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Incidence of Dyspnea and Assessment of Cardiac and Pulmonary Function in Patients With Stable Coronary Artery Disease Receiving Ticagrelor, Clopidogrel, or Placebo in the ONSET/OFFSET Study

Robert F. Storey, MD, DM,* Kevin P. Bliden, BS,† Shankar B. Patil, MD,* Arun Karunakaran, MD,* Rosemary Ecob, MA,* Kathleen Butler, MD, MS,‡ Renli Teng, PhD,‡ Cheryl Wei, PhD, MS,‡ Udaya S. Tantry, MD,† Paul A. Gurbel, MD,† on behalf of the ONSET/OFFSET Investigators

Sheffield, United Kingdom; Baltimore, Maryland; and Wilmington, Delaware

Objectives We prospectively assessed cardiac and pulmonary function in patients with stable coronary artery disease (CAD) treated with ticagrelor, clopidogrel, or placebo in the ONSET/OFFSET (A Multi-Centre Randomised, Double-Blind, Double-Dummy Parallel Group Study of the Onset and Offset of Antiplatelet Effects of AZD6140 Compared With Clopidogrel and Placebo With Aspirin as Background Therapy in Patients With Stable Coronary Artery Disease) study.

Background Ticagrelor reduces cardiovascular events more effectively than clopidogrel in patients with acute coronary syndromes. Dyspnea develops in some patients treated with ticagrelor, and it is not known whether this is associated with changes in cardiac or pulmonary function.

Methods In all, 123 stable aspirin-treated CAD patients randomly received either ticagrelor (180 mg load, then 90 mg twice daily; n = 57), clopidogrel (600 mg load, then 75 mg daily; n = 54), or placebo (n = 12) for 6 weeks in a double-blind, double-dummy design. Electrocardiography, echocardiography, serum N-terminal pro-brain natriuretic peptide, and pulmonary function tests were performed before (baseline) and 6 weeks after drug administration and/or after development of dyspnea.

Results After drug administration, dyspnea was reported by 38.6%, 9.3%, and 8.3% of patients in the ticagrelor, clopidogrel, and placebo groups, respectively ($p < 0.001$). Most instances were mild and/or lasted <24 h, although 3 patients discontinued ticagrelor because of dyspnea. Eight of 22 and 17 of 22 ticagrelor-treated patients experiencing dyspnea did so within 24 h and 1 week, respectively, after drug administration. In all treatment groups, and in ticagrelor-treated patients with dyspnea, there were no significant changes between baseline and 6 weeks in any of the cardiac or pulmonary function parameters.

Conclusions Dyspnea is commonly associated with ticagrelor therapy, but was not associated in this study with any adverse change in cardiac or pulmonary function. (A Multi-Centre Randomised, Double-Blind, Double-Dummy Parallel Group Study of the Onset and Offset of Antiplatelet Effects of AZD6140 Compared With Clopidogrel and Placebo With Aspirin as Background Therapy in Patients With Stable Coronary Artery Disease [ONSET/OFFSET]; NCT00528411) (J Am Coll Cardiol 2010;56:185–93) © 2010 by the American College of Cardiology Foundation

From the *Department of Cardiovascular Science, University of Sheffield, and NIHR Cardiovascular Biomedical Research Unit, Sheffield, United Kingdom; †Sinai Center for Thrombosis Research, Baltimore, Maryland; and ‡AstraZeneca Research and Development, Wilmington, Delaware. This work was funded by AstraZeneca LP, Wilmington, Delaware. Dr. Storey has received honoraria, consultancy fees, and/or institutional research grants from AstraZeneca, Eli Lilly, Daiichi Sankyo, Schering-Plough, The Medicines Company, Novartis, and Teva. Drs. Butler, Teng, and Wei are employees of AstraZeneca. Dr. Gurbel has received research grants, honoraria, and/or consultancy fees from Haemoscope, AstraZeneca, Schering-Plough, Medtronic, Lilly/Sankyo, Sanofi, Boston Scientific, and Bayer.

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Abbreviations and Acronyms

ADP = adenosine diphosphate

AUC_{0-8} = area-under-the-plasma concentration time curve over 8 hours

CAD = coronary artery disease

C_{max} = maximum plasma drug concentration

CYP = cytochrome P450

FEV_1 = forced expiratory volume at 1 s

FVC = forced vital capacity

Ticagrelor (formerly AZD6140), the first reversibly binding oral $P2Y_{12}$ receptor antagonist, inhibits activation of the $P2Y_{12}$ receptor by adenosine diphosphate (ADP) in a noncompetitive fashion (1). The action of ticagrelor differs from that of the thienopyridines clopidogrel and prasugrel, which require hepatic conversion to active metabolites that bind irreversibly to the platelet $P2Y_{12}$ receptor (2). Recently, in the PLATO (Platelet Inhibition and Patient Outcomes) study, ticagrelor was shown to be more efficacious than clopidogrel in the prevention of myocardial infarction and death after acute coronary syndrome (3). In 2 phase II studies, dyspnea was noted to occur as a side effect to ticagrelor in a dose-dependent fashion (4,5); and in the PLATO study, there was a 6% absolute excess of dyspnea in ticagrelor-treated patients compared with patients treated with clopidogrel (3). The mechanism for this side effect is unknown, although preliminary data indicate that ticagrelor has an off-target effect on adenosine reuptake (6), and it is known that intravenous adenosine infusion can cause transient dyspnea in the absence of bronchoconstriction (7).

We report here results from the randomized, double-blind assessment of the ONSET/OFFSET (A Multi-Centre Randomised, Double-Blind, Double-Dummy Parallel Group Study of the Onset and Offset of Antiplatelet Effects of AZD6140 Compared With Clopidogrel and Placebo With Aspirin as Background Therapy in Patients With Stable Coronary Artery Disease) study of the antiplatelet effects of ticagrelor versus clopidogrel in patients with stable coronary artery disease, which was conducted both to characterize further the onset and offset of action of ticagrelor compared with clopidogrel (reported elsewhere [8]) and to prospectively assess cardiac and pulmonary function in ticagrelor- and clopidogrel-treated patients with stable coronary artery disease (CAD).

Methods

Study population. Between October 17, 2007, and March 5, 2009, 154 patients with documented stable CAD were entered into the study in centers in the U.S. and the United Kingdom. The appropriate institutional review boards approved the study protocol, and patients provided written informed consent before beginning study procedures.

Patients were eligible if they were 18 years of age or older and had documented CAD, defined as any of the following: stable angina pectoris with objective evidence of CAD, history of myocardial infarction, or history of cardiac revascularization. Patients were also required to have been taking daily aspirin therapy (75 to 100 mg). Exclusion criteria were as follows: history of acute coronary syndromes in the past year; prior diagnosis by a physician of congestive heart failure, chronic obstructive pulmonary disease, chronic or active asthma, or other cardiopulmonary disease that could affect the interpretation of cardiopulmonary data; cardiac ejection fraction <35%; forced expiratory volume in 1 s (FEV_1) or forced vital capacity (FVC) below the lower limit of the normal age- and sex-adjusted range at baseline; use of tobacco products in the last month; and current use of any moderate or strong cytochrome P450 (CYP) 3A inhibitors, strong CYP 3A inducers, or CYP 3A substrates with a narrow therapeutic index.

Study design. The complete study design is presented elsewhere (8). Briefly, eligible patients were randomly assigned to receive either ticagrelor (90-mg tablet) or clopidogrel (75-mg capsule) in an approximately 1:1 double-blind, double-dummy fashion, although a smaller proportion of patients were also randomly allocated to receive placebo. Ticagrelor patients were given a loading dose of ticagrelor 180 mg (two 90-mg tablets) as well as 8 clopidogrel placebo capsules followed by a ticagrelor 90-mg tablet 12 h later. Patients were then given ticagrelor 90 mg twice daily and clopidogrel placebo once in the morning for 6 weeks. Clopidogrel patients received a 600-mg loading dose (eight 75-mg capsules) as well as 2 ticagrelor placebo tablets followed by a further ticagrelor placebo tablet 12 h later. Thereafter, patients were administered 75-mg clopidogrel once daily and ticagrelor placebo twice daily for the duration of the study. Placebo patients received loading doses of both dummy agents, followed by 1 ticagrelor placebo after 12 h and then ticagrelor and clopidogrel placebo doses for the remaining 6 weeks. All patients continued on background aspirin therapy (75 to 100 mg once a day) during the treatment period. Patients were followed up for 10 days after discontinuation of study drug and, if necessary, were contacted after this time point to determine the duration of adverse events.

The primary objectives of the main study were to determine the onset and offset of the antiplatelet effect of ticagrelor relative to clopidogrel, and the sample size was determined accordingly (8). The pre-specified subanalysis reported in this paper was designed to determine whether ticagrelor therapy is associated with any significant change in cardiopulmonary function and included all patients who received at least 1 dose of study drug. In support of this objective, investigators were required to record as an adverse event any reports of shortness of breath occurring either at rest or on exertion (referred to here as dyspnea).

All adverse events, including dyspnea, were graded as mild (awareness of sign or symptom but easily tolerated), moderate (discomfort sufficient to cause interference with normal activities), or severe (incapacitating, with inability to perform normal activities). Investigators were also required to indicate whether they thought adverse events, including dyspnea, were possibly or likely related to study medication.

Cardiac and pulmonary assessment. Cardiac and pulmonary function were assessed at baseline (before study medication) and after 6 weeks of treatment. Patients were requested to contact the investigator if they had shortness of breath after commencing study medication to allow the scheduling of earlier assessment. Cardiac measurements included sitting blood pressure, heart rate, electrocardiography, echocardiographic assessment of left ventricular ejection fraction, and N-terminal pro-brain natriuretic peptide. Pulmonary function parameters included FEV_1, FVC, FEV_1/FVC, mean forced expiratory flow between 25% and 75% of the FVC ($FEF_{25–75}$), lung volume (forced residual capacity), total lung capacity (TLC), residual volume , minute ventilation, tidal volume, respiratory rate, single-breath diffusing capacity of lung for carbon monoxide, and oxygen saturation.

Serum biochemistry. Serum samples were collected at baseline, after 6 weeks of study medication, and 10 days after last dose of study medication. Additional serum samples were also collected if patients experienced dyspnea. Analysis of serum biochemistry was performed at local laboratories. The results for serum bicarbonate are presented here, because it acts as a marker of metabolic and respiratory pH homeostasis and is, therefore, relevant to possible etiology of dyspnea and pulmonary function.

Pharmacokinetic studies. Plasma levels of ticagrelor and AR-C124910XX, an active metabolite, were measured using validated bioanalytical methods by York Bioanalytical Solutions (York, United Kingdom). Pharmacokinetic parameters were assessed during onset and offset of study drug effect and included maximum plasma drug concentration (C_{max}) and area-under-the-plasma concentration time curve over 8 h post-dosing ($AUC_{0–8}$).

Statistical analysis. Statistical analyses were performed by QDS (King of Prussia, Pennsylvania) under the direction of Biostatistics at AstraZeneca (Wilmington, Delaware) using SAS version 8.0 (SAS Institute Inc., Cary, North Carolina). Fisher's exact test was used to compare proportions with dyspnea in the different groups and categorical demographic data. For the cardiopulmonary parameters, analysis was performed by the analysis of covariance model for each cardiopulmonary function percentage change from baseline, fitting fixed-effect term for treatment group, with center and center-by-treatment interaction as covariates. Serum bicarbonate levels, cardiac, and pulmonary data also were summarized by descriptive statistics for all patients and were plotted across time points for patients with a dyspnea event. Pharmacokinetic parameters for ticagrelor and its active metabolite AR-C124910XX and plasma concentration data were summarized using descriptive statistics, including geometric mean and coefficient of variations. Log-transformed C_{max} and $AUC_{0–8}$ for ticagrelor and AR-C124910XX were analyzed using a *t* test between ticagrelor-treated patients with and without dyspnea.

Results

Study population. In all, 154 patients were screened and provided informed consent; of these, 123 were randomized to study treatment and were included in the safety cohort, which was used for the analysis of cardiac and pulmonary function. The treatment groups were generally well balanced with respect to demographic and other baseline characteristics although there were nonsignificant trends toward differences between the groups in proportions of patients who had diabetes mellitus or were receiving calcium-channel blockers and nitrates (Table 1).

Incidence of dyspnea. After study drug administration, dyspnea was reported by 38.6%, 9.3%, and 8.3% of patients in the ticagrelor, clopidogrel and placebo groups, respectively (ticagrelor vs. clopidogrel, $p < 0.001$; ticagrelor vs. placebo, $p < 0.05$; clopidogrel vs. placebo, p = NS). Dyspnea judged by the investigator to be likely or possibly due to the study drug occurred in 24.6%, 3.7%, and 0% in the ticagrelor, clopidogrel, and placebo groups, respectively (ticagrelor vs. clopidogrel, $p < 0.01$). The timing, duration, and severity of the dyspnea in the different groups are illustrated in Figure 1. Only 3 cases of dyspnea in the ticagrelor group and 1 case in the clopidogrel group were judged to be moderate, whereas the rest were mild in intensity. Eight of 22 cases of dyspnea in the ticagrelor group occurred within 24 h of ticagrelor administration, and 17 of 22 of the cases occurred within 1 week. In contrast, 4 of 5 dyspnea cases in the clopidogrel group occurred >1

Table 1 Demographic and Baseline Characteristics According to Treatment Group

Characteristic	Ticagrelor (n = 57)	Clopidogrel (n = 54)	Placebo (n = 12)
Age (yrs)			
Mean ± SD	62 ± 9	65 ± 8	64 ± 8
Range	41–79	42–83	44–79
Female	14 (25)	14 (26)	2 (17)
Race			
Caucasian	51 (90)	48 (89)	9 (75)
Black/African American	4 (7)	5 (9)	3 (25)
Asian	1 (2)	1 (2)	0 (0)
Hawaiian	1 (2)	0 (0)	0 (0)
Former smoker	29 (51)	27 (50)	7 (58)
Dyslipidemia	54 (95)	52 (96)	12 (100)
Hypertension	44 (77)	39 (72)	9 (75)
Diabetes mellitus	12 (21)	10 (19)	5 (42)
Concomitant medications			
Statins	49 (86)	50 (93)	11 (92)
Beta-blockers	39 (68)	42 (78)	9 (75)
Diuretics	20 (35)	18 (33)	4 (33)
Calcium-channel blocker	17 (30)	9 (17)	2 (17)
ACE inhibitors	10 (18)	8 (15)	2 (17)
Organic nitrates	6 (11)	12 (22)	0 (0)
Proton pump inhibitor	16 (28)	16 (30)	3 (25)

Values are n (%) unless otherwise indicated. All p values = NS for ticagrelor versus clopidogrel.
ACE = angiotensin-converting enzyme.

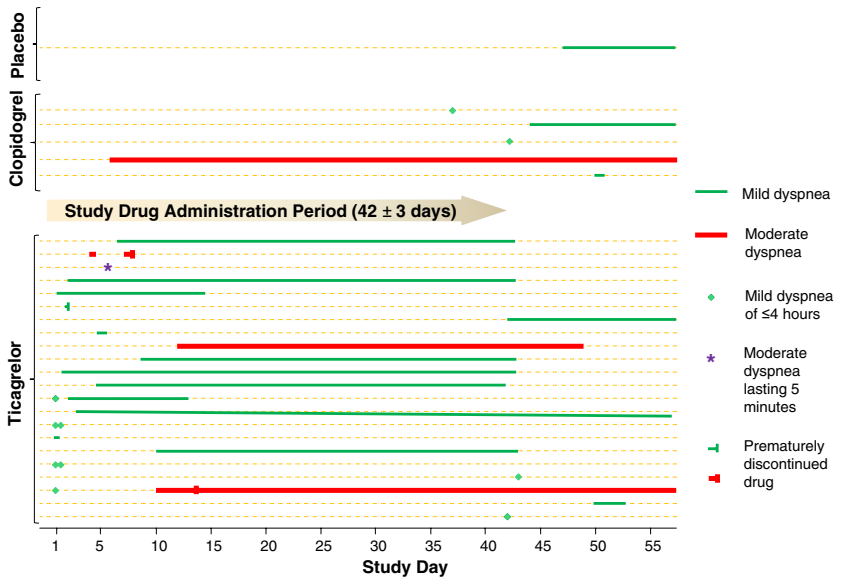

Figure 1 **Timing, Duration, and Severity of Dyspnea in Placebo, Clopidogrel, and Ticagrelor Groups**

Subjects administered placebo (n = 1), clopidogrel (n = 5), and ticagrelor (n = 22) who had any episode of dyspnea are indicated by the **faint dashed lines**. Study medication was administered on day 1 and continued until day 40 to 46. Episodes of transient dyspnea are denoted by **markers**, and more sustained or repeated episodes are denoted by **solid lines**. **Green lines** = mild dyspnea; **red lines** = moderate dyspnea; **green diamonds** = mild dyspnea ≤4 h; **blue asterisk** = moderate dyspnea of 5 min; **green blocks** and **red blocks** = premature discontinuation of drug.

week after clopidogrel administration. Some cases lasted <24 h whereas others persisted over the course of the study, with most of these cases in the ticagrelor group resolving upon cessation of ticagrelor administration. In 1 case in the placebo group, 2 cases in the clopidogrel group, and 3 cases in the ticagrelor group, dyspnea was persistent at the end of the study follow-up. Three ticagrelor patients experiencing dyspnea discontinued treatment as a result of this, compared with no patients taking clopidogrel or placebo.

Cardiac and pulmonary function. There were no obvious changes in any of the cardiac measurements, including blood pressure, heart rate, ejection fraction, and N-terminal pro-brain natriuretic peptide, in any of the groups between baseline and week 6 (Table 2). As expected in this population, electrocardiograms at baseline showed a wide range of abnormalities, and there were no adverse trends noted in any of the groups during the course of the study (data not shown). Similarly, there were no obvious changes in any of the pulmonary parameters, including measures of ventilation and respiratory rate, spirometry, lung volume, lung diffusion capacity, and blood oxygen saturation, between the 2 time points in any of the groups (Table 3). Statistical analysis of percent change from baseline for all the cardiac and pulmonary measurements showed there was no statistically significant difference between any of the treatment groups, and there was no significant effect of center or center by treatment interaction (data not shown).

In the cohort of patients who had dyspnea, study treatment did not affect any of the cardiac measurements or pulmonary parameters (Figs. 2A to 2I, Table 4). A small number of patients had additional cardiac and pulmonary assessments conducted at extra visits for assessment of dyspnea between baseline and 6 weeks. Six ticagrelor-treated patients had early assessment of cardiac and pulmo-

Table 2 **Cardiac Function Assessment**

	Ticagrelor (n = 57)		Clopidogrel (n = 54)		Placebo (n = 12)	
Parameter	Baseline	6 Weeks	Baseline	6 Weeks	Baseline	6 Weeks
Systolic BP, mm Hg	132 ± 17	132 ± 17	133 ± 16	132 ± 17	125 ± 20	121 ± 16
Diastolic BP, mm Hg	77 ± 10	77 ± 10	75 ± 10	74 ± 11	71 ± 9	70 ± 7
Heart rate, beats/min	66 ± 11	66 ± 13	63 ± 10	63 ± 11	70 ± 11	65 ± 10
Ejection fraction, %	58 ± 9	61 ± 8	62 ± 8	62 ± 7	60 ± 10	61 ± 10
NT-proBNP, pmol/ml	163 ± 184	140 ± 170	186 ± 227	214 ± 313	145 ± 145	141 ± 145

Values are mean ± SD.
BP = blood pressure; NT-proBNP = N-terminal pro-brain natriuretic peptide.

Table 3 Pulmonary Function Assessment

	Ticagrelor (n = 57)		Clopidogrel (n = 54)		Placebo (n = 12)	
Parameter	Baseline	6 Weeks	Baseline	6 Weeks	Baseline	6 Weeks
FEV_1, l	2.8 ± 0.7	2.8 ± 0.7	2.8 ± 0.8	2.7 ± 0.8	2.9 ± 0.7	3.0 ± 0.7
FVC, l	3.7 ± 0.9	3.7 ± 0.9	3.7 ± 1.1	3.8 ± 1.0	4.0 ± 0.9	4.0 ± 0.9
FEV_1/FVC	75 ± 7	75 ± 6	73 ± 7	73 ± 6	73 ± 7	74 ± 8
$FEF_{25–75}$, %	2.9 ± 1.3	2.8 ± 1.3	2.7 ± 1.2	2.7 ± 1.2	2.5 ± 1.2	2.9 ± 1.4
V_E, l/min	12.9 ± 4.0	13.7 ± 3.6	12.2 ± 3.6	13.1 ± 5.5	12.1 ± 4.1	11.5 ± 3.5
V_T, l/min	0.96 ± 0.33	0.92 ± 0.26	0.89 ± 0.32	0.93 ± 0.39	0.89 ± 0.27	0.83 ± 0.33
FRC, l	2.8 ± 0.9	2.7 ± 0.7	2.9 ± 0.9	2.8 ± 0.9	2.9 ± 0.7	2.78 ± 1.0
TLC, l	5.8 ± 1.3	5.7 ± 1.2	5.8 ± 1.4	5.9 ± 1.4	6.1 ± 1.0	6.0 ± 1.4
RV, l	1.9 ± 0.8	1.9 ± 0.6	2.0 ± 0.6	2.0 ± 0.6	1.9 ± 0.4	1.9 ± 0.8
RR, breaths/min	15 ± 2	15 ± 3	14 ± 3	15 ± 2	16 ± 2	15 ± 1
D_LCO_{SB}, %	17 ± 9	16 ± 8	17 ± 11	17 ± 8	16 ± 6	16 ± 7
SpO_2, %	97 ± 2	98 ± 1	97 ± 2	97 ± 1	98 ± 1	99 ± 1

Values are mean ± SD.

D_LCO_{SB} = single-breath diffusing capacity of lung for carbon monoxide; $FEF_{25–75}$ = mean forced expiratory flow between 25% and 75% of the FVC; FEV_1 = forced expiratory volume in 1 second; FRC = forced residual capacity; FVC = forced vital capacity; RR = respiratory rate; RV = residual volume; SpO_2 = blood oxygen saturation measured by pulse oximetry; TLC = total lung capacity; V_E = minute ventilation; V_T = tidal volume.

nary function as a result of dyspnea, and there was no evidence of any adverse trends (Table 5). In particular, there was no evidence on spirometry of transient bronchospasm in the ticagrelor-treated patients, even in 2 of the patients who discontinued study medication due to dyspnea (individual data not shown separately).

Serum bicarbonate levels. Serum bicarbonate levels showed no significant evidence of metabolic acidosis developing after study drug administration. Mean serum bicarbonate levels at baseline, at 6 weeks, and at 10 days after dose were 27.2 ± 2.2 mmol/l, 26.2 ± 2.3 mmol/l, and 27.2 ± 2.3 mmol/l, respectively, in the ticagrelor group; 27.5 ± 1.9 mmol/l, 26.5 ± 2.5 mmol/l, and 27.1 ± 2.5 mmol/l, respectively, in the clopidogrel group; and 26.3 ± 2.6 mmol/l, 26.4 ± 3.3 mmol/l, and 27.6 ± 2.1 mmol/l, respectively, in the placebo group. For patients who experienced dyspnea during the study, the mean serum bicarbonate levels at baseline, at 6 weeks, and at 10 days after dose were 27.0 ± 2.6 mmol/l, 25.4 ± 2.1 mmol/l, and 26.8 ± 2.4 mmol/l, respectively, in the ticagrelor group; 26.5 ± 0.84 mmol/l, 25.2 ± 4.7 mmol/l, and 28.5 ± 1.0 mmol/l, respectively, in the clopidogrel group; and for the 1 patient with dyspnea in the placebo group, 25.0 mmol/l, 29.0 mmol/l, and 29.0 mmol/l, respectively. Seven patients in the ticagrelor group who had dyspnea in the first 24 h had serum bicarbonate measured at 24 h after the first dose and had serum bicarbonate levels of 26.3 ± 3.2 mmol/l at this time point.

Relationship between dyspnea and pharmacokinetic data. Differences between pharmacokinetic parameters C_{max} and AUC_{0-8} in the ticagrelor group were not statistically significant between dyspnea and nondyspnea groups at drug onset (first dosing) or offset (last dosing), although there was a nonsignificant trend toward higher ticagrelor levels in the patients with dyspnea: geometric mean (coefficient of variation) C_{max} at onset was 1,249 ng/ml (24%) in patients with dyspnea and 1,170 ng/ml (46%) in patients without dyspnea ($p = 0.54$); at offset, the values were 890 ng/ml (50%) and 669 ng/ml (59%), respectively ($p = 0.07$). Mean AUC_{0-8} at onset was 5,903 $ng \cdot h^{-1} \cdot ml^{-1}$ (23%) in patients with dyspnea and 5,351 $ng \cdot h^{-1} \cdot ml^{-1}$ (43%) in patients without dyspnea ($p = 0.33$); at offset, mean AUC_{0-8} was 5,003 $ng \cdot h^{-1} \cdot ml^{-1}$ (53%) and 3,772 $ng \cdot h^{-1} \cdot ml^{-1}$ (61%), respectively ($p = 0.081$). No differences between dyspnea and nondyspnea groups were seen with respect to the plasma concentrations of AR-C124910XX, an active metabolite of ticagrelor, and there was no trend toward higher levels in the dyspnea group (data not shown).

Discussion

This is the first study to prospectively examine cardiac and pulmonary function before and during treatment with ticagrelor. As in previous studies of ticagrelor in patients with atherosclerotic disease (3–5), dyspnea was observed in a significant proportion of patients after commencement of ticagrelor. The incidence of dyspnea in ticagrelor-treated patients was greater in this study than in previous studies, which could be due to chance or could reflect the fact that both investigators and patients were informed of the potential occurrence of dyspnea and the reasons for cardiac and pulmonary investigation, thus increasing their awareness of the symptom and the probability of recording this as an adverse event. Some of the episodes were mild and so transient that it is quite likely these could have been overlooked in previous clinical studies, either because of lack of awareness of this side effect in the first phase 2 study in stable patients (4) or because of the numerous other distractions in the early phase of treatment in the 2 acute coronary syndrome studies (3,5). The pattern of dyspnea varied widely, from very brief episodes lasting minutes to sustained or intermittent episodes occurring over several weeks, with

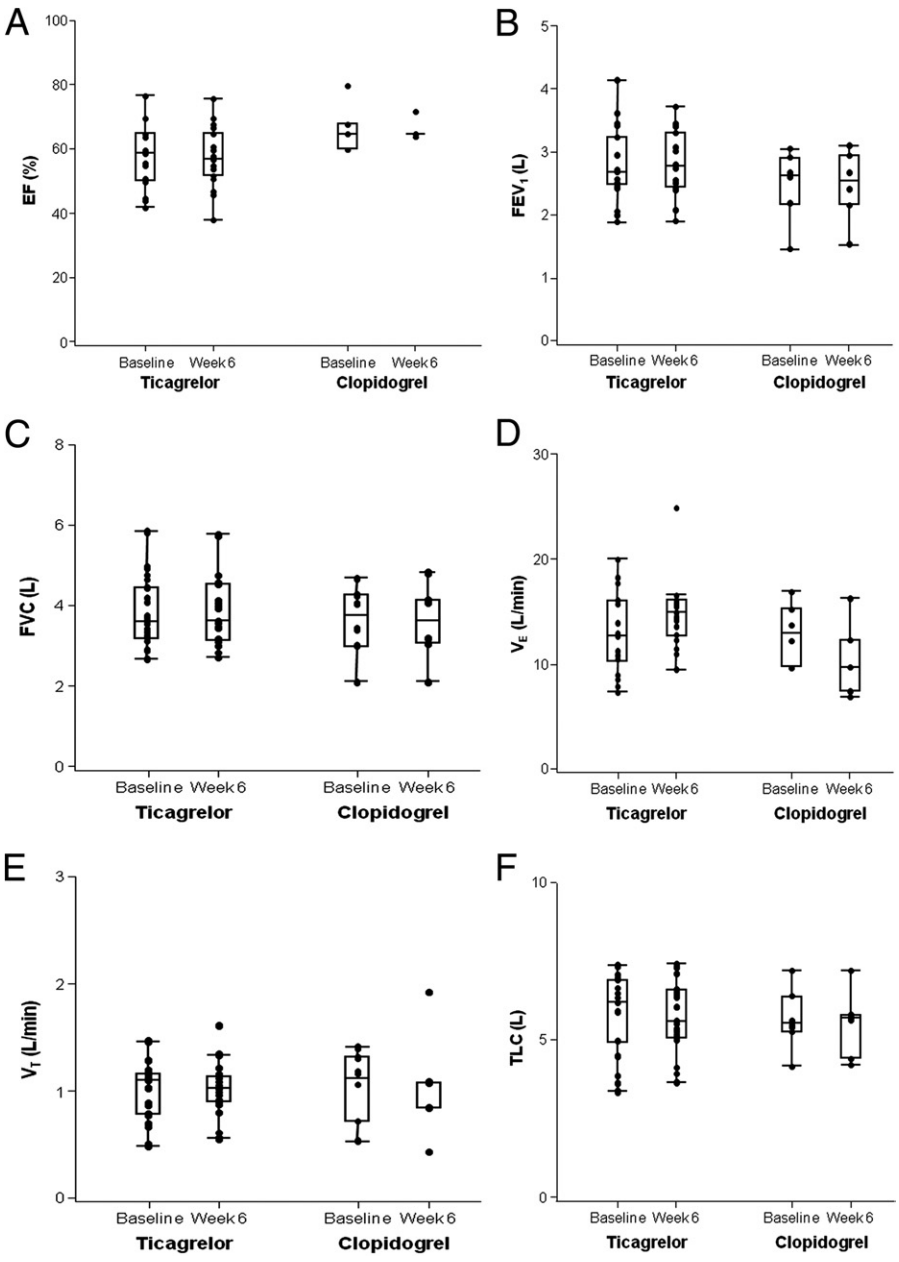

Figure 2 **Cardiac and Pulmonary Parameters in Ticagrelor- and Clopidogrel-Treated Patients With Dyspnea**

Measurements were made at baseline before drug administration and after 6 weeks of treatment with ticagrelor 90 mg twice daily or clopidogrel 75 mg daily. **(A)** Ejection fraction (EF). **(B)** Forced expiratory volume in 1 s (FEV_1). **(C)** Forced vital capacity (FVC). **(D)** Minute ventilation (V_E). **(E)** Tidal volume (V_T). **(F)** Total lung capacity (TLC). *Continued on next page.*

most episodes being reported as mild but some leading to discontinuation of study medication. Most of the sustained episodes in the ticagrelor group resolved upon cessation of ticagrelor, and there was little difference between the 2 active treatment groups in the proportions of patients who had persistent dyspnea despite discontinuation of the study medication. These observations provide reassurance about the reversibility of ticagrelor-related dyspnea with decline in plasma levels of ticagrelor.

To determine whether ticagrelor induced any changes in cardiac function, we performed measurements of heart rate and electrical activity, blood pressure, left ventricular ejection fraction, and serum N-terminal pro-brain natriuretic peptide and found no significant changes in any of these

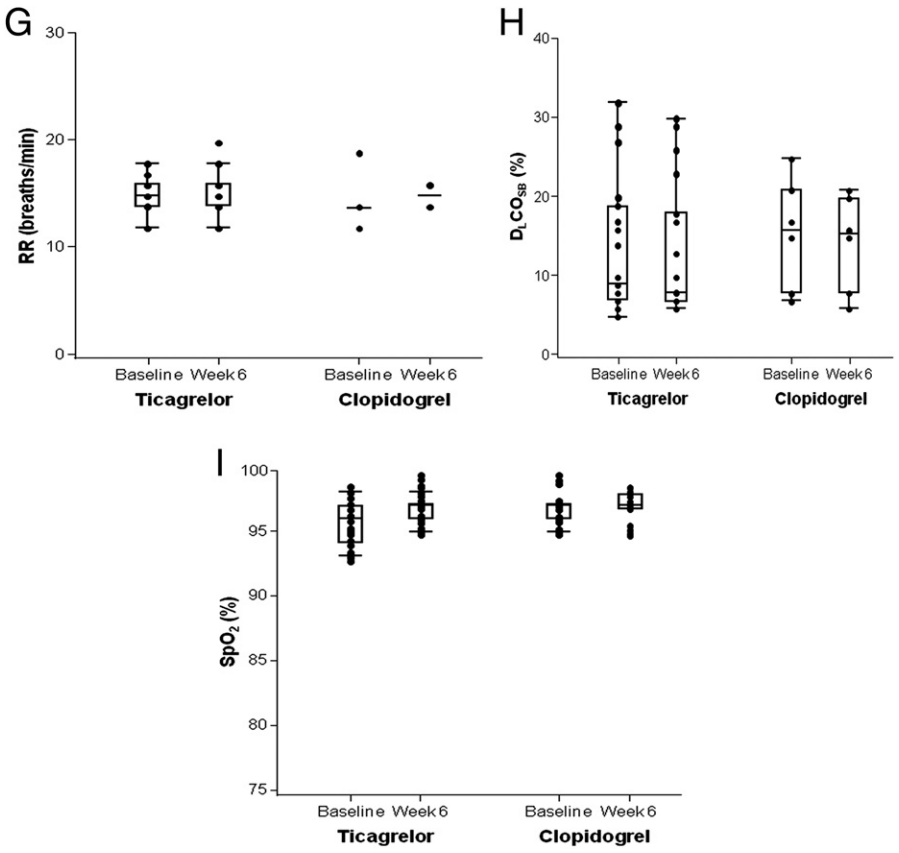

Figure 2 Continued

(G) Respiratory rate (RR). **(H)** Single-breath diffusing capacity for the lungs using carbon monoxide (D_LCO_{SB}). **(I)** Blood oxygen saturation measured by pulse oximetry (SpO_2). The **boxes** represent the interquartile ranges and median, and the **error bars** show standard deviation, superimposed on scatter plots of individual patients. The p value was not significant for all comparisons.

measurements during treatment, even in patients who had dyspnea after commencing ticagrelor. In addition, a wide range of parameters assessing different aspects of pulmonary function were examined, including established markers for assessing the presence and severity of bronchoconstriction and interstitial lung disease, and again, none of these parameters showed any significant change during treatment with ticagrelor, including in patients with ticagrelor-related dyspnea. There was also no evidence that metabolic acidosis, a cause of dyspnea, was induced by ticagrelor therapy as judged by serum bicarbonate levels.

Phase II studies of ticagrelor demonstrated that the incidence of ticagrelor-related dyspnea is dose dependent, suggesting that plasma levels of ticagrelor and/or its metabolites influence the likelihood of an individual developing this side effect (4,5). In this study, there was only a nonsignificant trend toward higher ticagrelor levels in patients who had dyspnea compared with patients who did not, suggesting that factors other than plasma ticagrelor level play a substantial role in the likelihood of ticagrelor-related dyspnea. Further analyses of the PLATO study data are warranted to explore what clinical factors may contribute to ticagrelor-related dyspnea.

The reversible nature of ticagrelor-related dyspnea and the lack of any evidence of cardiac or pulmonary pathology associated with this provide preliminary reassurance about the nature of this side effect. Although the mechanism for the dyspnea is unproven, a number of observations support the hypothesis that adenosine may mediate it. Preliminary data have suggested that ticagrelor inhibits adenosine uptake into erythrocytes, leading to changes in regional blood flow similar to those obtained with dipyridamole (6), another inhibitor of adenosine reuptake (9). Burki et al. (7) showed that intravenous infusion of adenosine to healthy volunteers can induce dyspnea without any associated bronchoconstriction, which can occur in asthmatic patients administered adenosine. They suggested that adenosine-induced dyspnea may be due to stimulation of lung receptors, most likely vagal C fibers. Adenosine administration can also induce bradycardia and, in both the DISPERSE2 (Dose Confirmation Study Assessing Anti-Platelet Effects of AZD6140 vs Clopidogrel in NSTEMI) study and the

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PLATO study, ticagrelor treatment was associated with an increased incidence of ventricular pauses on Holter monitoring (3,5), leading to speculation that dyspnea and increased propensity to ventricular pauses induced by ticagrelor may have the same underlying cause.

Three of 57 patients receiving ticagrelor discontinued treatment as a result of dyspnea in this study, higher than the rate of discontinuation due to dyspnea in the PLATO study (3). Again, this may be due to chance or may reflect less motivation to tolerate the dyspnea in view of the low probability of therapeutic gain during relatively short-term administration in a stable population as well as the demands of the intensive requirements of the study protocol.

Study limitations. Patients with recent acute coronary syndrome, cardiac failure, or significant lung disease including asthma were excluded from this study, and further analyses and/or studies are warranted to assess the response to ticagrelor therapy in these groups. The study was not of sufficient size to assess fully the relationship between dyspnea and plasma ticagrelor levels. The study was also not of sufficient size to properly assess whether ticagrelor-related dyspnea is a benign phenomenon, and further analysis of data from the PLATO study is required to explore the relationship between this dyspnea and clinical outcomes.

Conclusions

Dyspnea is commonly associated with ticagrelor therapy, often arising during the first week of treatment, and is usually mild or moderate in severity and often transient despite continued treatment. Ticagrelor treatment was not associated with any adverse changes in cardiac or pulmonary function after 6 weeks of treatment in this study of patients who were free of active lung disease at commencement of the study, including patients who had dyspnea during therapy. Further studies of ticagrelor in patients with active lung disease are now warranted.

Table 4 Cardiac and Pulmonary Assessments at Baseline and 6 Weeks for Patients Reporting Dyspnea Episode

	Ticagrelor		Clopidogrel	
Parameter	Baseline (n = 22)	6 Weeks (n = 19)	Baseline (n = 6)	6 Weeks (n = 6)
Ejection fraction, %	57 ± 9	58 ± 9	66 ± 7	66 ± 3
NT-proBNP, pmol/ml	147 ± 144	154 ± 221	257 ± 317	260 ± 195
FEV_1, l	2.8 ± 0.7	2.8 ± 0.5	2.5 ± 0.6	2.5 ± 0.6
FVC, l	3.9 ± 0.8	3.8 ± 0.8	3.6 ± 0.9	3.6 ± 1.0
FEV_1/FVC, %	73 ± 8	74 ± 5	70 ± 7	70 ± 7
V_E, l/min	13 ± 4	15 ± 3	13 ± 3	10 ± 4
V_T, l/min	1.0 ± 0.3	1.0 ± 0.2	1.0 ± 0.3	1.0 ± 0.5
TLC, l	5.9 ± 1.2	5.8 ± 1.1	5.7 ± 1.0	5.5 ± 1.1
RR, breaths/min	15 ± 2	16 ± 2	14 ± 3	15 ± 1
D_LCO_{SB}, %	14 ± 9	13 ± 8	16 ± 7	14 ± 6
SpO_2, %	97 ± 2	97 ± 1	98 ± 1	98 ± 1

Values are mean ± SD.
Abbreviations as in Tables 2 and 3.

Table 5 Early Cardiac and Pulmonary Function Assessments Due to Dyspnea in Ticagrelor-Treated Patients

Parameter	n	Days of Treatment	Baseline	Post-Treatment
Ejection fraction, %	5	16 ± 6	66 ± 10	63 ± 3
NT-proBNP, pmol/ml	5	19 ± 9	141 ± 70	126 ± 76
FEV_1, l	6	19 ± 8	2.5 ± 0.3	2.5 ± 0.2
FVC, l	6	19 ± 8	3.5 ± 0.4	3.4 ± 0.4
FEV_1/FVC	6	19 ± 8	72 ± 8	74 ± 7
RR, breaths/min	5	16 ± 6	15 ± 1	13 ± 2
D_LCO_{SB}, %	6	19 ± 8	9 ± 5	9 ± 5

Values are mean ± SD.
Abbreviations as in Table 3.

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Reprint requests and correspondence: Dr. Robert F. Storey, Department of Cardiovascular Science, University of Sheffield, Beech Hill Road, Sheffield S10 2RX, United Kingdom. E-mail: r.f.storey@sheffield.ac.uk.

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APPENDIX

ONSET/OFFSET Investigators: U.S.: Dr. Paul A. Gurbel (principal investigator), Sinai Center for Thrombosis Research, Baltimore, Maryland; Dr. Dean J. Kereiakes, Christ Hospital Heart and Vascular Center and Lindner Research Center, Cincinnati, Ohio; Dr. Cordel Paris, Dolby Research LLC, Baton Rouge, Louisiana; Dr. Drew Purdy, Black Hills Clinical Research Center, Rapid Center, South Dakota; Dr. Vance Wilson, Cardiology Consultants, Daytona Beach, Florida; Dr. Gary S. Ledley, Hahnemann University Hospital, Philadelphia, Pennsylvania; Dr. Albert Yataco, International Research Center, Baltimore, Maryland. UK: Dr. Robert F. Storey, NIHR Cardiovascular Biomedical Research Unit, Centre for Biomedical Research, Northern General Hospital, Sheffield.