Case

- 56 y old man was admitted with NSTEMI
- On admission
  - Stable hemodynamics
  - High-sensitivity cardiac troponin T – 0.9 (ULN<0.013)
  - GRACE>140
  - Preloaded with clopidogrel 600mg along with other standard ACS medications according to local protocol.

  On the next morning cardiac catheterization revealed large oblique marginal artery branch narrowed to ~90%. DES was implanted and switch to ticagrelor had been recommended.

Case – cont'

- On the third hospital day the patient complained of dyspnea.

Question 1

– How to assess dyspnea severity?

Dyspnea assessment

- No gold standard, more than 30 different methods are used.

- 3 most popular and easy:
  – Visual analogue scales (VAS);
  – Numerical rating scales (NRS);
  – Modified Borg scale.

Bausewein et al, Respiratory Medicine, 2007

Modified Borg Scale

0	NOTHING AT ALL (just noticeable)
0.5	VERY VERY SLIGHT
1	VERY SLIGHT
2	SLIGHT
3	MODERATE
4	SOMEWHAT SEVERE
5	SEVERE
6	
7	VERY SEVERE
8	
9	VERY VERY SEVERE (almost maximal)
10	MAXIMAL

Question 2

– Work-up for dyspnea

Work-up for dyspnea in ACS patient

- Physical exam (exclude wheezing/prolonged expirium/wet crackles);

- ECG (to exclude re-ischemia/arrhythmias);

- Pulse and blood pressure, noninvasive oxygen saturation, invasive blood gas analysis;

- Chest X-ray (exclude pulmonary congestion, infiltrate, pneumothorax, etc.)

Case – cont'

- Physical exam was unremarkable;
- His blood gases were without evidence of hypoxemia/acidosis;
- Chest X-ray was without the signs of pulmonary congestion/infiltrate; lung hyperinflation c/w COPD was diagnosed;
- His history was remarkable for current smoking, COPD and occasional use of inhaled bronchodilators.

Question 3:

– Will you continue on ticagrelor or

– Discontinue ticagrelor and switch to clopidogrel or prasugrel

Ticagrelor: Dyspnea reported more frequently

	Ticagrelor 90 mg bid N = 9235 n (%) of patients	Clopidogrel 75 mg qd N = 9186 n (%) of patients
Patients with at least 1 event	1270 (13.8)	721 (7.8)
MedDRA Preferred Term		
Dyspnea	1104 (12.0)	598 (6.5)
Dyspnea exertional	176 (1.9)	127 (1.4)
Dyspnea at rest	9 (0.1)	3 (<0.1)
Nocturnal dyspnea	8 (0.1)	4 (<0.1)
Dyspnea paroxysmal nocturnal	6 (0.1)	5 (0.1)

PLATO: Dyspnea

All patients	Ticagrelor (n=9,235)	Clopidogrel (n=9,186)	p value[*]
Dyspnea, %			
Any	13.8	7.8	<0.001
With discontinuation of study Tx.	0.9	0.1	<0.001

*p values were calculated using Fischer's exact test

Timing, Duration, and Severity of Dyspnea in Placebo, Clopidogrel, and Ticagrelor Groups
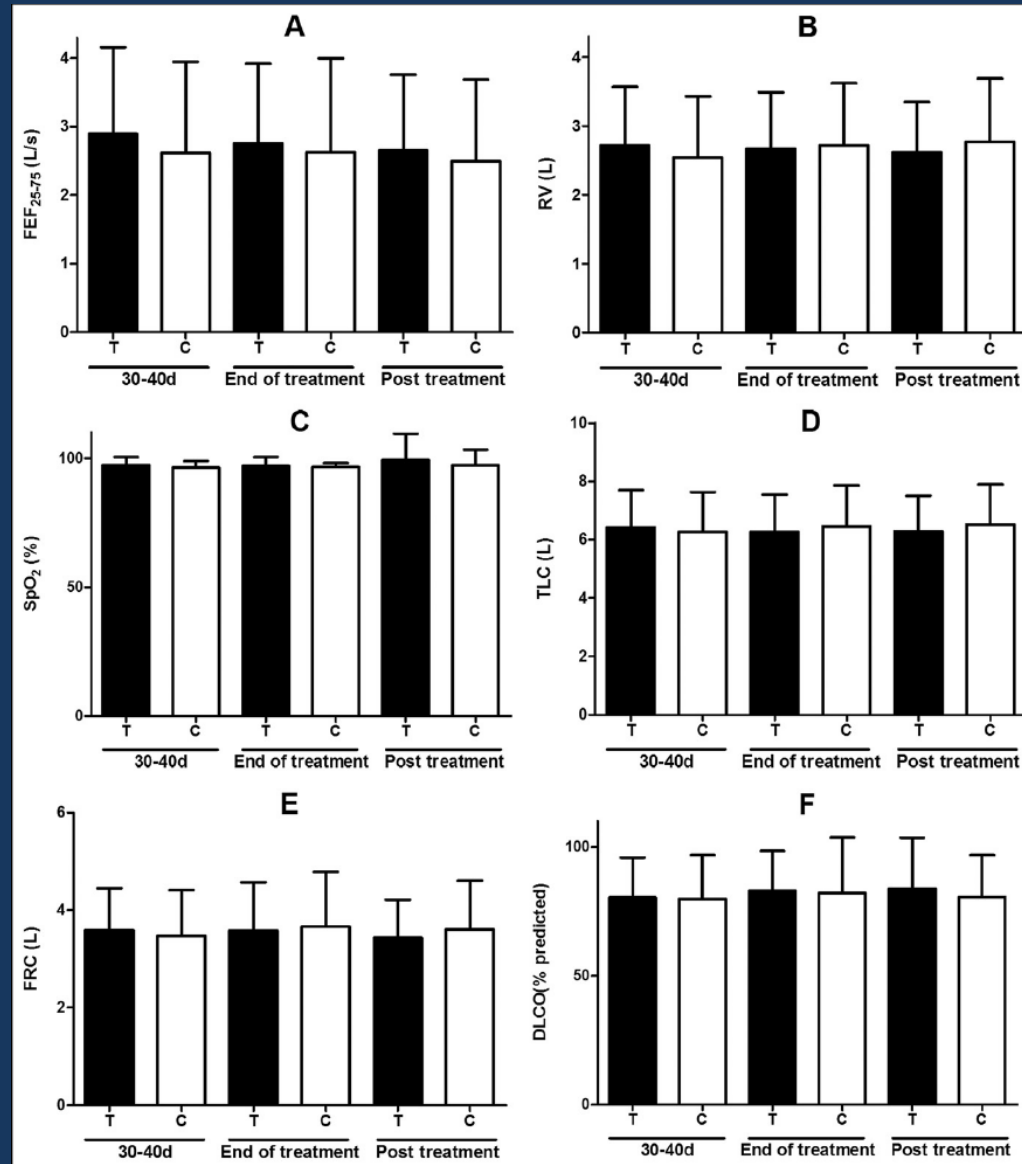

Storey RF et al, JACC 2010
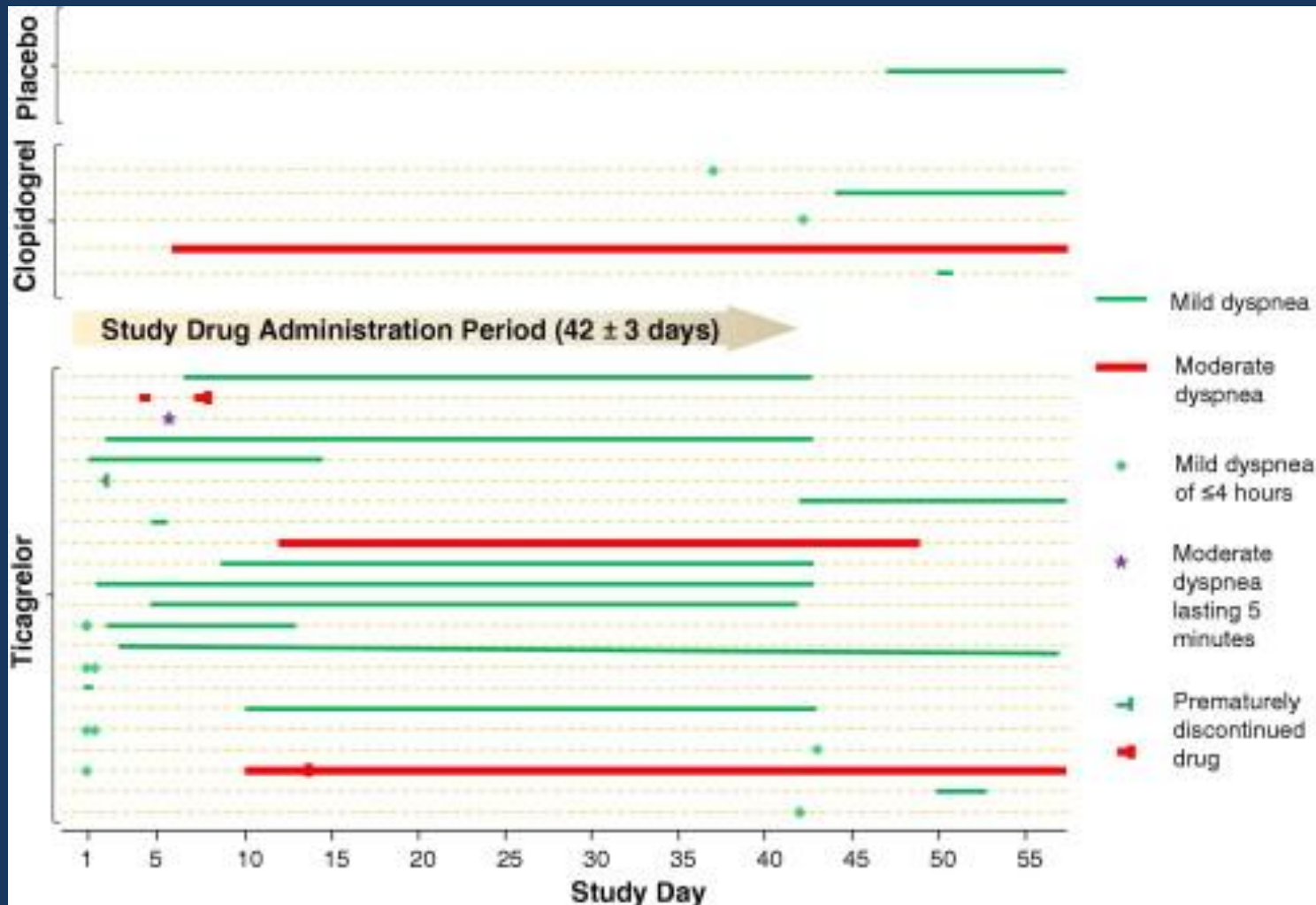
Cardiovascular Parameters in Patients With Dyspnea: Ejection Fraction
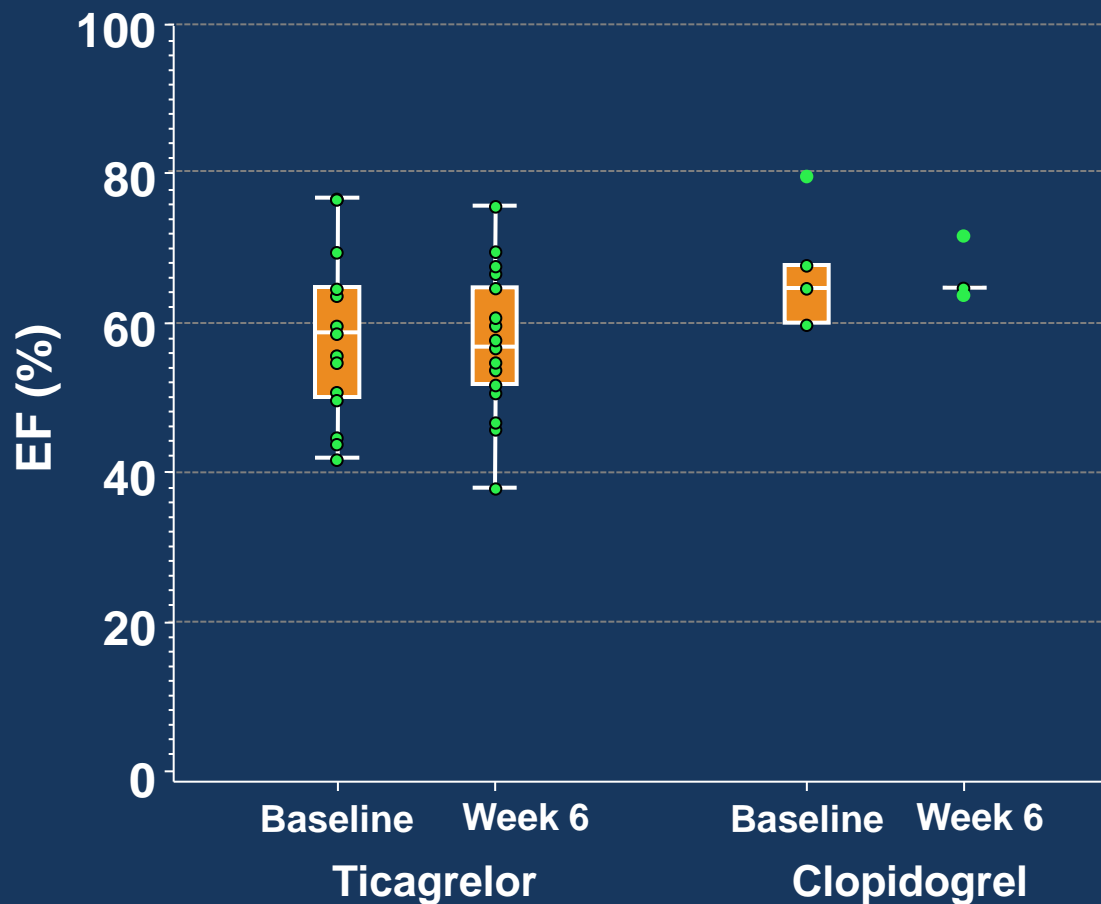
Boxes represent scatter plots of individual patient data; error bars show standard deviation

P = not significant for all parameters.
EF=ejection fraction

Storey RF et al.,JACC, 2010

Ticagrelor efficacy maintained in patients with history of COPD/Asthma/HF at baseline

Kaplan-Meier Estimated Rate (%)

Ticagrelor (249 / 1708)
Clopidogrel (291 / 1693)

18.78%
15.33%

Tic vs. Clop	HR	95% CI	p-value
	0.84	(0.71, 1.00)	0.044

Days from Randomization
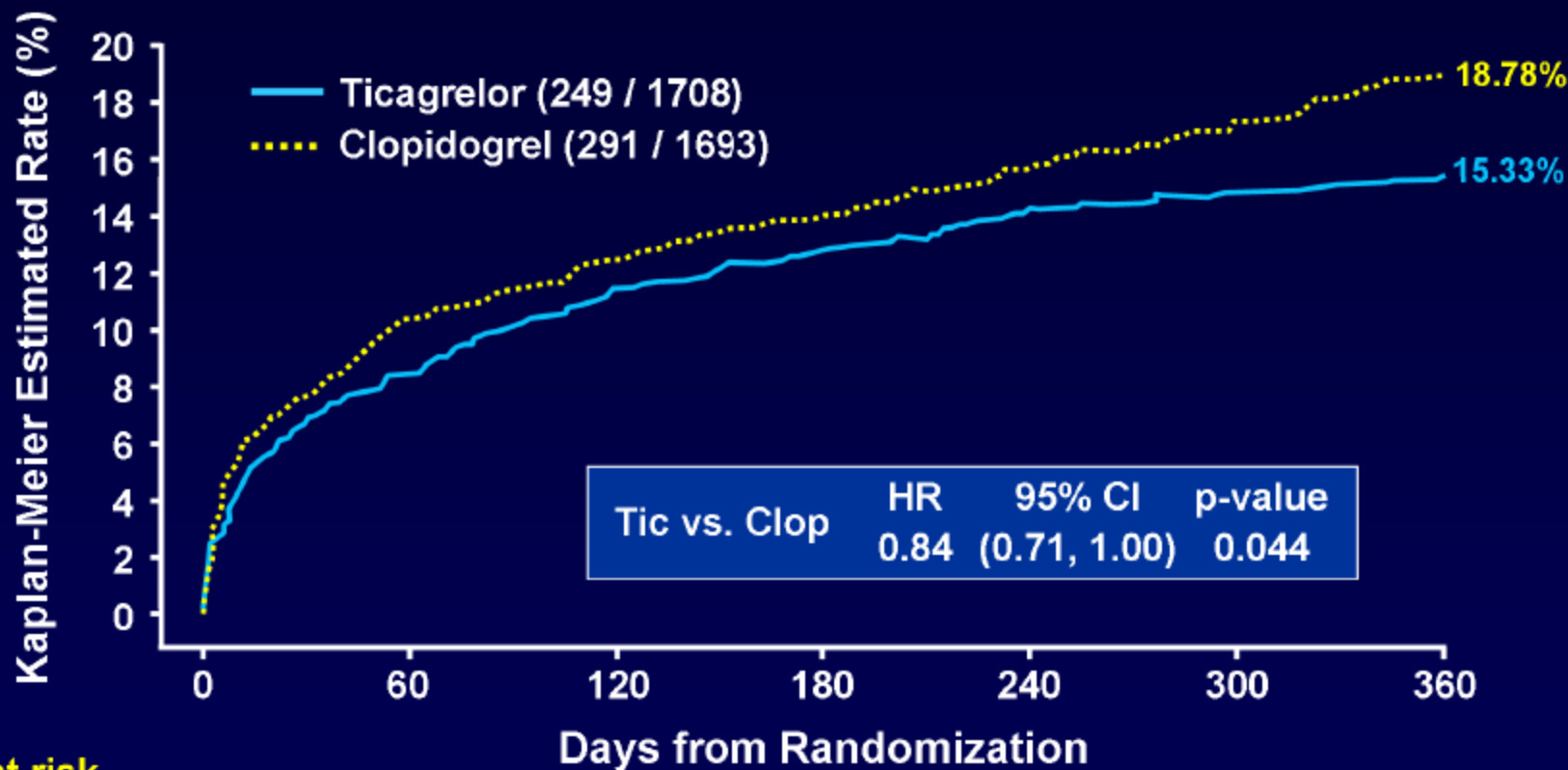
No. at risk

Ticagrelor	1708	1526	1466	1415	1150	880	712
Clopidogrel	1693	1489	1444	1391	1121	845	675

Wallentin et al., NEJM, 2009

Clinical Outcomes of Patients Reporting Dyspnea Post Randomization Compared with Those not Reporting Dyspnea, According to Treatment Group

n (K–M %)	Ticagrelor, n = 9235			Clopidogrel, n = 9186		
	Dyspnoea, n = 1339	No dyspnoea, n = 7896	P-value	Dyspnoea, n = 798	No dyspnoea, n = 8388	P-value
Primary composite endpoint (%)	151 (11.9)	701 (9.4)	<0.001	117 (15.7)	882 (11.2)	0.008
Myocardial infarction (%)	112 (8.7)	393 (5.4)	0.008	83 (11.3)	515 (6.6)	0.173
Stroke (%)	21 (1.7)	102 (1.4)	0.423	9 (1.3)	95 (1.2)	0.278
CV death (%)	39 (3.3)	306 (4.1)	<0.001	37 (4.8)	391 (5.0)	0.036
Total mortality (%)	47 (3.9)	342 (4.6)	<0.001	48 (6.4)	443 (5.7)	0.007
Major bleed (%)	164 (13.7)	797 (11.2)	0.591	96 (13.5)	833 (11.0)	0.436
Major or minor bleed (%)	256 (21.4)	1083 (13.7)	0.117	136 (18.8)	1079 (14.2)	0.032

Storey RF et al, EHJ, 2011

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Storey RF et al, EHJ, 2011

Clinical Outcomes of Patients Reporting Dyspnea Post Randomization According to Treatment Group, *Excluding Patients with Dyspnea AE Following the Secondary Endpoint of Non-Fatal Myocardial Infarction*

	Ticagrelor, *n* = 1293	Clopidogrel, *n* = 753	Unadjusted HR (95% CI)	P-value	Adjusted HR (95% CI)	P-value
	Patients with events (K–M%)	Patients with events (K–M%)				
Primary composite endpoint	106 (8.8)	72 (10.4)	0.84 (0.62, 1.13)	0.254	0.91 (0.67, 1.23)	0.542
Myocardial infarction	66 (5.4)	38 (5.7)	0.99 (0.66, 1.47)	0.956	1.01 (0.68, 1.52)	0.945
Stroke	19 (1.6)	7 (1.0)	1.55 (0.65, 3.69)	0.320	1.62 (0.68, 3.87)	0.279
CV death	36 (3.1)	35 (4.8)	0.59 (0.37, 0.93)	0.024	0.72 (0.45, 1.16)	0.179
Total mortality	43 (3.7)	45 (6.2)	0.54 (0.36, 0.83)	0.004	0.67 (0.44, 1.02)	0.060
Major bleed	151 (13.1)	87 (12.6)	1.01 (0.78, 1.32)	0.915	1.03 (0.79, 1.35)	0.802
Major or minor bleed	239 (20.7)	126 (18.4)	1.12 (0.90, 1.39)	0.293	1.14 (0.91, 1.41)	0.252

Kaplan-Meyer Curves for Events Between 31 and 360 Days with or without Onset of Dyspnea up to 30 Days Post Randomization
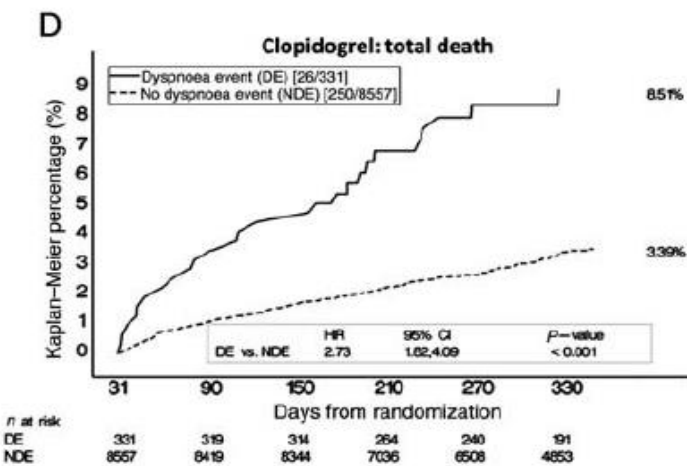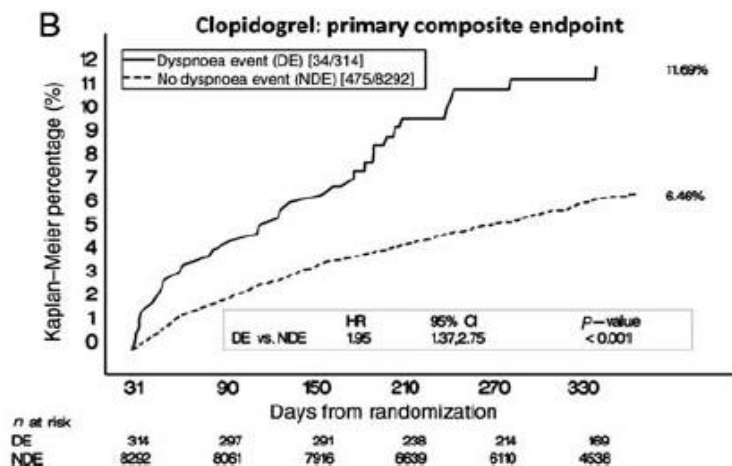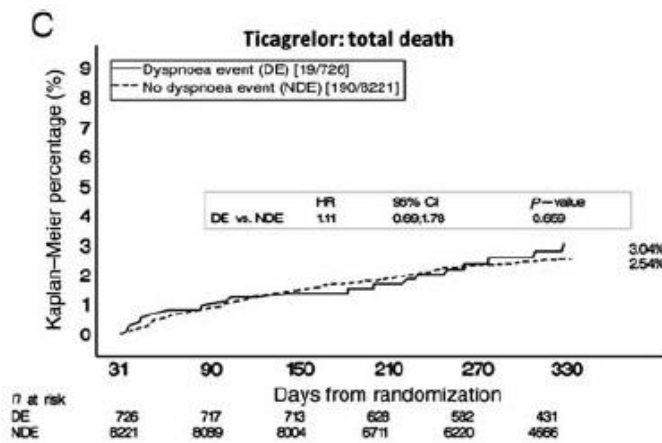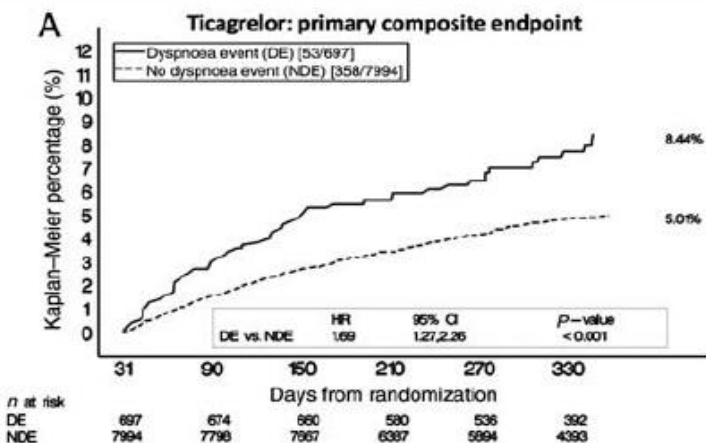
Why Does Ticagrelor Induce Dyspnea?

- Adenosine **is dyspnogenic** and its effect is mediated by activation of **vagal C fibers** *(Burki, Chest, 2010)*

- Tentative explanation for dyspnea during treatment with ticagrelor is that it may be caused by increased levels of extracellular adenosine.

- Ticagrelor has been shown to inhibit adenosine uptake

- Dipiridamole is another potent adenosine uptake inhibitor without prominent dyspnea effect.

- In the trial of iv dipiridamole use for thalium SPECT imaging was associated with 2.6% incidence of dyspnea *(Ranhosky et al, Circulation, 1990)*.

Cattaneo,Faioni, Thromb Haemost , 2012

Why Does Ticagrelor Induce Dyspnea?

- ***Hypothesis***: ticagrelor-induced dyspnea is mediated by inhibition of the $P2Y_{12}$ receptors (expressed by cells different from platelets).

- P2Y12 was shown to be expressed in neuronal tissues and to inhibit neuronal signaling, through the inhibition of cyclic adenosine monophosphate (cAMP) generation.

- Therefore, it can be predicted that inhibitors of P2Y12 will increase ***neuronal signaling***.

- Experimental evidence indicates that it is biologically plausible that inhibition of P2Y12 increases the conductivity of vagal C-fibers and, hence, the sensation of dyspnea.

Another hypothesis…

- Ticagrelor, in addition to inhibiting adenosine reuptake, also induces *ATP release from human RBCs in a dose-dependent manner.*

- It is suggested that the combined effects of ticagrelor on both ATP release and adenosine reuptake collectively result in circulating plasma levels of adenosine high enough to induce dyspnea and transient ventricular pauses.

Ohman J, et al. BBRC, 2012

Dyspnea Associated with Ticagrelor

- Usually mild to moderate

- No measured changes in pulmonary function

- Patients with baseline cardiopulmonary disease were not at an increased relative risk of dyspnea

- Risk factors for dyspnea were similar between treatment groups

- 9 in 1000 patients discontinued ticagrelor due to dyspnea

- Benefit of ticagrelor is maintained in patients at risk for dyspnea and those who experience dyspnea

Case – cont'

- Our patient developed only moderate and tolerable dyspnea which actually subsided in a few days. So the treatment had been continued.

Regulatory bodies' recommendations

- The European Union prescribing information states that ticagrelor should be used *with caution* in patients with history of asthma and/or COPD.

- The United States prescribing information states that after excluding underlying diseases that may require treatment, if dyspnea is determined to be related to ticagrelor, *no specific treatment is required and ticagrelor can be continued without interruption*

If the patient develops severe dyspnea after ticagrelor?

- The single dose of infused theophylline may be helpful (5mg/kg) for 20 minutes

Thank you for the attention

Backup slides

Ticagrelor adverse event profile

	Ticagrelor 90 mg bid N = 9235 n (%) of patients	Clopidogrel 75 mg qd N = 9186 n (%) of patients
Any AE	6714 (72.7)	6398 (69.6)
Mild	5655 (61.2)	5292 (57.6)
Moderate	3322 (36.0)	3073 (33.5)
Severe	1019 (11.0)	1061 (11.6)
Any SAE	1864 (20.2)	1866 (20.3)
SAE with outcome of Death	218 (2.4)	285 (3.1)
Leading to study drug discontinuation	687 (7.4)	500 (5.4)
SAE	259 (2.8)	218 (2.4)

Cardiovascular and Renal Drugs Advisory Committee Meeting, FDA, 2010