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Pharmacokinetics and Pharmacodynamics of Ticagrelor in Patients with Stable Coronary Artery Disease

Results from the ONSET-OFFSET and RESPOND Studies

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Abstract

Background and Objectives: Ticagrelor, the first reversibly binding oral $P2Y_{12}$ receptor antagonist, improves outcomes in patients with acute coronary syndromes (ACS) compared with clopidogrel. In the ONSET-OFFSET study (parallel group trial) and the RESPOND study (crossover trial), the pharmacodynamic effects of ticagrelor were compared with clopidogrel in patients with coronary artery disease (CAD). We now report the pharmacokinetic analyses of ticagrelor, and the exposure-inhibition of platelet aggregation (IPA) relationships from these studies.

Patients and Methods: Patients were treated with ticagrelor (180 mg loading dose, 90 mg twice daily maintenance dose) or clopidogrel (600 mg loading dose, 75 mg once daily maintenance dose) in addition to aspirin (acetylsalicylic acid) [75–100 mg once daily]. Ticagrelor administration was for 6 weeks in ONSET-OFFSET. In RESPOND, ticagrelor was given for 14 days before or after 2 weeks of clopidogrel in patients classified as clopidogrel responders or non-responders. Pharmacokinetics and IPA were evaluated following the loading and last maintenance doses. Exposure-IPA relationships were evaluated using a sigmoid maximum effect (E_{max}) model.

Outcome Measures: The outcome measures were ticagrelor and AR-C124910XX (active metabolite) pharmacokinetics and exposure-IPA relationships in both trials, including the effect of prior clopidogrel exposure, and effects in clopidogrel responders and non-responders in RESPOND.

Results: In ONSET-OFFSET, maximum (peak) plasma concentration (C_{max}), time to C_{max} (t_{max}) and area under the plasma concentration-time curve from time 0 to 8 hours (AUC_8) for ticagrelor were 733 ng/mL, 2.0 hours and 4130 ng • h/mL, respectively; and for AR-C124910XX were 210 ng/mL, 2.1 hours and 1325 ng • h/mL, respectively. E_{max} estimates were IPA >97%. Trough plasma ticagrelor (305 ng/mL) and AR-C124910XX (121 ng/mL) concentrations were 5.2 and 7.7 times higher than respective concentration producing 50% of maximum effect (EC_{50}) estimates. In RESPOND, ticagrelor mean C_{max} and AUC_8 following 2-week dosing were comparable between clopidogrel responders (724 ng/mL and 3983 ng • h/mL, respectively) and non-responders (764 ng/mL and 3986 ng • h/mL, respectively). Pharmacokinetics of ticagrelor were unaffected by prior clopidogrel dosing. E_{max} estimates were IPA >96% for both responders and non-responders. Trough plasma concentrations were sufficient to achieve high IPA.

Conclusions: Ticagrelor pharmacokinetics in stable CAD patients were comparable to previous findings in stable atherosclerotic and ACS patients, and were not affected by prior clopidogrel exposure or clopidogrel responsiveness. Ticagrelor effectively inhibited platelet aggregation, and trough plasma concentrations of ticagrelor and AR-C124910XX were sufficient to result in high IPA in stable CAD patients.

Background

Ticagrelor, the first reversibly binding oral $P2Y_{12}$ receptor antagonist,[1-4] was recently approved for use in the EU[5] and the US[6] for adult patients with acute coronary syndromes (ACS); ticagrelor has been approved in more than 40 countries. Phase III data from the PLATO (PLATelet inhibition and patient Outcomes) trial in ACS patients, with or without ST-segment elevation, showed that ticagrelor treatment (180 mg loading dose then 90 mg twice daily) significantly reduced the rate of the composite of myocardial infarction, stroke and death from vascular causes compared with clopidogrel (300–600 mg loading dose then 75 mg once daily).[7] This composite endpoint occurred in 9.8% (ticagrelor group) and 11.7% (clopidogrel group) of patients (hazard ratio 0.84, 95% CI 0.77, 0.92; $p < 0.001$).[7]

Healthy volunteer studies have provided extensive information on ticagrelor pharmacokinetics and pharmacodynamics. Ticagrelor exhibited linear and predictable pharmacokinetics with single doses up to 1260 mg.[8,9] Following multiple doses, maximum ticagrelor plasma concentrations were achieved within 1.5–3.0 hours, and the elimination half-life ($t_{½}$) ranged from 6.2 to 13.1 hours.[10] Ticagrelor (100–400 mg) produced near-complete inhibition of platelet aggregation (IPA) [88–95%] by 2 hours post-dosing.[8,9]

Clopidogrel requires metabolic activation via a multistep process involving several cytochrome P450 (CYP) isoenzymes.[11,12] In contrast, ticagrelor can directly bind to the $P2Y_{12}$ receptor, thereby inhibiting adenosine diphosphate (ADP)-induced platelet aggregation (PA).[13] *In vitro* studies have demonstrated that ticagrelor binds reversibly to $P2Y_{12}$ receptors, with rapid receptor kinetics (e.g. mean ± standard error of the mean dissociation constant [K_{off}]: $8.7 \pm 1.4 \times 10^{-4}$ s^{-1}; time to achieve 50% K_{off} [$t_{½(off)}$] 13.5 ± 1.9 min).[13] In a mass balance study, ticagrelor was metabolized to at least ten metabolites, with AR-C124910XX being the major component.[14] This active metabolite, formed mainly by CYP3A4/5 isoenzymes,[15] has a similar potency to ticagrelor and has plasma concentrations approximately one-third that of the parent compound.[9,14]

Two phase II ticagrelor studies, DISPERSE (Dose-finding Investigative Study to assess the Pharmacodynamic Effects of AZD6140 in atheRoSclErotic disease) and DISPERSE-2 (Dose confIrmation Study assessing anti-Platelet Effects of AZD6140 versus clopidogRel in non–STsegment Elevation myocardial infarction), have confirmed the consistent and predictable pharmacokinetic profiles of ticagrelor and AR-C124910XX in patients with either stable atherosclerosic disease[3] or ACS.[16] Furthermore, both trials demonstrated that IPA was greater and less variable with ticagrelor than with standard-dose clopidogrel (300 mg load/75 mg once-daily maintenance) in such patients.

Two randomized, multicentre, clinical trials have evaluated the antiplatelet activity, safety and tolerability of ticagrelor versus high-loading dose clopidogrel (both with concomitant aspirin [acetylsalicylic acid; 75–100 mg once daily] as background therapy) in patients with stable coronary artery disease (CAD). In these trials, the PLATO trial dose of ticagrelor was evaluated. In the randomized, double-blind ONSET-OFFSET (ONSET and OFFSET of the antiplatelet effects of ticagrelor versus clopidogrel in patients with stable coronary artery disease [NCT00528411; parallel group trial]) trial, IPA with ticagrelor was more rapid and greater than with clopidogrel; mean ± standard deviation final-extent IPA at 2 hours after first dose: 88 ± 15% versus 38 ± 33%, respectively ($p < 0.0001$).[17] In the RESPOND (REsponse to ticagrelor in clopidogrel non-responders and ReSPONDers and the effect of switching therapies [NCT00642811; crossover trial]) study, the ticagrelor antiplatelet effect was similar in patients responsive or non-responsive to clopidogrel.[18]

Secondary objectives of ONSET-OFFSET and RESPOND included evaluation of ticagrelor pharmacokinetics and the exposure-IPA relationships of ticagrelor and AR-C1249XX in patients with stable CAD. Results of these pre-planned sub-analyses from both studies are reported herein.

Methods

Detailed methodology for ONSET-OFFSET and RESPOND has been published previously.[17,18]

Patients

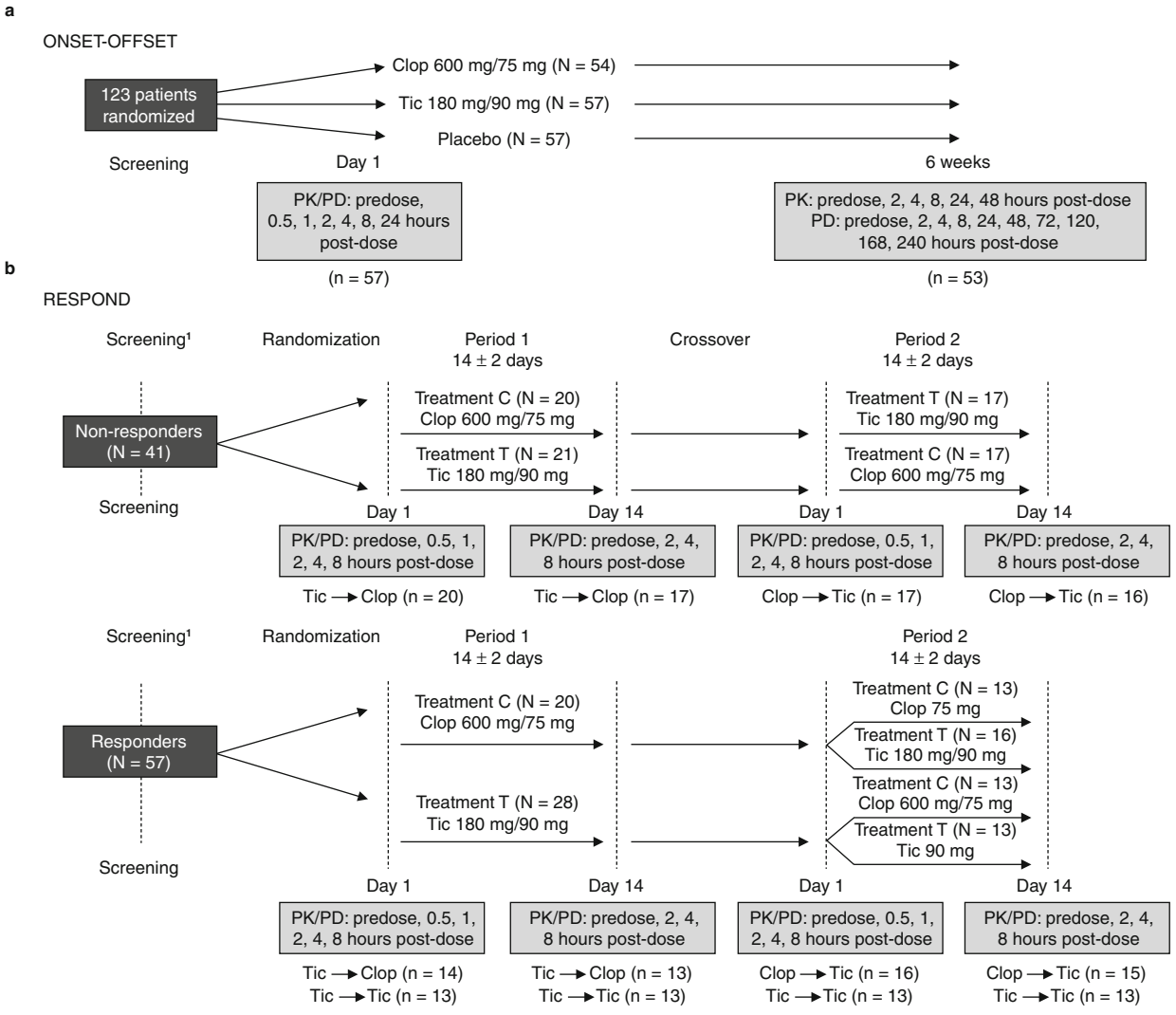
Patients were enrolled in the US and Europe. Key inclusion criteria were ≥18 years of age with documented stable CAD and stable aspirin therapy (75–100 mg once daily). In both studies, key exclusion criteria were ACS within 12 months of screening; a history of bleeding diathesis or severe pulmonary disease; pregnancy; concomitant therapy with moderate or strong CYP3A inhibitors or strong inducers in the prior 14 days; atrial fibrillation, coronary stent, mitral stenosis or prosthetic heart valve requiring antithrombotic treatment; and platelet count <100 000/mm^3 or haemoglobin <10 g/dL. In addition, smokers were excluded in ONSET-OFFSET, whereas in RESPOND patients who were currently smoking >1 pack per day were excluded. Both studies were performed in accordance with standard ethical principles; written consent was obtained from all patients.

Study Designs and Treatments

ONSET-OFFSET was a randomized, double-blind, double-dummy, parallel-group multicentre study to evaluate the onset and offset of ticagrelor antiplatelet effect versus clopidogrel or placebo. Patients treated with ticagrelor received a single oral loading dose (180 mg) in the morning on day 1, followed by a maintenance dose (90 mg) 12 hours later. For 6 weeks thereafter, ticagrelor was administered at 90 mg twice daily (figure 1a).

RESPOND was a multicentre, randomized, double-blind, double-dummy crossover study to compare the antiplatelet effects of ticagrelor with clopidogrel in patients previously identified as either responsive or non-responsive to clopidogrel (figure 1b). Non-responsiveness to clopidogrel was defined as ≤10% absolute change in maximum-extent PA, induced by 20 μmol/L ADP,[18] between pre-dose and 6–8 hours post-dosing with clopidogrel 300 mg at screening.

In period 1, responders and non-responders received either ticagrelor (180 mg loading dose then 90 mg twice daily) or clopidogrel (600 mg loading dose then 75 mg once daily) for 14 days. For period 2, all non-responders switched treatments and were treated for a further 14 days. In period 2, half of the responders switched treatments, with the remaining patients



1 Patients were dosed with study drug >14 days after screening.

Fig. 1. Study designs of (**a**) ONSET-OFFSET and (**b**) RESPOND. The N values are the number of patients randomized to treatments indicated, and the n values are the number of patients with evaluable pharmacokinetic/pharmacodynamic data and may differ from the number of patients who were randomized and treated. **Clop** = clopidogrel; **PD** = pharmacodynamic; **PK** = pharmacokinetic; **Tic** = ticagrelor.

Table I. Demographic and key baseline characteristics of patients in ONSET-OFFSET and RESPOND (RESPOND data reproduced from Gurbel et al.,[18] with permission)

Characteristic	ONSET-OFFSET (n = 53–57)	RESPOND	
		Non-responders (n = 41)	Responders[a] (n = 57)
Gender, male [n (%)]	43 (75)	28 (68)	48 (84)
Mean age [years (SD)]	62 (9)	66 (7)	64 (9)
Race [n (%)]			
White	51 (90)	38 (93)	49 (86)
Black/African American	4 (7)	3 (7)	5 (9)
Other	2 (4)	0 (0)	3 (5)
Mean BMI [kg/m^2 (SD)]	31 (5)	30 (4)	29 (5)
Mean baseline creatinine [μmol/L (SD)]	91 (24)	93 (26)	88 (18)
Current smoker [n (%)]	0	2 (5)	15 (26)
Hypertension [n (%)]	44 (77)	33 (81)	46 (81)
Diabetes mellitus [n (%)]	12 (21)	9 (22)	16 (28)
HbA_{1c} [>6.0% (baseline)]	6 (11)	6 (15)	14 (25)
Dyslipidaemia [n (%)]	54 (95)	38 (93)	54 (95)
Concomitant medications [n (%)]			
Statins	49 (86)	35 (85)	53 (93)
β-Blockers (β-adrenoceptor antagonists)	39 (68)	29 (71)	40 (70)
Diuretics	20 (35)	15 (37)	19 (33)
ACE inhibitors	10 (18)	10 (24)	10 (18)
Nitrates	6 (11)	8 (20)	7 (12)
Proton pump inhibitors	16 (28)	10 (24)	11 (19)
Calcium channel antagonists	17 (30)	8 (20)	16 (28)
Angiotensin II antagonists	11 (19)	10 (24)	10 (18)

a The only statistically significant difference between non-responders and responders was smoking, $p < 0.007$.[18]

BMI = body mass index; **HbA_{1c}** = glycosylated haemoglobin; **SD** = standard deviation.

continuing with treatment as in period 1. These patients did not receive a loading dose of study drug at the start of period 2.

All patients in both ONSET-OFFSET and RESPOND received concomitant aspirin (75–100 mg once daily).

Pharmacokinetic Evaluations

Blood sampling times were 0 (pre-dose), 0.5, 1, 2, 4, 8 and 24 hours after a single loading dose (180 mg) of ticagrelor on day 1 in ONSET-OFFSET (figure 1a), and at 0 (pre-dose), 0.5, 1, 2, 4 and 8 hours post-dosing on day 1 in periods 1 and 2 in RESPOND (figure 1b). Following maintenance dosing with ticagrelor (90 mg twice daily), blood samples were collected at 0 (pre-dose), 2, 4, 8, 24 and 48 hours post-dosing after the last dose at 6 weeks in ONSET-OFFSET (figure 1a). In RESPOND, blood sampling times, after ticagrelor maintenance dosing, were 0 (pre-dose), 2, 4 and 8 hours post-dosing on day 14 in periods 1 and 2 (figure 1b).

For ticagrelor and AR-C124910XX evaluations, venous blood samples (2 mL) were collected into lithium-heparinized tubes, mixed and placed on ice immediately. Within 30 minutes of collection, blood samples were centrifuged (10 min, 4°C, $1500 \times g$) and the plasma stored at −20°C until analysis.

Plasma concentrations of ticagrelor and AR-C124910XX were quantified using a validated reverse-phase liquid chromatography/tandem mass spectrometry method. Mean intra-batch accuracy was 91.9–109.0% (ticagrelor) and 86.8–109.2% (AR-C124910XX); intra-batch precision was 4.0–8.4% and 5.2–16.9%, respectively. Lower limits of quantification were 5 ng/mL (ticagrelor) and 2.5 ng/mL (AR-C124910XX).[19]

Pharmacodynamic Assessment

Blood sampling times for IPA assessment included 0 (pre-dose), 0.5, 1, 2, 4 and 8 hours after a single loading dose (180 mg) of ticagrelor on day 1 in both trials (figure 1). After the last ticagrelor dose at 6 weeks in ONSET-OFFSET, blood samples were collected for 10 days (figure 1a). IPA (20 μmol/L ADP-induced, final extent) in platelet-rich plasma was assessed, as described previously.[18,20]

Data Analyses

Pharmacokinetic parameters were estimated by noncompartmental methods using WinNonlin Professional (Pharsight Corporation, Mountain View, CA, USA). Key pharmacokinetic parameters calculated for ticagrelor and AR-C124910XX were maximum (peak) plasma concentration (C_{max}); time to C_{max} (t_{max}); area under the plasma concentration-time curve (AUC) from time 0 to 8 hours (AUC_8; calculated by the linear trapezoidal rule); and trough (minimum) plasma drug concentration over the dosing interval (C_{trough}) [ONSET-OFFSET].

Pharmacokinetic parameters and plasma concentration data for each moiety (ticagrelor and AR-C124910XX) were summarized using descriptive statistics. The latter also included geometric mean and coefficient of variation (CV) for all parameters, except for t_{max} which was summarized using median (range) values. Geometric mean ratio and 95% confidence intervals (Hodges-Lehman) were calculated for AUC and C_{max} comparisons between clopidogrel responders and non-responders.

Final-extent IPA was calculated using the formula $(PA_{BL} - PA_T)/PA_{BL}$, where PA_{BL} is the mean pre-dose baseline response, and PA_T is the mean PA response at time T. Mean IPA (percentage) was plotted versus time.

The relationship between IPA and ticagrelor, and AR-C124910XX concentrations was assessed using a sigmoid maximal effect model: $IPA = (E_{max}C^{\gamma})/(C^{\gamma} + EC^{\gamma}_{50})$, where E_{max} = maximum effect, EC_{50} = concentration producing 50% of maximum effect, γ = sigmoidicity or shape factor and C = plasma concentration.

Results

Patient Disposition and Baseline Characteristics

A total of 155 patients with stable CAD were randomized to ticagrelor treatment: ONSET-OFFSET, n = 57; RESPOND, n = 98.

In ONSET-OFFSET, all patients who were randomized to ticagrelor treatment received at least one dose of ticagrelor, and five of these patients discontinued (one for incorrect enrolment; four due to adverse events [dyspnoea, n = 2; exertional dyspnoea, n = 1; sleep disorders, n = 1]). Pharmacokinetic data were available for all ONSET-OFFSET patients on day 1 (n = 57) and 53 patients at week 6. Pharmacodynamic data were available for up to 53 patients in the intent-to-treat analysis set (n = 54); 3/57 patients were excluded to form the full intent-to-treat set as baseline PA values were not available.

In RESPOND, 41 non-responders and 57 responders received at least one dose of ticagrelor. Overall, seven non-responders discontinued (five for adverse events [ticagrelor treatment: gastrointestinal haemorrhage, n = 1; hypotension, n = 1; ECG T-wave inversion, n = 1; clopidogrel treatment: dyspnoea, n = 1; myalgia, n = 1], one for protocol non-compliance, one for other reasons) and three responders discontinued (one

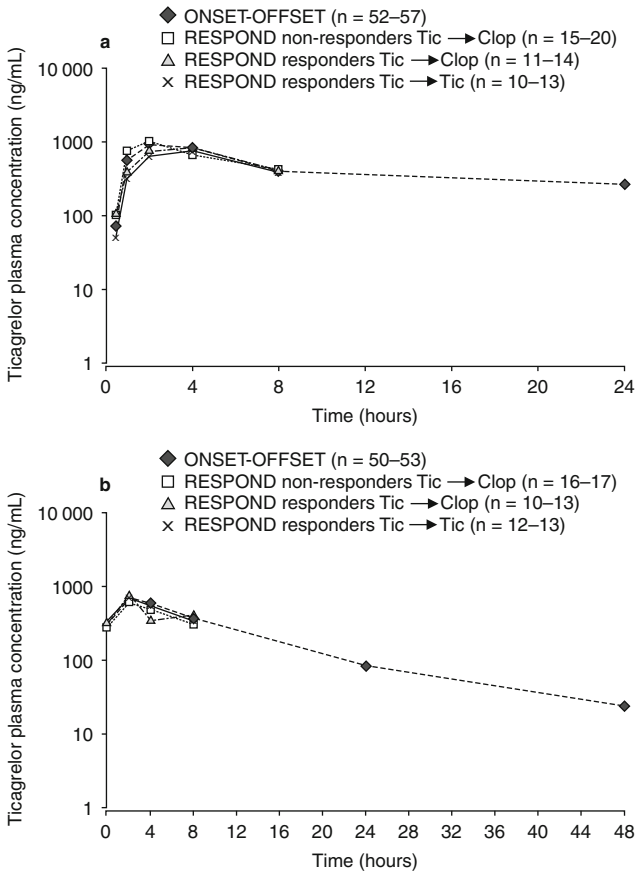


Fig. 2. Mean (geometric) plasma concentration-time curves of ticagrelor after (**a**) a single ticagrelor 180 mg loading dose and (**b**) the last 90 mg maintenance dose (6 weeks in ONSET-OFFSET; day 14 in RESPOND). n values are the range of patient numbers with quantifiable samples. Note that the x-axes show different time scales. **Clop** = clopidogrel; **Tic** = ticagrelor.

for adverse events [ticagrelor treatment: bradycardia], one developed study-specific discontinuation criteria, one for other reasons). Pharmacokinetic data were available for 80 patients (37 non-responders, 43 responders). Pharmacodynamic data were available for 97 patients (40 non-responders, 57 responders). Exposure-IPA analyses were available for 79 patients (36 non-responders, 43 responders).

Patient demographics were similar between the two trials, and the majority were Caucasian males. Key baseline characteristics were also similar in both trials, and were well balanced between non-responders and responders in RESPOND (table I).

Ticagrelor Pharmacokinetics

After a single 180 mg loading dose of ticagrelor, absorption was rapid (figure 2a) and the median t_{max} for ticagrelor was approximately 2 hours in both ONSET-OFFSET and RESPOND (table II). The ticagrelor C_{max} and AUC_8 values were broadly comparable between both trials (table II). Formation of AR-C124910XX was also rapid (figure 3a), with a median t_{max} of 2.0–3.8 hours (table II) in both studies. Overall, exposure (C_{max} and AUC_8) to the active metabolite was approximately 21% that of the parent compound, after a single loading dose of ticagrelor (table II).

Mean plasma concentration-time profiles of ticagrelor (figure 2b) and AR-C124910XX (figure 3b) at steady state demonstrated that after multiple ticagrelor dosing (90 mg twice daily) [i.e. 6 weeks in ONSET-OFFSET; 14 or 28 days in RESPOND] absorption of ticagrelor and conversion to AR-C124910XX were rapid. These profiles were broadly consistent between the two studies given the large variability of the data. Key pharmacokinetic parameters (C_{max}, AUC_8, t_{max}) for ticagrelor were broadly comparable between ONSET-OFFSET and RESPOND (table II). Overall, exposure (AUC_8) to the active metabolite after multiple ticagrelor dosing was approximately one-third that of the parent compound. In the ONSET-OFFSET study,

Table II. Pharmacokinetic parameters of a single loading dose (day 1) and after last maintenance dose of ticagrelor in ONSET-OFFSET and RESPOND

Parameter	Single dose[a]				Steady state[b]			
	ONSET-OFFSET[c]	RESPOND (day 1, period 1)[d]		GMR [95% CI][e]	ONSET-OFFSET[c]	RESPOND (day 14, period 1)[d]		GMR [95% CI][e]
		Responders[c]	Non-responders[c]			Responders[c]	Non-responders[c]	
Ticagrelor								
n[f]	52–57	10–13	15–20		52–53	12–13	16–17	
C_{max} (ng/mL)	1197 (39)	1039 (49)	1179 (41)	0.88 (0.65, 1.20)	733 (58)	715 (54)	688 (44)	1.04 (0.73, 1.47)
AUC_8 (ng • h/mL)	5539 (37)	4614 (46)	5170 (39)	0.89 (0.67, 1.20)	4130 (59)	3599 (45)	3707 (52)	0.97 (0.68, 1.40)
t_{max} (h)[g]	2.0 (0.9–23.9)	2.1 (1.0–4.1)	2.0 (1.0–8.0)		2.0 (0.0–4.2)	2.0 (0.0–4.0)	2.1 (1.9–4.0)	
AR-C124910XX								
n[f]	34–57	5–13	10–20		48–53	12–13	16–17	
C_{max} (ng/mL)	243 (40)	199 (30)	241 (51)	0.83 (0.61, 1.12)	210 (46)	187 (31)	247 (57)	0.76 (0.54, 1.06)
AUC_8 (ng • h/mL)	1254 (39)	940 (30)	1255 (52)	0.75 (0.55, 1.02)	1325 (42)	1096 (26)	1539 (51)	0.71 (0.52, 0.98)
t_{max} (h)[g]	2.0 (0.9–24.2)	3.8 (2.0–8.1)	2.0 (1.0–8.0)		2.1 (0.0–8.0)	2.0 (1.8–8.0)	2.0 (0.0–4.0)	

a After a single loading dose of ticagrelor 180 mg.

b After last maintenance dose of ticagrelor 90 mg twice daily after 6 weeks of dosing in ONSET-OFFSET and after 14 days of dosing in RESPOND.

c Values are expressed as geometric mean (CV%) unless otherwise specified.

d Data are shown for ticagrelor→ticagrelor group for responders and ticagrelor→clopidogrel group for non-responders. Data for ticagrelor→clopidogrel in responders are shown in tables III and IV.

e GMR of clopidogrel responders to non-responders.

f Number (or range) of patients with quantifiable pharmacokinetic samples.

g Values are expressed as median (range).

AUC_8 = area under the plasma concentration-time curve from time 0 to 8 hours; **C_{max}** = maximum (peak) plasma concentration; **CV** = coefficient of variation; **GMR** = geometric mean ratio; **t_{max}** = time to C_{max}.

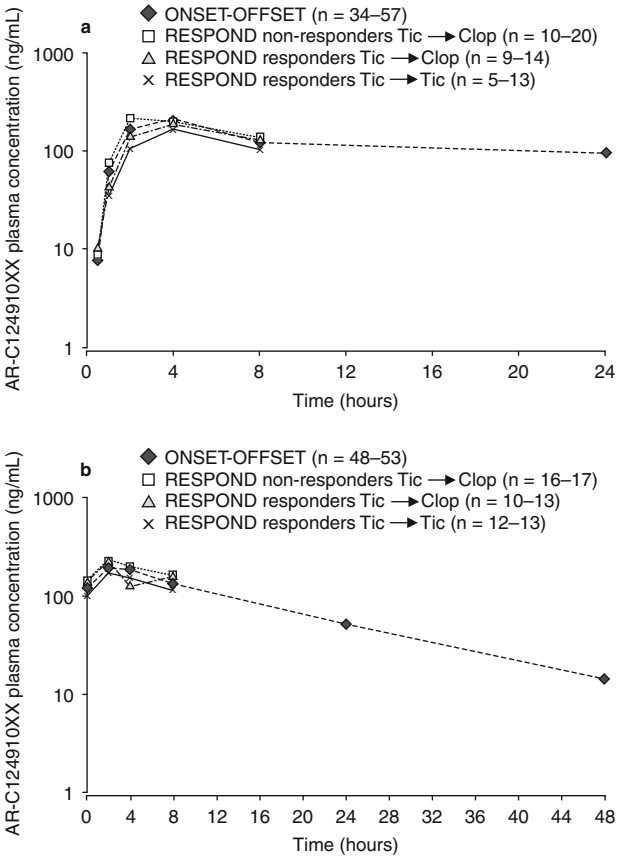


Fig. 3. Mean (geometric) plasma concentration-time curves of AR-C124910XX after (**a**) a single ticagrelor 180 mg loading dose and (**b**) the last 90 mg maintenance dose (6 weeks in ONSET-OFFSET; day 14 in RESPOND). n values are the range of patient numbers with quantifiable samples. Note that the x-axes show different time scales. **Clop** = clopidogrel; **Tic** = ticagrelor.

the median (range) $t_{½}$ values, calculated at the end of the 6-week maintenance period, were 9.8 (5.6–16.5) and 12.4 (7.3–22.8) hours, respectively.

Effect of Prior Administration of Clopidogrel on Ticagrelor Pharmacokinetics

In the RESPOND trial, pharmacokinetic measurements for the parent and active metabolite after a single ticagrelor loading dose were comparable in patients without prior clopidogrel administration (day 1, period 1, ticagrelor → clopidogrel group) and those who received 14 days of clopidogrel (day 1, period 2, clopidogrel → ticagrelor group) [table III]. Mean plasma concentration-time profiles of ticagrelor (figure 4a) and AR-C124910XX (figure 4b) were unaffected by 14 days of prior exposure to clopidogrel. Similarly, after 14 days of multiple dosing, ticagrelor and AR-C124910XX pharmacokinetic parameters were also unchanged by prior clopidogrel dosing (table IV).

Pharmacokinetics of Ticagrelor in Clopidogrel Responders and Non-Responders

Although plasma concentrations of both analytes were highly variable, following a single 180 mg loading dose of ticagrelor, the plasma concentration profiles of the parent compound (figure 2a) and active metabolite (figure 3a) were generally comparable between CAD patients who were responsive and non-responsive to clopidogrel. Geometric mean ratios and the 95% confidence interval indicated that the mean C_{max} and AUC_8 values for both ticagrelor and AR-C124910XX were either slightly lower (the reason for this observation was that the 180 mg loading dose of ticagrelor was not given systematically) in clopidogrel responders versus non-responders (ticagrelor → ticagrelor group; table II) or comparable in clopidogrel responders (ticagrelor → clopidogrel group; table III) versus non-responders.

Single-dose ticagrelor pharmacokinetics were also unaffected in patients who had no prior exposure to clopidogrel versus those who had clopidogrel for 14 days before ticagrelor (table III, figure 4). This observation was noted in both clopidogrel responders and non-responders (table III, figure 4).

Steady-state pharmacokinetic parameters (i.e. after 2-week maintenance dosing) of ticagrelor were comparable between the clopidogrel responder and non-responder subgroups in RESPOND (tables II and IV). Geometric mean ratios and the 95% confidence interval indicated that the mean C_{max} and AUC_8 values for AR-C124910XX were either slightly lower in clopidogrel responders (ticagrelor → ticagrelor group; table II) or comparable (ticagrelor → clopidogrel group; table IV) versus non-responders, reflecting the data variability. Ticagrelor and AR-C124910XX pharmacokinetic parameters at steady state were unaffected in clopidogrel responders and non-responders following clopidogrel dosing for 14 days versus no prior exposure to clopidogrel (table IV).

Pharmacodynamics

In both ONSET-OFFSET and RESPOND, a single loading dose of ticagrelor (180 mg) rapidly inhibited PA within 30 minutes of dosing (figure 5a). Final-extent IPA was shown to reach a maximum at 2 hours post-dosing in both studies, and the effect was sustained for the duration evaluated (i.e. 24 and 8 hours post-dosing for ONSET-OFFSET and RESPOND, respectively). The IPA profiles in response to ticagrelor were

Table III. Pharmacokinetic parameters of ticagrelor and AR-C124910XX on day 1 after dosing of ticagrelor 180 mg in patients who had either received or not received 14 days of clopidogrel (RESPOND)

Parameter	Ticagrelor as initial treatment (ticagrelor → clopidogrel; day 1, period 1)[a]			Ticagrelor after 14 days of clopidogrel (clopidogrel → ticagrelor; day 1, period 2)[b]			GMR [95% CI][c]	
	Responders[d]	Non-responders[d]	GMR [95% CI][e]	Responders[d]	Non-responders[d]	GMR [95% CI][e]	Responders	Non-responders
Ticagrelor								
n[f]	11–14	15–20		14–16	14–17			
C_{max} (ng/mL)	1203 (39)	1179 (41)	1.02 (0.77, 1.35)	1192 (53)	1140 (31)	1.05 (0.78, 1.40)	0.99 (0.71, 1.39)	0.97 (0.76, 1.23)
AUC_8 (ng • h/mL)	5243 (34)	5170 (39)	1.01 (0.79, 1.31)	4991 (44)	4860 (25)	1.03 (0.81, 1.31)	0.95 (0.72, 1.27)	0.94 (0.76, 1.17)
t_{max} (h)[g]	2.0 (1.0–8.0)	2.0 (1.0–8.0)		2.0 (0.5–4.0)	2.0 (0.5–4.0)			
AR-C124910XX								
n[f]	9–14	10–20		10–16	9–17			
C_{max} (ng/mL)	244 (37)	241 (51)	1.01 (0.74, 1.38)	238 (48)	262 (40)	0.91 (0.67, 1.23)	0.98 (0.72, 1.33)	1.09 (0.81, 1.46)
AUC_8 (ng • h/mL)	1196 (33)	1255 (52)	0.95 (0.75, 1.30)	1189 (40)	1229 (33)	0.97 (0.75, 1.24)	0.99 (0.76, 1.30)	0.98 (0.74, 1.30)
t_{max} (h)[g]	2.0 (1.0–8.0)	2.0 (1.0–8.0)		2.0 (1.0–4.0)	2.1 (2.0–4.1)			

a A single loading dose of ticagrelor 180 mg in clopidogrel-naïve patients.

b A single loading dose of ticagrelor 180 mg in patients who had received clopidogrel for 14 days.

c GMR of ticagrelor after 14 days of clopidogrel to ticagrelor as initial treatment separately for clopidogrel responders and non-responders.

d Values are expressed as geometric mean (CV%) unless otherwise specified.

e GMR of clopidogrel responders to non-responders.

f Number (or range) of patients with quantifiable pharmacokinetic samples.

g Values are expressed as median (range).

AUC_8 = area under the plasma concentration-time curve from time 0 to 8 hours; **C_{max}** = maximum (peak) plasma concentration; **CV** = coefficient of variation; **GMR** = geometric mean ratio; **t_{max}** = time to C_{max}.

comparable in CAD patients classified as either responsive or non-responsive to clopidogrel.

Offset of IPA following ticagrelor administration was assessed in ONSET-OFFSET (figure 5b).[17] Final-extent IPA increased for 2 hours after the final dose of ticagrelor then rapidly declined between 8 and 48 hours post-dosing. IPA continued to decrease thereafter and reached low concentrations by 120 hours post-dosing (figure 5b). For final-extent IPA, the slope of offset (4–72 hours after the last dose) was –1.04 IPA %/h.[17]

Exposure-Inhibition of Platelet Aggregation Relationships

In both ONSET-OFFSET and RESPOND, the exposure-IPA analyses showed that IPA declined with decreasing plasma concentrations of ticagrelor and its active metabolite (table V).

In the ONSET-OFFSET study, pooling the onset (0–24 hours post-first dose) and the offset (0–48 hours post-last dose) data, the model estimated high E_{max} values (IPA >97%) using either ticagrelor alone or ticagrelor plus AR-C124910XX plasma concentrations (table V). For the offset phase (4–48 hours post-last dose), the model also estimated high E_{max} values (IPA >100%) with both ticagrelor and ticagrelor plus AR-C124910XX plasma concentrations (table V). C_{trough} for ticagrelor in the ONSET-OFFSET study was 305 ng/mL (CV 110%). This concentration was 5.20-fold and 4.99-fold higher than the EC_{50} estimates for the pooled onset/offset (0–24 hours post-first dose and 0–48 hours post-last dose) and offset (0–48 hours post-last dose) data, respectively (table V). C_{trough} for AR-C124910XX in ONSET-OFFSET was 121 ng/mL (CV 65%), which was 7.71-fold higher than the EC_{50} estimate for the pooled onset/offset (0–24 hours post-first dose and 0–48 hours post-last dose), i.e. 15.7 (standard error 1.8) ng/mL.

Steady-state plasma concentrations in the RESPOND study following ticagrelor dosing at 90 mg twice daily, particularly in clopidogrel responders, were within a narrow range (data not

shown), so day 14 data were insufficient for an accurate estimation of E_{max} model parameters. Therefore, parameters were calculated using day 1 data following a ticagrelor 180 mg loading dose. Data for non-responders were more variable than that for responders. Based on the clopidogrel → ticagrelor day 1, period 2 data, the sigmoid E_{max} model estimated high E_{max} values (IPA >96%), which were comparable between non-responders and responders, with ticagrelor or ticagrelor plus AR-C124910XX plasma concentrations (table V). For both responders and non-responders, the EC_{50} values were low (table V). Although higher EC_{50} values were noted for non-responders than for responders, the 95% confidence intervals were very wide for non-responders (table V). Mean pre-dose plasma concentrations of ticagrelor on day 14 were 286.9–306.0 ng/mL (non-responders) and 130.5–326.2 ng/mL (responders), which were much higher than the ticagrelor EC_{50} estimates shown in table V.

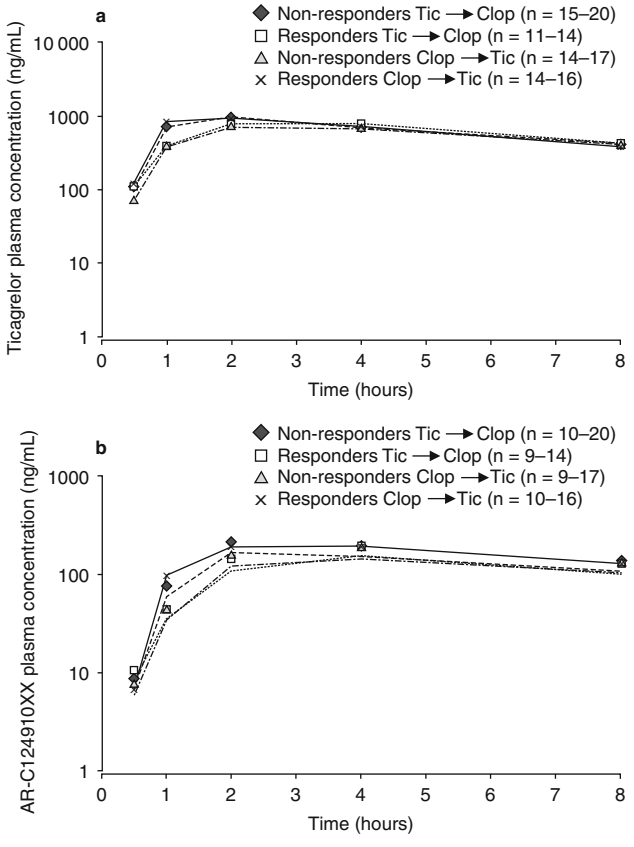


Fig. 4. Mean (geometric) plasma concentration-time curves of (**a**) ticagrelor and (**b**) AR-C124910XX in patients who received ticagrelor 180 mg (loading dose) initially or 24 hours after receiving 14 days of clopidogrel. n values are the range of patient numbers with quantifiable samples. Data for ticagrelor → clopidogrel (non-responders and responders) from figures 2a and 3a are repeated in figures 4a and 4b, respectively, for ease of comparison. **Clop** = clopidogrel; **Tic** = ticagrelor.

Discussion

Both ONSET-OFFSET and RESPOND investigated ticagrelor in stable CAD patients[17,18] at the clinical dose regimen approved in the EU,[5] which was the same regimen that was used in the phase III PLATO study.[7] Given the identical dosing regimen and similar patient demographics, pharmacokinetic and IPA data were compared across both studies to provide an assessment of these parameters in a larger CAD patient population. The sample size provided a more robust evaluation of key ticagrelor pharmacokinetic parameters in CAD patients. Importantly, the patient characteristics were typical of patients previously recruited in large cardiovascular outcome trials.[7,21,22]

Following a single oral ticagrelor 180 mg dose, C_{max}, t_{max} and AUC_8 were broadly comparable (i.e. overlapping variation of data) in ONSET-OFFSET and RESPOND. Although AUC_8 was not a standard drug-exposure parameter in the ticagrelor development programme, the collection of pharmacokinetic blood samples for longer than 8 hours post-dose in the ONSET-OFFSET and RESPOND studies was not feasible in these patients due to the other multiple demands of the studies and blood volumes required. Despite this limitation, the AUC values reported herein are comparable with previous data following a single ticagrelor dose in healthy subjects (200 mg; mean AUC [standard deviation {SD}]: ticagrelor 8213 [2114] ng • h/mL; AR-C124910XX: 3722 [1668] ng • h/mL),[9] and in patients with stable atherosclerosis (200 mg; mean AUC [CV]: ticagrelor 7581 [35%] ng • h/mL; AR-C124910XX: 1753 [32%] ng • h/mL)[3] or ACS (180 mg; mean AUC [SD]: ticagrelor 6104 [4012] ng • h/mL; AR-C124910XX: 1584 [560] ng • h/mL).[16]

After multiple dosing (ticagrelor 90 mg twice daily), ticagrelor and AR-C124910XX pharmacokinetic parameters were broadly comparable between ONSET-OFFSET (after 6 weeks of dosing) and RESPOND (after 14 days of dosing). Both C_{max} and t_{max} in these studies were also comparable with results reported for healthy volunteers. For example, following ticagrelor 100 mg twice daily for 5 days (n = 13) mean (CV) C_{max} and median t_{max}, respectively, were 626 (46%) ng/mL and 2 hours for ticagrelor, and 219 (49%) ng/mL and 3 hours for AR-C124910XX.[10] Comparable data were also reported following ticagrelor multiple dosing in patients with stable atherosclerosis (100 mg twice daily for 14 days),[3] and ACS patients (90 mg twice daily for 28 days).[16]

In RESPOND, ticagrelor pharmacokinetics were evaluated before and after clopidogrel dosing. Following a single ticagrelor loading dose, key pharmacokinetic parameters and the plasma concentration versus time curves of both ticagrelor and

Table IV. Pharmacokinetic parameters of ticagrelor and AR-C124910XX after 14 days (steady state) of ticagrelor 90 mg twice daily dosing, in patients who had either received or not received 14 days of clopidogrel (RESPOND)

Parameter	Ticagrelor as initial treatment (ticagrelor → clopidogrel; day 14, period 1)[a]			Ticagrelor after 14 days of clopidogrel (clopidogrel → ticagrelor; day 14, period 2)[b]			GMR [95% CI][c]	
	Responders[d]	Non-responders[d]	GMR [95% CI][e]	Responders[d]	Non-responders[d]	GMR [95% CI][e]	Responders	Non-responders
Ticagrelor								
n[f]	10–13	16–17		14–15	16			
C_{max} (ng/mL)	851 (60)	688 (44)	1.24 (0.86, 1.78)	724 (19)	764 (39)	0.95 (0.76, 1.18)	0.85 (0.62, 1.16)	1.11 (0.84, 1.48)
AUC_8 (ng • h/mL)	4183 (56)	3707 (52)	1.13 (0.77, 1.66)	3983 (21)	3985 (36)	1.00 (0.80, 1.24)	0.95 (0.70, 1.30)	1.08 (0.79, 1.46)
t_{max} (h)[g]	2.0 (1.8–7.3)	2.1 (1.9–4.0)		2.0 (1.8–4.0)	2.0 (1.8–4.0)			
AR-C124910XX								
n[f]	10–13	16–17		14–15	16			
C_{max} (ng/mL)	245 (51)	247 (57)	0.99 (0.68, 1.46)	223 (33)	234 (37)	0.95 (0.74, 1.22)	0.91 (0.67, 1.24)	0.95 (0.69, 1.31)
AUC_8 (ng • h/mL)	1413 (51)	1539 (51)	0.92 (0.64, 1.33)	1332 (32)	1388 (31)	0.96 (0.76, 1.21)	0.94 (0.68, 1.30)	0.90 (0.67, 1.21)
t_{max} (h)[g]	2.0 (1.8–4.0)	2.0 (0.0–4.0)		2.0 (1.8–8.0)	2.0 (0.0–7.8)			

a Ticagrelor given at 90 mg twice daily for 14 days in clopidogrel-naïve patients.

b Ticagrelor given at 90 mg twice daily for 14 days in patients who had received clopidogrel for 14 days.

c GMR of ticagrelor after 14 days of clopidogrel to ticagrelor as initial treatment separately for clopidogrel responders and non-responders.

d Values are expressed as geometric mean (CV%) unless otherwise specified.

e GMR of clopidogrel responders to non-responders.

f Number (or range) of patients with quantifiable pharmacokinetic samples.

g Values are expressed as median (range).

AUC_8 = area under the plasma concentration-time curve from time 0 to 8 hours; **C_{max}** = maximum (peak) plasma concentration; **CV** = coefficient of variation; **GMR** = geometric mean ratio; **t_{max}** = time to C_{max}.

AR-C124910XX were comparable before and after 14 days of clopidogrel dosing. Thus, these data demonstrate that prior exposure to clopidogrel did not affect the absorption and metabolism of ticagrelor. Another aspect of the RESPOND design is the characterization of ticagrelor pharmacokinetics in patients classified as clopidogrel non-responders and responders. Again, the pharmacokinetic profile of ticagrelor and its active metabolite were comparable in these two groups after both single and multiple ticagrelor dosing, and regardless of order of exposure to clopidogrel. Thus, our findings suggest that ticagrelor pharmacokinetics are not significantly associated with the responsiveness to clopidogrel.

Since clopidogrel and ticagrelor were administered sequentially in RESPOND, this allowed some characterization of the potential interaction between the two drugs. In clopidogrel non-responders switching from clopidogrel to ticagrelor, an enhancement of IPA was seen;[18] however, a limitation of RESPOND was that IPA was only evaluated for 8 hours post-dosing so the full extent of this apparent interaction is unclear. Similarly, in the DISPERSE-2 trial greater IPA was seen following ticagrelor administration to ACS patients who had previously received clopidogrel compared with those who were clopidogrel-naïve.[16] These findings are suggestive of a positive pharmacodynamic interaction between ticagrelor and clopidogrel.

In contrast, a healthy volunteer study investigating potential interactions between clopidogrel and cangrelor,[23] a reversible $P2Y_{12}$ inhibitor structurally similar to ticagrelor,[24] showed that simultaneous administration of cangrelor with clopidogrel resulted in a lower-than-expected sustained platelet inhibition in response to clopidogrel.[23] In contrast, sequential administration of clopidogrel after cangrelor resulted in the sustained platelet inhibition expected with clopidogrel. These pharmacodynamic findings indicate a negative interaction between clopidogrel and cangrelor when these agents are given together.[23] The interaction between ticagrelor and clopidogrel when given together on IPA has not been studied.

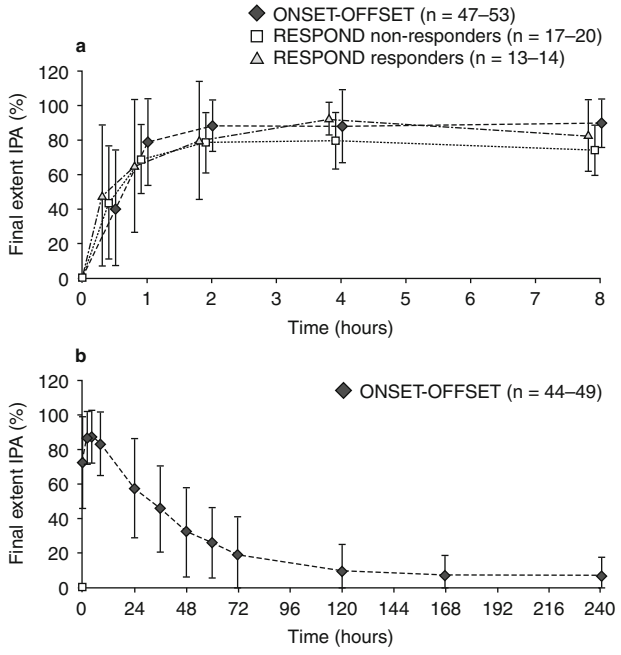


Fig. 5. Mean (± standard deviation) final extent inhibition of platelet aggregation (induced by 20 μmol/L adenosine diphosphate) time curves of (**a**) onset of effect after initial loading dose (180 mg) ticagrelor (ITT analysis) and (**b**) offset of effect after 6 weeks administration of ticagrelor 90 mg twice daily (ITT analysis).[17] n values are the range of patient numbers with IPA data. Data shown in figure 5a were collected at timepoints indicated in the Methods section, but are displaced in the figure to avoid overlap. Note that the x-axes show different time scales. **IPA** = inhibition of platelet aggregation; **ITT** = intent-to-treat.

The present exploration of exposure-IPA relationships demonstrated that the final-extent IPA during onset correlated with ticagrelor plus AR-C124910XX plasma concentrations in patients with CAD. This association is as expected, given that ticagrelor exerts its antiplatelet activity by binding directly to the $P2Y_{12}$ receptor.[13] During the offset phase, IPA declined with decreasing plasma concentrations of ticagrelor. However, from the present data, it is not possible to interpret the reasons why IPA was measurable at later timepoints (i.e. from 48 hours post-last dose) when ticagrelor concentrations were not quantifiable in plasma.

High E_{max} values for final-extent IPA were estimated by the sigmoid E_{max} model applied to both studies. In ONSET-OFFSET, these values were IPA >97%, indicating that ticagrelor can completely inhibit the final PA response to ADP in patients with stable CAD. Moreover, the model estimated EC_{50} values for ticagrelor and AR-C124910XX that were only approximately 19% and 13%, respectively, of the trough plasma concentrations of analytes. This finding supports the recommended ticagrelor dosing regimen (180 mg loading dose/90 mg twice daily), illustrating that the plasma concentrations of the parent drug and active metabolite are sufficiently high to achieve and sustain high concentrations of IPA in patients with CAD. This observation is also supported by the findings from RESPOND. High E_{max} values for ticagrelor, which were

Table V. Summary of pharmacokinetic/pharmacodynamic model estimates (based on sigmoid maximum effect model) for pharmacokinetic/pharmacodynamic relationship between inhibition of platelet aggregation (20 μmol/L adenosine diphosphate induced; final extent)

Parameter	Compound	E_{max} (%)[a]	EC_{50} (ng/mL)[a]	Gamma[a]
ONSET-OFFSET	Ticagrelor	98.6 ± 3.8	58.6 ± 8.2	0.82 ± 0.09
(n = 49); 0–24 h post-first dose + 0–48 h post-last dose		(91.2, 106)	(42.5, 74.7)	(0.65, 1.00)
	Ticagrelor + AR-C124910XX	97.6 ± 3.5	89.4 ± 10.9	0.93 ± 0.10
		(90.8, 104)	(68.0, 111)	(0.74, 1.12)
ONSET-OFFSET	Ticagrelor	106 ± 8.3	61.1 ± 16.8	0.70 ± 0.12
(n = 49); 4–48 h post-last dose		(90.0, 123)	(28.2, 94.1)	(0.46, 0.94)
	Ticagrelor + AR-C124910XX	105 ± 8.1	96.0 ± 23.3	0.78 ± 0.14
		(89.5, 121)	(50.1, 142)	(0.51, 1.05)
RESPOND non-responders	Ticagrelor	99.2 ± 10.6	18.0 ± 10.5	0.56 ± 0.16
(n = 17)[b]		(78.1, 120)	(-2.9, 38.9)	(0.24, 0.88)
	Ticagrelor + AR-C124910XX	96.9 ± 8.8	21.9 ± 10.4	0.62 ± 0.18
		(79.3, 114)	(1.19, 42.7)	(0.27, 0.97)
RESPOND responders	Ticagrelor	99.7 ± 9.3	3.0 ± 1.2	0.50 ± 0.25
(n = 16)[b]		(81.1, 118)	(0.6, 5.4)	(–0.01, 1.01)
	Ticagrelor + AR-C124910XX	98.0 ± 7.4	4.5 ± 1.6	0.58 ± 0.29
		(83.3, 113)	(1.4, 7.7)	(0.003, 1.16)

a Values are means ± standard error (95% CI).

b RESPOND: non-responder and responder data presented are for day 1 of ticagrelor treatment in clopidogrel → ticagrelor sequence.

EC_{50} = concentration producing 50% of maximum effect; **E_{max}** = maximum effect.

comparable between responders (IPA ≥98%) and non-responders (IPA > 97%), indicate that ticagrelor can inhibit PA in patients responsive or non-responsive to clopidogrel. Indeed, in RESPOND the antiplatelet effect of ticagrelor was not greatly affected by patient responsiveness to clopidogrel.[18] Ticagrelor at 180 mg loading dose/90 mg twice daily also resulted in sufficiently high plasma concentrations of the parent drug required for IPA in RESPOND, since minimum ticagrelor concentrations were many fold higher than the model estimated ticagrelor EC_{50} values for both responders and non-responders.

Conclusions

In conclusion, the present subanalyses showed that pharmacokinetics of ticagrelor in patients with stable CAD were comparable to those seen previously. Ticagrelor (180 mg loading dose then 90 mg twice daily) effectively inhibited PA, and trough plasma concentrations of ticagrelor (90 mg twice daily) and AR-C124910XX were sufficient to achieve high IPA in stable CAD patients. Ticagrelor pharmacokinetics were unaffected by prior exposure to clopidogrel and were comparable in patients defined as responsive and non-responsive to clopidogrel. Collectively, these findings provide further evidence that ticagrelor is associated with a faster and superior onset of antiplatelet effects in patients, including those who are clopidogrel non-responders, and that therapy can safely be switched from clopidogrel to ticagrelor.

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