

Chewed ticagrelor tablets provide faster platelet inhibition compared to integral tablets: The inhibition of platelet aggregation after administration of three different ticagrelor formulations (IPAAD-Tica) study, a randomised controlled trial.

Dimitrios Venetsanos, Sofia Sederholm Lawesson, Eva Swahn and Joakim Alfredsson

Journal Article



N.B.: When citing this work, cite the original article.

Original Publication:

Dimitrios Venetsanos, Sofia Sederholm Lawesson, Eva Swahn and Joakim Alfredsson, Chewed ticagrelor tablets provide faster platelet inhibition compared to integral tablets: The inhibition of platelet aggregation after administration of three different ticagrelor formulations (IPAAD-Tica) study, a randomised controlled trial., *Thrombosis Research*, 2017. 149, pp.88-94.

<http://dx.doi.org/10.1016/j.thromres.2016.10.013>

Copyright: Elsevier

<http://www.elsevier.com/>

Postprint available at: Linköping University Electronic Press

<http://urn.kb.se/resolve?urn=urn:nbn:se:liu:diva-133985>



li.u LINKÖPINGS
UNIVERSITET

Chewed ticagrelor tablets provide faster platelet inhibition compared to integral tablets.

The Inhibition of Platelet Aggregation after Administration of three Different Ticagrelor formulations (IPAAD-Tica) Study, a randomised controlled trial.

Dimitrios Venetsanos¹, Sofia Sederholm Lawesson¹, Eva Swahn¹, Joakim Alfredsson¹

¹Department of Cardiology and Department of Medical and Health Sciences, Linköping University, Linköping, Sweden.

Total word count 4475

Email addresses

dimitrios.venetsanos@liu.se

sofia.lawesson@liu.se

eva.swahn@liu.se

joakim.alfredsson@liu.se

Conflicts of interest

D. Venetsanos reports that he has no relationships relevant to the contents of this paper to disclose.

S.S. Lawesson reports that she has no relationships relevant to the contents of this paper to disclose.

E. Swahn reports receiving lecture fees from AstraZeneca.

J. Alfredsson reports serving on advisory board, and receiving lecture fees and a research grant from AstraZeneca.

Corresponding author: Dimitrios Venetsanos, MD

Department of Medical and Health Sciences, Division of Cardiovascular medicine
Linköping University Hospital
SE-581 85 Linköping
SWEDEN

Telephone: +46 101030000

Fax: +46 101032171

Email: dimitrios.venetsanos@liu.se

Abstract

Aims

To provide pharmacodynamic data of crushed and chewed ticagrelor tablets, in comparison with standard integral tablets.

Methods

Ninety nine patients with stable angina were randomly assigned, in a 3:1:1 fashion, to one of the following 180 mg ticagrelor loading dose (LD) formulations: A) Integral B) Crushed or C) Chewed tablets. Platelet reactivity (PR) was assessed with VerifyNow before, 20 and 60 minutes after LD. High Residual platelet reactivity (HRPR) was defined as > 208 P2Y12 reaction units (PRU).

Results

There was no significant difference in PRU values at baseline. PRU 20 minutes after LD were 237 (182 - 295), 112 (53 - 238) and 84 (29 - 129) and 60 minutes after LD, 56 (15 - 150), 51 (18 - 85) and 9 (7 - 34) in integral, crushed and chewed ticagrelor LD, respectively ($p < 0.01$ for both). Chewed ticagrelor tablets resulted in significantly lower PRU values compared to crushed or integral tablets at 20 and 60 minutes. Crushed ticagrelor LD resulted in significantly lower PRU values compared to integral tablets at 20 minutes whereas no difference was observed at 60 minutes.

At 20 minutes, no patients had HRPR with chewed ticagrelor compared to 68% with integral and 30% with crushed ticagrelor LD ($p < 0.01$).

Conclusion

With crushed or chewed ticagrelor tablets a more rapid platelet inhibition may be achieved, compared to standard integral tablets. We also show that administration of chewed tablets is feasible and provides faster inhibition than either crushed or integral tablets.

CLINICAL TRIAL REGISTRATION: European Clinical Trial Database (EudraCT number 2014-002227-96).

Keywords: pharmacodynamic, chewed, crushed, VerifyNow, platelet, aggregation.

Introduction

Platelets play a fundamental pathophysiological role in patients with acute coronary syndrome. Following an atherosclerotic plaque rupture or erosion, platelet aggregation leads to thrombus formation and an acute ischemic event. (1) Ticagrelor is a direct acting and reversibly binding P2Y₁₂ receptor inhibitor that is highly recommended in clinical guidelines for treatment of patients with acute coronary syndromes (ACS). (2-4) In patients with stable angina pectoris (SAP), administration of 180 mg loading dose (LD) of ticagrelor resulted in a more rapid and stronger inhibition of platelet reactivity (PR) compared to clopidogrel. Within 30 minutes, ticagrelor administration led to the same degree of inhibition of PR as that achieved 8 hours after a 600 mg LD of clopidogrel. (5) However, in patients with ST segment elevation myocardial infarction (STEMI), where fast and effective platelet inhibition is even more important, a delayed onset of action of platelet inhibitors, and a wider variability of drug response has been demonstrated. Beside the higher baseline PR in STEMI patients, a limited or delayed intestinal absorption of orally administered drugs is another major contributor to this observation.(6-8)

Previous pharmacokinetic studies have demonstrated that chewable aspirin and crushed clopidogrel administration increased the rate of drug absorption compared to integral tablets, when administered orally. (9,10) Recently, crushed ticagrelor tablets, administered orally or via a naso-gastric tube, has been shown to be feasible and resulted in increased plasma concentration of ticagrelor and its active metabolite at an earlier time point compared to integral tablets.(11,12) As the plasma concentration of ticagrelor and its active metabolite is linearly associated with the degree of platelet inhibition, (2) administration of crushed or chewed ticagrelor may provide a more rapid onset of drug action. Nevertheless, limited pharmacodynamic data of novel methods of ticagrelor administration exist and data regarding chewed ticagrelor have not been reported.

Thus, the aim of our study was to provide pharmacodynamic data of two novel ways of ticagrelor administration, crushed and chewed tablets, in comparison with the standard, integral tablets administration.

Material and Methods

Study design and population

This was a single center, open-label, randomized, investigator initiated, pharmacodynamic study. Patients > 18 year of age, with stable angina pectoris, scheduled for outpatient coronary angiography, were randomly assigned, at least 90 minutes before the intervention, in a 3:1:1 fashion (according to a computer generated randomization list) to one of the following treatment modalities: A) Integral ticagrelor tablets, 180 mg LD B) Crushed ticagrelor tablets, 180 mg LD or C) Chewed ticagrelor tablets, 180 mg LD. The allocation sequence was concealed from the researcher enrolling and assessing participants in sequentially numbered, sealed envelopes. Exclusion criteria were: pregnancy or lactation, known allergy to the study medication, chronic therapy with ticagrelor, prasugrel, clopidogrel or ticlopidine, treatment with warfarin or new oral anticoagulants (NOAC) within 4 days before admission, active bleeding, bleeding diathesis or coagulopathy, history of gastrointestinal or genitourinary bleeding in the last 2 months, history of intracranial bleeding, major surgery in the last 4 weeks, known relevant hematological deviation (severe anemia, severe thrombocytopenia), known severe liver disease or severe renal failure, increased risk of bradycardia or inability to chew tablets.

Administration of the different ticagrelor formulations.

All three groups received two tablets of ticagrelor (180 mg) and 150 mL of water. In the first group (A), two integral ticagrelor tablets were administered as an oral dose, followed by 150 mL of water. In the second group (B), two ticagrelor tablets (180 mg) were placed in a point-of-care (POC) crushing device and crushed. The total content of the crushed tablets was transferred to a dosing cup, 50 mL of water was added and the suspension was mixed before drinking. Afterwards, 100 mL of water was administered. In the third group (C), the patient was instructed to chew two tablets of ticagrelor for at least 10-15 seconds followed by oral administration of 150 mL of water.

Blood sampling for platelet aggregation measurements

Platelet aggregation assessment was performed at three time-points: before administration of ticagrelor (baseline, sample 1) 20 ± 5 minutes (sample 2) and 60 ± 10 minutes (sample 3) after administration of ticagrelor. In all cases, the blood samples were drawn from a recently inserted venous catheter for repeated sampling or by direct venipuncture. The first 2-3 ml of blood was discarded to avoid platelet aggregation and then blood was collected in 3.2 % citrated tubes. Platelet aggregation was measured with the VerifyNow P2Y12

(Accumetrics Inc, San Diego, CA) POC test. The test has been described in detail earlier.(13) Briefly, VerifyNow is a turbidimetric test which measures agonist-induced aggregation as an increase in light transmittance. The system contains a lyophilised preparation of human fibrinogen-coated beads, which causes a change in light transmittance by agonist-induced platelet aggregation.

Platelet reactivity (PR) results are reported in arbitrary P2Y12 reaction units (PRU). The percent inhibition of platelet reactivity (IPR) was defined as: $[(PRU \text{ baseline} - PRU \text{ sample 1 or 2})/PRU \text{ baseline}] \times 100$. Based on a recently published consensus document, high residual platelet reactivity (HRPR) was defined as $PR > 208$ PRU (non-responders).(14) Patients with PR values ≤ 208 were considered as responders to the drug.

Outcome

We report residual platelet reactivity, percent IPR and proportion of patients with HRPR at baseline, 20 and 60 minutes.

Safety outcomes include TIMI major, minor or minimal bleeding within 24 hours after randomization.

Sample Size Calculation

In the ONSET/OFFSET study,(5) around 50% of patients had HRPR 30 minutes after LD ticagrelor (integral tablets). A recent study (15) has shown that administration of crushed ticagrelor tablets resulted in a mean plasma concentration of ticagrelor that was four to five times higher at 30 minutes compared with plasma concentration after administration of integral tablets. We assumed that chewed ticagrelor tablets would have at least as fast uptake as crushed ones. Given the antiplatelet effect of ticagrelor is linearly related to the blood concentration of ticagrelor,(2) we also assumed that 20% of patients with the novel ways of ticagrelor administration (crushed and chewed) would have HRPR 20 minutes after administration of LD. A sample of 100 patients (60 patients in the integral, 20 patients in the crushed and 20 patients in the chewed group) would give an 80% power to detect statistically significant differences in the HRPR rates.

Study population

Between November 2014 and July 2015, 102 patients were included in the study. Three patients were excluded due to technical reasons (e.g. inability to run the VerifyNow assay). Ninety nine eligible patients were included in the final analysis.

Ethics

The study was approved by the local ethical review board (Dnr 2014/334-31) and was conducted according to the declaration of Helsinki. All patients provided written informed consent before enrollment. The study has been registered at the European Clinical Trial Database (EudraCT number 2014-002227-96).

Statistical analysis

Continuous variables are presented as median and interquartile range. Categorical variables are presented as counts and percentages. The Kolmogorov-Smirnov test was used to test for normality of the distribution of PR values. Baseline characteristics were compared according to randomised treatment by Fisher's exact test for categorical variables and Kruskal-Wallis test for continuous variables. Friedman's test was used for within group comparisons of PR over time. PR and IPR of the three groups of patients were compared using Kruskal-Wallis test. Pairwise comparisons of the groups were performed with Mann Whitney U test. Percentage of HRPR in the three groups was compared using Chi-squared test. Pairwise comparisons were also performed using the same test. A p-value <0.05 was considered to indicate statistical significance. Due to the relatively small number of hypotheses being tested under the pairwise comparison, the likelihood of type I error was estimated as low and adjusted p values were not used. A forward stepwise binary logistic regression analysis was used to identify independent predictors of HRPR at 20 minutes after administration of ticagrelor. Known and potential predictors of HRPR were included in the model, in accordance with previous studies. (16,17) Variables included in the model were age, gender, diabetes, Body Mass Index (BMI), smoking status, estimated glomerular filtration (eGFR) by the MDRD formula, platelet count, treatment with beta blockers or diuretics, PR at baseline and randomization group as a dichotomous variable (integral tablets versus crushed or chewed tablets).(16,18). Odds ratios (OR) with 95% confidence intervals (CI) are presented for the significant predictors.

Statistical analysis was performed by using SPSS software, release23.0 (SPSS Inc).

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Results

Baseline characteristics are presented in Table 1. There were no significant differences between the groups.

Table 1

Baseline characteristics and medication at arrival

	Group A, Integral tablets n=60	Group B, Crushed tablets n=20	Group C, Chewed tablets n=19	P value*
Male	49 (81.7)	14 (70.0)	14 (73.7)	0.46
Age, median (25 th -75 th percentile)	67.5 (59.0 - 74.0)	66.5 (58.8 - 73.3)	69.0 (60.0 - 73.0)	0.85
BMI, median (25 th - 75 th percentile)	26.5 (24.6 - 28.7)	25.5 (23.3 - 26.9)	25.7 (23.6 - 26.8)	0.20
Diabetes	15 (25.0)	2 (10.0)	3 (15.8)	0.32
Hypertension	41 (68.3)	12 (60.0)	14 (73.7)	0.66
Hyperlipidemia	44 (73.3)	12 (60.0)	10 (52.6)	0.19
Previous myocardial infarction	13 (21.7)	4 (20.0)	2 (10.5)	0.64
Previous CABG	6 (6.7)	2 (10.0)	1 (5.3)	0.86
Previous PCI	17 (28.3)	4 (20.0)	3 (15.8)	0.54
Nonsmoker	26 (43.3)	11 (55.0)	8 (42.1)	0.66
Estimated GFR median (25 th -75 th percentile)	84.6 (78.0 - 94.4)	78.3 (73.5 - 98.4)	84.4 (74.0 - 97.5)	0.69
Medication at arrival				
Aspirin	55 (91.7)	19 (95.0)	17 (89.5)	0.77
Beta blockers	40 (66.7)	16 (80.0)	12 (63.2)	0.45
ACE/ARB inhibitors	36 (60.0)	10 (50.0)	10 (52.6)	0.69
Diuretics	6 (10.0)	3 (15.0)	4 (21.1)	0.34
Proton Pump Inhibitors	14 (23.3)	4 (20.0)	3 (15.8)	0.89
NSAID last 24 hours	1 (1.7)	0 (0.0)	1 (5.3)	0.39

Data are presented as numbers and percentages if not otherwise stated.

BMI Body Mass Index, CABG Coronary Artery Bypass Grafting, PCI Percutaneous Coronary Intervention, ACE Angiotensin Converting Enzyme, ARB Angiotensin II Receptor Blocker, NSAID Non-Steroidal Anti-inflammatory Drugs, MDRD Modification of Diet in Renal Disease, GFR Glomerular Filtration Rate.

*p-values for comparison of the three groups by using Fishers exact tests for categorical variables and Kruskal-Wallis test for continuous variables.

Residual Platelet reactivity: PRU values over time for the three groups are presented in Figure 1. There was no difference in PRU values at baseline (median (IQR) 273 (237 - 304), 272 (249 - 313) and 259 (225 - 314), $p=0.87$), between the integral, crushed and chewed group, respectively). PRU 20 minutes after the LD were 237 (182 - 295), 112 (53 - 238) and 84 (29 - 129) and 60 minutes after LD, 56 (15 - 150), 51 (18 - 85) and 9 (7 - 34) in integral, crushed and chewed ticagrelor LD, respectively ($p<0.01$ at both time-points). At 20 and 60 minutes after the LD, chewed ticagrelor resulted in significantly lower PRU values compared to other two treatment modalities. Crushed ticagrelor achieved significantly lower PRU values compared to integral tablets 20 minutes after the LD whereas no difference was observed at 60 minutes (Figure 2).

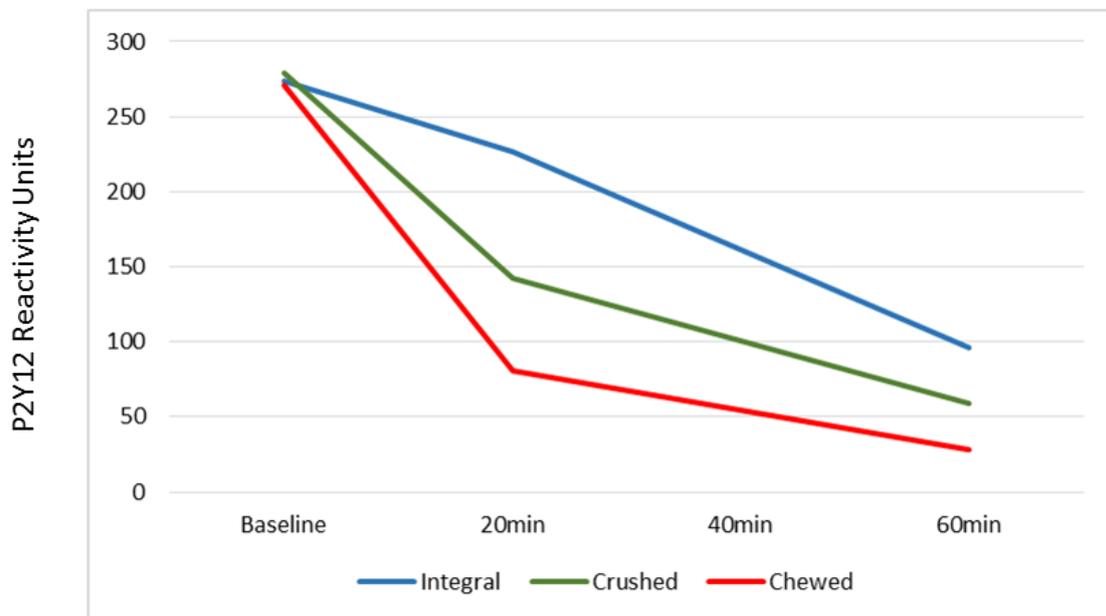


Figure 1

Mean values (standard deviation) of P2Y12 platelet reactivity unit (PRU) for integral vs crushed vs chewed ticagrelor: 274 (54), 279 (43), 271 (50) at baseline, 227 (100), 142 (90), 81 (56) 20 minutes after loading dose and 96 (106), 59 (46), 28 (41) 60 minutes after loading dose of 180 mg ticagrelor.

No significant reduction in PRU was observed in the integral ticagrelor group within 20min ($p = 0.52$). PRU was significantly reduced between 20 and 60 min in the integral ticagrelor group ($p < 0.01$) and between all the time points in the crushed and chewed ticagrelor group, (p values not shown). Comparisons by using Friedman's test.

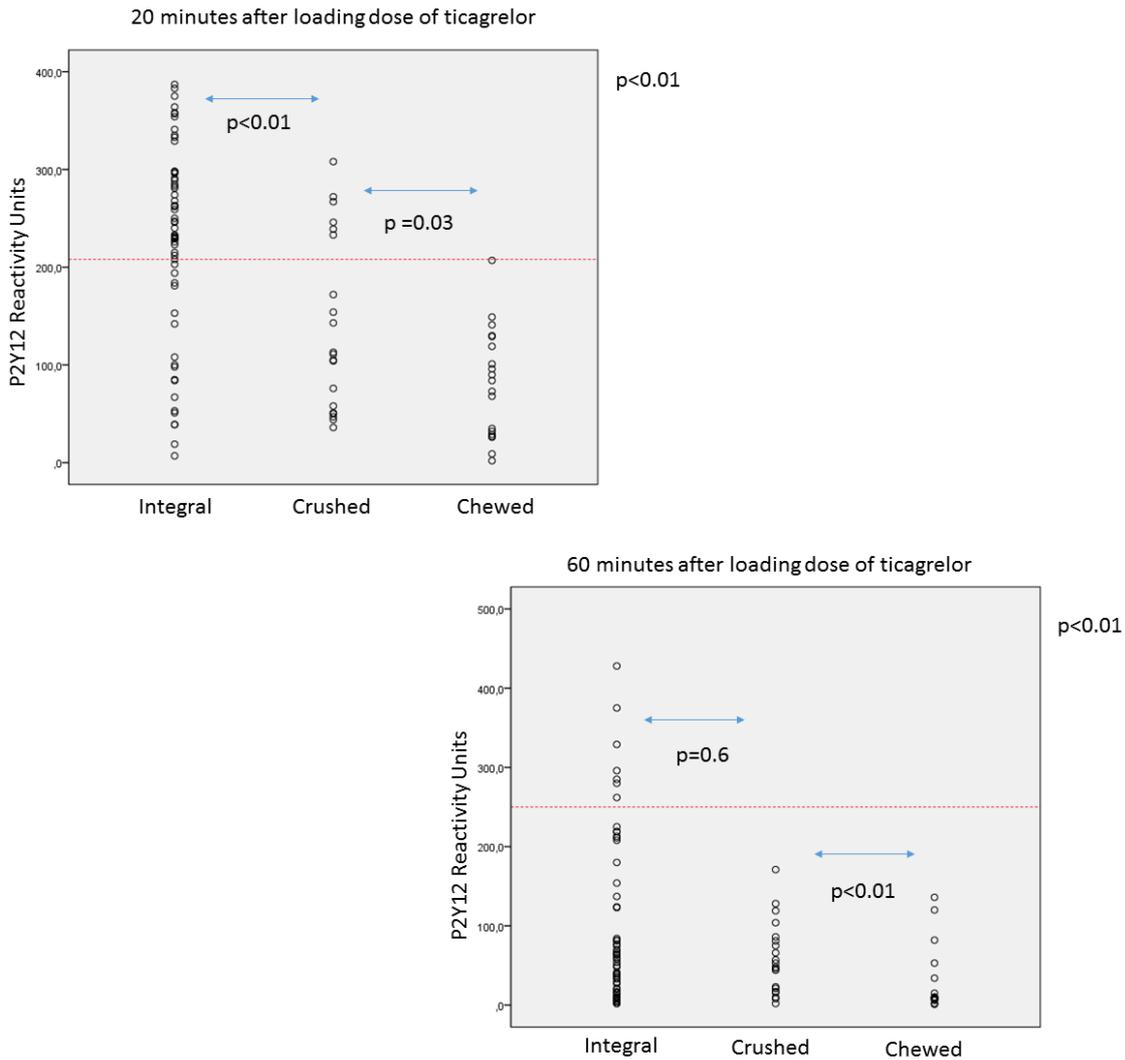


Figure 2

Inhibition of platelet reactivity in the three groups 20 and 60 minutes after integral, crushed and chewed loading dose (180mg) of ticagrelor. P2Y12 reactivity unit, obtained by Verify Now. The red dashed line represents the cut-off value for the definition of the high residual platelet reactivity (208 P2Y12 reactivity units). P-values outside the boxes represent comparison between all groups by Kruskal-Wallis test whereas p values inside the boxes represent pairwise comparisons between groups by Mann Whitney U.

Percent Inhibition of Platelet Reactivity: We also calculated percent IPR values in order to correct for potential differences in baseline PRU. At 20 minutes, both crushed and chewed ticagrelor led to a significantly higher percent IPR compared to integral ticagrelor and chewed ticagrelor led to a higher percent IPR compared to crushed ticagrelor. Sixty minutes after the LD, all three groups achieved a substantial IPR (above 80%). However, the degree

of IPR was significantly higher with chewed ticagrelor compared to the other formulations (Figure 3).

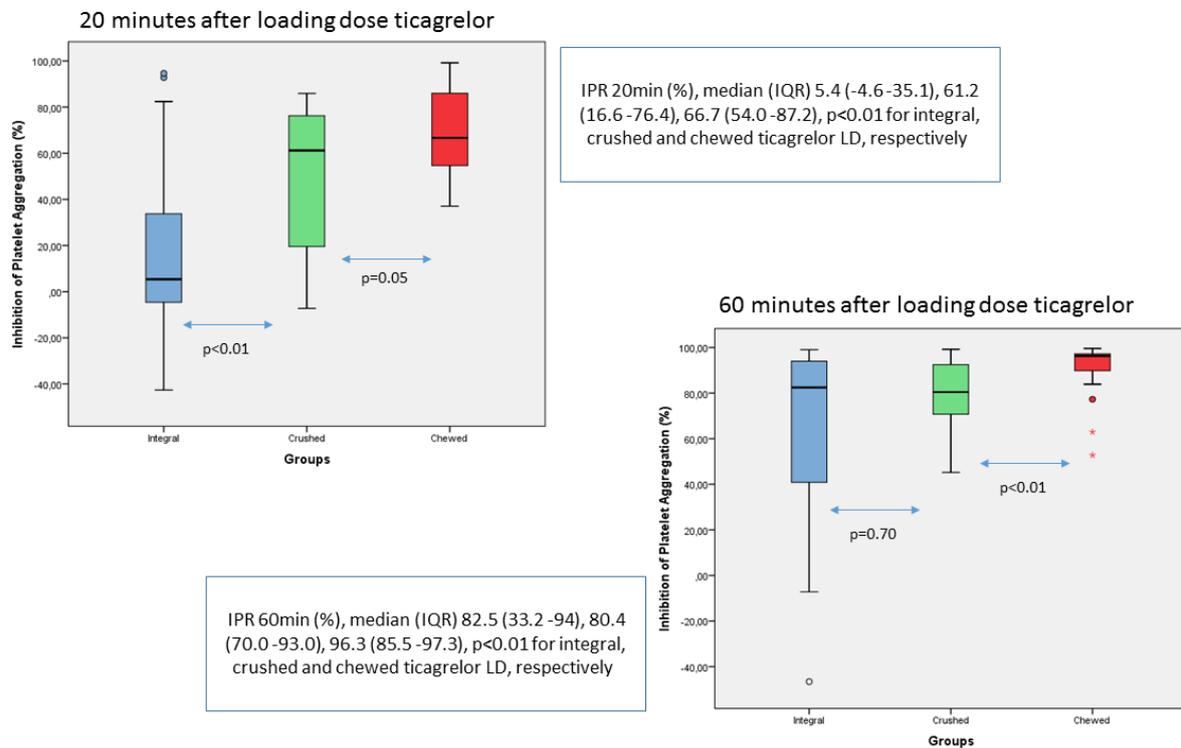


Figure 3

Percent Inhibition of Platelet Reactivity (IPR) 20 and 60 minutes after integral, crushed and chewed loading dose (180mg) of ticagrelor. P-values for pairwise comparison of the three groups by Mann Whitney U test.

High Residual Platelet Reactivity: The percentage of patients with HRPR at different time points in the integral, crushed and chewed ticagrelor groups are presented in Figure 4. HRPR rates differed significantly between the three groups 20 and 60 minutes after the LD. No patient in the chewed ticagrelor group had HRPR 20 minutes after the LD, significantly lower than in the crushed as well as the integral tablet groups. At the same time point, 68.3% of patients in the integral ticagrelor group and 30% of patients in the crushed ticagrelor groups had HRPR. After 60 minutes, none of the patients in the crushed or the chewed ticagrelor groups had HRPR compared to 20% of patients in the integral ticagrelor group, a significantly higher rate than the two other groups.

In a multivariate analysis including potential predictors of HRPR, integral ticagrelor administration (vs. crushed/chewed tablets combined) was the most powerful predictor of

HRPR (OR for HRPR: 12.63; 95% CI: 4.22 - 37.76). The other significant predictors of HRPR had a modest effect; PRU value at baseline (OR: 1.01; 95% CI: 1.00 – 1.02) and BMI (OR: 1.15; 95% CI: 1.00 – 1.32).

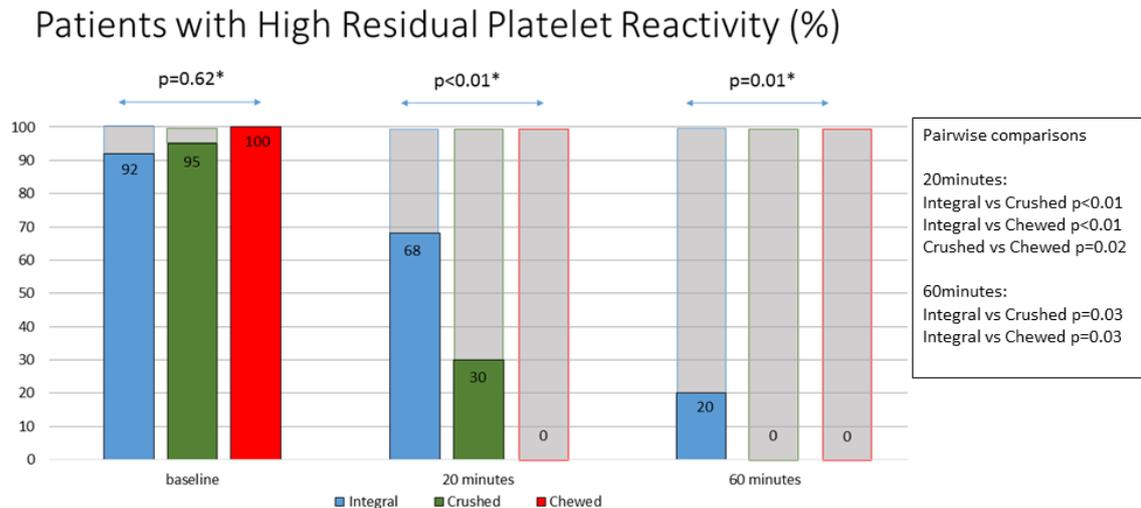


Figure 4

High Residual platelet reactivity (defined as > 208 platelet reactivity units) at baseline and 20 and 60 minutes after ticagrelor administration.*P-values for comparison of the three groups by Chi-squared test. Pairwise comparison between groups by chi-squared.

Safety outcome: One patient in the integral ticagrelor and one in the crushed ticagrelor group had a TIMI minor bleeding. One patient in the chewed ticagrelor group had a TIMI minimal bleeding.

Discussion

Our study shows that LD of crushed or chewed ticagrelor tablets achieved a more rapid and more effective platelet inhibition compared to LD of standard integral tablets. In addition, and to the best of our knowledge, for the first time, we show that administration of chewed ticagrelor tablets is feasible and may provide a faster and stronger platelet inhibition than administration of either crushed or integral tablets.

The chewed ticagrelor LD achieved impressive platelet inhibition properties. Within 20 minutes after LD, no patient had HRPR and a very low residual PR was observed (median PR

84 PRU). One hour after the LD, the median residual PR was 9 PRU, an exceptionally low value, not previously observed at any time point in a stable population treated with 180 mg LD ticagrelor followed by 90mg b.i.d. as a maintenance dose. (5) As the degree of platelet inhibition by ticagrelor is linearly related to the plasma concentration of the drug, (2) our data indicate that chewed ticagrelor achieved the most rapid and the highest rate of drug absorption. Furthermore, the faster and stronger platelet inhibition with chewed ticagrelor compared to crushed ticagrelor implies that other mechanisms than the mechanical “fractioning” of the tablets may have contributed to the improved absorption of the chewed ticagrelor. Initiation of enzymatic metabolic degradation of the tablet in the mouth due to the prolonged contact of the drug with the saliva as well as enhanced oral transmucosal absorption of the drug may be explanations for our results. These data may be of clinical importance in STEMI patients. According to an earlier trial, more than half of the STEMI patients treated with LD of integral ticagrelor still have HRPR up to 4 hours after administration of the drug.(7) Given the fact that suboptimal platelet inhibition is an important predictor of ischemic complications, such as stent thrombosis, (19) there is a time window after primary PCI, in which patients are at increased risk for ischemic complications. In the ATLANTIC trial, despite a short median time between pre-hospital and in-hospital administration of ticagrelor, prehospital administration significantly reduced the risk of stent thrombosis, suggesting that fast and strong platelet inhibition at the time of PCI is clinically important. (20). A significantly faster and stronger platelet inhibition, by overcoming the delayed intestinal absorption of orally administered drugs, with chewed ticagrelor administration may improve clinical outcomes compared to integral tablets. A recent study in STEMI patients confirmed the superior pharmacodynamic properties of crushed ticagrelor compared to integral tablets. (17) Crushed tablet preparation in the prehospital setting, such as in the ambulance, may be cumbersome whereas chewed ticagrelor administration is more comfortable and according to our data, may provide a more effective platelet inhibition compared to crushed ticagrelor administration. Theoretically, a stronger platelet inhibition at the time of PCI may increase the risk of bleeding. In the ATLANTIC trial, prehospital administration of ticagrelor appeared to be safe, compared to inhospital administration. In our study, the risk of bleeding was not increased with crushed or chewed ticagrelor administration.

With a small study population, other factors than the randomized treatment may be important. Therefore, we performed a multivariate analysis including potential confounders. Integral ticagrelor administration was the most powerful predictor of HRPR (OR: 12.63; 95% CI: 4.22 - 37.76). The only other independent predictors of HRPR had a modest effect; PRU value at baseline (OR: 1.01; 95% CI: 1.00 – 1.02) and BMI (OR: 1.15; 95% CI: 1.00 – 1.32). Low responsiveness to clopidogrel in obese patients has previously been described. (21) Taking into account that ticagrelor LD is just the daily maintenance dose of the drug, while clopidogrel LD is 8-fold and prasugrel LD is 6-fold the daily dose, higher risk for HRPR in obese patients after ticagrelor administration might be due to a lower concentration of the drug. This finding should be taken into account when fast and strong platelet inhibition is desirable in an obese patient. However, at least in this setting, the tablet formulation appears much more important than BMI.

Cangrelor is a new intravenous ADP receptor blocker with immediate onset of platelet inhibition. (22) Cangrelor administration may solve the problem of delayed onset of action of orally administered drugs in STEMI patients. However, it is not yet available in many countries and cost implications should be taken into consideration. Therefore, novel ways of ticagrelor administration, with improved pharmacodynamics remain important. Furthermore, given the very short plasma half-life (three to five minutes) of cangrelor and the rapidly reversible antiplatelet effect on withdrawal, chewed ticagrelor administration may serve as the optimal transitioning strategy from intravenous cangrelor, minimizing the time lapse of inadequate platelet inhibition and additionally reduce the need for prolonged cangrelor infusion after primary PCI that would substantially increase the cost.

Finally, our data may have important clinical implications in patients with SAP referred to coronary angiography or in patients with non-STEMI undergoing coronary angiography soon after the first medical contact. Based on results from prior clinical trials, unselective preloading with clopidogrel or new ADP receptors blockers such as prasugrel, before coronary anatomy is known, is no longer recommended and administration of ADP receptor blockers in the catheterization laboratory when ad hoc PCI is planned should be preferred. (23,24) However, given the long time-delay between administration of integral tablets and efficient platelet inhibition, in patients with moderate to high risk for ischemic complications, this strategy may increase the risk of periprocedural myocardial infarction or

acute stent thrombosis. In addition, awareness of the delayed onset of action may lead to an increased use of glycoprotein IIb/IIIa inhibitors, and consequently increased risk of bleeding. Fast and potent platelet inhibition with chewed ticagrelor administration in the catheterization laboratory may be a practicable strategy in these cases.

In this study we confirm earlier knowledge regarding pharmacodynamic properties of integral and crushed ticagrelor LD. In a previous study,⁽⁵⁾ patients with stable angina were randomised to ticagrelor versus clopidogrel loading dose. Within 60 minutes, 80% inhibition of PR was observed in the ticagrelor group in accordance with our results in the integral ticagrelor group. A recent study compared crushed versus integral ticagrelor tablets in STEMI patients.⁽¹⁷⁾ Crushed ticagrelor provided earlier inhibition of platelet aggregation than integral tablets. At 60 minutes, 63% in the integral ticagrelor group and 35% in the crushed ticagrelor group had HRPR. In our study, compared to integral ticagrelor, 50% lower rate of HRPR was observed with crushed ticagrelor at 20 minutes. Lower baseline PRU values and earlier onset of drug action in our stable population may explain the difference between the two studies.

With these data, we expand earlier knowledge on the importance of ticagrelor formulations for pharmacodynamic results.

Limitations

There are several limitations with our study. First, the most important limitation is the relatively small sample size, mainly in the crushed and chewed ticagrelor subgroups. We assumed that crushed and chewed ticagrelor would have similar pharmacodynamic properties and would be included as one group in the analysis. Despite the small numbers of patients, statistically significant differences in outcome between the subgroups could be identified. However, given the small sample size, only one method of platelet aggregation reported (VerifyNow), and the fact that comparison between chewed and crushed tablets derived from a post-hoc analysis, the difference between crushed and chewed tablets should be interpreted with caution and be regarded as hypothesis generating only. Second, we did not have pharmacokinetic data. Earlier studies have provided pharmacokinetic data for crushed ticagrelor indicating a linear relationship between plasma concentration of ticagrelor and effect on aggregation. Therefore we think it is reasonable to assume that

faster and stronger inhibition of platelet activity with chewed tablets is caused by a faster and higher absorption after administration.

Conclusion

Novel ways of oral ticagrelor administration are feasible. Chewed ticagrelor tablets as a LD resulted in a faster and stronger platelet inhibition than integral tablets and in addition appeared to be faster than crushed tablets. This may have important clinical implications in STEMI patients and in cases when fast and potent platelet inhibition is desirable.

Acknowledgements

The authors would like to thank all patients who took part in this study, all nurses in the outpatient clinic at Linköping University Hospital for their participation in the data collection and E. Logander, research nurse, for her important contribution during the study design.

References

1. Santos-Gallego CG, Picatoste B, Badimon JJ. Pathophysiology of acute coronary syndrome. *Current atherosclerosis reports* 2014;16:401.
2. Husted S, Emanuelsson H, Heptinstall S et al. Pharmacodynamics, pharmacokinetics, and safety of the oral reversible P2Y12 antagonist AZD6140 with aspirin in patients with atherosclerosis: a double-blind comparison to clopidogrel with aspirin. *European heart journal* 2006;27:1038-47.
3. Levine GN, Bates ER, Bittl JA et al. 2016 ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients With Coronary Artery Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Journal of the American College of Cardiology* 2016;68:1082-115.
4. Windecker S, Kolh P, Alfonso F et al. [2014 ESC/EACTS Guidelines on myocardial revascularization]. *Kardiologia polska* 2014;72:1253-379.
5. Gurbel PA, Bliden KP, Butler K et al. Randomized double-blind assessment of the ONSET and OFFSET of the antiplatelet effects of ticagrelor versus clopidogrel in patients with stable coronary artery disease: the ONSET/OFFSET study. *Circulation* 2009;120:2577-85.
6. Alexopoulos D, Xanthopoulos I, Gkizas V et al. Randomized assessment of ticagrelor versus prasugrel antiplatelet effects in patients with ST-segment-elevation myocardial infarction. *Circulation Cardiovascular interventions* 2012;5:797-804.
7. Parodi G, Valenti R, Bellandi B et al. Comparison of prasugrel and ticagrelor loading doses in ST-segment elevation myocardial infarction patients: RAPID (Rapid Activity of Platelet Inhibitor Drugs) primary PCI study. *Journal of the American College of Cardiology* 2013;61:1601-6.
8. Kubica J, Adamski P, Ostrowska M et al. Morphine delays and attenuates ticagrelor exposure and action in patients with myocardial infarction: the randomized, double-blind, placebo-controlled IMPRESSION trial. *European heart journal* 2016;37:245-52.
9. Nordt SP, Clark RF, Castillo EM et al. Comparison of three aspirin formulations in human volunteers. *The western journal of emergency medicine* 2011;12:381-5.

10. Zafar MU, Farkouh ME, Fuster V et al. Crushed clopidogrel administered via nasogastric tube has faster and greater absorption than oral whole tablets. *Journal of interventional cardiology* 2009;22:385-9.
11. Crean B, Finnie C, Crosby A. Evaluation of crushed ticagrelor tablet doses: recovery following crushing and naso-gastric tube passage ex vivo. *Drugs in R&D* 2013;13:153-7.
12. Teng R, Carlson G, Hsia J. An open-label, randomized bioavailability study with alternative methods of administration of crushed ticagrelor tablets in healthy volunteers. *International journal of clinical pharmacology and therapeutics* 2015;53:182-9.
13. Price MJ. Bedside evaluation of thienopyridine antiplatelet therapy. *Circulation* 2009;119:2625-32.
14. Tantry US, Bonello L, Aradi D et al. Consensus and update on the definition of on-treatment platelet reactivity to adenosine diphosphate associated with ischemia and bleeding. *Journal of the American College of Cardiology* 2013;62:2261-73.
15. G Carlson RT, J Hsia. Crushing ticagrelor tablets accelerates exposure compared with intact tablets. *J Am Coll Cardiol* 2014;63(12_S):doi:101016/s0735-1097(14)60229-1 April 2014.
16. Verdoia M, Sartori C, Pergolini P et al. Prevalence and predictors of high-on treatment platelet reactivity with ticagrelor in ACS patients undergoing stent implantation. *Vascular pharmacology* 2015.
17. Alexopoulos D, Barampoutis N, Gkizas V et al. Crushed Versus Integral Tablets of Ticagrelor in ST-Segment Elevation Myocardial Infarction Patients: A Randomized Pharmacokinetic/Pharmacodynamic Study. *Clinical pharmacokinetics* 2015.
18. Alexopoulos D, Gkizas V, Patsilinakos S et al. Double versus standard loading dose of ticagrelor: onset of antiplatelet action in patients with STEMI undergoing primary PCI. *Journal of the American College of Cardiology* 2013;62:940-1.
19. Bonello L, Pansieri M, Mancini J et al. High on-treatment platelet reactivity after prasugrel loading dose and cardiovascular events after percutaneous coronary intervention in acute coronary syndromes. *Journal of the American College of Cardiology* 2011;58:467-73.
20. Montalescot G, van 't Hof AW, Lapostolle F et al. Prehospital ticagrelor in ST-segment elevation myocardial infarction. *The New England journal of medicine* 2014;371:1016-27.
21. Siller-Matula JM, Christ G, Lang IM et al. Multiple electrode aggregometry predicts stent thrombosis better than the vasodilator-stimulated phosphoprotein phosphorylation assay. *Journal of thrombosis and haemostasis : JTH* 2010;8:351-9.
22. Bhatt DL, Stone GW, Mahaffey KW et al. Effect of platelet inhibition with cangrelor during PCI on ischemic events. *The New England journal of medicine* 2013;368:1303-13.
23. Bellemain-Appaix A, O'Connor SA, Silvain J et al. Association of clopidogrel pretreatment with mortality, cardiovascular events, and major bleeding among patients undergoing percutaneous coronary intervention: a systematic review and meta-analysis. *JAMA : the journal of the American Medical Association* 2012;308:2507-16.
24. Montalescot G, Bolognese L, Dudek D et al. Pretreatment with prasugrel in non-ST-segment elevation acute coronary syndromes. *The New England journal of medicine* 2013;369:999-1010.

