Design and rationale for the Minimizing Adverse haemorrhagic events by TRansradial access site and systemic Implementation of angioX program

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Background Transradial intervention (TRI) and bivalirudin infusion compared with transfemoral coronary intervention or unfractionated heparin plus glycoprotein IIb/IIIa inhibitors decrease bleeding complications in patients with acute coronary syndromes (ACS). Although bleeding is thought to be associated with worse outcomes, it remains unclear whether TRI and bivalirudin both independently lower ischemic or combined ischemic and bleeding complications in ACS patients undergoing contemporary invasive management.

Hypotheses The primary objectives of the MATRIX program are to assess whether TRI or bivalirudin as compared, respectively, with transfemoral coronary intervention (MATRIX access site) or unfractionated heparin plus provisional glycoprotein IIb/IIIa inhibitors, (MATRIX antithrombin) decrease the 30-day incidence of an ischemic (ie, death, myocardial infarction or stroke) or an ischemic and bleeding composite end point across the whole spectrum of ACS patients, including clarifying the optimal duration of bivalirudin infusion after percutaneous coronary intervention (MATRIX treatment duration).

Study design The MATRIX (NCT01433627) study, which incorporates 3 randomized comparisons in a nonfactorial manner and primary end points at 30 days and clinical follow-up ≤1 year, is a large-scale, multicenter study with blind event adjudication conducted at approximately 100 European sites. With 8,200 patients in the randomized comparison of access sites and 6,800 individuals participating in the randomized comparison of antithrombin regimens, this study will have ≥85% power for the primary end points.

Summary The MATRIX program aims at conclusively ascertaining the role of TRI and bivalirudin infusion in the whole spectrum of ACS patients undergoing contemporary invasive management. (Am Heart J 2014;168:838-845.e6)
segment elevation ACS or stable coronary artery disease or in patients with ST-segment elevation myocardial infarction (STEMI) receiving a balanced proportion of TRI and TFI. Limited data exist on the value of bivalirudin, used at currently approved regimen, versus heparin alone in contemporary practice. Hence, the benefit of bivalirudin across the whole spectrum of ACS patients, especially if they are receiving a concomitant bleeding-avoidance strategy such as TRI and/or UFH alone, remains controversial.

**Transradial versus transfemoral access site: a critical appraisal of the evidence**

The RIVAL trial was a randomized multicenter trial, where patients with ACS were randomly assigned (1:1) to radial or femoral artery access. The primary outcome, which was a composite of death, MI, stroke, or non-coronary artery bypass graft–related major bleeding at 30 days, occurred in 128 (3.7%) of 3,507 patients in the radial access group compared with 139 (4.0%) of 3,514 in the femoral access group (hazard ratio [HR] 0.92; P = .50). There was a significant interaction for the primary outcome with benefit for radial access in highest tertile volume radial centers (HR 0.49; 95% CI) (P = .0015) and in patients with ST-segment elevation MI (HR 0.60; 0.38-0.94) (P = .026). The benefit observed for TRI in STEMI patients was driven by a reduction in mortality (1.3% vs 3.2%; P = .006), with similar rates of MI, stroke, and major bleeding complications. In this patient group, the use of bivalirudin was low and heterogeneously distributed across groups (2.3% in the radial vs 4.1% in the femoral group; P = .0253). In contrast, among patients with non-ST-segment elevation acute coronary syndrome (NSTEACS), the primary outcome occurred in 3.8% randomized to RA intervention compared with 3.5% randomized to femoral artery intervention (HR: 1.11; 95% CI: 0.83-1.48) (P = .49), with mortality showing a worrisome trend toward a 66% increase in the TRI group (P = .082).

The RIFLE-STECAS study randomized 1,001 acute ST-segment elevation acute coronary syndrome patients undergoing primary/rescue percutaneous coronary intervention (PCI). The 30-day rate of cardiac death, stroke, MI, target lesion revascularization (TLR), and bleeding occurred in 68 patients (13.6%) in the radial arm and 105 patients (21.0%) in the femoral arm (P = .003). Compared with femoral, radial access reduced cardiac mortality (5.2% vs 9.2%; P = .020) and bleeding (7.8% vs 12.2%; P = .026). Bivalirudin was used in only 8% of patients, and GPIS were used in 69% of patients. In the more recent STEMI-RADIAL study, no clear mortality benefit was observed in 707 randomly allocated to either TRI or TFI largely receiving UFH and GPI in 45% of cases.

After these pivotal studies, many issues remain open. The mortality advantage provided by TRI in some of the conducted studies has not been clearly reproduced in others, and the magnitude of the benefit reported in some positive studies appears higher than that observed for some major life-saving interventions in STEMI patients, including the implementation acute revascularization and type thereof. Moreover, the low or no use of bivalirudin, which has itself been shown to reduce mortality in the STEMI patient population, questions the external validity of these findings in a more contemporary pharmacologic environment. Finally, the numerical excess of fatal events in NSTEACS patients randomized to TRI in the RIVAL study is worrisome and deserves further investigation.

**Bivalirudin as the foundation anticoagulant in ACS patients undergoing PCI: a critical appraisal of the evidence**

In the HORIZONS-AMI trial, bivalirudin monotherapy demonstrated statistical superiority versus UFH plus GPI for the 2 primary end points of net adverse clinical outcomes (9.2% vs 12.1%; P = .006) and major bleeding (4.9% vs 8.3%; P = .0001). Treatment with bivalirudin rather than heparin plus a GPI also reduced 30-day cardiac mortality (1.8% vs 2.9%; relative risk [RR] [95% CI] = 0.62 [0.40-0.95]) (P = .028) and all-cause mortality (2.1% vs 3.1%; RR [95% CI] = 0.66 [0.44-1.00]) (P = .047), with nonsignificantly different rates of reinfarction, target vessel revascularization, and stroke. The rate of acute stent thrombosis was significantly higher among patients assigned to bivalirudin.

The ACUITY trial randomized a total of 13,819 patients with NSTEACS. The use of bivalirudin in NSTEACS patients alone was superior to heparins plus GPI, for the net clinical outcome end point (death, MI, unplanned revascularisation, or major bleeding) (10.1% vs 11.7%; P = .0147) and for major bleeding using the ACUITY scale (3.0% vs 5.7%; P < .0001). Yet, in this study, bivalirudin alone did not affect mortality despite the fact that there was a reduction in bleeding events similar to that seen in the HORIZONS-AMI study (with both trials using the same definition for bleeding events). The mortality benefit observed in the HORIZONS-AMI study seems to be related to the patients’ risk status, with those showing a higher Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications score (ie, being at greater risk for death), deriving the greatest relative and absolute benefit from the treatment with bivalirudin as compared with heparin plus GPI. Hence, the apparently discrepant findings on the effect of bivalirudin on mortality observed in HORIZONS-AMI and ACUITY trials may reflect a roughly 2-fold greater risk of death at 30 days noted in the former as compared with the latter study. Alternatively, the vulnerability to bleeding events may differ in STEMI versus NSTEACS patients. However, this interpretation is challenged by the findings of OASIS-5 study, which recruited only NSTEACS patients, and it reported a clear mortality benefit in favor of fondaparinux, which concomitantly cut hemorrhagic events.
The more recent EUROMAX study, where TRI and TFI were equally represented and the addition of GPI to UFH was left at discretion of the treating physician, failed to show a mortality advantage with bivalirudin at 30 days.17 Interestingly, EUROMAX showed a reduction of major bleeding complications in the bivalirudin arm, which seems consistent with that observed in previous trials, where the use of TRI was negligible and GPIs were protocol mandated.

Multiple studies have raised some issues with respect to the value of bivalirudin in preventing ischemic events, including the occurrence of acute stent thrombosis in STEMI or the incidence of peri-procedural MI in the setting of P2Y12 naive NSTEACS patients. As GPIs in the comparator arm in all these studies were either mandated by the protocol or implemented in the vast majority of patients, a possible interpretation of these findings is that bivalirudin-treated patients, despite drug's capability to inhibit thrombin-dependent platelet activation, remain critically dependent on P2Y12 pathway inhibition to minimize the ischemic risk. This hypothesis is supported by growing evidence showing that clopidogrel, even at 600 mg loading dose and/or given at first medical contact, cannot rapidly provide a measurable degree of platelet inhibition at the time of PCI in STEMI; and even prasugrel or ticagrelor do not seem to entirely overcome this limitation in the very first hours after administration in STEMI patients. On the other hand, it has been suggested that prolonging bivalirudin infusion well after PCI may effectively and safely overcome the lack of adequate P2Y12 inhibition, whereas allowing thereafter a gradual bridging with oral P2Y12 inhibitors. Yet, in EUROMAX, despite protocol-mandated prolongation of bivalirudin after PCI, which was largely dosed at 0.25 mg/kg per hour, the incidence of acute ST remained higher in the bivalirudin arm. Hence, it remains to be assessed if concomitant or early administration of more potent P2Y12 inhibitors and/or prolonged full regimen bivalirudin post-PCI infusion mitigates this risk.

The HEAT PPCI trial recruited 1,829 STEMI patients over a 22-month period at a single UK hospital and randomized them bivalirudin, to be stopped at the end of the procedure or UFH, with abciximab to be considered in both study arms only for bailout scenarios.18 At 4 weeks, the primary efficacy end point (major adverse cardiovascular events, defined as all-cause mortality, cerebrovascular accident, reinfarction, or unplanned cardiovascular events, defined as all-cause mortality, cerebrovascular accident, reinfarction, or unplanned PCI in the previous 30 d)

### Inclusion criteria for NSTEACS

- All 3 must be present for eligibility
- History consistent with new or worsening ischemia, occurring at rest or with minimal activity
- Enrollment within 7 days of the most recent symptoms
- Planned coronary angiography with indication to PCI

### Exclusion criteria

- Age ≥60 years
- Troponin T or I or creatine kinase–MB above the upper limit of normal
- Electrocardiograph changes compatible with ischemia, ie, ST depression of ≥1 mm in 2 contiguous leads, T-wave inversion >3 mm, or any dynamic ST shifts

### Inclusion criteria for STEMI

- Both criteria must be present for eligibility
- Chest pain for >20 min with an electrocardiographic ST-segment elevation ≥1 mm in ≥2 contiguous leads or with a new left bundle-branch block or with ST-segment depression of ≥1 mm in ≥2 of leads V1-V3 with a positive terminal T wave

### Exclusion criteria

- Any of the following:
  - Patients who cannot give informed consent or have a life expectancy of <30 d
  - Allergy/intolerance to bivalirudin or UFH
  - Treatment with low molecular weight heparin within the past 6 h
  - Treatment with any GPI in the previous 3 d
  - Absolute contraindications or allergy that cannot be premedicated to iodinated contrast or to any of the study medications including both aspirin and clopidogrel
  - Contraindications to angiography, including but not limited to severe peripheral vascular disease.
  - If it is known, a creatinine clearance <30 mL/min or dialysis dependent
  - Previous enrolment in this study
  - PCI in the previous 30 d

### Design of the MATRIX program

The HEAT PPCI trial recruited 1,829 STEMI patients over a 22-month period at a single UK hospital and randomized them bivalirudin, to be stopped at the end of the procedure or UFH, with abciximab to be considered in both study arms only for bailout scenarios.18 At 4 weeks, the primary efficacy end point (major adverse cardiovascular events, defined as all-cause mortality, cerebrovascular accident, reinfarction, or unplanned PCI in the previous 30 d) was used in >80% of the cases in both treatment groups, and bailout GPI use was similar in both groups, at 13.5% in the bivalirudin group and 15.5% in the heparin-treated patients. The results of this single-center investigator pinpoint the importance of reevaluating the value of bivalirudin in current contemporary practice.

To further examine the role of access site selection and bivalirudin administration across the whole spectrum of ACS intended for an early invasive strategy, including clarifying the optimal duration of bivalirudin infusion in patients undergoing PCI, the MATRIX program has been initiated (see Appendix A for study organization). The design of this large-scale, multicenter, prospective, study with blind event adjudication, conducted at approximately 100 sites in Europe, which incorporates 3 random comparisons and ≤1 year of clinical follow-up, appears in Figure 2. Principal inclusion and exclusion criteria are shown in the Table, whereas study algorithms for STEMI or NSTEACS patients are...
reported in Figures 1 and 2. Patency of the ulno-palmar arches, according to the modified Allen and Barbeau tests will be assessed in the TRI population only after access site randomization has occurred so to avoid a selection bias.

Randomization, staged procedures, and access site management

Concealed allocation of study treatment is performed via a Web-based interactive randomization system available at www.cardiostudy.it/matrix. Randomization is achieved with computer-generated random sequence with a random block size stratified according to type of ACS (STEMI, non-ST segment elevation myocardial infarction, or unstable angina) and intended or ongoing P2Y12 inhibitor (ie, clopidogrel vs ticagrelor or prasugrel).

To account for the expected ≥30% patients with NSTEACS who will not undergo PCI after angiography and to minimize the risk that this may unbalance the distribution of patients with respect to the tested pharmacologic options, randomization to either bivalirudin or standard of care will mainly occur after the decision to proceed to PCI has been taken after coronary angiography. Hence, a 2-step randomization process (access site before angiography followed by antithrombin selection only in those undergoing PCI) will mainly occur in NSTEACS patients. If anticoagulation is deemed necessary to obtain tomographic (ie, intravascular ultrasound or optical coherence tomography) or functional (ie, FFR) information and PCI is considered likely, patients can be randomized to the antithrombin agent before the decision to proceed to PCI is taken. Finally, to reach inclusion of ACS patients as consecutive as possible, in selected cases where upstream (ie, before coronary angiography) therapy is deemed necessary by investigators (ie, due to hemodynamic instability, ongoing symptoms or objective signs of ongoing ischemia despite full antianginal medical therapy, and anticipated delay to catheterization), the full treatment scheme (access site and pharmacologic treatment), upon investigator’s request, can be provided before angiography. Per protocol, this option has to be offered in cases where the delay to the catheter laboratory is expected to exceed 60 minutes. On the other hand, (i) to avoid any possible treatment delay, (ii) to facilitate early initiation of study treatment if deemed necessary, and (iii) acknowledging that PCI in these patients is performed in ≥85% of the cases, randomization to access site and antithrombin selection will occur at a single time point in STEMI. In all cases where randomization to pharmacologic regimen is taking place, duration of bivalirudin infusion (ie, to be stopped at the end of PCI or to be continued thereafter) is simultaneously disclosed.

Access site management after diagnostic or therapeutic procedures is left to the discretion of the treating physician as per institutional guidelines, and closure devices are allowed as per local practice. Staging is allowed with no restriction with respect to timing. The study protocol mandates that both access site and pharmacologic regimen remain consistent to original randomization scheme during staged procedures.
Concomitant medications and treatment protocol

Concomitant adjunctive antithrombotic and nonantithrombotic medications including aspirin, P2Y12 inhibitor, statin, β-blocker, and angiotensin-converting enzyme inhibitor are strongly encouraged and to be implemented according to guidelines. In patients with STEMI, UFH administration at any time before randomization will be allowed and recorded in the case report form for subsequent stratified analyses. Patients with NSTEACS will be eligible for inclusion provided last UFH bolus or UFH continuous infusion has been administered or stopped, respectively, ≥2 hours before arterial sheath insertion and activated clotting time is not >200 seconds. Patients who received fondaparinux before randomization can be included irrespective of the timing of the last given dose, whereas patients who received enoxaparin or other low molecular weight heparin can be randomized only provided last subcutaneous injection has been administered ≥6 hours before. Similarly, patients who received treatment with a GPI before randomization in the previous 3 days are not eligible.

Control group for antithrombin program. Unfractionated heparin should be dosed according to guidelines, that is, 70 to 100 U/kg in patients not receiving GPI and 50 to 70 U/kg in patients receiving GPI. Unfractioned heparin infusion post-PCI is highly discouraged. Subsequent UFH titration based on activated clotting time, which is not protocol mandated, is left to the discretion of the treating physician, in respect of current European practice. Glycoprotein IIb/IIIa inhibitors can be added on top of UFH at discretion of the treating physician. Based on current registry data in recruiting countries, we expect a prevalence of GPI used on top of UFH in the range of 30%, with a possible gradient for the use of this therapy in STEMI versus NSTEACS. All 3 GPls available on the market can be given at discretion of the treating physician based on the following recommended regimen: tirofiban at 25 μg/kg followed by an infusion of 0.15 μg/kg per minute for ≤24 hours, eptifibatide at two 180 μg/kg boluses with a 10-minute interval followed by an infusion of 2.0 μg/kg per minute for ≤96 hours, and abciximab with a bolus of 0.25 mg/kg followed by an infusion of 0.125 μg/kg per minute for 12 hours (maximum dose, 10 μg/min). Although the protocol encourages the postbolus infusion of GPls as per current label, shorter treatment duration or a bolus-only regimen is also allowed by the protocol and left to the discretion of the investigator.

Study group for antithrombin program. Bivalirudin should be given upon enrolment as bolus of 0.75 mg/kg followed immediately by an infusion of 1.75 mg/kg per hour. This infusion should be run continuously until completion of PCI at which time the infusion should be reduced to a
dose of 0.25 mg/kg per hour for ≥6 hours in the prolonged infusion arm or stopped upon removal of the angioplasty guide wire in the short infusion arm. An optional higher dose infusion of 1.75 mg/kg per hour is also permitted for ≤4 hours in the prolonged infusion arm only, which is consistent with the approved product label. Patients who do not undergo PCI and are to be medically managed may continue the infusion of 0.25 mg/kg per hour for ≤72 hours at the investigator’s discretion. Patients who have been randomized to bivalirudin may only have a “bail out” GPI administered during PCI for the following 2 reasons only:

- The presence of a “giant” thrombus adjacent to the stent or in the coronary vessel (length >2× that of the diameter of the coronary vessel) after PCI in the absence of a mechanical obstruction.
- Sustained no reflow (TIMI 0-1 flow in the absence of a mechanical obstruction, refractory to intracoronary nitrates, adenosine, or a calcium-channel blocker delivered intracoronary to the distal coronary bed via an infusion catheter).

Measures to minimize/avoid bias

The study is open label. Despite the obvious benefits of a double-blind design, the access site cannot be concealed to the operator or to the other patient medical and paramedical staff. Similarly, the concealment of the pharmatherapeutic strategy in this study would require a double dummy approach, which may realistically delay the active treatment especially in the setting of STEMI patients in whom all efforts must be taken not to retard time to reperfusion. An independent clinical events committee (CEC) will adjudicate all primary clinical end points plus bleeding events and stent thrombosis. The committee members and the CEC management team will be blinded to access site and randomized therapy. Another measure to avoid or minimize bias introduced by the open-label design will include use of objective measures for repeat MI and bleeding end points. To minimize selection bias after randomization, follow-up will be sought for all randomized patients, and primary analyses will be performed according to the intention-to-treat principle, where all patients are analyzed according to the allocated rather than received intervention.

Hypotheses and power analysis

The MATRIX program has prespecified 3 independent randomized comparisons:

- The appraisal of TRI over TFI (MATRIX access site).
- The assessment of bivalirudin, either stopped or continued after PCI as compared with UFH plus provisional GPs (MATRIX antithrombin).
- The value of prolonging bivalirudin infusion either at the dose of 0.25 mg/kg per hour for ≥6 hours or at 1.75 mg/kg per hour is for ≤4 hours versus stopping it at the end of the procedure (MATRIX treatment duration).

**MATRIX access site—end points and sample size.**

This randomized comparison will use on 2 coprimary end points at 30 days. It is expected that the incidence of the first coprimary end point (death, MI, or stroke) on an intention-to-treat basis will be in the range of 4.2% and 6% (RR: 0.70) in the transradial and transfemoral groups, respectively. The expected background event rate for the first coprimary end point in the range of 5% has been assumed based on the 30-day findings reported by 2 large and multinational investigations assessing the value of new P2Y12 inhibitors in the context of an heterogeneous ACS patient population including both patients with and without ST-segment elevation MI.19,20 Similarly, the incidence of the second coprimary end point (death, MI, stroke, or bleeding event) on an intention-to-treat basis is projected to be in the range of 6.3% and 9.0% (RR: 0.70) in the transradial and transfemoral group, respectively. Hence, 4,100 patients per group will provide >90% and >99% power for the first and the second coprimary end point, respectively, with an α error set at 2.5%. The final sample size was driven by power analysis for the MATRIX antithrombin comparison program, taking into consideration the fact that NSTEACS patients will be largely eligible to this comparison only if proceeding to PCI.

**MATRIX antithrombin—end points and sample size.**

This randomized comparison will use 2 coprimary end points at 30 days. It is expected that the incidence of the first coprimary end point (death, MI, or stroke) on an intention-to-treat basis will be in the range of 4.2% and 6% (RR: 0.70) in the bivalirudin and UFH group, respectively. Similarly, the incidence of the second coprimary end point (death, MI, stroke, or BARC 3 or 5) on an intention-to-treat basis is projected to be in the range of 6.3% and 9.0% (RR: 0.70) in the bivalirudin and UFH group, respectively. Hence, 3,400 patients per group will provide >85% and >95% for the first and the second coprimary end point, respectively, with an α error set at 2.5%.

**MATRIX treatment duration—end points and sample size**

This randomized comparison will use 1 primary outcome, the composite of death, MI, stroke, urgent target vessel revascularization, stent thrombosis, and type 3 and 5 type BARC bleeding at 30 days. One thousand seven hundred patients per group per will provide >86% power to assess superiority of prolonged post-PCI bivalirudin infusion versus no post-PCI infusion assuming a background event rate in the range of respectively 7.0% and 10% (risk ratio: 0.70), with an α error set at 5.0%.

Secondary end points will include each component of the primary end points; cardiac mortality; type 1, 2, or 4 BARC events; bleeding according to the TIMI or GUSTO scales; the length and costs of hospitalization; the need for surgical access site repair/intervention; and/or blood
products transfusion throughout follow-up. Definitions of components of primary and secondary end points are detailed in Appendix C.

Data analysis
Primary analyses will be performed according to the intent-to-treat principle in all subjects according to their assigned study treatment. Only end point events adjudicated by the CEC will be used in the primary secondary analyses.

Primary and secondary outcomes will be analyzed as time-to-first event using the Mantel-Cox method accompanied by log-rank tests to calculate corresponding P values. Survival curves will be constructed using Kaplan-Meier estimates. Analyses will be stratified according to prespecified subgroups including age, sex, presenting syndrome, use of GPI, type of P2Y12 inhibitor, renal function, and operator/center transradial volume. Tests for interaction between the subgroups will be performed. As sensitivity analyses, Cox proportional hazard models including as covariates, the treatment group and the stratification factors (presenting syndrome and type of P2Y12 inhibitor analyzed as dummy variable clopidogrel vs ticagrelor or prasugrel) will be carried out to estimate HRs and 95% CIs comparing the tested treatment options.

As the decisions to use GPI in the control group or which bivalirudin regimen to implement in the prolonged bivalirudin infusion arm are not randomized, both univariate as well as propensity-based multivariable adjustment will be carried out at exploratory level.

Follow-up
Patients return for study visits at 30 days and then 1 year (last study visit). During follow-up visits, patients are assessed for adverse events, 12-lead electrocardiogram recordings, and questioned on their compliance with secondary prevention medications. Patency of the RA will be assessed by the presence of radial pulse as well as by the use of the reverted Barbeau test.

Operator criteria for eligibility
Transradial intervention requires specific skills and dedicated training. Therefore, scope of this study is not to investigate the learning curve of the technique, rather assessing the comparative efficacy and safety of transradial technique versus transfemoral intervention in the context of fully trained interventional cardiologists having been properly exposed to both treatment options. Against this background, single operators qualify for the study provided: (i) they are familiar and have been exposed to transfemoral intervention as senior cardiologist in the past for ≥2 years, (ii) they have performed in the last 12 months ≥50% of intervention in ACS transradially, and (iii) the number of transradial coronary intervention within the previous 12 months is ≥75.

On-treatment platelet reactivity substudy
Immediately before PCI, VerifyNow P2Y12 assay will be performed to blindly collect platelet reaction units base, platelet reaction units post, and percentage of P2Y12 inhibition. Main scope of the current substudy is to assess the association of residual on-treatment platelet reactivity to adverse events and its interaction with the 2 tested pharmacologic strategies (ie, bivalirudin monotherapy, either given as short or post-PCI prolonged infusion vs UFH ± GPI). Other prespecified substudies will be detailed in separate publications.

Study timelines, role of funding and conclusions
The first patient was randomized at the coordinating center in October 2011, whereas enrolment phase is project to be completed at current recruitment pace by quarter 3 2014. The MATRIX program is sponsored by the Gruppo Italiano Studi Emodinamica, which received research grants from The Medicines Company and Terumo for its conduct. The Eustrategy organization is responsible for the data management, whereas the Institute of Social and Preventive Medicine and Clinical Trials Unit Bern, Department of Clinical Research, University of Bern, will carry out data lock and subsequent independent statistical analyses. The 2 supportive companies have no role in the development of the protocol, operations of the trial, analysis of the data and decision, and publish the results. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper, and its final contents. The MATRIX program aims at conclusively ascertaining the role of TRI and bivalirudin infusion in the whole spectrum of ACS patients undergoing contemporary invasive management.

References


Appendix A. MATRIX program study organization

Study sponsors: Gruppo Italiano Studi Emodinamica (GISE) and EUSTRATEGY (co-sponsor)

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Appendix C. Definitions of clinical outcomes

The following end points will be adjudicated by the CEC: death; myocardial infarction; stroke; transient ischemic attack; bleeding; coronary stent thrombosis; urgent target vessel coronary revascularization.

Death
All deaths will be adjudicated by the CEC. Deaths will be considered cardiac unless an unequivocal non-cardiac cause can be established. Specifically, any unexpected death, even in patients with coexisting potentially fatal non-cardiac disease (e.g. cancer, infection), should be classified as cardiac.

Cardiac death. Any death due to immediate cardiac cause (e.g. MI, low output failure, fatal arrhythmia). Sudden death and death of unknown cause will be classified as cardiac death. This includes all procedure related deaths including those related to concomitant treatment.

Vascular death. Death due to cerebrovascular disease, pulmonary embolism, ruptured aortic aneurysm, dissecting aneurysm, or other vascular cause.

Non-cardiovascular death
Any death not covered by the above definitions, including death due to infection, sepsis, pulmonary causes, accident, malignancy, suicide or trauma.

Myocardial infarction
All occurrences of MI up to and including the 1-year time point will be adjudicated by the CEC.
Serial ECGs, the presence of symptoms consistent with myocardial ischemia, and biomarkers of myocardial necrosis should be obtained for each suspected recurrent MI.

A diagnosis of an end point MI is made when the following criteria are met:
MI <24 hours of randomization in patients with STEMI or in patients with NSTEMI in whom cardiac markers before randomization are not available or higher than URL and still in the ascending phase (i.e. markers are not stable or decreasing in two or more assessments taken before the suspected event)
• Presumed ischemic symptoms (such as chest pain) and either
• New ST segment elevation of $\geq 1$ mm in $\geq 2$ contiguous leads, or presumably new left bundle branch block.

and/or

• Angiographic complications including but not limited to re-occlusion of a previously patent coronary artery or bypass graft, no reflow (i.e. new onset of vessel closure or compromise defined as TIMI 0/1 flow after baseline TIMI 2/3 flow) or slow reflow (i.e. TIMI 2 flow after baseline TIMI 3 flow), sustained distal embolization, sustained side-branch closure of a vessel $\geq 2$ mm in diameter.

MI 24 hours to 7 days OR in patients in whom cardiac markers are stable or decreasing in two or more assessments taken before the suspected event

Presumed ischemic symptoms (such as chest pain) and either if cardiac markers are in the descending phase, a new re-elevation in biomarkers $>20\%$ above the prior documented valley level (troponin I or T should be used first, if not available the second option is for CK-MB mass and if CK-MB not available total CK should be used) or
If cardiac markers are normal or returned to normal, use the definition for subsequent ischemic events >7 days

MI >7 days
If the suspected MI occurs >7 days after randomization, the 2007 Universal Definition of MI will be used. Under these conditions any one of the following criteria meets the diagnosis for myocardial infarction:

Type 1 MI. Spontaneous myocardial infarction related to ischaemia due to a primary coronary event such as plaque erosion and/or rupture, fissuring, or dissection.
Type 2 MI. Myocardial infarction secondary to ischaemia due to either increased oxygen demand or decreased supply, e.g. coronary artery spasm, coronary embolism, anaemia, arrhythmias, hypertension, or hypotension.

Type 1 and type 2 MI requires the detection of a rise and/or a fall of cardiac biomarkers (preferably troponin) with $\geq 1$ value above the 99th percentile of the upper reference limit (URL) together with evidence of myocardial ischemia with at least one of the following:
• Symptoms of ischemia. In the absence of pain, new ST segment changes indicative of ischemia, acute pulmonary edema, ventricular arrhythmias, or hemodynamic instability presumed to be
ischemic in origin, will constitute sufficient evidence of ischemia.

- ECG changes indicative of new ischemia (new ST-T changes or new LBBB) or development of pathological Q waves in the ECG;
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

Type 3 MI. Sudden, unexpected cardiac death, involving cardiac arrest, often with symptoms suggestive of myocardial ischemia, and accompanied by presumably new ST elevation, or new LBBB, and/or evidence of fresh thrombus by coronary angiography and/or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood.

Type 4a MI. For percutaneous coronary interventions (PCI) in patients with normal or abnormal and stable/falling baseline troponin values an increases of troponin biomarkers greater than 3 x 99th percentile URL in ≥1 blood sample is designated as defining PCI related myocardial infarction. A subtype related to a documented stent thrombosis is recognized (type 4b MI).

Type 5 MI. For coronary artery bypass grafting (CABG) in patients with normal or abnormal and stable/falling baseline troponin values, increases of troponin biomarkers greater than 5 x 99th percentile URL in ≥1 blood sample plus either new pathological Q waves or new LBBB, or angiographically documented new graft or native coronary artery occlusion, or imaging evidence of new loss of viable myocardium is designated as defining CABG-related myocardial infarction.

An MI will be also defined by the presence of pathological findings of an acute myocardial infarction on autopsy.

Q wave definition. New Q waves are defined as Q waves with a duration of >0.04 seconds in ≥2 contiguous leads that were not present on previous ECGs. These ECG criteria are only valid in the absence of left bundle branch block (LBBB), Wolff Parkinson White syndrome (WPW), paced rhythm or other artifacts that would preclude an ECG definition of myocardial infarction.

(c) Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in the presence of biomarker elevation with or without other defining factors of myocardial infarction (clinical, ECG, biochemical) and in the absence of a non-ischemic cause may also be used to define a re-infarction. A wall motion abnormality alone does not define infarction.

Note: There may be patients who have a suspected reinfarction who have insufficient data to adjudicate the event according to the definitions outlined in this charter (eg. symptom duration is missing). For these patients, an MI may be adjudicated by the CEC when there is a preponderance of clinical evidence based on signs, symptoms, ECG changes, angiographic and biomarkers data.

Cerebrovascular accident (stroke or TIA)

Cerebrovascular accidents are composed by stroke and transient ischemic attacks (TIA).

A stroke is defined as a sudden, focal neurological defect resulting from a cerebrovascular cause, resulting in death or lasting greater than 24 hours, that is not due to a readily identifiable cause such as a tumor, infection or trauma. All suspected strokes will be adjudicated using all available clinically relevant information including imaging studies to classify all strokes as:

- Haemorrhagic stroke - a stroke with focal collections of intracranial blood
- Ischemic stroke - a stroke without focal collections of intracranial blood
- Unknown - no imaging or autopsy data are available

A TIA is defined as a new, transient episode of neurological dysfunction (usually 1 to 2 h), always within 24 h caused by focal brain, spinal cord, or retinal ischemia, without acute infarction at neuroimaging.

Stent thrombosis

The incidence of ST will be assessed up to and including the 1 year time point. Stent thrombosis should be reported as a cumulative value at the different time points and with the different separate time points. Time 0 is defined as the time point after the guiding catheter has been removed.

Timing

- Acute stent thrombosis: 0-24 hours post stent implantation
- Subacute stent thrombosis: >24 hours-30 days post stent implantation
- Late stent thrombosis: >30 days-1 year post stent implantation

Likelihood of an accurate diagnosis

We recognize three categories of evidence in defining stent thrombosis: definite, probable, and possible.

Definite (is considered either by angiographic or pathologic confirmation).

Angiographic confirmation of stent thrombosis is considered to have occurred if:
1) Thrombolysis In Myocardial Infarction (TIMI) flow is:
   a) TIMI flow grade 0 with occlusion originating in
      the stent or in the segment 5 mm proximal or
      distal to the stent region in the presence of a
      thrombus(*).
   b) TIMI flow grade 1, 2, or 3 originating in the stent or
      in the segment 5m proximal or distal to the stent
      region in the presence of a thrombus(*).
      And at least one of the following criteria, has been
      fulfilled within a 48 hours time window:
   2) New onset of ischemic symptoms at rest (typical chest
      pain with duration ≥20 minutes or requiring medical
      treatment)
   3) New ischemic ECG changes suggestive of acute
      ischemia
   4) Typical rise and fall in cardiac biomarkers

   The incidental angiographic documentation of stent
   occlusion in the absence of clinical signs or symptoms is
   not considered a confirmed stent thrombosis (silent
   occlusion).

   (*) Intracoronary thrombus [Ellis et al., Mabin et al.,
   Capone et al.]

   **Non-occlusive thrombus.** Intracoronary thrombus is
   defined as a (spheric, ovoid or irregular) non-calcified
   filling defect or lucency surrounded by contrast material
   (on three sides or within a coronary stenosis) seen in
   multiple projections, or persistence of contrast material
   within the lumen, or a visible embolization of intralum-
   inal material downstream.

   **Occlusive thrombus.** A TIMI 0 or TIMI 1 intra-stent or
   proximal to a stent up to the most adjacent proximal side
   branch or main branch (if originating from the side
   branch).

   Pathologic confirmation of stent thrombosis.
   Evidence of recent thrombus within the stent deter-
   mined at autopsy.
   Probable:
   Clinical definition of probable stent thrombosis is
   considered to have occurred after intracoronary stenting
   in the following cases:

   1) Any unexplained death within the first 30 days.
   2) Irrespective of the time after the index procedure any
      myocardial infarction (MI), which is related to
      documented acute ischemia in the territory of the
      implanted stent without angiographic confirmation of
      stent thrombosis and in the absence of any other
      obvious cause.

   Possible:
   Clinical definition of possible stent thrombosis is
   considered to have occurred with any unexplained death
   following intracoronary stenting until the end of the
   follow-up period.

Bleeding
The primary bleeding classification used in the study will
be the Bleeding Academic Research Consortium (BARC).
The TIMI and GUSTO classification will be also assessed.
BARC classification

Type 0 No evidence of bleeding.
Type 1 Bleeding that is not actionable and does not cause
the patient to seek unscheduled performance of
studies, hospitalization, or treatment by a health
Care professional. Examples include, but are not
limited to, bruising, hematoma, nosebleeds, or
hemorrhoidal bleeding for which the patient does
not seek medical attention. Type 1 bleeding may
include episodes that lead to discontinuation of
medications by the patient because of bleeding
without visiting a health care provider.

Type 2 Any clinically overt sign of hemorrhage (e.g.,
more bleeding than would be expected for a
clinical circumstance; including bleeding found
by imaging alone) that is actionable, but does not
meet criteria for type 3 BARC bleeding, type 4
BARC bleeding (CABG-related), or type 5 BARC
bleeding (fatal bleeding). The bleeding must
require diagnostic studies, hospitalization or
behavior by a health care professional. In
particular, the bleeding must meet at least one of
the following criteria:

1) Requiring intervention: defined as a health
Care professional-guided medical treatment or
percutaneous intervention to stop or treat
bleeding, including temporarily or perma-
nently discontinuing a medication or study
drug. Examples include, but are not limited to,
coiling, compression, use of reversal agents
(e.g. vitamin K, protamine), local injections to
reduce oozing, or a temporary/permanent
cessation of antiplatelet, antithrombin, or
fibrinolytic therapy;

2) Leading to hospitalization or an increased level
of care: defined as leading to or prolonging
hospitalization or transfer to a hospital unit
capable of providing a higher level of care or;

3) Prompting evaluation: defined as leading to an
unscheduled visit to a healthcare professional
resulting in diagnostic testing (laboratory or
imaging). Examples include, but are not limited to,
hematocrit testing, Hemoccult testing,
endoscopy, colonoscopy, computed tomogra-
phy scanning, or urinalysis. A visit or phone call
to a healthcare professional where neither
testing nor treatment is undertaken does not
constitute type 2 bleeding.

Type 3 Clinical, laboratory, and/or imaging evidence of
bleeding with specific healthcare provider re-
sponses, as listed below:
Type 3a
- Any transfusion with overt bleeding
- Overt bleeding plus hemoglobin drop ≥3 to <5 g/dL* (provided hemoglobin drop is related to bleeding)
Type 3b
- Overt bleeding plus hemoglobin drop ≥5 g/dL* (provided hemoglobin drop is related to bleeding)
- Cardiac tamponade
- Bleeding requiring surgical intervention for control (excluding dental/nasal/skin/hemorrhoid)
- Bleeding requiring intravenous vasoactive drugs
Type 3c
- Intracranial hemorrhage (does not include microbleeds or hemorrhagic transformation; does include intraspinal).
- Subcategories: confirmed by autopsy or imaging or lumbar puncture (LP)
- Intra-ocular bleed compromising vision

*Hb drop should be corrected for intracurrent transfusion, where 1 unit of packed red blood cells or 1 unit of whole blood would be expected to increase Hb by 1 g/dl.

Type 4 CABG-related bleeding.
- Perioperative intracranial bleeding within 48 hours
- Reoperation following closure of sternotomy for the purpose of controlling bleeding
- Transfusion of ≥5 units of whole blood or packed red blood cells within a 48 hour period**
- Chest tube output ≥2L within a 24 hour period.

Note: If a CABG-related bleed is not adjudicated as at least a type 3 severity event, it will be classified as ‘not a bleeding event’.

** Only allogeneic transfusions are considered as transfusions for CABG-related bleeds. Cell saver products will not be counted.

Type 5 Fatal bleeding. Fatal bleeding is bleeding that directly causes death with no other explainable cause. BARC fatal bleeding is categorized as either definite or probable as follows:
Type 5a Probable fatal bleeding: Bleeding that is clinically suspicious as the cause of death, but the bleeding is not directly observed and there is no autopsy or confirmatory imaging.
Type 5b Definite fatal bleeding: Bleeding that is directly observed (either by clinical specimen – blood, emesis, stool, etc.- or by imaging) or confirmed on autopsy.

The site of fatal bleeding is further categorized as intracranial, gastrointestinal, retroperitoneal, pulmonary, pericardial, gastrourinary, or other. BARC fatal bleeding is meant to capture deaths that are directly due to bleeding with no other cause. The time interval from the bleeding event to the death should be considered with respect to likely causality, but there is no specific time limit proposed. Bleeding that is contributory but not directly causal to death is not classified as fatal bleeding, but may be categorized as other forms of bleeding. Bleeding that leads to cessation of antithrombotic or other therapies may be contributory, but again, would not be classified as fatal bleeding. Bleeding associated with trauma or with surgery may be fatal, depending on whether it was determined to be directly causal or not.

TIMI classification
Major bleeding is defined as [Bovil et al, 1991]:
- Intracranial haemorrhage
- Bleeding associated with a decrease in Hgb >5g/dL (3.1 mmol/L) (or 15% of haematocrit)
- Haemorrhagic death
- Cardiac tamponade

Minor bleeding is defined as [Bovil et al, 1991]:
- Blood loss that is spontaneous and observed as gross haematuria or haematemesis
- Observed (ie, haeme-positive coffee ground emesis, haeme-positive melaena, haematoma or retroperitoneal bleeding)
- Spontaneous or non-spontaneous blood loss associated with a haemoglobin >3 g/dL (1.8 mmol/L) and <5 g/dL (3.1 mmol/L) (or a haematocrit decrease of 9% and <15%)
- Haemoglobin decrease >4 g/dL (2.5 mmol/L) and <5 g/dL (3.1 mmol/L) (or 12% of haematocrit and <15%) with, despite attempts, no bleeding site identified

GUSTO classification
Severe or life-threatening is defined as [GUSTO investigators, 1993]:
- Either intracranial haemorrhage or bleeding that causes hemodynamic compromise and requires intervention

Moderate is defined as [GUSTO investigators, 1993]:
- Bleeding that requires blood transfusion but does not result in hemodynamic compromise

Urgent target vessel revascularization (uTVR)
Urgent target vessel revascularization (uTVR) is defined as 1 or more episodes of rest pain, presumed to be ischemic in origin, which results in either urgent repeat PCI or urgent CABG of the target vessel (as defined above). In the absence of pain, new ST segment changes
(a new ST segment shift $\geq 0.05$ mV (0.5 mm) on a 12-lead ECG), indicative of ischemia, acute pulmonary edema, ventricular arrhythmias, or hemodynamic instability presumed to be ischemic in origin, will constitute sufficient evidence of ischemia. To be considered urgent, the repeat PCI or CABG will be initiated within 24 hours of the last episode of ischemia and not be identified as planned/staged. The episode of ischemia leading to urgent repeat PCI must occur following completion of the index PCI and guide wire removal. CABG initiated within 24 hours of PCI (index or repeat) due to an unsatisfactory result, even in the absence of documented ischemia, will also be considered a uTVR end point.