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Efficacy of Clotinab in Acute Myocardial Infarction Trial-ST Elevation Myocardial Infarction (ECLAT-STEMI)

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Background: This study investigated the efficacy and the safety of the upstream glycoprotein (Gp) IIb/IIIa inhibitor (clotinab; ISU ABXIS, Seoul, Republic of Korea) under 600-mg clopidogrel pretreatment compared with provisional use in ST-elevation myocardial infarction (STEMI).

Methods and Results: A total of 786 STEMI patients were randomized to upstream use in the emergency room (ER) (n=392) or provisional use during percutaneous coronary intervention (PCI) (n=394). All patients were prescribed 600-mg clopidogrel in the ER. The primary endpoint was the 30-day incidence of composite events including death, nonfatal myocardial infarction, target vessel revascularization, and stroke. There was no significant difference in the events that occurred in 40 patients (10.2%) in the upstream arm and 55 patients (14.0%) in the provisional arm during the 30 days (odds ratio 0.70, 95% confidence interval 0.45–1.08). Major bleeding was higher in the upstream arm (1.5% vs. 0%, P=0.02). However, there was a significant reduction in 30-day composite events in the upstream arm in the high-risk population (Killip class ≥II or GRACE score >140).

Conclusions: The upstream use of clotinab under a 600-mg clopidogrel loading may not significantly reduce cardiac events following primary PCI but may improve the clinical outcome in high-risk patients. (*Circ J* 2012; **76:** 405–413)

Key Words: Angioplasty; Clotinab; Myocardial infarction; Percutaneous coronary intervention

Glycoprotein IIb/IIIa inhibitors (GPI) are known to effectively reduce platelet aggregation, which improves microvascular function and clinical outcomes following PCI.[1,2] However, there is controversy over the beneficial effect of GPI.[3–5] The optimal time of administration of GPI could be a significant factor in the clinical and the angiographic benefits.[6,7] Previous studies showed that the early use of GPI before a procedure might be lead to favorable outcomes and better tissue perfusion.[5,6]

Clotinab (ISU ABXIS, Seoul, Republic of Korea) was produced by expressing the antiplatelet Gp IIb/IIIa DNA in Chinese hamster's ovary cells, essentially an identical active ingredient as abciximab. Recent studies demonstrated that clotinab has similar ex vivo antiplatelet effects, clinical outcomes, and safety profiles to abciximab in patients with acute coronary syndrome (ACS).[8,9]

Although a recent study using abciximab under 600-mg clopidogrel pretreatment showed no reduction in infarction size, more data may be needed to demonstrate the benefit of early use of GPI.[10] Therefore, this study investigated whether the upstream use of clotinab had additional benefits in ST elevation myocardial infarction (STEMI) patients undergoing primary PCI compared with "physician-guided provisional use", even after pretreatment with a 600-mg loading dose of clopidogrel.

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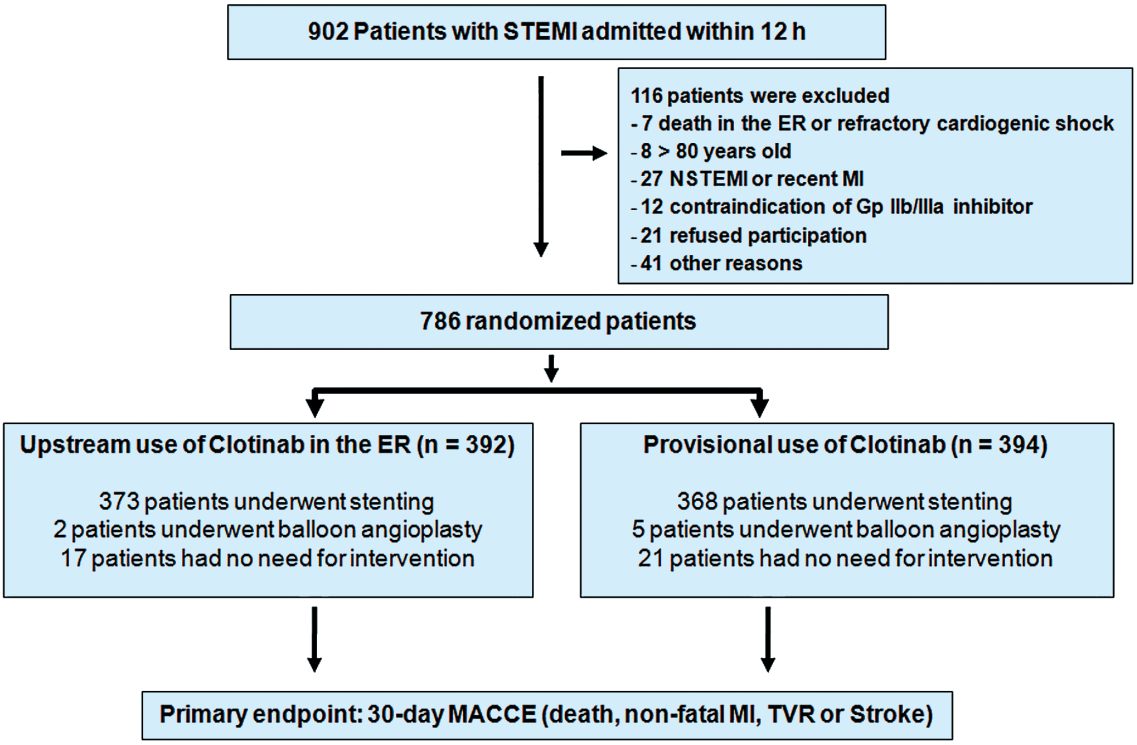

Figure 1. Study protocol of the ECLAT-STEMI Trial (ECLAT-STEMI, Efficacy of CLotinab in Acute myocardial infarction Trial-ST Elevation Myocardial Infarction).

Methods

Study Population

The ECLAT-STEMI (Efficacy of CLotinab in Acute myocardial infarction Trial–ST Elevation Myocardial Infarction) study is a multicenter, prospective, randomized, single-blind clinical trial performed at 31 Korean institutions (Figure 1). Inclusion criteria were the presence of symptoms <12 h, ST-segment elevation of at least 0.1 mV in 2 contiguous leads of the ECG or new-onset left bundle branch block, and age between 18 and 80 years. Exclusion criteria were cardiogenic shock; history of major surgery, trauma, or significant bleeding within recent 6 weeks; history of cerebrovascular attack within past 2 years, or with a significant residual neurological deficit; severe or malignant hypertension (systolic blood pressure (SBP) >180 mmHg or diastolic blood pressure (DBP) >105 mmHg); been administered oral anticoagulants within past 7 days; and known allergy to heparin, aspirin, clopidogrel, or abciximab. The study protocol was approved by the institutional review board of each participating institution, and written consent was given by all patients.

Between August 2007 and December 2008, 902 STEMI patients were screened in this study; 116 patients were excluded (7 died in the emergency room (ER) or from refractory cardiogenic shock, 27 with non-STEMI or STEMI ≥12 h after symptom onset, 8 were over 80 years old, 12 had a contraindication to GPI, 21 refused to participate, and 41 had other exclusion criteria). The eligible patients (n=786) were randomized to the upstream arm (n=392) or the provisional arm (n=394). They were assigned in a 1:1 ratio using a Web-based computer-generated randomization sequence with blocks at 31 centers.

Study Protocol and Procedure

The patients were pretreated in the ER before PCI with chewable aspirin (200 mg) and clopidogrel (600-mg loading). Those allocated to the upstream arm received intravenous clotinab in the ER with a bolus of 0.25 mg/kg followed by a continuous infusion of 0.125 μg/(kg×min) (up to a maximal dose of 10 μg/min) for 12 h. Those allocated to the provisional arm received intravenous or intracoronary clotinab during the procedure at the operator's discretion. Intravenous heparin (5,000 U) was injected in the ER, and activated clotting time (ACT) was checked before procedure in the catheterization lab. According to the ACT, patients received intravenous heparin to reach an ACT >200 s in the upstream arm and >300 s in the provisional arm. Procedural success was defined as a reduction of the stenosis to <30% residual narrowing and Thrombolysis In Myocardial Infarction (TIMI) grade 3 flow. After PCI, aspirin (100 mg/day) was continued indefinitely and clopidogrel (75 mg/day) was administered for at least 12 months; clinical follow-up at 1 and 12 months was performed by office visit or telephone with all study patients. In the follow-up assessment performed independently, treatment assignment was not disclosed.

Angiographic and Electrocardiographic Analysis

All interventions were performed with a standard technique. Pre- and post-PCI angiograms were reviewed in an angiographic core laboratory (Yonsei University Health System, Seoul, Republic of Korea). The angiographic parameters were

Table 1. Baseline Clinical Characteristics

	Upstream group (n=392)	Provisional group (n=394)	P value
Age (years)	57.9±11.4	58.8±11.7	0.33
Male	310 (79.1%)	317 (80.5%)	0.63
BMI (kg/m^2)	24.2±2.7	24.2±3.0	0.83
Diabetes mellitus	75 (19.1%)	80 (20.3%)	0.68
Hypertension	194 (49.5%)	217 (55.1%)	0.12
Hypercholesterolemia	201 (51.3%)	204 (51.8%)	0.89
Current smoker	198 (50.5%)	210 (53.3%)	0.43
Family history of CAD	29 (7.7%)	27 (7.3%)	0.81
Previous MI	8 (2.0%)	13 (3.3%)	0.27
Previous PCI	19 (4.8%)	19 (4.8%)	0.99
Previous CVA	14 (3.6%)	15 (3.7%)	0.86
Pain-to-balloon time (min)*	209 (136–324)	218 (140–343)	0.68
Door-to-balloon time (min)*	73.0 (59.0–97.0)	68.0 (55.0–92.0)	0.07
Clopidogrel loading-to-balloon time (min)	65.5 (50.0–88.0)	60.0 (47.0–84.0)	0.07
Randomization-to-balloon time (min)†	58.5 (44.0–82.0)	53.0 (40.0–77.0)	0.07
Peak CK-MB (U/L)	208±148	213±163	0.67
LVEF (%)†	51.3±11.2	50.9±11.5	0.62

Values are presented as n (%) or mean±SD.
BMI, body mass index; CAD, coronary artery disease; MI, myocardial infarction; PCI, percutaneous coronary intervention; CVA, cerebrovascular accident; CK-MB, creatine kinase-myocardial band isoenzyme; LVEF, left ventricular ejection fraction.
*These parameters were evaluated in 746 patients who underwent PCI from among 786 patients.
†LVEF was evaluated during admission after primary PCI.

analyzed using TIMI flow grade before and after PCI, corrected TIMI frame count (cTFC), and myocardial blush grade (MBG) by 2 experienced observers, as in previous reports.[11–13]

Cardiac Enzyme Assay

Blood samples were collected before and 4 times every 6 h, 3 times every 8 h, and 2 times every 12 h after PCI to measure creatine kinase–myocardial band isoenzyme (CK-MB) levels for the detection of periprocedural enzyme re-elevation; further measurements were performed in cases of postprocedural symptoms suggestive of myocardial ischemia. Normal limits of CK-MB and troponin T or I were defined according to each center.

Endpoints

The primary endpoint was the occurrence of major adverse cardiac and cerebrovascular events (MACCE) (death, reinfarction, target vessel revascularization, or stroke) during the first 30 days. Reinfarction was defined by protocol as: (1) occurring within 24 h of index PCI with re-elevation of CK-MB by at least 33% or 100% from the preceding nadir (which was ≥2 or <2 times normal, respectively) and reaching at least >3 times normal value in association with ischemic symptoms, and (2) after 24 h, MI was defined as new pathological Q waves or re-elevation of CK-MB to >3 times normal (24 h to discharge) or >2 times normal (after hospital discharge).[14] Spontaneous MI was also evaluated according to the universal definition.[15] Target vessel revascularization included bypass surgery or repeat PCI of the target vessels. The diagnosis of stroke was confirmed by an imaging study, such as magnetic resonance imaging or computer tomography, and neurologic symptoms. Secondary endpoints after PCI were as follows: (1) final TIMI flow, (2) cTFC, and (3) MBG. Bleeding complication was classified according to the TIMI criteria, which categorizes it as major or minor bleeding.[16] Proposed standard definitions of stent thrombosis by the Academic Research Consortium (ARC) were used.[17] MACCE were evaluated according to risk with Killip class and Global Registry of Acute Coronary Syndrome (GRACE) risk score.[18] All events were adjudicated and classified by an Event Adjudication Committee blinded to the randomization group.

Sample Size Calculation and Statistical Analysis

Calculation of the sample size was based on a 2-sample and 2-sided test. Based on previous studies, the MACCE rate was assumed to be 11.5% in the provisional arm, considering the beneficial effect of the provisional clotinab and the 600-mg clopidogrel loading on the MACCE rate in the ADMIRAL study (14.6%).[4] The MACCE rate of the early clotinab arm was assumed to be 5.5%, considering approximately 10.0% reduction of events when compared with the ADMIRAL study (6.0%). Therefore, the difference in event-free survival for MACCE at 30 days was 6.0%, which was based on a previous study and taking into consideration the 600-mg clopidogrel loading before primary PCI setting (94.5% for the upstream arm vs. 88.5% for the provisional arm). Using a 2-sided alpha level of 0.05 and statistical power of 90%, 338 patients in the upstream arm and 338 patients in the provisional arm were studied. Based on a 15% follow-up loss, a total of 780 patients were analyzed.

All analyses were performed on the basis of intention-to-treat analysis considering all data, including those of this trial, as randomized. Treatment crossover did not take place in 30 days. Values are expressed as mean±SD or median (25^{th} to 75^{th} percentiles). Comparisons of categorical variables were made using χ^2 test and Fisher's exact test when the expected frequency was less than 5. Student's t-test was used to compare continuous variables for normally distributed values, otherwise the Mann-Whitney U test was used. In addition, post hoc analysis was performed according to Killip class or GRACE score as a measure of risk level. Heterogeneity of

Table 2. Angiographic and Periprocedural Characteristics

	Upstream group (n=392)	Provisional group (n=394)	P value
Target vessel (n, %)			0.63
Left main	3 (0.8%)	4 (1.0%)	
LAD	212 (54.1%)	209 (53.0%)	
LCX	48 (12.2%)	39 (10.0%)	
RCA	129 (32.9%)	142 (36.0%)	
Severity of CAD (n, %)			
Left main disease	13 (3.4%)	14 (3.7%)	0.86
No significant disease	13 (3.3%)	11 (2.8%)	0.44
1-VD	200 (51.0%)	180 (45.7%)	
2-VD	103 (26.3%)	117 (29.7%)	
3-VD	76 (19.4%)	86 (21.8%)	
Type B2 or C (n, %)	256 (65.3%)	271 (68.8%)	0.30
Bifurcation (n, %)	36 (9.2%)	31 (7.9%)	0.51
Initial TIMI grade (n, %)			
0	192 (49.0%)	225 (57.1%)	0.02
1	54 (13.8%)	39 (9.9%)	0.09
2	64 (16.3%)	49 (12.4%)	0.12
3	82 (20.9%)	80 (20.3%)	0.83
Type of PCI (n=746)			0.25
POBA	2 (0.5%)	3 (0.8%)	
Stent	373 (99.5%)	368 (99.2%)	
Type of stent			0.46
DES	370 (99.2%)	363 (98.6%)	
BMS	3 (0.8%)	5 (1.4%)	
Stent diameter (mm)	3.3±0.4	3.3±0.4	0.98
Stent length (mm)	25.3±6.9	24.6±6.5	0.17
Maximal pressure (mmHg)	13.1±3.1	13.3±3.4	0.29
Thrombectomy	92 (23.5%)	87 (22.1%)	0.64
Glycoprotein IIb/IIIa inhibitor	392 (100.0%)	160 (40.6%)	<0.001
IABP use	14 (3.6%)	20 (5.1%)	0.30
IVUS use	75 (19.1%)	67 (17.0%)	0.44

Values are presented as n (%) or mean±SD.
LAD, left anterior descending artery; LCX, Left circumflex artery; RCA, right coronary artery; TIMI, Thrombolysis In Myocardial Infarction; POBA, plain-old balloon angioplasty; DES, drug-eluting stent; BMS, bare metal stent; IABP, intra-arterial balloon pump; IVUS, intravascular ultrasound. Other abbreviations see in Table 1.

treatment differences across risk groups was checked by assessing the interaction between the assigned treatment and the risk group according to various subsets, including Killip class or GRACE score with respect to the endpoint of interest. Results are expressed as mean±SD unless otherwise specified. All analyses were verified using the Statistical Analysis System software (SAS; 9.1.3., SAS Institute, Cary, NC, USA). A P value <0.05 was considered statistically significant.

Results

Baseline Characteristics

Baseline clinical characteristics in the upstream and the provisional arms are shown in Table 1. The left ventricular ejection fraction during admission after PCI was comparable between the 2 arms (51.3 vs. 50.9%, P=0.62). The pain-to-balloon time was not different (median: 209 vs. 218 min, P=0.68), but the door-to-balloon time tended to be longer in the upstream arm (median 73.0 vs. 68.0 min, P=0.07). Median clotinab administration-to-balloon time in the upstream arm was 49.5 (34.0–72.3) min.

Angiographic and Periprocedural Findings (Table 2)

TIMI grade 0 before PCI was observed in 417 patients (53.1%) and was significantly lower in the upstream arm [192 (49.0%) vs. 225 (57.1%), P=0.02]. Intracoronary thrombi were seen in 256 (65.3%) and 267 patients (67.8%) in the upstream and provisional arms, respectively. Clotinab was used during PCI in 160 patients (40.6%) of the provisional arm. Aspiration thrombectomy and intra-arterial balloon pump were used in 179 (22.8%) and 34 patients (4.3%).

Primary Endpoint (Table 3)

MACCE at 30 days occurred in 40 (10.2%) and 55 patients (14.0%) in the upstream and provisional arms (P=0.14), respectively, which was not significantly different overall or for each cardiac event. Re-elevation of the cardiac enzymes in the periprocedural period occurred in 70 patients [upstream arm vs. provisional arm: 30 (7.7%) vs. 40 (10.2%), P=0.22]. In addition, the composite events at 30 days, including death or MI, did not differ significantly between the 2 arms [40 (10.2%) vs. 50 (12.7%), P=0.27].

The incidence of in-hospital MACCE tended to be lower in

Table 3. Incidence of Major Adverse Cardiac Events

	Upstream group (n=392)	Provisional group (n=394)	OR (95%CI)	P value
In-hospital				
Death				
Any cause	5 (1.3%)	9 (2.3%)	0.55 (0.18–1.67)	0.27
Cardiovascular	4 (1.0%)	8 (2.0%)	0.50 (0.15–0.17)	0.25
Reinfarction	31 (7.9%)	40 (10.2%)	0.76 (0.47–1.24)	0.27
TVR	2 (0.5%)	5 (1.3%)	0.40 (0.08–2.07)	0.26
Stroke	0 (0%)	2 (0.5%)	–	0.50
MACCE	36 (9.2%)	52 (13.2%)	0.65 (0.42–1.02)	0.07
30 days				
Death				
Any cause	7 (1.8%)	10 (2.5%)	0.70 (0.26–1.85)	0.47
Cardiovascular	6 (1.5%)	8 (2.0%)	0.75 (0.26–2.18)	0.60
Reinfarction	33 (8.4%)	41 (10.4%)	0.79 (0.49–1.28)	0.34
TVR	4 (1.0%)	5 (1.3%)	0.80 (0.21–3.01)	0.74
Stroke	0 (0%)	3 (0.8%)	–	0.25
MACCE	40 (10.2%)	55 (14.0%)	0.70 (0.45–1.08)	0.14
ARC definite or probable stent thrombosis at 12 months	11 (2.9%)	12 (3.2%)	0.85 (0.37–1.91)	0.81

Values are presented as n (%) or mean ± SD.
OR, odds ratio; CI, confidence interval; TVR, target vessel revascularization; MACCE, major adverse cardiac and cerebrovascular event; ARC, Academic Research Consortium.

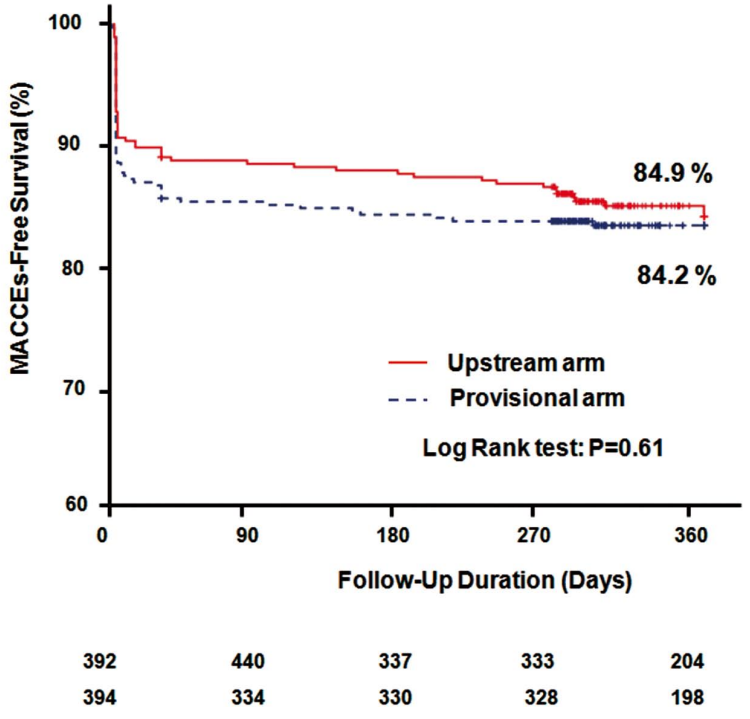

Figure 2. Kaplan Meier 12-month MACCE-free survival after primary PCI. MACCE-free survival at 12 months was not significantly different between the 2 groups. MACCE, major adverse cardiac and cerebrovascular events; PCI, percutaneous coronary intervention.

Table 4. Immediate Postprocedural Outcomes and Bleeding Events

	Upstream group (n=375)	Provisional group (n=371)	P value
Final TIMI flow grade	2.92±0.34	2.91±0.34	0.34
TIMI grade III	352 (93.9%)	344 (92.7%)	0.53
No reflow	23 (6.1%)	34 (9.2%)	0.12
Corrected TIMI frame count*	32.7±19.7	32.8±20.0	0.99
Blush grade*	2.09±1.09	1.97±1.12	0.13
Blush grade 3*	167 (48.4%)	150 (43.0%)	0.15
Bleeding events	(n=392)	(n=394)	
TIMI major bleeding	6 (1.5%)	0 (0%)	0.02
TIMI minor bleeding	18 (4.6%)	9 (2.3%)	0.08
Thrombocytopenia			
<50,000 cells/mm^3	5 (1.3%)	1 (0.3%)	0.12
<20,000 cells/mm^3	1 (0.3%)	0 (0%)	0.50

Values are presented as n (%) or mean±SD.
Abbreviations see in Tables 1,2.
*TIMI frame count and blush grade were evaluated in 696 of 746 patients who underwent PCI.

the upstream arm compared with the provisional arm (36 (9.2%) vs. 52 (13.2%), P=0.07, Table 3), but the occurrence of MACCE during 12 months was quite similar between the 2 groups (Figure 2).

In addition, the prevalence of definite or probable stent thrombosis was not different between the 2 arms. The incidence of spontaneous MI using the universal definition was also not different between the 2 groups [upstream arm vs. provisional arm: 1 (0.3%) vs. 0 (0%), P=0.50, in-hospital; 3 (0.8%) vs. 1 (0.3%), P=0.37, at 30 days; and 8 (2.0%) vs. 5 (1.3%) at 12 months, P=0.40].

Secondary Endpoints (Table 4)

TIMI 3 flow was obtained for 696 patients (93.3%), which was also not significantly different between groups. MBG showed a higher trend in the upstream arm, but cTFC was not significantly different between groups. Peak CK-MB level was also not significantly different (208±148 vs. 213±167, P=0.67) between groups. However, the incidence of both TIMI major bleeding [6 (1.5%) vs. 0 (0%), P=0.02) and minor bleeding (18 (4.6%) vs. 9 (2.3%), P=0.08] was higher in the upstream arm. Severe thrombocytopenia (<50,000 cell/mm^3) was observed in 6 patients [5 (1.3%) vs. 1 (0.3%), P=0.12], and profound thrombocytopenia (<20,000 cell/mm^3) was experienced by only 1 patient treated with clotinab in the upstream arm.

Clinical Outcome According to Subgroup Including Killip Class and GRACE Score (Figure 3)

The 30-day MACCE was analyzed in different subgroups according to age, sex, diabetes, infarct location, multivessel disease, interval from pain onset to admission, interval clopidogrel to balloon, Killip class and GRACE score. The upstream use of clotinab had a beneficial effect on the reduction of 30-day MACCE in patients ≤60 years old. Interestingly, the upstream use of clotinab had also a favorable effect on the reduction of 30-day MACCE among the high-risk population (Killip class ≥II and GRACE score >140) (16/141 (11.3%) vs. 26/117 (22.2%), P=0.02 and 19/152 (12.5%) vs. 31/141 (22.0%), P=0.03). Additionally, the rate of in-hospital and 30-day net adverse clinical outcomes (MACCE+major bleeding) was significantly lower in the upstream arm of the high-risk population (14/141 (9.9%) vs. 24/117 (20.9%), P=0.01 and 16/141 (11.3%) vs. 25/115 (21.7%), P=0.02 in Killip class ≥II and 16/152 (10.5%) vs. 30/141 (21.3%), P=0.01 and 19/152 (12.7%) vs. 31/137 (22.0%), P=0.03 in GRACE risk score >140), although there were not any differences of clinical outcomes in the overall population and low-risk groups.

Discussion

The ECLAT-STEMI study is a prospective randomized trial to compare the clinical benefits and the incidence of bleeding between upstream use and physician-guided provisional use as a real clinical practice pattern of clotinab under 600-mg clopidogrel pretreatment. The upstream use of clotinab might not be significantly associated with a reduction in the incidence of MACCE at 30 days. Significant bleeding, including TIMI major, was more commonly observed in the upstream arm. However, the in-hospital MACCE tended to be lower in the upstream arm and the upstream use of clotinab might show a favorable effect on clinical outcome in high-risk patients.

Early pharmacologic reperfusion has been of main interest for reducing the ischemic time and compensating the delayed action of clopidogrel in primary PCI of STEMI.[19,20] Previous study has shown the beneficial effects of obtaining TIMI III flow before primary PCI in STEMI.[21] However, the clinical benefits of upstream use of GPIs is controversial based on large clinical trials and meta-analysis.[7,22,23] Timing of GPI infusion could be an important factor in the different results. The FINESSE trial (Facilitated Intervention with Enhanced Reperfusion Speed to Stop Events) failed to demonstrate any benefits on clinical outcome with upstream use of GPIs.[22] Another large randomized trial in patients with STEMI did not show any benefit of abciximab before PCI under 600-mg clopidogrel loading.[10] However, the On-Time 2 trial (Ongoing Tirofiban in Myocardial Evaluation) showed that prehospital initiation of tirofiban improved ST-segment resolution and clinical outcome after primary PCI.[7] In the first 2 trials, abciximab was started >200 min after the onset of symptoms, but in the On-Time 2 trial, the median time between symptom onset and tirofiban was 76 min.[7] In addition, subgroup analysis in that trial showed that the largest effectwas in patients who received tirofiban shortly after symptom onset.[7] The median time from onset of pain to clotinab administration of this study was over 120 min, which could be a reason for the lack of

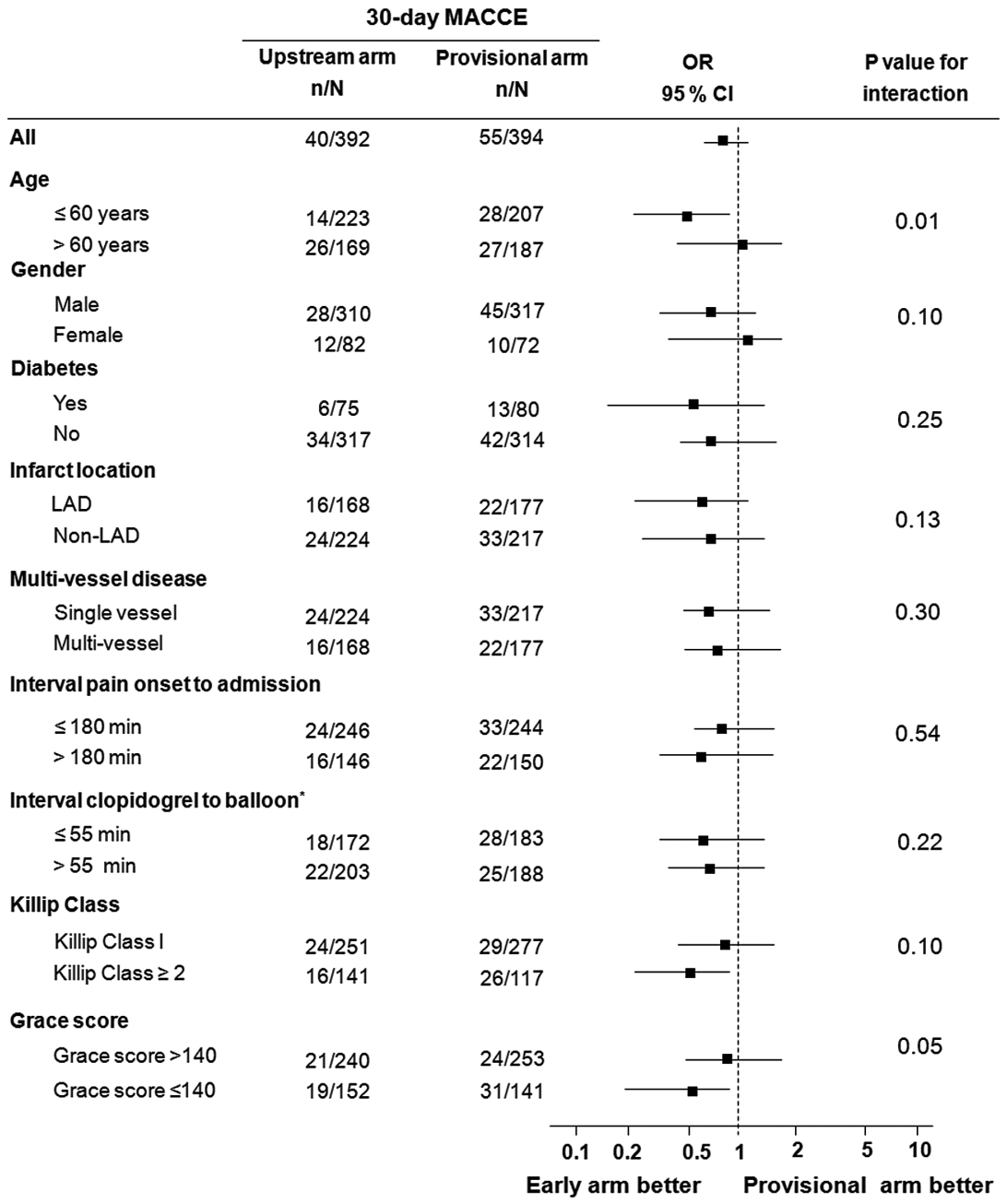

Figure 3. The 30-day clinical outcomes in various subgroups. Upstream use of clotinab shows a favorable effect on reducing the 30-day clinical events in patients aged ≤60 years, Killip class ≥II and GRACE score >140. *These parameters were evaluated in 746 patients who underwent percutaneous coronary intervention from among 786 patients. CI, confidence interval; MACCE, major adverse cardiac and cerebrovascular events; OR, odds ratio.

clinical benefit. Another issue is the delayed action of clopidogrel, which takes more than 2 h to achieve sufficient inhibition of platelet aggregation even with a 600-mg loading dose before PCI.[20] Hence, early GPI administration theoretically could be useful for suppressing platelet activity during primary PCI because door-to-balloon time is usually within 90 min. The present trial also evaluated the efficacy of upstream GPI administration to overcome the delayed action of clopidogrel, and this was compared with active control (provisional use of clotinab), which could well reflect the real clinical situation. Overall, upstream clotinab was not associated with a reduction in the incidence of adverse cardiovascular events but rather, increased bleeding complications compared with the provisional use of clotinab during PCI. This finding suggests that upstream clotinab may not improve clinical outcomes in unselected patients if bleeding complication is considered. However, this strategy showed beneficial effects for improving clinical outcome in the high-risk population (Killip

class ≥II or GRACE risk score >140). The upstream use of clotinab could be considered an option for the high-risk group in STEMI to decrease clinical events, and previous studies also report favorable results for the upstream use of abciximab.[24,25] The further analysis in the FINESSE trial suggested that a combination (abciximab plus half-dose reteplase) before PCI might have a substantial benefit in high-risk patients with a large infarct area and TIMI score ≥3 in STEMI.[22,26,27] Furthermore, a recent study and meta-analysis reported a significant relationship between the patient's risk profile and clinical outcome, and suggested the use of conjunctive pharmacologic treatment, including GPIs, to improve the outcomes in those high-risk patients.[28] The favorable effect of the GPI might be related to rapid inhibition of platelets in patients with high risk, whose thrombotic complications significantly outweighs the risk of bleeding complications. In the present study, the initial TIMI grade 0 was significantly lower in the upstream arm, which could also explain the reduction in in-hospital clinical events in the high-risk patients, because early reperfusion could be critical especially in the high-risk group in STEMI.

The beneficial role of microvascular perfusion was investigated using TIMI grade, cCTF, and MBG in the upstream use. Some parameters showed a favorable trend with upstream use, but no significant improvement in myocardial perfusion was observed in this study.

Study Limitations

One of the limitations in this study is that the sample size might not be sufficient to evaluate the effects of upstream clotinab on clinical events, because the overall cohort was at low or intermediate risk, with the overall 30-day, all-cause mortality at 2.2%. Therefore, beneficial effects of the upstream use of clotinab might be underestimated because of insufficient sample size, and a large randomized trial with sufficient sample size or involving high-risk patients is needed to confirm the findings. Second, serial cardiac enzyme measurements were not available in all patients. Therefore, reinfarction defined as a re-elevation of cardiac enzymes may not have been detected in some patients. Third, this was not a double-blind study. Fourth, cTFC and MBG could be evaluated in 696 patients (93.9%) only, because of poor image quality. Fifth, the upstream use of clotinab had a favorable effect in high-risk patients, but this finding needs to be confirmed with a large population study with sufficient power because this finding was derived from a subanalysis.

Conclusions

Although the upstream use of clotinab in the ER before primary PCI failed to decrease clinical events compared with its provisional use at the time of PCI in the ECLAT-STEMI study, a beneficial effect cannot be excluded based on the sample size. In addition, the reduction of MACCE associated with provisional use was significant in high-risk subgroups such as patients with Killip class >II or GRACE score >140.

A larger clinical trial, adequately powered for key clinical endpoints, is needed to determine the role in clinical practice of upstream use of clotinab on a background of 600-mg clopidogrel pretreatment.

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Disclosures

None of the authors have any conflicts of interest to declare.

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