

Supplement

Supplementary Table 1A. Event rates for pulmonary and sepsis AE according to individual terms

Event	MedDRA Preferred Term Name	Ticagrelor N=9235 no. of events (%)	Clopidogrel N=9186 no. of events (%)
Pulmonary AE	Lower respiratory tract infection	22 (0.2)	23 (0.3)
	Lung infection	13 (0.1)	11 (0.1)
	Pleural disorders	122 (1.3)	135 (1.5)
	Pneumonia	209 (2.3)	227 (2.5)
	Respiratory failure	27 (0.3)	29 (0.3)
Pulmonary AE on-treatment	Lower respiratory tract infection	16 (0.2)	18 (0.2)
	Lung infection	10 (0.1)	11 (0.1)
	Pleural disorders	83 (0.9)	104 (1.1)
	Pneumonia	162 (1.8)	204 (2.2)
	Respiratory failure	18 (0.2)	22 (0.2)
Septic AE	Bacteraemia	8 (0.1)	5 (0.1)
	Sepsis	37 (0.4)	41 (0.4)
	Septic	6 (0.1)	12 (0.1)
Septic AE on-treatment	Bacteraemia	6 (0.1)	5 (0.1)
	Sepsis	29 (0.3)	30 (0.3)
	Septic	3 (0.0)	9 (0.1)

Pulmonary AE are grouped according to MedDRA high-level group name of 'PLEURAL DISORDERS' or MedDRA preferred term names containing 'PNEUMONIA', 'RESPIRATORY FAILURE', 'LOWER RESPIRATORY TRACT INFECTION' or 'LUNG INFECTION'. AE rates include individuals who had more than one type of event but individual rates do not count the same individual twice.

On-treatment: An event/adjudicated death with onset not later than 7 days after the last recorded dose of active study drug

Septic AE consist of MedDRA preferred term names containing 'SEPSIS', 'SEPTIC' or 'BACTERAEMIA'

Supplementary Table 1B. Incidence of pulmonary and sepsis AEs and associated mortality according to treatment group in those who did not or did have CABG surgery during the study

Event	CABG surgery during study?	Ticagrelor N=9235 no. of events (%)	Clopidogrel N=9186 no. of events (%)
Pulmonary AE	No	244 (2.6)	267 (2.9)
	Yes	125 (1.4)	123 (1.3)
Death following pulmonary AE	No	42 (0.5)	74 (0.8)
	Yes	5 (0.1)	10 (0.1)
Pulmonary AE on-treatment	No	193 (2.1)	232 (2.5)
	Yes	82 (0.9)	99 (1.1)
Death after pulmonary AE with continuing treatment	No	10 (0.1)	39 (0.4)
	Yes	0 (0.0)	4 (0.0)
Death on-treatment following pulmonary AE	No	21 (0.2)	36 (0.4)
	Yes	0 (0.0)	6 (0.1)
Sepsis AE	No	30 (0.3)	42 (0.5)
	Yes	20 (0.2)	15 (0.2)
Sepsis AE on-treatment	No	24 (0.3)	34 (0.4)
	Yes	14 (0.2)	10 (0.1)
	Total	38 (0.4)	44 (0.5)
Death attributed to sepsis	No	5 (0.1)	12 (0.1)
	Yes	2 (0.0)	11 (0.1)
Pulmonary or sepsis AE	No	266 (2.9)	287 (3.1)
	Yes	139 (1.5)	133 (1.4)
Death following pulmonary or sepsis AE	No	51 (0.6)	82 (0.9)
	Yes	9 (0.1)	15 (0.2)
Pulmonary or sepsis AE on-treatment	No	213 (2.3)	251 (2.7)
	Yes	94 (1.0)	107 (1.2)

Event	CABG surgery during study?	Ticagrelor N=9235 no. of events (%)	Clopidogrel N=9186 no. of events (%)
Death attributed to sepsis following pulmonary AE	No	0 (0.0)	7 (0.1)
	Yes	1 (0.0)	4 (0.0)
Death attributed to sepsis after pulmonary AE with continuing treatment	No	0 (0.0)	5 (0.1)
	Yes	0 (0.0)	2 (0.0)
Death attributed to sepsis following pulmonary AE on-treatment	No	0 (0.0)	6 (0.1)
	Yes	1 (0.0)	4 (0.0)
Sepsis AE following pulmonary AE on-treatment	No	5 (0.1)	15 (0.2)
	Yes	3 (0.0)	4 (0.0)
Death on-treatment following pulmonary or septic AE	No	28 (0.3)	38 (0.4)
	Yes	0 (0.0)	8 (0.1)

Supplementary Table 1C. Adjudication of deaths following pulmonary or sepsis AEs as ‘cardiovascular’ or ‘non-cardiovascular’

Event	CV/non-CV death	Ticagrelor N=9235 no. of events (%)	Clopidogrel N=9186 no. of events (%)
Death following pulmonary AE on-treatment	Non-CV death	13 (0.1)	19 (0.2)
	CV death	20 (0.2)	52 (0.6)
	Total	33 (0.4)	71 (0.8)
Death attributed to sepsis	Non-CV death	5 (0.1)	16 (0.2)
	CV death	2 (0.0)	7 (0.1)
	Total	7 (0.1)	23 (0.3)
Death following pulmonary or sepsis AE	Non-CV death	24 (0.3)	32 (0.3)
	CV death	36 (0.4)	65 (0.7)
	Total	60 (0.6)	97 (1.1)

Supplementary Table 1D. Incidences of sepsis AEs that *did not* follow a pulmonary AE

Event	MedDRA Preferred Term Name ^a	Ticagrelor N=9235 no. of events (%)	Clopidogrel N=9186 no. of events (%)
Sepsis AE that did not follow pulmonary AE	Bacteraemia	5 (0.1)	5 (0.1)
	Sepsis	31 (0.3)	26 (0.3)
	Septic	5 (0.1)	7 (0.1)

Supplementary Table 2. Effect of baseline factors on pulmonary AE on-treatment

	OR (95% CI)	P-value
Treatment group, Ticagrelor vs Clopidogrel	0.83 (0.70-0.98)	0.0262
Age (yrs), per 1-yr increase	1.04 (1.03-1.05)	<.0001
Gender, female vs male	0.73 (0.60-0.88)	0.0014
Weight, per 1-kg increase	1.00 (0.99-1.00)	0.3867
Asthma, no vs yes	0.47 (0.33-0.67)	<.0001
COPD, no vs yes	0.60 (0.46-0.79)	0.0002
Diabetes mellitus, no vs yes	0.71 (0.60-0.85)	0.0002
Habitual smoker, no vs yes	0.88 (0.72-1.07)	0.1936
Congestive heart failure, no vs yes	0.80 (0.60-1.08)	0.1437
Non-haemorrhagic stroke, no vs yes	0.64 (0.46-0.89)	0.0079
Chronic renal disease, no vs yes	0.59 (0.44-0.79)	0.0004
Peripheral arterial disease, no vs yes	0.86 (0.64-1.15)	0.3085
Clopidogrel pre-rand, no vs yes	0.83 (0.71-0.98)	0.0300

P-values and odds ratios (OR) from multivariable logistic regression for modelling the probability of pulmonary AE on-treatment using treatment group and baseline factors (gender, age, weight, asthma, chronic obstructive pulmonary disease (COPD), diabetes, smoker, congestive heart failure (CHF), non-haemorrhagic stroke, chronic renal disease, peripheral arterial disease (PAD) and clopidogrel pre-randomization) as independent variables

The odds ratios (OR) for the baseline factor are calculated according to not present vs. present (binary factors) and per 1 unit increase (continuous factors)

Supplementary Table 3. Effect of baseline factors on death following pulmonary AE on-treatment

	OR (95% CI)	P-value
Treatment group, Ticagrelor vs Clopidogrel	0.47 (0.31-0.72)	0.0004
Age (yrs), per 1-yr increase	1.07 (1.04-1.09)	<.0001
Gender, female vs male	0.66 (0.43-1.03)	0.0704
Weight, per 1-kg increase	0.96 (0.95-0.98)	<.0001
Asthma, no vs yes	0.82 (0.29-2.29)	0.6986
COPD, no vs yes	0.46 (0.26-0.81)	0.0070
Diabetes mellitus, no vs yes	0.43 (0.29-0.64)	<.0001
Habitual smoker, no vs yes	0.72 (0.45-1.17)	0.1878
Congestive heart failure, no vs yes	0.88 (0.47-1.64)	0.6811
Non-haemorrhagic stroke, no vs yes	0.36 (0.20-0.64)	0.0006
Chronic renal disease, no vs yes	0.51 (0.28-0.93)	0.0272
Peripheral arterial disease, no vs yes	0.87 (0.46-1.64)	0.6700
Clopidogrel pre-rand, no vs yes	1.21 (0.80-1.83)	0.3578

P-values and odds ratios from multivariable logistic regression for modelling the probability of death following pulmonary AE on-treatment using treatment group and baseline factors (gender, age, weight, asthma, COPD, diabetes, smoker, CHF, non-haemorrhagic stroke, chronic renal disease, PAD and clopidogrel pre-randomization) as independent variables

The odds ratios (OR) for the baseline factors are calculated according to not present vs. present (binary factors) and per 1 unit increase (continuous factors)

Supplementary Table 4. Incidence of leukopaenia and neutropaenia during the study according to treatment group

Time point	Ticagrelor 90mg bd	Clopidogrel 75mg od
Total leukocyte counts		
<i>Randomisation</i>	<i>n = 8168</i>	<i>n = 8114</i>
Total leukocyte count < 3.0 x 10 ⁹ /L, n (%)	10 (0.1)	12 (0.1)
<i>1 month</i>	<i>n = 3792</i>	<i>n = 3807</i>
Total leukocyte count < 3.0 x 10 ⁹ /L, n (%)	3 (0.08)	3 (0.08)
<i>3 months</i>	<i>n = 3357</i>	<i>n = 3387</i>
Total leukocyte count < 3.0 x 10 ⁹ /L, n (%)	3 (0.09)	1 (0.03)
<i>6 months</i>	<i>n = 2736</i>	<i>n = 2685</i>
Total leukocyte count < 3.0 x 10 ⁹ /L, n (%)	0	6 (0.22)
Differential neutrophil counts		
<i>Randomisation</i>	<i>n = 7808</i>	<i>n = 7785</i>
Neutrophil count < 1.5 x 10 ⁹ /L, n (%)	6 (0.08)	8 (0.1)
<i>1 month</i>	<i>n = 3576</i>	<i>n = 3600</i>
Neutrophil count < 1.5 x 10 ⁹ /L, n (%)	2 (0.06)	7 (0.19)
<i>3 months</i>	<i>n = 3164</i>	<i>n = 3202</i>
Neutrophil count < 1.5 x 10 ⁹ /L, n (%)	6 (0.19)	3 (0.09)
<i>6 months</i>	<i>n = 2565</i>	<i>n = 2539</i>
Neutrophil count < 1.5 x 10 ⁹ /L, n (%)	2 (0.08)	7 (0.28)