (62.96)
	Moderate	2 (50)	1 (33.3)	1 (16.7)	5 (35.7)	9 (33.3)
	Severe	0	0	0	1 (7.14)	1 (3.7)

Supplementary Table S5 (c): Clinical events at 6 months.

Clinical event	Placebo	Aspirin	Ticagrelor	DAPT	Total
Any hospitalisation during study period (for heart problems) Yes	3 (10.7%)	4 (14.3%)	3 (13.0%)	4 (17.4%)	14 (13.7%)
Exacerbation of COPD Yes	13 (46.4%)	15 (53.6%)	13 (56.5%)	10 (43.5%)	51 (50.0%)
Pneumonia or chest infections Yes	2 (7.1%)	1 (3.6%)	0 (0.0%)	2 (8.7%)	5 (4.9%)
Diagnosis of angina (stable) Yes	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.3%)	1 (1.0%)
Begun taking aspirin/other blood thinners or cholesterol tablets Yes	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.3%)	1 (1.0%)
Any flare ups of their chest requiring antibiotics/and or steroids Yes	12 (42.9%)	13 (46.4%)	14 (60.9%)	11 (47.8%)	50 (49.0%)
Started any new medication for their heart and lungs Yes	1 (3.6%)	2 (7.1%)	1 (4.3%)	2 (8.7%)	6 (5.9%)

Supplementary Table S6 (a): Reported SAEs on ITT population.

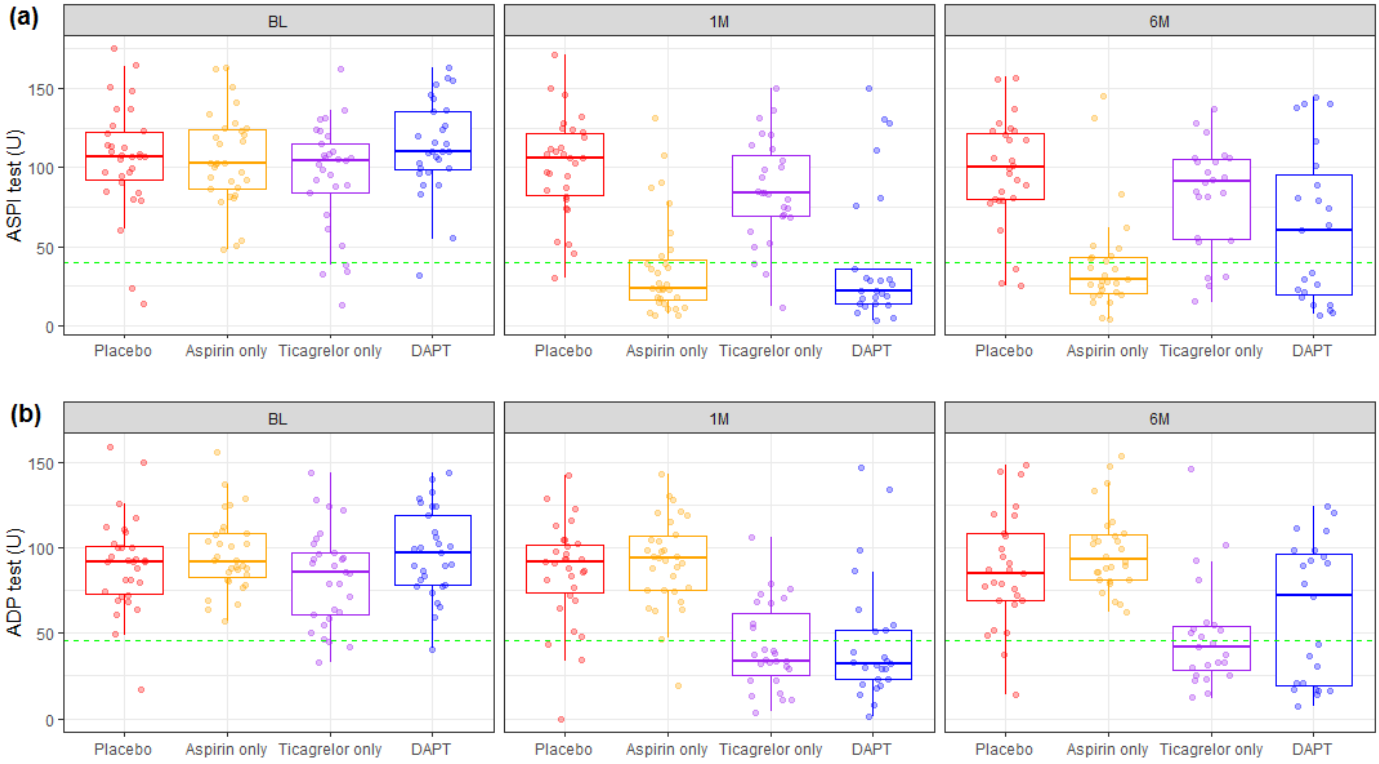
Related to treatment	Severity	Placebo n(%)	Aspirin n(%)	Ticagrelor n(%)	DAPT n(%)	Total
Unrelated	**Mild**	0	0	0	0	0
	Moderate	1 (9.09)	1 (14.29)	2 (33.3)	3 (42.86)	7 (22.58)
	Severe	10 (90.9)	6 (85.7)	4 (66.7)	4 (57.1)	24 (77.4)

Supplementary Table S6 (b): Tabulation of SAEs according to pre-defined categories.

Predefined Category	Severity	Placebo	Aspirin	Ticagrelor	DAPT	Total
Exacerbation of COPD n(%)	**Total**	6	1	2	1	10
	Mild	0	0	0	0	0
	Moderate	1 (16.7)	0	1 (50)	0	2 (20)
	Severe	5 (83.3)	1 (100)	1 (50)	1 (100)	8 (80)
Pneumonia n(%)	**Total**	1	2	0	1	4
	Mild	0	0	0	0	0
	Moderate	0	0	0	0	0
	Severe	1 (100)	2 (100)	0	1 (100)	4 (100)
Death n(%)	**Total**	1	0	1	0	2
Other n(%)	**Total**	3	3	2	3	11
	Mild	0	0	0	0	0
	Moderate	0	1 (33.3)	1 (50)	1 (33.3)	3 (27.27)
	Severe	3 (100)	2 (66.7)	1 (50)	2 (66.7)	8 (72.7)
Hospitalisation † n(%)	**Total**	0	1	1	2	4
	Mild	0	0	0	0	0
	Moderate	0	0	0	2 (100)	2 (50)
	Severe	0	1 (100)	1 (100)	0	2 (50)

† these patients were categorised as hospitalised rather than the reason for an SAE. Please see line listing for more details. NB. From the line listing and paper forms it appears that patients should have been categorised as Other, Exacerbation of COPD, Exacerbation of COPD and Stable Angina for the Aspirin only arm, Ticagrelor only arm and DAPT arm respectively.

Supplemental Figure S1



Boxplots of the (a) ASPI test and the (b) ADP test split by treatment groups over time (ITT analysis set).

The green dashed line indicated the threshold below which patients are considered to be responders