Safety and Efficacy of Intense Antithrombotic Treatment and Percutaneous Coronary Intervention Deferral in Patients With Large Intracoronary Thrombus

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The optimal management of a large intracoronary thrombus in patients with acute coronary syndromes without an urgent need of revascularization is unclear. We investigated whether deferring percutaneous coronary intervention (PCI) after a course of intensive antithrombotic therapy (ATT) (glycoprotein IIb/IIIa inhibitors, enoxaparin, aspirin, and clopidogrel) improves the outcomes compared with immediate PCI. We studied 133 stable patients with ACS and a large intracoronary thrombus and without an urgent need for revascularization at angiography. The angiographic and in-hospital outcomes of a prospective cohort of 89 patients who had undergone deferred angiography with or without PCI after ATT (d-PCI) were compared with a historical cohort of 44 patients who had undergone immediate PCI, matched for age, gender, and Thrombolysis In Myocardial Infarction thrombus grade. The absolute thrombus volume was measured before and after ATT using dual quantitative coronary angiography. All d-PCI patients remained stable during ATT (60.0 ± 30.8 hours). A significant reduction in the Thrombolysis In Myocardial Infarction thrombus grade (4, range 4 to 5, vs 3, range 2 to 4; p <0.001), thrombus volume (51.1, range 32.1 to 83, vs 38.1, range 21.7 to 50.7 mm^3; p <0.001), stenosis severity (73.8 ± 25.8% vs 60.3 ± 32.5%; p <0.001) and better Thrombolysis In Myocardial Infarction flow (2, range 0 to 3, vs 3, 1.5 to 3; p <0.001) were noted after ATT. PCI, stenting, and thrombus aspiration were performed less frequently in the d-PCI group (76.4% vs 100%, p <0.001; 70.8% vs 93.2%, p = 0.003; and 21% vs 100%, p <0.001, respectively). However, distal embolization and slow and/or no-reflow were more common during immediate PCI (31.8% vs 9%; p = 0.001). No life-threatening or severe hemorrhagic complications were observed, although the rate of mild and/or moderate bleeding was similar between the 2 groups (6.8% in immediate PCI vs 7.9% in d-PCI; p = 0.829). In conclusion, compared with immediate PCI, d-PCI after ATT in selected, stabilized patients with ACS and a large intracoronary thrombus and without an urgent need for revascularization is probably safe and associated with a reduction in thrombotic burden, angiographic complications, and the need of revascularization. These benefits were observed without an increase in hemorrhagic complications. © 2013 Elsevier Inc. All rights reserved. (Am J Cardiol 2013;111:1745−1750)

In patients with acute coronary syndromes (ACS), a large intracoronary thrombus (LIT) increases the risk of distal embolization, no-reflow, abrupt closure, stent thrombosis, repeat revascularization, myocardial infarction, and death.[1−4] Antithrombotic and antiplatelet therapies can reduce the thrombotic burden, and thrombectomy and embolic protection devices can effectively remove variable fractions of LIT. However, their effectiveness is often suboptimal[5]; therefore, the optimal treatment of LIT remains a major, unsolved problem frequently faced during percutaneous coronary intervention (PCI). Although in some presentations of ACS, such as acute ST-elevation myocardial infarction, PCI must be performed ad hoc, and thrombus burden reduction relies mainly on thrombectomy, the risk/benefit ratio of performing immediate PCI in patients with ACS and LIT who are clinically stable and without an urgent need of revascularization is less clear. Accordingly, the aim of the present study was to investigate whether in stable patients with ACS and LIT and without an urgent need for revascularization, deferral of PCI (d-PCI) after a course of intensive antithrombotic therapy (ATT), would be effective in reducing the thrombotic load and improve the in-hospital outcomes compared with ad hoc immediate PCI.

Table 1
Baseline patient characteristics

Variable	Total Population (n = 133)	d-PCI (n = 89)	i-PCI (n = 44)	p Value
Age (yrs)	58 ± 13	58 ± 13	58 ± 12	0.866
Men	115 (87)	77 (87)	38 (86)	0.981
Diabetes mellitus	25 (19)	20 (23)	5 (11)	0.123
Presentation				0.051
Unstable angina pectoris	11 (8)	11 (12)	0	
Non−STEMI	68 (51)	43 (48)	25 (57)	
STEMI (subacute phase)	54 (41)	35 (39)	19 (43)	
Peak troponin during admission (ng/ml)	9 (2−27)	8 (2−27)	10 (3−25)	0.564
Ejection fraction (%)	58 ± 15	57 ± 15	59 ± 13	0.543
Glycoprotein IIb/IIIa inhibitors before angiography	25 (19)	13 (15)	12 (27)	0.079
No. of coronary arteries narrowed				0.160
1	95 (71)	61 (69)	34 (77)	
2	26 (20)	17 (19)	9 (21)	
3	12 (9)	11 (12)	1 (2)	
Thrombus location				0.180
Left anterior descending artery	47 (35)	27 (30)	20(46)	
Circumflex artery	15 (11)	11 (12)	4 (9)	
Right coronary artery	66 (50)	46 (52)	20 (46)	
Saphenous vein graft	5 (4)	5 (6)	0	
TIMI flow	2 (0−3)	2 (0−3)	1 (0−3)	0.080
TIMI thrombus grade	4 (4−5)	4 (4−5)	4 (4−5)	0.289
Absolute thrombotic volume (mm^3)*	32 (51−83)	56 (38−90)	35 (26−79)	0.148
Stenosis grade (%)	79 ± 23	74 ± 26	90 ± 11	<0.001

Data are presented as mean ± SD, median (25th−75th percentile), or n (%).

i-PCI = immediate percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction; TIMI = Thrombolysis In Myocardial Infarction.

* Calculated using dual quantitative coronary angiography in 44 patients suitable for this analysis.

Table 2
Influence of antithrombotic therapy on angiographic features in patients with deferred percutaneous coronary intervention (d-PCI) (n = 89)

Variable	Before ATT	After ATT	p Value
TIMI flow	2 (0−3)	3 (1.5−3)	<0.001
TIMI thrombus grade	4 (4−5)	3 (2−4)	<0.001
Absolute thrombotic volume (mm^3)*	51 (32−83)	38 (22−51)	<0.001
Stenosis grade (%)	74 ± 26	61 ± 36	<0.001
Stenosis length (mm)	14 ± 8	10 ± 7	<0.001
Totally occluded vessel	29 (33)	18 (20)	<0.001

Data are presented as mean ± SD, median (25th−75th percentile), or n (%).

* Calculated using dual quantitative coronary angiography in 44 patients suitable for this analysis.[10]

no need for urgent revascularization, as judged by the operator. Primary PCI, ongoing/recurrent angina, hemodynamic instability, and unstable arrhythmias were the exclusion criteria.

The treatment group consisted of a prospective cohort of patients with ACS, LIT, and controlled symptoms who underwent deferred PCI (d-PCI), after a period of intensive ATT and antiplatelet therapy. ATT consisted of glycoprotein IIb/IIIa inhibitors, enoxaparin, aspirin, and clopidogrel for 48 hours after the diagnostic angiography but before PCI. Their angiographic and in-hospital outcomes were compared with those of a historical cohort of patients, with controlled symptoms, who had been treated ad hoc with PCI (immediate PCI) at our institution during the same period. The control patients were ≈ 1:2 frequency-matched for age, gender, and Thrombolysis In Myocardial Infarction thrombus grade.

Coronary angiograms were analyzed off-laboratory by experienced personnel before and after PCI. According to Yip et al,[7] LIT was diagnosed if ≥1 of the 6 following features were present: (1) cutoff pattern of occlusion in the infarct-related artery, (2) accumulated thrombus (>5 mm) proximal to the occlusion, (3) the presence of floating thrombus, (4) persistent dye stasis distal to the obstruction, (5) thrombus in the infarct-related artery >4 mm, and (6) incomplete obstruction with the presence of accumulated thrombus >3 times the infarct-related artery luminal diameter. Coronary flow was assessed using the Thrombolysis In Myocardial Infarction flow grade classification[8] (Thrombolysis In Myocardial Infarction grade 0 to 3). The Thrombolysis In Myocardial Infarction thrombus grade scale[9] was used to assess the change in thrombotic burden before and after the interventions: grade 0, no angiographic characteristics of thrombus; grade 1, possible thrombus, seen as reduced contrast density, haziness, irregular lesion contour, or a smooth convex "meniscus" at the site of total occlusion suggestive, but not diagnostic, of thrombus; grade 2, definite thrombus, with the greatest dimensions ≤$\frac{1}{2}$ the vessel diameter; grade 3, definite thrombus, with the greatest linear dimension >$\frac{1}{2}$ but <2 vessel diameters; grade 4, definite thrombus, with the largest dimension ≥2 vessel diameters; and grade 5, total occlusion. To assess the effect of ATT on thrombotic burden, the absolute thrombus volume was measured using dual quantitative coronary angiography before and after ATT in cases suitable for this analysis (Thrombolysis In Myocardial Infarction flow ≥1

Methods

Patients admitted with ACS, LIT, and controlled symptoms, who were hemodynamically stable and without an urgent need for revascularization, were included in the present study. ACS were defined according to current clinical practice guidelines.[6] Subacute ST-elevation myocardial infarction was defined as a history of typical chest pain lasting for >30 minutes, with ST-segment elevation >1 mm in 2 consecutive leads or new-onset complete left bundle branch block and arriving to the hospital >12 hours after the onset of symptoms. Unstable angina was defined as at rest, new-onset, progressive, or postinfarct chest pain, and non−ST-elevation myocardial infarction as the occurrence of troponin elevation with electrocardiographic changes or angina. The definition of controlled symptoms required the presence of all of the following at angiography: the absence of anginal symptoms or signs of acute heart failure, significant arrhythmias, complications of myocardial infarction, arrival to the hospital >12 hours after symptom onset, and
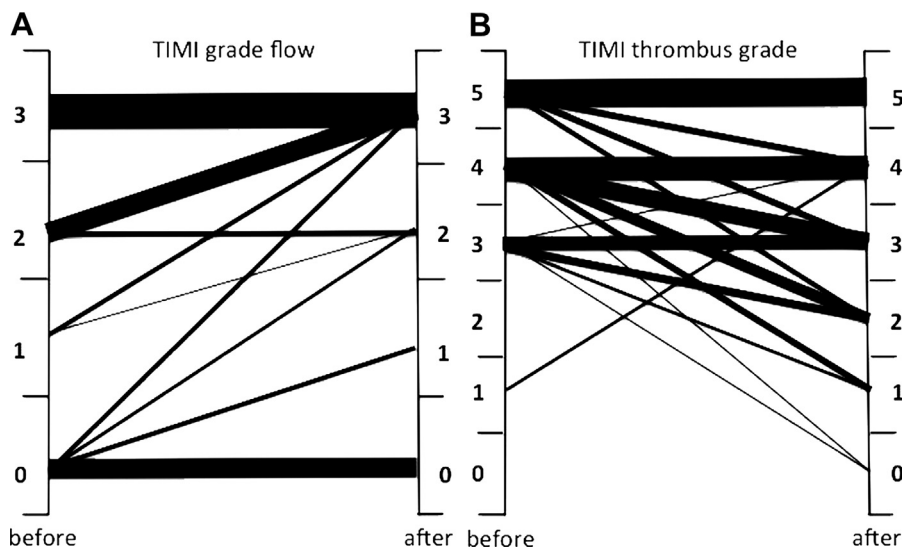
Figure 1. Influence of ATT on Thrombolysis In Myocardial Infarction (TIMI) flow grade *(A)* and TIMI thrombus grade *(B)* in patients with d-PCI. *(A)* Changes in TIMI grade flow after ATT. *(B)* Changes produced in TIMI thrombus grade. The diameter of the connector is proportional to the number of patients in each situation.
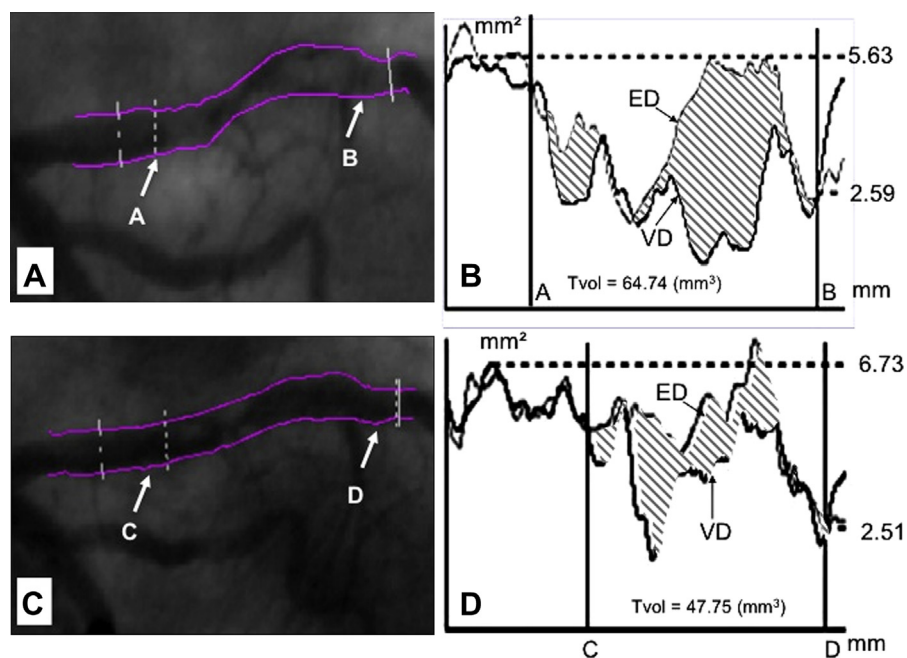

Figure 2. Dual quantitative coronary angiography analysis data from 1 patient, performed according to the technique validated by Aleong et al,[10] of a stenosis containing a large intracoronary thrombus in the proximal left anterior descending artery before and after ATT. Stenosis before *(A)* and after *(C)* treatment with luminal edges reconstructed and the thrombus borders demarcated using the CAAS-II system within *segment A−B*. Corresponding area plots before *(C)* and after *(D)* treatment, with the thrombus borders defined by the *solid outer lines* within *segment C−D*. The *shaded area* indicates the mismatch between edge detection (ED)- and video densitometry (VD)-derived luminal areas in both graphs caused by intracoronary thrombus. Tvol = thrombus volume.

and absence of significant vessel foreshortening or overlapping). A detailed description of the development and validation of dual quantitative coronary angiography for thrombus volume quantification has been previously published.[10] In brief, dual quantitative coronary angiography calculates the intracoronary thrombus volume by combining 2 quantitative coronary angiographic modalities: edge detection and video densitometry. The discrepancy between the luminal volumes calculated with both techniques

constitutes an estimate of thrombotic volume. The CAAS-II quantitative coronary angiography system (Pie Medical, Einthoven, The Netherlands) was used.

The angiographic complications recalled were defined as follow.[7] Distal embolization was defined as the presence of filling defects in or cut-off of a distal branch; slow flow as Thrombolysis In Myocardial Infarction flow grade 2 at the end of the procedure; and, finally, no reflow as Thrombolysis In Myocardial Infarction grade ≤ 1 flow in the distal
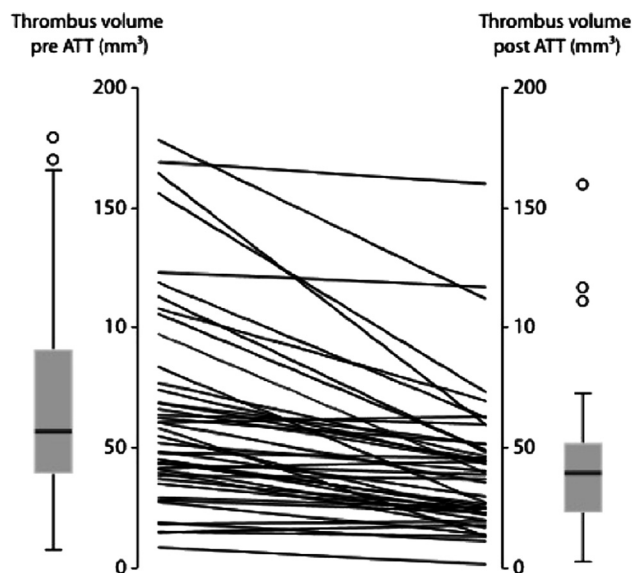
Figure 3. Modification of absolute thrombotic volume with ATT showing observed change in thrombotic volume, estimated using dual quantitative angiography in patients suitable for this analysis (n = 44). Data are shown as box plots, with individual pre- and post-ATT thrombus volumes linked by connectors. Data from 1 coronary artery with pre- and post-ATT thrombotic volume of 330 and 301 mm^3, respectively, were not plotted.

infarct-related artery in the absence of an occlusion at the treatment site or evidence of distal embolization. The clinical complications and in-hospital evolution were reviewed, including recurrent angina, hemodynamic instability, and urgent revascularization during the ATT period. Hemorrhagic complications were collected as defined by the Global Utilization of Streptokinase and Tissue-Plasminogen Activator for Occluded Coronary Arteries (GUSTO) investigators[11]: (1) severe or life-threatening, intracranial hemorrhage or bleeding that causes hemodynamic compromise and requires intervention, (2) moderate, bleeding requiring blood transfusion but not causing hemodynamic instability, and (3) mild, bleeding not meeting the criteria for severe or moderate bleeding.

All continuous variables are presented as the mean ± SD or median (interquartile range), according to their normal or not normal distribution. Categorical variables are presented as numbers or percentages. Before the statistical analysis, the normalcy and homogeneity of the variances were tested using the Kolmogorov-Smirnov and Levene tests. Continuous variables were compared using the *t* test or Mann-Whitney *U* test, as appropriate. Categorical variables were compared using Pearson's chi-square or Fisher's exact test, as appropriate. A paired *t* test or Wilcoxon test was used to compare the angiographic differences before and after ATT and PCI. A p value <0.05 was considered significant. The SPSS, version 20.0 (SPSS, Chicago, Illinois), statistical software package was used for all calculations.

Results

The baseline characteristics of the study population are listed in Table 1. Non−ST-elevation myocardial infarction was the dominant cause of admission. About 40% of

Table 3
Procedural data in patients with deferred-percutaneous coronary intervention (d-PCI) and controls

Procedural Characteristics	Total Population (n = 133)	d-PCI (n = 89)	i-PCI (n = 44)	p Value
PCI	112 (84)	68 (76)	44 (100)	<0.001
Thrombus aspiration	63 (47)	19 (21)	44 (100)	<0.001
Stent implantation	104 (78)	63 (71)	41 (93)	0.003
Direct stenting	64 (48)	39 (61)	25 (61)	0.997
Stents (n)	1 (1−1)	1 (0−1)	1 (1−1)	0.078
Total stent length (mm)	18 (15−25)	19 (15−28)	18 (15−24)	0.193
Angiographic complications	22 (17)	8 (9)	14 (32)	0.001
Distal embolization	10 (8)	3 (3)	7 (16)	0.010
No reflow	7 (5)	2 (2)	5 (11.4)	0.027
Slow flow	5 (3.8)	3 (3.4)	2 (4.5)	0.738

Data are presented as mean ± SD, median (25th−75th percentile), or n (%).

patients (n = 54) were in the subacute phase of ST-elevation myocardial infarction treated either with fibrinolysis (9%, n = 12) or had not received reperfusion therapy owing to a late (>12 hours) arrival to the hospital and controlled symptoms. Most patients had 1-vessel disease, with a preponderance of LIT in the right coronary artery. No significant differences with the controls were observed for diabetes, hypertension, dyslipidemia, and smoking or in the cause of admission, number of diseased vessels, thrombus location, or pre-PCI treatment with glycoprotein IIb/IIIa inhibitors. Patients in the d-PCI group were more likely to have a greater stenosis grade. Thrombotic vessel occlusion was found in 29 (33%) d-PCI and 21 (48%) immediate PCI patients (p = 0.090).

All d-PCI patients remained asymptomatic and without recurrent angina during the ATT period (60 ± 31 hours). Tirofiban was the most frequently used glycoprotein IIb/IIIa inhibitor (63%), followed by abciximab (33%). The angiographic data for the d-PCI group are listed in Table 2. After the ATT period, the Thrombolysis In Myocardial Infarction grade flow, TTG, and other indexes of thrombotic burden and coronary flow significantly improved (Figure 1 and Table 2). The number of vessels completely occluded by LIT decreased significantly with ATT. In the 44 patients suitable for this analysis, dual quantitative coronary angiography (Figure 2) demonstrated a significant reduction in the absolute thrombus volume of 37% (Figure 3).

Because of the angiographic improvement in lesion characteristics, PCI was performed less frequently in the d-PCI group than in the immediate PCI group (Table 3). Stenting was also more frequent in the immediate PCI group, although no significant differences were observed in the total number of stents used per patient or in the total stent length. Thrombus aspiration was performed in all immediate PCI but in only 19 d-PCI (21%) procedures. However, distal embolization and slow and/or no reflow occurred more frequently during immediate PCI. d-PCI was therefore protectively associated against these complications (odds ratio 0.18, 95% confidence interval 0.06 to 0.49; p <0.001). Finally, hemorrhagic complications were observed in 10 patients (7.5%), of which none were severe

or life-threatening. The use of intense ATT in the d-PCI group was not associated with an increase in mild and/or moderate hemorrhagic complications, which occurred in 3 (7%) immediate PCI and 7 (8%) d-PCI patients (p = 0.829).

Discussion

The main finding of the present study was that, in selected, stabilized patients with ACS and LIT and, compared with the immediate PCI group, d-PCI after intensive ATT appeared to be safe and to be associated with an objective reduction in thrombotic burden, a decreased number of angiographic complications, and a reduced need for revascularization. These benefits were observed without an increase in hemorrhagic complications.

LIT has been associated with an increased rate of angiographic complications during PCI, including impaired final Thrombolysis In Myocardial Infarction flow, no reflow, abrupt closure, distal embolization, side branch occlusion, microcirculatory obstruction, and subacute stent thrombosis.[2,12,13] Also, residual thrombus after PCI has been associated with greater rates of restenosis.[14,15] More importantly, it seems that these angiographic, LIT-related complications can translate into clinical events, because these patients are at a greater risk of in-hospital and 6-month myocardial infarction and death.[2] The reported pharmacologic and mechanical treatments aimed at reducing the effect of LIT during PCI have included unfractionated and low-molecular-weight heparin, glycoprotein IIb/IIIa inhibitors, thrombolytic drugs, ultrasound thrombolysis, manual thrombectomy, rheolytic thrombectomy, embolic protection devices, distal occlusive devices, covered stents, and heparin-coated stents, among others.[16,17] All have had variable rates of success.[5]

The strategy followed in our study was effective in reducing the thrombotic load. Because of the significantly greater number of nonoccluded vessels and an overall reduction in the thrombotic volume, PCI was simpler and, in some cases, deemed no longer required. Furthermore, that the incidence of distal embolism and no reflow was lower in patients undergoing d-PCI, despite the lower use of aspiration devices, raises the hypothesis that the more friable fractions of thrombus were lysed during ATT. Therefore, the benefit of ATT for the d-PCI group might have come not only from an absolute reduction in the thrombotic volume, but also because this could be produced at the expense of lyses of the most dangerous fraction of the heterogeneous thrombotic mass.

A characteristic worth noting of the included patients with ST-segment elevation myocardial infarction was that all were considered not eligible for primary PCI (mainly "latecomers"), who were hemodynamically stable and asymptomatic at rest when LIT was diagnosed. In this specific subgroup of patients, in whom primary PCI was not indicated, PCI for a hemodynamically significant stenosis in a patent infarct artery even >24 hours after ST-segment elevation myocardial infarction has been shown to improve the final left ventricular size[18] and clinical outcomes.[19] We also found that ATT reduced the number of total occlusions, which also contributed to simplify PCI.

To keep a positive risk/benefit ratio in this particular clinical scenario, a reduction in thrombotic burden is highly desired before PCI. Several trials have shown that medical therapy is useful in this regard by interrupting the activated thrombogenesis. Previous studies have reported improvement of stenosis severity in patients with ACS associated with medical treatment,[20] with a decrease in periprocedural coronary thrombosis and abrupt closure associated with prolonged heparin infusion before PCI in patients with LIT.[21] Moreover, the angiographic substudies from the Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS) and c7E3 Fab Antiplatelet Therapy in Unstable Refractory Angina (CAPTURE) trials[22,23] demonstrated a reduction in thrombus burden in patients treated with 18 to 48 hours of glycoprotein IIb/IIIa therapy, and this was also observed as early as 90 minutes after abciximab saturation in the Thrombolysis In Myocardial Infarction 14 trial.[9]

A major question in our research was whether the benefit of decreasing the thrombotic burden would be outweighed by an increase in hemorrhagic and/or ischemic events resulting from ATT and delaying revascularization. Because no urgent revascularization was needed in the d-PCI group and the rate of hemorrhagic complications was comparable to that observed in the control group, our observations provide supporting evidence of the safety of this therapeutic strategy, although our findings were hypothesis generating owing to the nonrandomized design of our study.

Two small previous studies by Burzotta et al[24] and Cafri et al,[25] which included 28 patients in total, have addressed the value of d-PCI after a course of up-to-date ATT in patients with ACS and LIT. In agreement with our study, they observed that d-PCI was associated with a lower rate of angiographic complications without an increase in adverse clinical events or hemorrhagic complications. To the best of our knowledge, our study is the largest experience assessing d-PCI in stable patients with ACS, controlled symptoms, and LIT.

Our study had several limitations. It was a retrospective, nonrandomized study; thus, bias could not be ruled out and could have affected the selection of the controls despite matching for age, gender, and TTG. The present study was conducted at a center with several operators. The patient and angiographic characteristics might have influenced the operator to perform d-PCI. Our conclusions were limited by the relatively small sample size. Finally, it was a single-center experience; thus, the external reproducibility of our findings could be challenged. Despite these limitations, and remembering the hypothesis-generating character of our study, we believe that the observations gathered can contribute to initiate a new avenue of research in the increasingly larger number of patients with ACS.

Disclosures

The authors have no conflicts of interest to disclose.

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