I.F.C. Italian Federation of Cardiology

Oral aspirin or low dose of intravenous lysine acetylsalicylate in ST-elevation myocardial infarction undergoing primary percutaneous coronary intervention

Marco Ferlini[a], Sergio Leonardi[b,c], Alessandro Mandurino Mirizzi[a], Claudio Montalto[a,c], Gabriele Crimi[a], Alessandra Repetto[a], Barbara Marinoni[a], Alberto Somaschini[a,c], Maurizio Ferrario[a], Catherine Klersy[d] and Luigi Oltrona Visconti[a]

Background **A loading dose of aspirin (ASA) is recommended as soon as possible in patients presenting with ST-elevation myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention (pPCI), and both oral and intravenous administration can be considered. However, studies comparing the two routes of administration, as well as data about the use of low-intravenous dosages in this clinical setting are lacking.**

Aim **To compare the pharmacodynamic effect of an oral loading dose of 'noncoated' ASA 300 mg vs. an intravenous bolus injection of lysine acetylsalicylate 150 mg in patients with STEMI undergoing pPCI.**

Methods **This was a prospective single-center, open label, pharmacodynamic study, including nonconsecutive patients presenting at our catheterization laboratory with STEMI undergoing pPCI and not receiving ASA within the previous 7 days. Pharmacodynamic analyses were performed at five time points: baseline, and 1, 2, 4 and 12 h after the loading dose, and measured as ASA reaction units (ARU) by the Verify Now System. An ARU more than 550 was considered as nonresponsiveness to study drugs. The primary end point was the different rate of patients with ARU more than 550 at 2 h after the loading dose of oral vs. intravenous ASA. Secondary end points included the comparison of ARU more than 550 at the other time points and the comparison of continuous ARU at each time point.**

Results **The study was planned with a sample size of 68 patients, but it was prematurely stopped due to slow enrollment after the inclusion of 23 patients, 12 randomized to oral ASA and 11 to intravenous lysine acetylsalicylate. At 2 h the rate of patients with ARU more than 550 was numerically but not significantly higher in patients receiving oral ASA as compared with intravenous lysine acetylsalicylate (33 vs. 14.2%; Δ −0.19, 95% confidence interval −0.59–0.21, *P* = 0.58). The difference over time was NS (*P* = 0.98), though the prevalence of ARU more than 550 was higher at the other time points. Both routes of administration reduced ARU values over time, though with no overall significant difference between profiles (*P* overall = 0.48).**

Conclusion **In patients with STEMI undergoing pPCI the rate of nonresponsiveness to ASA was not different comparing an oral 'noncoated' loading dose of ASA with an intravenous bolus injection of lysine acetylsalicylate. However, as patient enrollment was prematurely terminated, this study is underpowered to draw a definite conclusion.**

J Cardiovasc Med 2021, **22**:000–000

Keywords: aspirin, intravenous, myocardial infarction, oral

[a]Division of Cardiology, [b]Coronary Care Unit, Fondazione IRCCS Policlinico San Matteo, [c]Department of Molecular Medicine, University of Pavia and [d]Clinical Epidemiology & Biometry Unit, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy

Correspondence to Marco Ferlini, MD, Division of Cardiology, Fondazione IRCCS Policlinico San Matteo, viale Golgi 19, 27100, Pavia, Italy
E-mail: marco.ferlini@gmail.com

Received 5 August 2020 **Revised** 3 December 2020
Accepted 23 January 2021

Introduction

A dual antiplatelet therapy including aspirin (ASA) and an oral inhibitor of the platelet P2Y12 receptor for adenosine 5′-diphosphate is mandatory in patients with acute coronary syndrome (ACS).[1] In case of ST-elevation myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention (pPCI), a loading dose of ASA is recommended as soon as possible to obtain a complete inhibition of thromboxane A2-dependent platelet aggregation, and both oral or intravenous administration can be considered.[2]

Although there is consensus about the 150–300 mg oral dose of a 'nonenteric-coated' formulation, a wide range of intravenous dosages have been purposed over the years[3] and data of comparison between the routes of administration are lacking. In healthy volunteers, an intravenous loading dose of lysine acetylsalicylate achieved a faster onset of platelet inhibition, with less intraindividual and

DOI:10.2459/JCM.0000000000001174

interindividual variability than oral ASA.[4] In patients with ACS, high dosages of intravenous ASA 250 or 500 mg was associated with a faster and higher platelet inhibition compared with a single oral dose of ASA 300 mg, but only 5% of the included patients presented with STEMI.[5]

A low-intravenous dose range of 75–150 mg is recommended by guidelines[2] based on pharmacokinetic considerations,[6] although this dosage was not investigated in pharmacodynamic or clinical study including patients with STEMI.

We aimed to compare the pharmacodynamic effect of 300 mg oral ASA with 150 mg of intravenous lysine acetylsalicylate, in patients with STEMI undergoing pPCI.

Methods

The present is a prospective, randomized, single-center, open label study to assess the pharmacodynamic effect of oral ASA vs. intravenous lysine acetylsalicylate in patients presenting with STEMI undergoing pPCI. The study was conducted at the Fondazione IRCCS Policlinico San Matteo in Pavia, Italy. The protocol (full text available as Supplementary Appendix, http://links.lww.com/JCM/A365) was designed by the principal investigator and approved by the statistician and the coinvestigators. The study complied with the Declaration of Helsinki and was approved by the Local Institutional Review Board; all patients gave their written informed consent before any study procedure. The protocol was approved by the National Italian Drug Agency (Agenzia Italiana del Farmaco, AIFA, Rome, Italy; EudraCT number 2015-001189-24).

The data that support the findings of the present analysis are available from the corresponding author upon reasonable request.

Patients presenting at our catheterization laboratory with STEMI and not receiving ASA within the previous 7 days including the loading dose by the emergency medical system were screened for study eligibility; further exclusion criteria were contraindications to ASA like hypersensitivity or history of allergic reactions; known hemorrhagic diathesis; previous hemorrhagic stroke; ongoing or planned treatment with glycoprotein IIa/IIIb inhibitors; inability to swallow.

After diagnostic angiography and confirmation of the need to proceed with pPCI, patients were randomly assigned 1:1 to receive either oral 'noncoated' ASA 300 mg or intravenous lysine acetylsalicylate 150 mg. Randomization was generated by the study statistician (C.K.) in randomized blocks generated using an algorithm reproducible with the Stata 16 software (StataCorp, College Station, Texas, USA). Masking was obtained using sealed opaque sequentially numbered envelopes.

Patients received the study drugs immediately after randomization but before the guide wire was passed through the culprit lesion. All patients received a loading dose of 70 IU/kg unfractionated heparin as per the local standard of care.

The additional antithrombotic therapy was at the discretion of the treating interventional cardiologist, including type and timing of the P2Y12 inhibitor loading dose. Coronary angiography was performed by either the femoral or the radial approach.

Pharmacodynamic assessments

Aspirin reactivity was measured with the VerifyNow System Aspirin Platelet Reactivity test (Accriva Diagnostics, Inc San Diego, California, USA) and quantified as the ASA reaction unit (ARU). In line with the reported cutoff value, an ARU more than 550 was considered as nonresponsiveness to study drugs.[7]

Pharmacodynamic assessments were performed at the following five time points: baseline (before loading dose administration of study drugs) and 1, 2, 4 and 12 h after the study drugs administration. Figure S1, http://links.lww.com/JCM/A364 shows a flow diagram of the study. All samples were taken by vein with a specific tube and were processed within 4 h of collection as recommended with the use of the VerifyNow System.

Outcomes

The rate of patients with ARU more than 550 at 2 h after the loading dose of study drugs was considered as the primary end point of the study. Secondary end points included the comparison of ARU more than 550 at the other time points and the comparison of continuous ARU at each time point.

An evaluation of the inhibition of platelet aggregation at baseline and 1 and 4 h after the study drugs administration was planned at study design but it was not performed for missing financial support and for logistic difficulties.

In-hospital occurrence of death (all-cause), ST and major bleeding information was collected. ST was defined according to the Academic Research Consortium criteria[8] and bleeding was classified with the thrombolysis in MI criteria.[9]

Statistical analysis

The Stata software was used for computation (version 16, StataCorp). A two-sided P value less than 0.05 was considered statistically significant. As all analyses are to be considered exploratory, no multiple tests correction is applied. Categorical variables were compared using the Fisher exact test. Continuous variables were described with mean and SD or median and interquartile range and compared with the Student t test or Mann–Whitney test, as appropriate. We computed the risk difference and mean difference, respectively, and 95% confidence intervals (CIs) to quantify the treatment effect. We used regression models for repeated measures (either logistic

or linear); we computed Huber–White robust standard errors to account for intrapatient correlation of measures. We assessed the interaction of treatment and time to compare the profile of ARU over time. Missing data were not imputed.

Based on residual platelet reactivity of oral P2Y12 inhibitors in patients with STEMI[10] and of nonresponsiveness to intravenous lysine acetylsalicylate in healthy volunteers,[4] we assumed an expected rate of nonresponder (ARU > 550) at 2 h of 50% with oral administration and of 16% with intravenous lysine acetylsalicylate. A planned enrollment of approximately 29 patients per arm is needed to achieve an 80% power (with a 0.05 alfa error) using a Chi-squared test; however, with this sample size a power of 72% will be achieved using a Fisher test. This led to an estimated sample size of approximately 68 patients (34 per arm), to maintain an 80% power.

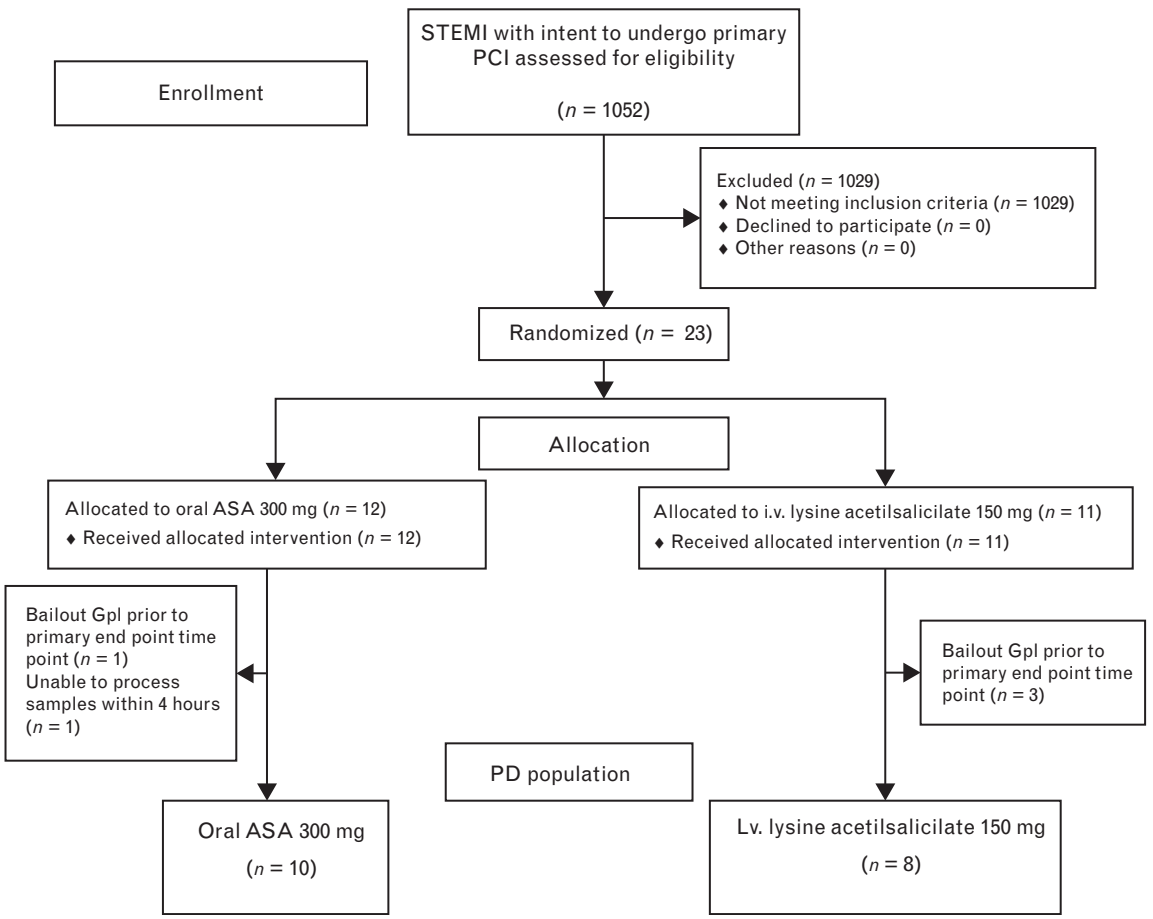
Results

Between January 2016 and November 2019 a total of 1052 patients with STEMI and intent to undergo primary PCI presented to our catheterization laboratory. Of these, 23 nonconsecutive patients met the inclusion/exclusion criteria and provided their written informed consent to participate in the study. They were then randomized into 12 to oral ASA 300 mg and 11 to intravenous lysine acetylsalicylate 150 mg. Figure 1 summarizes the study profile. Mean age of the population was 66 ± 13 years, 78% were male and 39% had an anterior MI. Full baseline characteristics are reported in Table 1.

No patients received an oral loading dose of P2Y12 inhibitor before the procedure, but it was administered in the catheterization laboratory immediately after the end of the PCI: most patients received ticagrelor, and the remaining 35% received clopidogrel.

Table 2 reports the pharmacological and procedural details of the study population: unfractioned heparin was used as the anticoagulant in all cases, the radial artery was the route of access in most patients and glycoprotein IIb/IIIa inhibitors (GpI) were required as bailout in four cases (one in the oral and three in the intravenous group). Morphine was administered to four

Fig. 1



Study profile. ASA, aspirin; GpI, glycoprotein IIb/IIIa inhibitors; PCI, percutaneous coronary intervention; PD, pharmacodynamic; STEMI, ST-elevation myocardial infarction.

Table 1 Baseline characteristics of the study population

Variables	Oral ASA, $n=12$	i.v. LA, $n=11$	*P* value
Age (years; mean ± SD)	67.7 ± 12.6	63.5 ± 12.8	0.44
Male sex, *n* (%)	10 (83)	8 (73)	0.54
BMI (kg/m^2, mean ± SD)	26.1 ± 3.15	28.8 ± 4.17	0.09
Current smoking, *n* (%)	3 (25)	3 (27)	0.9
Type 2 diabetes, *n* (%)	3 (25)	4 (36.3)	0.55
Hypercholesterolemia, *n* (%)	4 (33.3)	3 (27)	0.75
Arterial hypertension, *n* (%)	7 (58.3)	9 (81.8)	0.22
Previous PCI, *n* (%)	5 (41.6)	4 (36.3)	0.79
Previous MI, *n* (%)	1 (8.3)	2 (18)	0.48
Previous TIA/stroke, *n* (%)	2 (16.6)	0 (0)	0.16
eGFR (ml/min, mean ± SD)	73.7 ± 21.5	84.1 ± 24.8	0.29
Hemoglobin (g/dl, mean ± SD)	13.63 ± 1.38	13.74 ± 1.29	0.84
Platelet count (10^3/μl, mean ± SD)	236.75 ± 87.69	237.63 ± 83.84	0.98
Location of MI, *n* (%)			
Anterior	4 (33)	5 (45)	0.55
Inferior	7 (59)	4 (37)	0.29
Lateral	1 (8)	2 (18)	0.48
Time from symptom onset to randomization [min; median (IQR)]	265 (55–380)	280 (49–450)	0.68
Oral P2Y12 inhibitor			
Ticagrelor, *n* (%)	8 (66.6)	7 (63.6)	0.88
Clopidogrel, *n* (%)	4 (33.4)	4 (36.3)	0.88
Prasugrel, *n* (%)	0	0	–

ASA, aspirin; eGFR, estimated glomerular filtration rate; i.v., intravenous; IQR, interquartile range; LA, lysine acetylsalicylate; MI, myocardial infarction; PCI, percutaneous coronary intervention; TIA, transient ischemic attack.

patients (two in the oral and two in the intravenous group). In one case receiving intravenous lysine acetylsalicylate, despite an anterior ST-segment elevation and a suboptimal baseline thrombolysis in MI (TIMI) flow, we did not identify a significant stenosis on the left anterior descending, therefore no stent was implanted. Pre-PCI and final TIMI flows were not different between the two groups.

During hospitalization one patient experienced an acute ST, and one patient experienced major bleeding; both were enrolled in the oral arm.

Pharmacodynamic findings

The four patients receiving bailout GpI as well as one patient whose samples were unable to be processed within 4 h of collection were excluded from the pharmacodynamic assessment.

At 2 h the rate of patients with ARU more than 550 was numerically higher in patients receiving oral ASA compared with intravenous lysine acetylsalicylate (33 vs. 14.2%; Δ −0.19, 95% CI −0.59–0.21, $P=0.58$). The difference over time was NS ($P=0.98$), though the

Table 2 Pharmacological and procedural details

Variables	Oral ASA 300 mg, $n=12$	i.v. LA 150 mg, $n=11$	*P* value
Medications, *n* (%)			
UHF	12 (100)	11 (100)	–
Bivalirudin	0	0	–
GpI	1 (8)	3 (27)	0.23
Morphine	2 (17)	2 (18)	0.92
Ondansetron	1 (8)	3 (27)	0.23
Radial access, *n* (%)	9 (75)	10 (91)	0.31
Culprit vessel, *n* (%)			
LM	0	0	–
LAD	4 (34)	5 (45)	0.55
LCX	1 (8)	2 (18)	0.48
RCA	7 (58)	4 (37)	0.29
Thrombis aspiration, *n* (%)	4 (33)	3 (27)	0.75
Multivessel PCI, *n* (%)	0	0	–
Number of stents per patient (mean ± SD)	1.75 ± 1.48	1.18 ± 0.87	0.28
TIMI flow before PCI, *n* (%)			
0	8 (67)	6 (55)	0.55
1	0	1 (9)	0.29
2	3 (25)	3 (27)	0.9
3	1 (8)	1 (9)	0.95
TIMI flow at the end of PCI, *n* (%)			
0–1	0	0	–
2	1 (8)	0	0.33
3	11 (92)	11 (100)	0.33

ASA, aspirin; GpI, glycoprotein IIb/IIIa inhibitors; i.v., intravenous; LA, lysine acetylsalicylate; LAD, left anterior descending; LCX, left circumflex artery; LM, left main; PCI, percutaneous coronary intervention; RCA, right coronary artery; TIMI, thrombolysis in myocardial infarction; UHF, unfractioned heparin.

Table 3 Absolute values, of aspirin reaction unit measured by the VerifyNow Aspirin assay at different time points, with related mean difference and 95% confidence intervals comparing patients receiving oral aspirin vs. intravenous lysine acetylsalicylate

Time point	Oral ASA 300 mg	i.v. LA 150 mg	Mean difference	95% CI	*P* value
Baseline	618.7 ± 36.9	571 ± 59.4	47.09	−5.31–99.5	0.08
1 h	532.4 ± 105.7	450 ± 58.4	82.45	1.98–162.9	0.13
2 h	498.3 ± 111.15	450.29 ± 88.15	48.04	−58.83–154.9	0.45
4 h	502.2 ± 92.58	397.67 ± 64.4	104.58	13.06–196.09	0.02
12 h	480 ± 117.5	434.67 ± 93.6	45.3	−73.5–164.15	0.59

ASA, aspirin; CI, confidence interval; i.v., intravenous; LA, lysine acetylsalicylate.

prevalence of ARU more than 550 was higher at 1 h (36.3 vs. 12.5%, Δ −0.23, 95% CI −0.61–0.13, $P = 0.34$), at 4 h (37.5 vs. 0%, Δ −0.37, 95% CI −0.71 to −0.39, $P = 0.21$) and at 12 h (44.4 vs. 16.6%, Δ −0.27, 95% CI −0.72–0.16, $P = 0.58$).

At baseline there were no differences in ARU between the two groups: 618.7 ± 36.9 in the oral arm vs. 571 ± 59.4 in the intravenous arm (mean difference 47.09, 95% CI –5.31–99.5, $P = 0.08$). Table 3 reports the ARU values and the mean difference between the two groups at each time point. Although the numerical decrease was lower and slower in the oral group, no overall significant difference between profiles (Fig. 2, *P* overall = 0.48) was found.

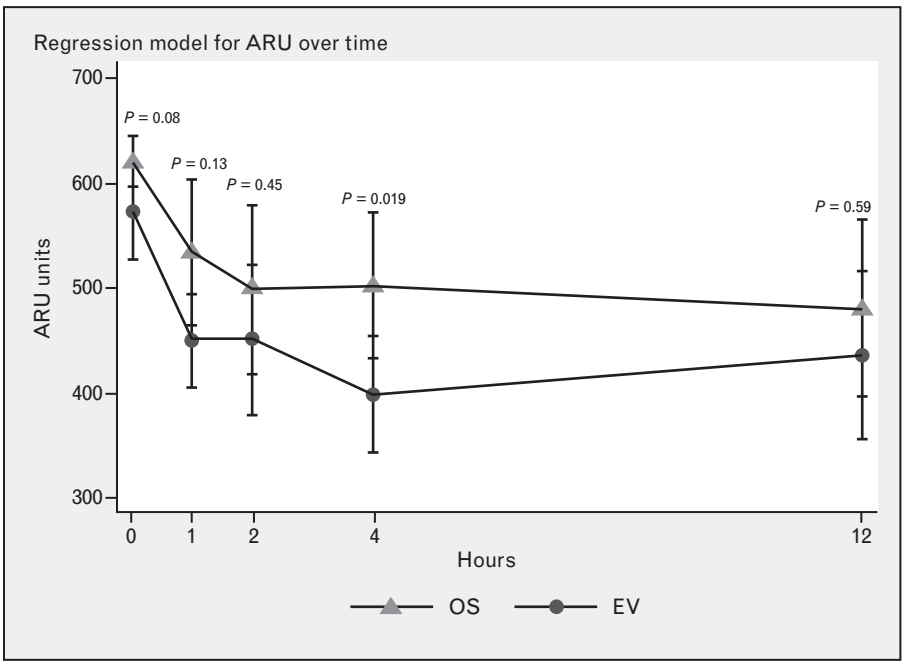
Discussion

For the first time in patients with STEMI, we compared the pharmacodynamic effect of a loading dose of oral ASA with an intravenous low-dose bolus injection of lysine acetylsalicylate. The key finding of the study is that, for the first 12 h, the rate of patients' nonresponsiveness to study drugs was not different between the two routes of administration.

Several studies have reported that an adequate inhibition of platelet aggregation in patients undergoing PCI is mandatory to prevent an increased risk of major adverse cardiovascular events.[11–13]

There is a lack of consensus regarding the definition of resistance to antiplatelet therapy in the clinical setting and routine platelet function testing to adjust antiplatelet therapy before or after PCI is not recommended.[1] The antiplatelet effect of ASA depends on its ability to irreversibly inhibit the enzyme cyclo-oxygenase-1 (COX-1) that is required for the conversion of arachidonic acid: therefore, a resistance to its intake should refer to

Fig. 2



Pharmacodynamic assessment over time measured by VerifyNow Aspirin Platelet Reactivity test after administration of oral (os) apirin 300 mg loading dose (triangles) and intravenous lysine acetylsalicylate 150 mg bolus injection (circles). Aspirin reaction unit measured by the VerifyNow Aspirin assay. Values are expressed as means. Error bars indicate standard 95% confidence intervals; *P* values indicate the comparisons between groups at each time point.

the inability to inhibit the platelet COX-1 activity.[14] About 8–45% of patients do not respond to therapy with ASA as determined by different laboratory tests, and these ASA-resistant patients are at increased risk of thrombotic events.[15–17] In consecutive patients undergoing PCI and on treatment with oral ASA 80–325 mg for at least 1 week, an ARU at least 550 was found in 19.2% of the cases, and these patients had a three times increased risk of periprocedural myocardial necrosis.[17] Lev *et al.*[18] reported an ARU at least 550 in 15.3% of patients undergoing elective PCI, from 20 to 24 h after receiving an oral dose of ASA 325 mg. However, these two studies included patients undergoing nonurgent PCI, and nonresponsiveness to ASA was assessed using a single measurement.

In our investigation we focused on patients with STEMI; in this population it has been widely reported that oral antiplatelet drugs such as P2Y12 inhibitors presented a late onset of action that could be overcome with the use of intravenous agents.[10,19] Furthermore, sedation, nausea, vomiting, shock condition and endotracheal intubation, that can be more frequent in emergent clinical settings, contribute to limiting the antiplatelet efficacy of oral agents.[20] Therefore, even in the case of ASA, an intravenous administration should be more efficacious in acute clinical settings. Current guidelines consider both the formulation of ASA in the acute phase of STEMI, but the recommended intravenous dosage was reduced over the years to the current range of 75–150 mg.[2,3] The dose reduction is based on pharmacokinetic considerations of a harmful inhibition of prostacyclin exposing systemic endothelial cells to high drug concentrations.[6,21] Previous data have already reported that lysine acetylsalicylate (320 mg oral or 450 mg intravenous) obtained a faster platelet inhibition compared with oral ASA, but they included respectively patients with stable coronary artery disease and healthy volunteers.[4,22] In patients with ACS, no significant pharmacodynamic difference was found when comparing two intravenous dosages of ASA 250 and 500 mg, although both provided greater platelet inhibition compared with oral administration.[5] Data on healthy volunteers reported the superiority of an intravenous dosage of 100 mg compared with an intravenous dosage of 25 and 50 mg.[23]

Particularly, our study is the only one that allows a direct comparison between the two routes of administration and that should not be affected by different dosages: given a 50% oral bioavailability of oral ASA,[5,6] the intravenous dose of 150 mg should correspond to the oral dose of 300 mg. We found that the intravenous lysine acetylsalicylate achieves an earlier and progressive reduction of nonresponsiveness up to absence at 4 h after administration; on the contrary with the oral ASA, the initial decrease of nonresponsiveness to 30–40% remained stable for up to 12 h. The difference in nonresponsiveness to ASA between the two routes of administration that we hypothesized at study design was found 4 h after the loading dose, therefore 2 h later than our assumption: whether this gap can be overcome with higher dosages cannot be excluded. However, the small difference in the continuous values of ARU was not overall significant and should be considered of unclear clinical significance and only hypothesis generating.

Different dosages of oral ASA have been used over time in different clinical and pharmacodynamic studies: our choice of an oral loading dose of 300 mg was based on the range recommended by guidelines,[1] in our daily clinical practice and in previous similar studies[4]; as for intravenous administration, an influence of different higher or lower dosages on results cannot be excluded.

Limitation

There are many limitations to our analysis. First, since the trial was terminated for slow enrollment without including the assumed sample size, its power is limited, and any result is to be considered inconclusive.

Second, we enrolled nonconsecutive patients from a very large population of STEMI: the wider use of ASA as first line medical treatment, before diagnostic angiography, left most patients unsuitable for inclusion; this determines a selection bias and an impossibility to generalize our findings.

Third, a binary outcome as the primary end point with a small sample size limits the study power and reduces the ability to draw any firm conclusion; however, our choice was influenced by the cutoff value of response to ASA that has been established with the use of the VerifyNow System.[7]

Despite the recommendations of guidelines,[2] no patients received an upstream loading dose of oral P2Y12, and about 35% of the enrolled patients were treated with clopidogrel. The decision to not pretreat patients with STEMI with these drugs is based on our daily clinical practice after a decision shared with the colleagues of the emergency medical system; on the contrary, we have no specific reason to provide for the choice of clopidogrel in more than one-third of the patients, but all concomitant medical therapies were left at the discretion of the treating physician.

The fact that not all patients received the same oral P2Y12 inhibitors can be considered as a further limitation: an influence of clopidogrel on the arachidonic acid-thromboxane A_2-COX pathway has been reported,[24,25] and almost 50% of ASA-resistant patients were also resistant to clopidogrel.[18] However, an influence on our results is unlikely as the rate of patients receiving clopidogrel was not different in the two groups; the very small sample size does not allow a comparison of ARU values in the subgroup of patients receiving clopidogrel rather than ticagrelor.

Finally, we did not perform any other platelet function testing and we did collect more samples to address eventual errors.

Conclusion

The current randomized study did not establish a significantly different pharmacodynamic effect between an oral loading dose of 'noncoated' ASA 300 mg and an intravenous bolus injection of lysine acetylsalicylate 150 mg in patients with STEMI undergoing primary PCI. However, as patient enrollment was prematurely terminated, the study is underpowered for a definitive conclusion. Future larger studies are required to establish the optimal regimen of ASA in this clinical setting.

Acknowledgements

Authors want to thank Monica Portolan for her kind support.

The costs of the current study have been supported by research funding of the Division of Cardiology, Fondazione IRCCS Policlinico San Matteo, Pavia.

Conflicts of interest

Outside the present work, M.F. received individual payment as consultant, for advisory board or as speaker at scientific congresses from: Astra Zeneca, Chiesi Farmaceutici, Biosensors, Bayer, Sanofi, Boeringher Ingelheim. L.O.V. received payment as an individual for consulting fee or honorarium from: Eli Lilly, Daiichi Sankyo, Astra Zeneca, Menarini, Bayer, Pfizer, BMS, Boehringer Ingelheim. Other authors have nothing to disclose.

There are no conflicts of interest.

References

1 Valgimigli M, Bueno H, Byrne RA, *et al.* 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS. *Eur Heart J* 2018; **39**:213–260.
2 Ibanez B, James S, Agewall S, *et al.* 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *Eur Heart J* 2018; **39**:119–177.
3 Van de Werf F, Bax J, Betriu A, *et al.* Management of acute myocardial infarction in patients presenting with persistent ST-segment elevation: the Task Force on the Management of ST-Segment Elevation Acute Myocardial Infarction of the European Society of Cardiology. *Eur Heart J* 2008; **29**:2909–2945.
4 Vivas D, Martín A, Bernardo E, *et al.* Impact of intravenous lysine acetylsalicylate versus oral aspirin on prasugrel-inhibited platelets: results of a prospective, randomized, crossover study (the ECCLIPSE Trial). *Circ Cardiovasc Interv* 2015; **8**:e002281.
5 Zeymer U, Hohlfeld T, Vom Dahl J, *et al.* Prospective, randomised trial of the time dependent antiplatelet effects of 500 mg and 250 mg acetylsalicylic acid i.v. and 300 mg p.o. in ACS (ACUTE). *Thromb Haemost* 2017; **117**:625–635.
6 Pechlaner C. Intravenous high-dose aspirin in acute coronary syndromes? *Crit Care Med* 2010; **38**:2267.
7 Nielsen HL, Kristensen SD, Thygesen SS, *et al.* Aspirin response evaluated by the VerifyNow Aspirin System and light transmission aggregometry. *Thromb Res* 2008; **123**:267–273.
8 Cutlip DE, Windecker S, Mehran R, *et al.* Clinical end points in coronary stent trials: a case for standardized definitions. *Circulation* 2007; **115**:v2344–v2351.
9 Rao AK, Pratt C, Berke A, *et al.* Thrombolysis in myocardial infarction (TIMI) trial-phase I: hemorrhagic manifestations and changes in plasma fibrinogen and the fibrinolytic system in patients treated with recombinant tissue plasminogen activator and streptokinase. *J Am Coll Cardiol* 1988; **11**:1–11.
10 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. *J Am Coll Cardiol* 2013; **61**:1601–1606.
11 Sofi F, Marcucci R, Gori AM, *et al.* Clopidogrel nonresponsiveness and risk of cardiovascular morbidity: an updated meta-analysis. *Thromb Haemost* 2010; **103**:841–848.
12 Krasopoulos G, Brister SJ, Beattie WS, Buchanan MR. Aspirin 'resistance' and risk of cardiovascular morbidity: a systematic review and meta-analysis. *BMJ* 2008; **336**:195–198.
13 Snoep JD, Hovens MM, Eikenboom JC. Clopidogrel nonresponsiveness in patients undergoing percutaneous coronary intervention with stenting: a systematic review and meta-analysis. *Am Heart J* 2007; **154**:221–231.
14 Sambu N, Curzen N. Monitoring the effectiveness of antiplatelet therapy: opportunities and limitations. *Br J Clin Pharmacol* 2011; **72**:683–696.
15 Grotemeyer KH, Scharafinski HW, Husstedt IW. Two-year follow-up of aspirin responder and aspirin nonresponder: a pilot study including 180 poststroke patients. *Thromb Res* 1993; **71**:397–403.
16 Gum PA, Kottke-Marchant K, Poggio ED, *et al.* Profile and prevalence of aspirin resistance in patients with cardiovascular disease. *Am J Cardiol* 2001; **88**:230–235.
17 Chen WH, Lee PY, Ng W, Tse HF, Lau CP. Aspirin resistance is associated with a high incidence of myonecrosis after nonurgent percutaneous coronary intervention despite clopidogrel pretreatment. *J Am Coll Cardiol* 2004; **43**:1122–1126.
18 Lev E, Patel R, Maresh K, *et al.* Aspirin and clopidogrel drug response in patients undergoing percutaneous coronary intervention: the role of dual drug resistance. *J Am Coll Cardiol* 2006; **47**:27–33.
19 Valgimigli M, Tebaldi M, Campo G, *et al.* Prasugrel versus tirofiban bolus with or without short postbolus infusion with or without concomitant prasugrel administration in patients with myocardial infarction undergoing coronary stenting: the FABOLUS PRO (Facilitation through Aggrastat By drOpping or shortening Infusion Line in patients with ST-segment elevation myocardial infarction compared to or on top of PRasugrel given at loading dOse) trial. *JACC Cardiovasc Interv* 2012; **5**:268–277.
20 Heestermans AA, van Werkum JW, Taubert D, *et al.* Impaired bioavailability of clopidogrel in patients with a ST-segment elevation myocardial infarction. *Thromb Res* 2008; **122**:776–781.
21 Rocca B, Petrucci G. Variability in the responsiveness to low-dose aspirin: pharmacological and disease-related mechanisms. *Thrombosis* 2012; **2012**:376721.
22 Gurfinkel EP, Altman R, Scazziota A, *et al.* Fast platelet suppression by lysine acetylsalicylate in chronic stable coronary patients: potential clinical impact over regular aspirin for coronary syndromes. *Clin Cardiol* 2000; **23**:697–700.
23 Husted SE, Kristensen SD, Vissinger H, *et al.* Intravenous acetylsalicylic acid – dose-related effects on platelet function and fibrinolysis in healthy males. *Thromb Haemost* 1992; **68**:226–229.
24 Armstrong PC, Dhanji AR, Truss NJ, *et al.* Utility of 96-well plate aggregometry and measurement of thrombin adhesion to determine aspirin and clopidogrel effectiveness. *Thromb Haemost* 2009; **102**:772–778.
25 Frelinger AL III, Furman MI, Linden MD, *et al.* Residual arachidonic acid-induced platelet activation via an adenosine diphosphate-dependent but cyclooxygenase-1- and cyclooxygenase-2-independent pathway: a 700 patient study of aspirin resistance. *Circulation* 2006; **113**:2888–2896.