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Timing of Angiography and Outcomes in High-Risk Patients With Non–ST-Segment–Elevation Myocardial Infarction Managed Invasively: Insights From the TAO Trial (Treatment of Acute Coronary Syndrome With Otamixaban)

Deharo, Pierre MD; Ducrocq, Gregory MD, PhD; Bode, Christoph MD; Cohen, Marc MD; Cuisset, Thomas MD, PhD; Mehta, Shamir R. MD; Pollack, Charles Jr MA, MD; Wiviott, Stephen D. MD; Elbez, Yedid MS; Sabatine, Marc S. MD, MPH; Steg, Philippe Gabriel MD

Informations sur l'auteur

Hopital La Timone, Marseille, France (P.D., T.C.).

Bristol Heart Institute, United Kingdom (P.D.).

Hôpital Bichat, Assistance Publique–Hôpitaux de Paris, France (G.D., Y.E., P.G.S.).

Département Hospitalo–Universitaire FIRE, INSERM U-1148, Paris, France (G.D., Y.E., P.G.S.).

FACT (French Alliance for Cardiovascular Clinical Trials), an F-CRIN network, INSERM U-1148, Paris, France (G.D., Y.E., P.G.S.).

Heart Center Freiburg University, Cardiology and Angiology I, Faculty of Medicine, Germany (C.B.).

Newark Beth Israel Medical Center, Rutgers–New Jersey Medical School, Newark (M.C.).

McMaster University and Population Health Research Institute, Hamilton Health Sciences, Ontario, Canada (S.R.M.).

Department of Emergency Medicine, Thomas Jefferson University, Philadelphia, PA (C.P.).

TIMI Study Group, Division of Cardiovascular Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA (S.D.W., M.S.S.).

Université Paris Diderot, Sorbonne-Paris Cité, France (P.G.S.).

NHLI, Royal Brompton Hospital, Imperial College, London, United Kingdom (P.G.S.).

The online-only Data Supplement is available with this article at

Abstract

Background: In patients with non–ST-segment–elevation myocardial infarction (NSTEMI) and GRACE (Global Registry of Acute Coronary Events) score >140, coronary angiography (CAG) is recommended by European and American guidelines within 24 hours. We sought to study the association of very early (ie, ≤12 hours), early (12–24 hours), and delayed (>24 hours) CAG in patients with NSTEMI with GRACE score >140 with ischemic outcomes.

Methods: The TAO trial (Treatment of Acute Coronary Syndrome With Otamixaban) randomized patients with NSTEMI and CAG scheduled within 72 hours to heparin plus eptifibatide versus otamixaban. In this post hoc analysis, patients with a GRACE score >140 were categorized into 3 groups according to timing of CAG from admission (<12, ≥12–<24, and ≥24 hours). The primary ischemic outcome was the composite of all-cause death and myocardial infarction within 180 days of randomization.

Results: CAG was performed in 4071 patients (<12 hours, n=1648 [40.5%]; 12–24 hours, n=1420 [34.9%]; ≥24 hours, n=1003 [24.6%]). With CAG ≥24 hours as a reference, CAG from 12 to 24 hours was not associated with a lower risk of primary ischemic outcome at 180 days (odds ratio, 0.96; 95% confidence interval, 0.75–1.23), whereas CAG <12 hours was associated with a lower risk of death and myocardial infarction (odds ratio, 0.71; 95% confidence interval, 0.55–0.91). Performing CAG <12 hours was also associated with a lower risk of death and myocardial infarction (odds ratio, 0.76; 95% confidence interval,

0.61–0.94; $P=0.01$) compared with CAG performed at 12 to 24 hours. No difference was observed in bleeding complications.

Conclusions: In patients with high-risk NSTEMI, undergoing CAG within the initial 12 hours after admission (as opposed to later, either 12–24 or ≥ 24 hours) was associated with lower risk of ischemic outcomes at 180 days.

Clinical Perspective

What Is New?

- In high-risk patients with non-ST-segment-elevation myocardial infarction (defined by a GRACE [Global Registry of Acute Coronary Events] score >140), a very early invasive strategy (ie, coronary angiography within the first 12 hours) was associated with a lower risk of ischemic outcomes (death and myocardial infarction) at 180 days compared with an early (12–24 hours) or a delayed (24–72 hours) strategy.
- Bleeding risk was not different among patients managed with very early, early, or delayed strategy.

What Are the Clinical Implications?

- In high-risk patients with non-ST-segment-elevation myocardial infarction, coronary angiography within 12 hours of admission may lead to improved outcomes, early optimization of antithrombotic treatments, and shorter hospitalization stays.
- These observations deserve prospective confirmation in a randomized trial.

Coronary angiography (CAG) plays a central role in the management of patients presenting with non-ST-segment-elevation myocardial infarction (NSTEMI), allowing confirmation of diagnosis and risk stratification and affecting the choice of revascularization strategy and antithrombotic therapy. However, the optimal timing of CAG in these patients is still a matter of debate. CAG followed if indicated by coronary revascularization is recommended for most patients within the first 72 hours of hospital admission.^{1,2} This strategy has led to a reduction of mortality, recurrent ischemic complications, and length of stay compared with a strategy of selective angiography.^{3,4} It has also been shown that an early invasive strategy (ie, within the first 24 hours) was associated with a further reduction in ischemic events (death, myocardial infarction [MI], and refractory angina) in high-risk patients (defined by GRACE [Global Registry of Acute Coronary Events] score >140) but not in low-risk patients (GRACE score ≤ 140) and is recommended in both American and European guidelines.^{1,2,5} In those patients with high-risk NSTEMI, the interest in further reducing the delay to an invasive strategy is uncertain. A series of small randomized trials have explored a strategy of “immediate” percutaneous coronary intervention (PCI) on hospital admission for patients with moderate- to high-risk NSTEMI and have yielded conflicting results.^{6–9} Instead of immediate PCI, which has challenging logistical implications (extending the burden of urgent angioplasty to patients who may not need it), it may be interesting to examine whether performing angiography with a view to intervention within a slightly wider time window (ie, the first 12 hours after admission, which allows the scheduling of most patients during the daytime, regardless of their time of admission) would be associated with improved outcomes.

Using the large contemporary cohort of patients with NSTEMI extracted from the TAO randomized trial (Treatment of Acute Coronary Syndrome With Otamixaban), we assessed in this post hoc analysis the association between a very early invasive strategy (ie, within 12

hours after admission) and clinical outcomes in patients with high-risk NSTEMI (defined by a GRACE risk score >140).

Methods

Study Population

The methods and results of the TAO trial have been previously described.^{10,11} Briefly, TAO was a large international trial randomizing patients with moderate- to high-risk NSTEMI with CAG planned in the first 72 hours to heparin plus eptifibatid versus otamixaban. Patients were randomized to the unfractionated heparin plus eptifibatid group or to 1 of 2 otamixaban dosing groups (intravenous bolus of 0.080 mg/kg followed by an infusion of either 0.100 or 0.140 mg/kg per hour) in a 1:1:1 ratio. A planned interim analysis performed after 1969 randomized patients in each group led the investigators to define the higher-dose otamixaban as optimal, to discontinue enrollment in the lower dose, and to continue enrollment in the higher dose until study end in a 1:1 ratio compared with heparin.

Patients with NSTEMI scheduled to undergo an invasive strategy (angiography and PCI, if indicated, to be performed at the latest within 72 hours) were eligible for the study.

The main exclusion criteria were a revascularization procedure already performed for the qualifying event, acute ST-segment elevation MI, receipt of a therapeutic dose of injectable anticoagulant for >24 hours before randomization, or treatment with abciximab. The main results of the trial have been previously published: Otamixaban did not reduce the rate of the primary outcomes of death plus MI but did increase bleeding compared with heparin plus eptifibatid.¹¹ From the TAO population, we selected patients with high-risk NSTEMI (ie, GRACE score >140) who make up the study cohort examined in the present analysis.

Timing of Angiography

For the purpose of the present analysis, patients with a GRACE score >140 and undergoing CAG were stratified into 3 groups according to the timing of CAG from the first ECG performed on admission: very early (ie, <12 hours), early (ie, ≥12–<24 hours), or delayed (ie, ≥24 hours) CAG.

Definitions and Outcomes

For the present analysis, the longest follow-up available was considered for the primary ischemic and bleeding outcomes.

Efficacy Outcomes

Clinical follow-up was performed at 7, 30, and 180 days. The primary ischemic outcome of the present analysis was the composite of all-cause death or new MI from randomization to day 180.

Secondary efficacy outcome measures included the same composite ischemic end point at days 7 and 30. All-cause death, cardiovascular death, nonfatal MI, rehospitalization, and prolongation of the hospitalization as a result of MI and stent thrombosis were analyzed separately at days 30 and 180. Stent thromboses were categorized according to the Academic Research Consortium classification,¹² and MIs were categorized according to the 2007 universal definition.¹³

Safety Outcomes

The primary safety outcome was TIMI (Thrombosis in Myocardial Infarction) significant bleeding (defined as the composite of TIMI major and minor bleeding) from randomization to day 30. Other safety outcome measures included coronary artery bypass graft (CABG)–related and non–CABG-related bleeding according to the TIMI classification, TIMI clinical bleeding, any clinical overt bleeding, TIMI bleeding requiring medical attention, and TIMI minimal bleeding at day 30. Bleeding (other than fatal) was not captured beyond day 30.

Key efficacy and safety outcomes, including all procedural complications, were adjudicated by a central clinical event committee (TIMI Study Group) unaware of study treatment assignments and, in the case of procedural complications, with review of the angiograms.

Ethics

All patients provided written informed consent. In each country, the study was approved by ethics committees in accordance with local guidelines.

Statistical Analysis

Patients were categorized into 3 groups according to the time to angiography from admission (defined by the time of the first ECG): <12, 12 to 24, and \geq 24 hours. Descriptive statistics are reported as means \pm SDs for continuous variables and patient numbers with percentages for categorical variables.

Categorical variables across groups were compared by $[\text{chi}]^2$ tests; continuous variables were compared by ANOVA.

Comparisons of event rates across groups were performed by $[\text{chi}]^2$ tests. Primary end points based on time to the inclusion were assessed by comparison of Kaplan-Meier–based cumulative incidence rates with the log-rank test. Multivariable logistic models for death and nonfatal MI were adjusted on the following predefined variables: age, sex, diabetes mellitus, previous PCI, creatinine concentration, systolic blood pressure, elevated biomarker at presentation, and heart failure. For bleeding complications, the route for arterial access (radial or femoral) was added to the model. The group undergoing CAG \geq 24 hours was used as the reference for group comparisons. Sensitivity analyses adding variables with the greatest imbalance between groups, excluding periprocedural MI (types 4b and 5), and exploring shorter delays were planned.

Results

Baseline and Procedural Characteristics

Of 13 229 patients randomized in the TAO trial, 13 073 (98.8%) had information on the time of first ECG and time of angiogram. Of those, 4071 patients (30.8% of the overall population) had a GRACE score $>$ 140 and underwent an invasive strategy. This group represents the study cohort ([Figure 1](#)). CAG was performed at an average of 17 hours after presentation. The delay between presentation and CAG was very early (ie, $<$ 12 hours) for 1648 patients (40.5%), early (ie, \geq 12– $<$ 24 hours) for 1420 patients (34.9%), and delayed (ie, \geq 24 hours) in 1003 patients (24.6%). Of note, the invasive strategy led to PCI in 3,171 patients (77.9%) and to CABG surgery in 42 patients (1.0%).

Table 1 describes the baseline characteristics of the patients stratified according to time from ECG to CAG. Briefly, mean age was 70.6 years; 64.0% of patients were male; and 91% of patients had elevated troponin at presentation. Except for a higher proportion of patients from Eastern Europe in the very early group, the baseline characteristics and presentations were well balanced between the groups. The time between the latest ischemic symptoms and randomization increased in parallel with time to angiography.

Procedural characteristics are reported in Table 2. Of the 4071 patients, 3171 (77.9%) underwent PCI during the index admission, corresponding to 1372 (43.3%) in the very early group, 1059 (33.4%) in the early group, and 740 (23.3%) in the delayed group. The access site used was more often the radial artery in the very early cohort (53.2% versus 47.5% in the early and 46.4% in the delayed cohort). Patients in the very early group were more likely to undergo culprit artery PCI only during the index procedure compared with patients in the other groups (62.1% versus 58.4% in the early and 57.8% in the delayed group; $P=0.01$). Despite a modest difference between groups in baseline TIMI flow, final angiographic results were similar across the 3 groups. As expected, the duration of anticoagulation increased with the delay to CAG.

Outcomes

Efficacy Outcomes

Unadjusted outcomes are presented in Tables 3 and 4. At 180 days, the unadjusted primary efficacy end point occurred in 177 patients (10.7%) in the very early cohort, 191 (13.5%) in the early cohort, and 137 (13.7%) in the delayed group ($P=0.03$). Unadjusted Kaplan-Meier curves are presented in Figure 2. Patients in the very early cohort experienced fewer ischemic events than patients in the early and delayed cohorts (<12 versus ≥ 12 – <24 hours, $P=0.03$; <12 versus ≥ 24 hours, $P=0.028$; ≥ 12 – <24 versus ≥ 24 hours, $P=0.91$; Figure 2). After adjustment, with CAG ≥ 24 hours (ie, delayed group) taken as a reference, CAG ≥ 12 to <24 hours (ie, early group) was not associated with a reduction of the primary outcome (adjusted odds ratio [OR] 0.96; 95% confidence interval [CI], 0.75–1.23; $P=0.76$), whereas CAG <12 hours (ie, very early group) was associated with a lower risk of death and MI (adjusted OR, 0.71; 95% CI, 0.55–0.91; $P<0.01$; Figure 3A). Performing CAG <12 hours was also associated with a lower risk of the primary end point (adjusted OR, 0.76; 95% CI, 0.61–0.94; $P=0.01$) compared with CAG performed 12 to 24 hours after admission (Figure 3B).

There was no difference in the rates of the composite ischemic outcome at 7 and 30 days or for unplanned revascularization, rehospitalization, or prolongation of the hospitalization as a consequence of recurrent MI at 30 and 180 days (Table 3). The incidence of nonfatal MI was numerically lower in the very early group and significantly lower at 180 days (6.3% versus 8.3% versus 8.8% in the very early, early, and delayed CAG groups, respectively; $P=0.03$).

Efficacy Outcomes: Sensitivity Analyses

A sensitivity analysis was performed examining the impact of shorter delays to CAG in the very early CAG group. With CAG ≥ 24 hours as a reference, the reduction in the incidence of the primary end point was consistent across all strata for very early angiography, albeit it became not statistically significant in patients undergoing CAG within 4 hours of admission (presumably because of the smaller sample size; Figure 4).

Because of an important imbalance between groups, we performed various sensitivity analyses by adding geographic origin and time between symptoms and admission to the multivariable logistic models. When geographic location was added to the multivariable logistic model, undergoing a CAG <12 hours was associated with numerically lower (although not significant) incidence of the primary outcome than CAG \geq 24 hours (10.75% versus 14.14%; $P=0.08$) and CAG \geq 12 to <24 hours (10.75% versus 13.34%; $P=0.04$; model 2 in Figure I in the online-only Data Supplement). Similar results were observed when the time between symptoms and admission was added to the multivariable logistic model (CAG <12 versus \geq 24 hours, $P<0.01$; and CAG <12 versus \geq 12–<24 hours, $P=0.06$; model 3 in the Figure I in the online-only Data Supplement).

When periprocedural MIs were excluded from the outcomes of interest (reducing power), there were numerically lower (although not significant) rates of the primary end point for CAG <12 hours compared with CAG \geq 12 to <24 hours (6.93% versus 8.15%; OR, 0.81; $P=0.12$) and CAG \geq 24 hours (6.93% versus 8.64%; OR, 0.79; $P=0.14$; Figure II in the online-only Data Supplement).

Safety Outcomes

The primary safety outcome occurred in 4.2% of the very early cohort patients, 3.2% of the early cohort, and 4.9% of the delayed group ($P=0.12$) at 30 days (Table 3). Figure 5 shows the incidence of the unadjusted primary safety end point at 30 days in the 3 groups (<12 versus \geq 12–<24 hours, $P=0.26$; <12 versus \geq 24 hours, $P=0.35$; \geq 12–<24 versus \geq 24 hours, $P=0.06$). After adjustment, with the group undergoing CAG \geq 24 hours used as reference, CAG <12 hours or between 12 and 24 hours was not associated with an excess risk of bleeding at 180 days (adjusted OR for the primary safety outcome, 0.85; 95% CI, 0.56–1.29; $P=0.44$; and adjusted OR, 0.70; 95% CI, 0.44–1.09; $P=0.11$; Figure 6A). Likewise, among patients with CAG performed within the first 24 hours, CAG in the first 12 compared with 12 to 24 hours was not associated with a difference in the primary safety end point (adjusted OR, 1.26; 95% CI, 0.85–1.85; $P=0.24$; Figure 6B).

Sensitivity analyses with geographic location and time between symptoms and admission added to the multivariable logistic model showed consistent findings (Figure III in the online-only Data Supplement).

No differences were observed in TIMI major, TIMI CABG- and non-CABG-related, and TIMI minor bleeding events at 30 days. The rates of any clinical overt bleeding, TIMI bleeding requiring medical attention, and TIMI minimal bleeding were all consistently and significantly lower in patients undergoing very early CAG than in the other groups.

Discussion

In the present analysis, among patients with high-risk NSTEMI, defined by a GRACE score >140 , a very early invasive strategy (ie, within the first 12 hours) was associated with a lower risk of death and MI at 180 days without an increase in bleeding risk compared with an early or a delayed strategy.

Several trials have addressed the issue of optimal timing for an invasive strategy in patients with NSTEMI. The TIMACS trial (Timing of Intervention in Acute Coronary Syndromes) showed a reduction in death, MI, or stroke at 6 months in patients with a GRACE score >140 with an early (\leq 24 hours) compared with a delayed (\geq 36 hours) invasive strategy, whereas there were no differences between early and delayed strategies in patients with low to intermediate risk.⁵ Moreover, in the ACUITY trial (Acute Catheterization and Urgent

Intervention Triage Strategy), delay to PCI >24 hours was an independent predictor of 30-day and 1-year mortality.¹⁴ From this evidence, American and European guidelines provide a Grade I recommendation for an early invasive strategy in the first 24 hours for high-risk NSTEMI only (ie, GRACE score >140, dynamic electrocardiographic changes, troponin rise) and 72 hours for others.^{1,2}

A meta-analysis including 10 trials from 2000 to 2016 has recently compared early (0.5–14 hours) and delayed (18.3–86 hours) strategies in 6397 patients with moderate- to high-risk NSTEMI ¹⁵ and found no difference in terms of mortality or MI but showed reduction in the risk of recurrent ischemia or refractory angina in the early arm. In contrast to the present study, that meta-analysis did not specifically focus on high-risk patients, who are more likely to benefit from a very early strategy. Moreover, this meta-analysis included studies with wide heterogeneity in terms of MI and bleeding definitions, making comparability difficult.

A strategy of immediate invasive management, similar to that implemented for primary PCI in patients with STEMI, has been tested in NSTEMI. The ISAR-COOL study (Intracoronary Stenting With Antithrombotic Regimen Cooling-Off) compared angiography within 6 hours with delayed angiography (3–5 days), demonstrating that the urgent approach was superior in preventing death or MI.⁶ Those results are supported by the recent RIDDLE-NSTEMI study (Immediate Versus Delayed Invasive Intervention for Non-STEMI Patients) in which an immediate strategy (1.4 versus 61 hours) reduced the composite of death and MI compared with a delayed invasive procedure, a benefit driven largely by a reduction in MI.⁹ In contrast, 2 other trials (OPTIMA [Immediate Versus Delayed Invasive Intervention for Non-STEMI Patients] and ABOARD [Angioplasty to Blunt the Rise of Troponin in Acute Coronary Syndromes Randomized for an Immediate or Delayed Intervention]) showed no benefit and even possible harm (increase in the incidence of ischemic events in OPTIMA) from an immediate invasive approach (0.5 and 1.1 hours to catheterization, respectively).^{7,8} These trials were of small to moderate size and do not provide a consistent signal of benefit or harm. Accordingly, even if not specifically tested in high-risk patients, an immediate invasive strategy for NSTEMI, similar to the approach used in primary PCI, is not considered to have established benefits but is associated with important logistical issues in terms of widespread implementation.

In our study, very early CAG was associated with a lower rate of ischemic outcomes (death and MI) at 180 days compared with an early or a delayed strategy. The different sensitivity analyses and the analyses of outcomes at 7 and 30 days showed consistent results with numerically lower rates of ischemic outcomes in patients undergoing CAG <12 hours. However, the differences observed were not significant. This might be the result of a substantial decrease in the number of events analyzed, leading to underpowered analyses.

The variation in MI definitions across studies and the difficulties in ascertaining recurrent MI in patients treated with PCI for an acute ongoing index MI make the comparison between trials difficult. An immediate invasive strategy can lead to harm, driven mainly by increasing the risk of PCI complications, given the fact that oral antiplatelet agents need at least 3 to 4 hours after a loading dose to be effective.¹⁶ However, only the OPTIMA trial reported an increased rate of procedure-related MI in patients undergoing immediate CAG for NSTEMI.⁷ On the other hand, the observed differences in events in the ISAR-COOL and RIDDLE NSTEMI trials were attributable mainly to lower rates of recurrent MI in the precatheterization period in patients with immediate intervention; no significant difference in outcomes were observed after discharge up to 1 year.^{6,9} In the present analysis, when periprocedural MIs were excluded, the difference did not remain significant despite a lower

incidence of the primary end point in the very early group compared with the 2 other groups (presumably a result of a smaller number of events and the associated lack of power).

In our cohort, neither the thrombus burden during the index procedure nor the final angiographic result differed according to the delay to CAG. Moreover, the number of thrombotic complications during the index procedure and bailout use of glycoprotein IIb/IIIa inhibitors did not differ between groups.

The ischemic benefit in high-risk patients treated during the first 12 hours seems to be maintained in the long term, with the difference increasing up to 180 days, compared with the early strategy. The benefit associated with the very early strategy appeared to be driven by a reduction of the incidence of MI throughout the follow-up, with the curves continuing to separate over time. These findings suggest that the benefit of a very early strategy is driven by the prevention of periprocedural MI and late MI.

Dual antiplatelet therapy and anticoagulants are recommended in NSTEMI until angiography is performed.^{1,2} A meaningful proportion of patients admitted with NSTEMI will not require a PCI and are exposed to a higher bleeding risk until the CAG is performed. In addition, in acute coronary syndromes, anticoagulation is typically discontinued after revascularization; therefore, patients receiving earlier PCI are likely to have a shorter duration of anticoagulation. Accordingly, in our cohort, the duration of anticoagulation increased proportionally with the delay of CAG. It is conceivable that early invasive assessment may allow a shorter exposure to anticoagulation and early decisions about the discontinuation of antithrombotic strategies and thus reduce the risk of bleeding complications. However, in our cohort, the time to the procedure was not associated with significant differences in the risk of bleeding complications at 30 days, as previously reported in the TIMACS, RIDDLE NSTEMI, and ACRYL trials and confirmed in the most recent meta-analysis.^{5,9,14,15}

Last, the duration of the index hospitalization was shorter in patients undergoing early invasive management, and this may translate to improved organization of care and potential financial benefits.

Limitations

Although multivariable adjustment was used to correct for measured differences between groups, we cannot exclude the presence of residual confounding, particularly with unmeasured variables. It is important to note that this study is a post hoc analysis, and our findings should therefore be interpreted as hypothesis generating.

Moreover, the TAO NSTEMI cohort was characterized by a high rate of use of femoral access for CAG (with significant differences between the 3 groups), a substantial rate of use of bare metal stents, and routine use of glycoprotein IIb/IIIa inhibitors in the heparin arm.^{1,2} Differences in management of NSTEMI such as greater use of radial access and drug-eluting stents or a lower rate of use of potent antiplatelet agents may affect ischemic and bleeding outcomes and the result of any comparison between groups based on time to CAG.

Last, when baseline geographic differences and time between symptoms and admission were added to the sensitivity model, the analyses, although consistent, did not reach statistical significance for the primary efficacy end point. This may reflect reduced statistical power with the reduction of the number of patients evaluated.

Conclusions

In patients with high-risk NSTEMI, undergoing CAG within the initial 12 hours (as opposed to between 12 and 24 or ≥ 24 hours after admission) was associated with a lower risk of ischemic outcomes at 180 days without an increase in bleeding risk. This observation deserves prospective confirmation and has potentially important implications for the organization of care.

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