Impact of SARS-CoV-2 positivity on clinical outcome among STEMI patients undergoing mechanical reperfusion: Insights from the ISACS STEMI COVID 19 registry

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A R T I C L E I N F O

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A B S T R A C T

Background and aims: SARS-Cov-2 predisposes patients to thrombotic complications, due to excessive inflammation, endothelial dysfunction, platelet activation, and coagulation/fibrinolysis disturbances. The aim of the present study was to evaluate clinical characteristics and prognostic impact of SARS-CoV-2 positivity among STEMI patients undergoing primary percutaneous coronary intervention (PPCI).

Methods: We selected SARS-CoV-2 positive patients included in the ISACS-STEMI COVID-19, a retrospective multicenter European registry including 6609 STEMI patients treated with PPCI from March 1st until April 30th, in 2019 and 2020. As a reference group, we randomly sampled 5 SARS-Cov-2 negative patients per each SARS-CoV-2 positive patient, individually matched for age, sex, and hospital/geographic area. Study endpoints were in-hospital mortality, definite stent thrombosis, heart failure.

Results: Our population is represented by 62 positive SARS-CoV-2 positive patients who were compared with a matched population of 310 STEMI patients. No significant difference was observed in baseline characteristics or the modality of access to the PCI center. In the SARS-CoV-2 positive patients, the culprit lesion was more often located in the RCA ($p < 0.001$). Despite similar pre and postprocedural TIMI flow, we observed a trend in higher

use of GP IIb-IIIa inhibitors and a significantly higher use of thrombectomy in the SARS-CoV-2 positive patients. SARS-CoV-2 positivity was associated with a remarkably higher in hospital mortality (29% *vs* 5.5%, $p < 0.001$), definite in-stent thrombosis (8.1% *vs* 1.6%, $p = 0.004$) and heart failure (22.6% *vs* 10.6%, $p = 0.001$) that was confirmed after adjustment for confounding factors.
Conclusions: Our study showed that among STEMI patients, SARS-CoV-2 positivity is associated with larger thrombus burden, a remarkably higher mortality but also higher rates of in-stent thrombosis and heart failure.

1. Introduction

As of September 8th, 2020, more than 27 million of cases of COVID-19 have been reported in over 185 countries and territories, resulting in more than 890,000 deaths, especially in Europe, the United States and Latin America.

It has been suggested that SARS-Cov-2 may be a direct and indirect cause of increased cardiovascular mortality during the COVID pandemic [1]. The indirect effects are mainly due to the fear of contagion that may refrain patients from activating the emergency system or do it but with a remarkable delay as compared to 2019 that reasonably increases mortality [2–6]. Furthermore, SARS-Cov-2 predisposes patients to thrombotic complications, both in the venous and arterial bed, due to excessive inflammation, endothelial dysfunction, platelet activation, and coagulation/fibrinolysis disturbances and therefore potentially causing plaque disruption and amplified thrombotic superimposition leading to myocardial infarction [7]. Small reports suggested a very high-mortality rate among SARS-Cov-2 positive patients [5,8]. Therefore, the aim of the present study was to evaluate clinical characteristics and prognostic impact of SARS-Cov-2 positivity among patients with ST-segment elevation myocardial infarction (STEMI) undergoing mechanical reperfusion enrolled in the International Study on Acute Coronary Syndromes – ST segment Elevation Myocardial Infarction (ISACS-STEMI) COVID-19.

2. Patients and methods

Our study population is represented by consecutive SARS-Cov-2 positive patients enrolled in the ISACS-STEMI COVID-19, a retrospective multicenter registry including 6609 STEMI patients enrolled by 77 high-volume European primary percutaneous coronary intervention (PCI) centers, that was conducted to compare STEMI patients treated from March 1st until April 30th, 2019 with those admitted within the same period of 2020 [9].

As reference group, we randomly sampled 5 SARS-Cov-2 negative patients per each SARS-Cov-2 positive patient, individually matched for age, sex, and geographic area. We collected demographic, clinical, procedural data, data on total ischemia time, door-to-balloon time, referral to primary PCI facility, PCI procedural data, in hospital outcome, including death. For this analysis, we collected, in addition to mortality, data on stent thrombosis (defined according to ARC definition), heart failure and major bleeding complications (BARC 3–5). We additionally collected detailed information on SARS-Cov-2 positive patients, including the presence of symptoms before or during the intervention, timing of SARS-Cov-2 diagnosis and the specific medications for COVID. The study was approved by the Ethical Committee of AOU Maggiore della Carità, Novara.

2.1. Statistics

Data analysis was performed with the SPSS Statistics Software 23.0 (IBM SPSS Inc., Chicago, Illinois). Quantitative variables were described using median and interquartile range. Absolute frequencies and percentages were used for qualitative variables. ANOVA or Mann-Whitney and chi-square test were used for continuous and categorical variables, respectively. Normal distribution of continuous variables was tested by the Kolmogorov-Smirnov test).

Multivariable logistic regression analyses were performed to identify the impact of SARS-Cov-2 positivity on in-hospital mortality, stent thrombosis, heart failure and major bleeding complications after adjustment for baseline confounding factors between the two groups. All significant variables (set at a p-value <0.1) were entered in block into the model. A $p < 0.05$ was considered statistically significant. The data coordinating center was established at the Eastern Piedmont University.

3. Results

We included a total of 62 SARS-CoV-2 positive patients who were compared with a matched cohort of 310 STEMI patients. Patients characteristics are described in Table 1. As detailed, no significant difference was observed in baseline characteristics, even though the SARS-CoV-2 positive patients tended to be less often smokers ($p = 0.055$), more often with cardiogenic shock at presentation ($p = 0.09$) and a direct access to the PCI Hospital ($p = 0.084$). No significant difference was observed in terms of ischemia time or door-to-balloon time. Supplementary Table 1S shows detailed characteristics of SARS-CoV-2 positive, in particular concerning the timing of diagnosis, symptoms and medical therapy. About 40% of patients had symptoms at admission, and in most of the patients (60%) the SARS-CoV-2 diagnostic tests were performed before or soon after the procedure. Hydroxychloroquine and chloroquine were the most frequently administrated therapies.

Table 2 shows angiographic and procedural characteristics. SARS-CoV-2 positive patients had more often the culprit lesion located in RCA, without any difference in pre and postprocedural TIMI flow or multivessel disease. However, a trend in higher use of IIb-IIIa inhibitors (33.9% *vs* 22.9%, $p = 0.07$) and a remarkable statistically significant higher use of thrombectomy (37.1% *vs* 20.6%, $p = 0.005$) were observed among the SARS-CoV-2 positive patients, suggesting a larger thrombus burden. No difference was observed in terms of pre and postprocedural TIMI flow. SARS-CoV-2 positive patients underwent more often orotracheal intubation during hospitalization as compared to negative patients (24.2% *vs* 5.7%, $p < 0.001$).

3.1. In-hospital outcome

Detailed data on clinical outcome are reported in Table 3. The SARS-CoV-2 positive patients had longer hospitalization (8 [4–15] *vs* 5 [3–7] days, $p < 0.001$) and more often needed orotracheal intubation (24.2% *vs* 5.7%, $p < 0.001$). SARS-CoV-2 positivity was associated with a remarkably higher in-hospital mortality (29% *vs* 5.5%, OR [95% CI] = 7.05 [3.38–14.7], $p < 0.001$) (Fig. 1), higher in-hospital definite in-stent thrombosis (8.1% *vs* 1.6%, OR [95% CI] = 5.35 [1.5–19], $p = 0.004$) (Fig. 2) and in-hospital heart failure (22.6% *vs* 10.6%., OR [95% CI] = 2.45[1.22–4.91], $p = 0.001$), without any difference in major bleeding complications. Among COVID positive patients, 10 out of 18 deaths were related to COVID. The results were confirmed after correction for baseline confounding factors (Table 3). No significant impact of chronic therapy with renin-angiotensin system inhibitors (RASI) at admission or its administration during hospitalization was observed on mortality among the SARS-CoV-2 positive patients. Figs. 1 and 2 show in-hospital mortality and in-stent thrombosis, respectively, according to combined SARS-CoV-2 positivity and use of thrombectomy, suggesting the potential beneficial effects of thrombectomy among SARS-CoV-2 positive patients. The use of Gp IIb/IIIa did not impact on mortality and stent thrombosis.

Table 1
Baseline demographic and clinical characteristics.

	SARS-CoV2 positive (n = 62)	SARS-CoV2 negative (n = 310)	*p* value
Age (median, IQR)	70 (62–76)	70 (62–75)	0.9[a]
Age > 75 year – n. (%)	18 (29)	80 (25.8)	0.59
Male gender – n. (%)	49 (79)	245 (79)	1.0
Medical hystory			
Diabetes mellitus- n (%)	10 (16.1)	67 (21.6)	0.33
Hypertension- n (%)	35 (56.5)	176 (56.8)	0.96
Hypercholesterolemia - n (%)	25 (40.3)	125 (40.3)	1.0
Active smoker – n (%)	14 (22.6)	109 (35.2)	0.055
Family history of CAD - n (%)	6 (9.7)	46 (14.8)	0.28
Previous STEMI- n (%)	8 (12.9)	29 (9.4)	0.39
Previous PCI – n (%)	12 (19.4)	49 (15.8)	0.49
Previous CABG - n (%)	1 (1.6)	14 (4.5)	0.29
Chronic therapy with RASI - n (%)	27 (43.5)	132 (42.6)	0.89
Geographic area			1.0
Italy – n (%)	21 (33.9)	105 (33.9)	
Iberian peninsula– n (%)	20 (32.3)	100 (32.3)	
Central Europe– n (%)	16 (25.8)	80 (25.8)	
Balkans– n (%)	3 (4.8)	15 (3.8)	
North-East Europe – n (%)	2 (3.2)	10 (3.2)	
Referral to primary PCI hospital			0.084
Type	23 (37.1)	73 (23.5)	
Direct access – n (%)	24 (38.7)	146 (47.1)	
Ambulance (from community) – n (%)	15 (24.2)	91 (29.4)	
Spoke– n (%)			
Time delays			
Ischemia time, median [25 - 75th]	200 [107–500]	179 [120–291]	0.26[a]
Total ischemia time	43 (69.4)	248 (80.5)	0.22
<6 h – n (%)	10 (16.1)	35 (11.4)	
6–12 h – n (%)	5 (8.1)	16 (5.2)	
12–24 h – n (%)	4 (6.5)	9 (2.3)	
>24 h – n (%)			
Total ischemia time > 12 h – n (%)	9 (14.5)	25 (8.1)	0.11
Door-to-balloon time, median [25 - 75th]	40 [28–65]	35 [23–68]	0.23[a]
Door-to-balloon time	17 (27.4)	111 (35.8)	0.11
<30 min - n (%)	17 (27.4)	102 (32.9)	
30-60 min– n (%)	28 (45.2)	97 (31.3)	
>60 min– n (%)			
Door-to-balloon time > 30 min (%)– n (%)	44 (73.3)	198 (64.1)	0.17
Clinical presentation			
Anterior STEMI– n (%)	25 (40.3)	146 (47.1)	0.33
Out-of-hospital cardiac arrest – n (%)	3 (4.8)	19 (6.1)	0.69
Cardiogenic shock– n (%)	9 (14.5)	24 (7.7)	0.09
Rescue PCI for failed thrombolysis – n (%)	2 (3.2)	4 (1.3)	0.27
Killip class – n (%)	45 (72.6)	245 (79)	0.15
I	5 (8.1)	34 [11]	
II	3 (4.8)	5 (1.6)	
III	9 (14.5)	26 (8.4)	
IV			

CAD = coronary artery disease; STEMI = ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention; CABG = coronary artery bypass graft.

[a] Mann-Whitney test.

4. Discussion

The main finding of the present study is that SARS-Cov-2 positivity is associated with larger use of IIb-III inhibitors and thrombectomy. Furthermore, it is associated with a remarkable higher in-hospital mortality, in-hospital definite stent thrombosis and heart failure, without any difference in major bleeding complications.

The outbreak of COVID-19 has rapidly spread across the world, with more than 7 million cases of COVID-19 in 185 countries and territories, resulting in more than 400,000 deaths, especially in Europe and United States.

SARS-Cov-2 has been suggested to increase cardiovascular mortality due to direct and indirect effects [1]. In particular, the inflammatory pathophysiological mechanisms triggering plaque disruption while producing a pro-thrombotic milieu [6] may potentially increase the risk of local micro thromboembolism, may impair reperfusion and increase the risk of in-stent thrombosis.

This is one of the largest reports describing characteristics and prognostic impact of SARS-Cov-2 positivity on outcome among STEMI patients undergoing mechanical reperfusion. No difference was observed in time delays. SARS-Cov-2 positive patients received more often Gp IIb/IIIa inhibitors and thrombectomy, potentially suggesting a larger thrombus burden than the control patients. SARS-Cov-2 positivity was associated with a remarkably higher in-hospital mortality, definite in-stent thrombosis and heart failure that was confirmed after adjustment for all baseline and procedural confounding factors.

The high mortality rates among STEMI patients associated with SARS-Cov-2 positivity is in step with previous findings from smaller reports and it is certainly not only a consequence of the pulmonary and systemic effects of COVID. In fact, the mortality rate in SARS-Cov-2 positive patients was still remarkably high even after the exclusion of COVID-related deaths (12.9%).

In a previous study [9] including 29 STEMI SARS-Cov-2 positivity patients (only 17 undergoing primary angioplasty), the authors observed

Table 2
Angiographic and procedural characteristics.

	SARS-CoV2 positive (n = 62)	SARS-CoV2 negative (n = 310)	*p* value
Radial access (%)	54 (87.1)	275 (88.7)	0.71 .72
Culpirt vessel	0 (0)	9 (2.9)	0.049
Left main – n (%)	25 (40.3)	142 (45.8)	
Left anterior descending artery – n (%)	4 (6.5)	453 (15.4)	
Circumflex – n (%)	31 (50)	103 (33.2)	
Right coronary artery – n (%)	1 (1.6)	1 (0.3)	
Anterolateral branch – n (%)			
Proximal lesion location – n (%)	31 (50)	142 (45.8)	0.55
In-stent thrombosis – n (%)	5 (8.1)	20 (6.5)	0.64
Multivesseldisease – n (%)	26 (41.9)	165 (53.2)	0.11
Preprocedural TIMI 0 flow – n (%)	36 (58.1)	193 (62.3)	0.21
Thrombectomy– n (%)	23 (37.1)	64 (20.6)	0.005
Stenting– n (%)	56 (90.3)	285 (91.9)	0.67
Drug-eluting stent– n (%)	56 (90.3)	277 (89.4)	0.82
Postprocedural TIMI 3 flow – n (%)	57 (91.9)	285 (91.9)	1.0
Gp IIb-IIIa inhibitors/cangrelor – n (%)	21 (33.9)	71 (22.9)	0.07
Bivalirudin– n (%)	0 (0)	0 (0)	1.0
Additional PCI	8 (13.1)	42 (13.7)	0.15
During the index procedure – n (%)	6 (9.8)	46 [15]	
Staged– n (%)			
DAPT therapy – n (%)	61 (98.4)	3.5 (98.4)	1.0
New ADP antagonists– n (%)	45 (72.6)	227 (73.2)	0.92
RASI– n (%)	37 (59.7)	239 (77.1)	0.004

TIMI = thrombolysis in myocardial infarction; DAPT = dual antiplatelet therapy; RASI: renin-angiotensin system inhibitors.

a mortality rate of 40%. Similar high mortality rates (28.6%) associated with SARS-Cov-2 positivity were observed in a larger Italian registry including about 465 STEMI patients treated both conservatively or by mechanical reperfusion [5].

The potential higher risk of stent thrombosis associated with SARS-Cov-2 positivity has been highlighted by anedoctical case reports [10–12]. In our study, SARS-Cov-2 positivity was independently associated with a 5 times higher risk of in-hospital definite stent thrombosis. This observation may potentially be a consequence of the larger thrombus burden and the potential specific mechanisms involved in plaque rupture among SARS-Cov-2 positive patients that may lead to an increased risk of thrombus formation and thrombotic complications. In fact, a previous *ex vivo* human autopsy study clearly demonstrated the role of residual thrombus burden and suboptimal stent implantation in unstable patients as a trigger of early stent thrombosis [13].

In our study, thrombectomy seemed to play favourably in SARS-Cov-2 positive subjects. Several randomized trials have investigated the benefits of thrombectomy in STEMI with conflicting results. After initial trials showing benefits in mortality [14,15], these findings have not been confirmed in large randomized trials [16,17]. However, thrombectomy seems to provide benefits in case of large thrombus burden and in terms of stent thrombosis [18,19]. In fact, a study clearly showed that thrombectomy was associated with better stent implantation, and a reduced metallization of coronary arteries, with shorter and larger stents [20]. These factors may favourably impact on the outcome in SARS-Cov-2 patients due to the potential mechanisms involved in plaque rupture that may increase the thrombotic milieu and therefore may support the use of thrombectomy.

In the last 2 decades, large attention has been focused on the use of Gp IIb/IIIa inhibitors in the context of STEMI patients, especially in the presence of large thrombus burden to prevent distal microembolisation, improve myocardial perfusion and reduce thrombotic complications [21,22]. In our study Gp IIb/IIIa inhibitors, while more frequently used in the SARS-Cov-2 positive patients, did not favourably impact on outcome. A potential risk in terms of bleeding and increased damage of the inflamed pulmonary tissue may in some way counterbalance the benefits in terms of thrombotic complications expected with the administration of Gp IIb/IIIa inhibitors.

Furthermore, in our study RASI did not impact on mortality among SARS-Cov-2 positive patients, and this is in step with recent large studies showing no impact on RASI on outcome of SARS-Cov-2 positive patients [23–25].

4.1. *Limitations*

Our study was based on a non-randomized design and retrospective data collection. Despite we randomly sampled the control group matched by age, gender and geographic location, we observed some

Table 3
In-hospital outcome.

	SARS-CoV2 positive (n = 62)	SARS-CoV2 negative (n = 310)	Odds ratio	95% CI	*p* value	Adjusted[a] odds ratio	95% CI	*p* value	Adjusted[b] odds ratio	95% CI	*p* value
Death – n (%)	18 (29)	17(5.5)	7.05	3.38–14.7	<0.001	5.25	2.03–13.55	0.001	9.33	3.01–28.03	<0.001
Definite stent thrombosis – n (%)	5 (8.1)	5 (1.6)	5.35	1.5–19	0.004	5.05	1.4–18.1	0.009	5.25	1.35–19.1	0.01
Heart failure – n (%)	14 (22.6)	33 (10.6)	2.45	1.22–4.91	0.01	2.35	1.15–5.05	0.02	2.5	1.25–5.85	0.009
Major bleeding complications (BARC 3–5) – n (%)	2 (3.3)	11 (3.7)	0.88	0.19–4.1	0.88	0.37	0.069–2.01	0.25	0.45	0.08–2.65	0.38

Adjustment for: [a]cardiogenic shock at presentation, smoking, referral to PCI hospital, culprit lesion location, Gp IIb-IIIa inhibitors, thrombectomy, RASI, in-hospital orotracheal intubation (p entry < 0.1); [b]culprit lesion location, thrombectomy, RASI, in-hospital orotracheal intubation (p entry < 0.05).

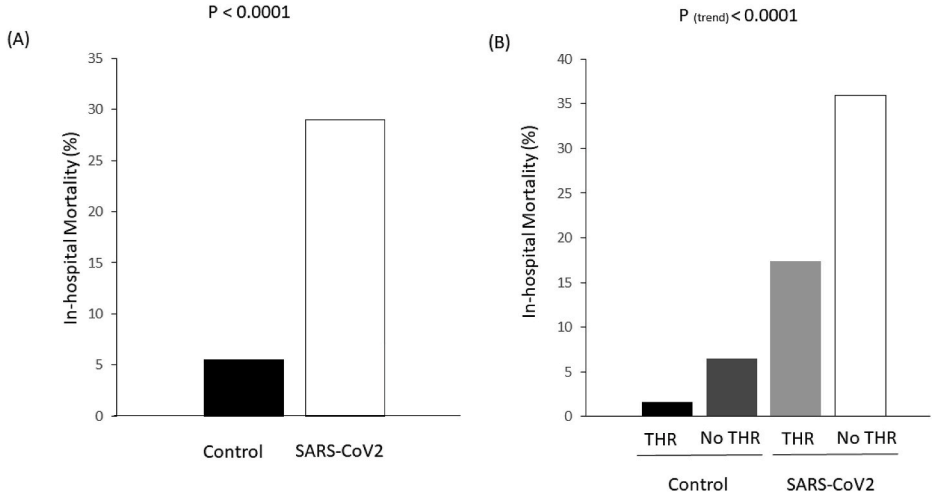

Fig. 1. Impact of SARS-Cov-2 positivity on in-hospital mortality (A). Outcome of patients according to SARS-Cov-2 positivity and use of thrombectomy (THR) suggesting potential benefits from thrombectomy especially among SARS-Cov-2 positive patients (B).

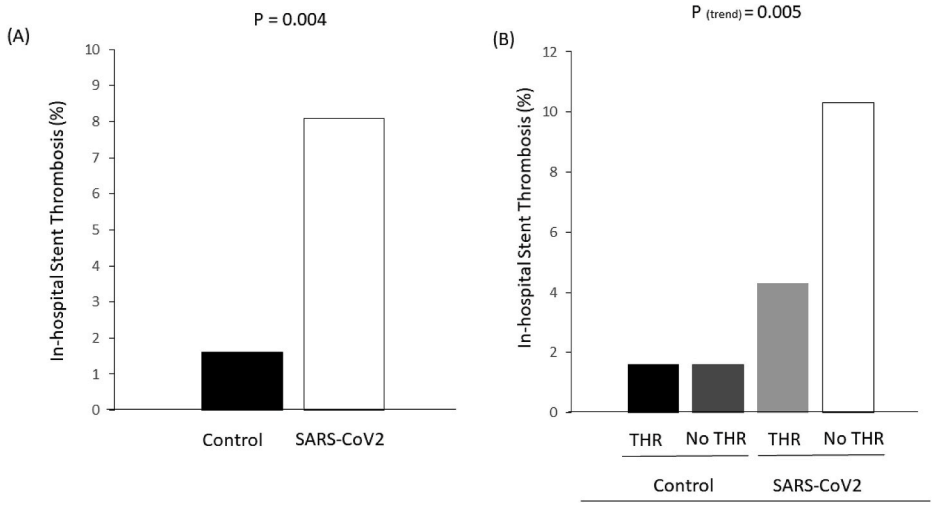

Fig. 2. Impact of SARS-Cov-2 positivity on in-hospital definite stent thrombosis (A). Outcome of patients according to SARS-Cov-2 positivity and use of thrombectomy suggesting potential benefits from thrombectomy especially among SARS-Cov-2 positive patients (B).

differences in baseline characteristics. However, our main results were confirmed after adjustment for all those baseline and procedural differences that may have played as confounders. We could not provide data on myocardial blush grade and thrombus score. In fact, a larger thrombus burden has been only hypothesized but not documented (by angiography and/or intracoronary imaging). Furthermore, we could have missed SARS-Cov-2 positive STEMI patients who died before reaching the cath lab with potential underestimation of the impact of SARS-Cov-2 positivity on mortality. We did not routinely collect data on oxygen saturation, oxygen supply, and ejection fraction at the onset of MI, hemodialysis, creatinine clearance, and prognostic scores such as APACHE and SOFA.

Our population was enrolled in the initial phase of COVID pandemic, with potential disparities in strategies concerning the use of nasopharingeal swabs that may have caused a potential selection bias. Furthermore, we did not routinely investigate the presence of PFO and therefore we cannot exclude any potential episode of paradoxical coronary embolization. However, being this one an extremely rare cause of STEMI, it cannot relevantly contribute to explain the observed larger thrombus burden in SARS-Cov-2 positive patients.

Finally, our population was relatively small, and therefore future larger investigations are certainly needed to further confirm our findings.

4.2. Conclusions

Our study showed that among STEMI patients SARS-Cov-2 positivity is associated with a remarkably higher mortality, but also higher in-stent thrombosis and heart failure. Moreover, the higher use of thrombectomy and Gp IIb/IIIa in SARS-Cov-2 positive patients may reflect the elevated thrombotic burden and the increased prothrombotic milieu of these patients. Future larger and well-powered studies are certainly needed to confirm our findings, and to evaluate the potential prognostic benefits from routine adjunctive thrombectomy and Gp IIb/IIIa inhibitors in SARS-Cov-2 positive patients.

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Author contributions

Authors included in the manuscript met all of the following conditions: 1) substantial contributions to the conception and design, acquisition of data, or analysis and interpretation of data; 2) drafting the article or revising it critically for important intellectual content; and 3) final approval of the version to be published.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.atherosclerosis.2021.06.926.

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