A randomized trial to compare the safety of rivaroxaban vs aspirin in addition to either clopidogrel or ticagrelor in acute coronary syndrome: The design of the GEMINI-ACS-1 phase II study

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Dual antiplatelet therapy (DAPT), the combination of aspirin and a P2Y12 inhibitor, given for 12 months remains the standard of care after presentation with acute coronary syndrome (ACS) because it has been shown to be associated with a significant reduction in ischemic events compared with aspirin monotherapy. The factor Xa inhibitor rivaroxaban was shown to be associated with a significant reduction in the composite of cardiovascular death, myocardial infarction, and stroke, and resulted in a nominal reduction in cardiovascular death, when added to background DAPT in the ATLAS ACS 2–TIMI 51 trial; however, there was excessive bleeding with this “triple-therapy” approach. The combination of rivaroxaban with P2Y12 inhibition in a “dual-pathway” approach may be an effective therapeutic regimen for the treatment of ACS, given the known importance of P2Y12 inhibition after stenting and intriguing data that the combination of an anticoagulant with clopidogrel after stenting in patients with atrial fibrillation appears an attractive option to this patient population. GEMINI-ACS-1 is a prospective, randomized, double-dummy, double-blind, active-controlled trial that will assess the safety of dual antithrombotic therapy (rivaroxaban [2.5 mg twice daily] + P2Y12 inhibitor) as compared with DAPT (aspirin [100 mg] + P2Y12 inhibitor) within 10 days of an ACS event in 3,000 patients. Patients will be randomized in a 1:1 ratio stratified by intended P2Y12 inhibitor use (clopidogrel 75 mg daily or ticagrelor 90 mg twice daily), with 1500 patients expected in each P2Y12 inhibitor strata. The primary end point is Thrombolysis in Myocardial Infarction clinically significant bleeding (major, minor, or requiring medical attention). The exploratory efficacy determination will be a composite of cardiovascular death, myocardial infarction, ischemic stroke, and stent thrombosis. GEMINI-ACS-1 will assess the safety and feasibility of dual antithrombotic therapy with rivaroxaban and a P2Y12 inhibitor compared with conventional DAPT for the treatment for patients with recent ACS. (Am Heart J 2016;174:120-8.)

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Background

Treatment of acute coronary syndrome

Dual antiplatelet therapy (DAPT) is central to the European Society of Cardiology1,2 and American Heart Association/American College of Cardiology3,4 practice guidelines for the treatment for patients with acute coronary syndrome (ACS).

Despite the use and development of novel more potent P2Y12 inhibitors, the residual risk of recurrent ischemic events remains unacceptably high, especially in the medically managed patient population.5,6 To mitigate this risk, a variety of “triple-therapy” approaches have been explored; however, the addition of either another antiplatelet agent (the protease-activated receptor-1 inhibitor vorapaxar) or oral anticoagulants at therapeutic
doses (apixaban,7 dabigatran,8 or darexaban9) was associated with a higher bleeding risk and modest nonstatistically significant impact on ischemic events.10

In contrast, the addition of rivaroxaban, at comparatively lower doses, to DAPT as explored in the Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Aspirin with or without Thienopyridine Therapy in Subjects with Acute Coronary Syndrome (ATLAS) program was associated with a 31% relative risk reduction (RRR) in the primary composite end point of cardiovascular death, myocardial infarction (MI), and stroke in the phase II ATLAS ACS-TIMI 51 trial.11 A clear dose-response relationship between the total daily dose of rivaroxaban and bleeding, coupled with a lack of greater efficacy at higher doses on ischemic events led to the selection of lower doses (2.5 and 5 mg twice daily) for assessment in a phase III trial (ATLAS ACS 2-TIMI 51), which demonstrated an RRR of 16% on ischemic events (24-month Kaplan-Meier rate of 8.9 and 10.7, respectively) in the 2.5-mg arm. Given a dose-dependent bleeding risk and preservation of ischemic effectiveness in the lowest-dose rivaroxaban arm (Table I), the European Society of Cardiology guidelines for ST-segment elevation MI (STEMI),2 non-ST-segment elevation (NSTEMI)–ACS,1 and myocardial revascularization12 suggest (level IIb) that low-dose rivaroxaban (2.5 mg twice daily) may be considered in addition to clopidogrel and aspirin in appropriate patients.1

### Alternative strategies: removing aspirin

Aspirin has been the cornerstone of treatment of antithrombotic events since the initial demonstration of a highly significant effect on mortality in patients with both non-STEMI (NSTEMI) and STEMI.14–17 Both theoretical and clinical findings suggest that alternative dual antithrombotic approaches combining a P2Y12 inhibitor with low-dose oral anticoagulation might retain effectiveness against ischemic events while reducing the bleeding risk observed with triple or DAPT therapies. First, although the use of a P2Y12 inhibitor after stenting appears important to reduce acute ischemic complications,18 the risks and benefits of aspirin in this setting have never been fully tested.

Second, the addition of a second antiplatelet agent adds significant bleeding risk, and aspirin, with direct gastrointestinal toxicity, leads directly to increased bleeding. In the STent Anticoagulation Restenosis Study (STARS), the addition of ticlopidine after percutaneous coronary intervention (PCI) resulted in a 3-fold increase in hemorrhagic complications with rates of bleeding similar to a strategy using full-dose warfarin,18 whereas the CURE trial demonstrated a 30% increase in major and a 2-fold increase in minor bleeding with aspirin and clopidogrel compared with aspirin alone.19

Third, the benefit of aspirin in addition to P2Y12 inhibition remains unproven. The Management of AThrombotic thrombosis with Clopidogrel in High-risk patients (MATCH) trial showed marked increases in minor, major, and life-threatening bleeding with relatively small improvements in ischemic events when aspirin was added to clopidogrel in patients with prior stroke.20

Finally, DAPT targets the action of products released on platelet activation via interaction with collagen, but does not inhibit direct platelet activation by potent agonists such as thrombin, which is generated in prothrombotic conditions such as MI (Figure 1).21–24 Rivaroxaban, by directly inhibiting factor Xa and prothrombinase complex activity, prolongs the time and suppresses the maximal extent of thrombin generation. In the ATLAS ACS-TIMI 46 trial, treatment with rivaroxaban was associated with reduced thrombin generation both acutely and at 6-month follow-up.25 In an in vivo rat shunt thrombosis model, rivaroxaban and clopidogrel were as effective as triple therapy and more effective in suppressing thrombus formation than any single agent, DAPT, or rivaroxaban and aspirin, while demonstrating lower bleeding times than DAPT or triple therapy.26 Finally, rivaroxaban and ticagrelor may act synergistically to reduce platelet aggregation. In an in vitro model, either agent alone resulted in ≥31% to ≥37% inhibition of tissue factor-induced platelet aggregation; however, the combination, even at submaximal dosing, resulted in >90% inhibition.27 These observations suggest that suppression of thrombin generation might be particularly effective at limiting ischemic events via both an anticoagulation effect as well as inhibition of thrombin-mediated platelet activation.

### Clinical trial results with dual-pathway inhibition

Clinical findings support the hypothesis that dual antithrombotic approaches warrant additional study. The What is the Optimal antiplatElet and anticoagulant therapy

| Table I. Comparison of ischemic and bleeding events in the ATLAS ACS 2–TIMI 51 trial by treatment group |
|--------------------------------------------------|--------------------------------------------------|------------------------------------------|----------|
| Composite of CV death, MI, stroke | 9.1 | 8.8 | 10.7 |
| Death, MI, stroke | 9.3 | 9.1 | 11.0 |
| Cardiovascular death | 2.7 | 4.0 | 4.1 |
| Stent thrombosis | 2.2 | 2.3 | 2.9 |
| Non-CABG TIMI major bleeding | 1.8 | 2.4 | 0.6 |
| TIMI minor bleeding | 0.9 | 1.6 | 0.5 |
| TIMI bleeding requiring medical attention | 12.9 | 16.2 | 7.5 |
| Intracranial hemorrhage | 0.4 | 0.7 | 0.2 |
| Fatal bleeding | 0.1 | 0.4 | 0.2 |

### Summary

- Rivaroxaban, by directly inhibiting factor Xa and prothrombinase complex activity, prolongs the time and suppresses the maximal extent of thrombin generation.
- Clinical findings support the hypothesis that dual antithrombotic approaches warrant additional study.
in patients with oral anticoagulation and coronary StentTing (WOEST) study compared the use of oral anticoagulation and clopidogrel alone with triple therapy in patients with an indication for oral anticoagulation after PCI. A dual-pathway approach was associated with a 64% RRR in bleeding (hazard ratio [HR] 0.36, 95% CI 0.26-0.50, \( P \leq 0.001 \)), and a lower rate of ischemic end points (11.1% vs 17.6; HR 0.60, 95% CI 0.38-0.94, \( P = .025 \)). These findings have spurred a variety of trials exploring the utility of dual-pathway strategy without aspirin in patients with atrial fibrillation undergoing PCI (Table II). To date, no safety concerns have been raised in these trials. In addition, 2 other ongoing post-PCI studies are comparing a ticagrelor alone approach with DAPT, starting either 1 month or 3 months after PCI. Although these trials will build on our understanding of the utility of long-term DAPT, they do not address the addition of alternative therapies after cessation of aspirin.

The GEMINI-ACS-1 clinical trial builds on these preclinical and clinical observations to explore the feasibility and safety of a dual antithrombotic strategy (rivaroxaban 2.5 twice daily with a P2Y12 inhibitor) in comparison with conventional DAPT (aspirin 100 mg QD).
daily with a P2Y12 inhibitor) for secondary prevention in patients with recent ACS.

**Methods**

**Study overview**

GEMINI-ACS-1 (NCT02293395) is a phase II, randomized, double-blind, double-dummy, active-controlled study assessing the safety and feasibility of rivaroxaban (2.5 mg twice daily) and a P2Y12 inhibitor compared with conventional DAPT (aspirin [100 mg] + P2Y12 inhibitor) in patients within 10 days of an ACS event. The study will be conducted at approximately 370 sites in 22 countries with proportional geographic representation (Figure 2).

GEMINI-ACS-1 was designed by an academic executive committee (Appendix A) comprising international experts in interventional cardiology and thrombosis/hemostasis and representatives from each of the sponsors. The executive committee will oversee the medical, scientific, and operational conduct of the study, and review and approve analyses for publication. A steering committee (Appendix A) comprising the executive committee and individual country leaders will provide feedback on country-specific issues related to applicability of the trial and regional practices, and formulate substudy analysis initiatives.

GEMINI-ACS-1 adheres fully to the ethical principles of the Declaration of Helsinki, the specifications of the International Conference on Harmonization, and Good Clinical Practice, including the requirement for each subject’s informed consent before initiating any study procedure.

**Study population**

GEMINI-ACS-1 will enroll approximately 3,000 patients with recent (<10 days) ACS. Patients with unstable angina, NSTEMI, and STEMI treated with medical therapy alone, PCI, or coronary artery bypass graft (CABG) surgery are eligible. Key inclusion and exclusion criteria are shown in Table III. Notably, patients younger than 55 years must have diabetes or have had an MI prior to the index presentation, and patients with NSTEMI or unstable angina must fulfill enrichment criteria to ensure a population at risk for future events.

Patients will receive at least 1 dose of DAPT with aspirin and a P2Y12 inhibitor prior to randomization and, in those undergoing PCI, an additional dose after PCI. All patients should be intended to be treated with DAPT for their ACS event and agree to provide a genetic sample for CYP2C19 testing.

**Randomization and treatment.** Randomization will be 1:1 stratified by intended P2Y12 inhibitor use (clopidogrel 75 mg daily or ticagrelor 90 mg twice daily), with approximately 1,500 patients in each P2Y12 inhibitor strata. The study will use a double-blind, double-dummy design. Patients will be provided with drug packs containing either aspirin (100 mg) or matching placebo taken once daily, and rivaroxaban or matching placebo taken twice daily. Dosing of aspirin was based on analyses indicating either greater or identical ischemic benefit but a bleeding hazard associated with higher aspirin dosing. All patients must receive a dose of DAPT prior to randomization. Patients undergoing PCI must receive 2 doses of DAPT, including a minimum of 1 dose post-PCI. Patients post-CABG surgery may be enrolled once able to tolerate DAPT, but not within 12 hours of CABG surgery. Study drug will be provided on the day of randomization and will be taken on a 12-hour schedule. All study drugs and P2Y12 inhibitors will be provided by the sponsor for the duration of the study.

All patients will be treated for 12 months or until the study treatment end date, defined as 180 days after the last subject is randomized. At the end of the treatment phase, or on permanent discontinuation of study drug, all patients will be instructed to receive treatment with aspirin (unless contraindicated) starting on the day after the last dose of study drug. The duration of continued background treatment with a P2Y12 inhibitor will be left to the discretion of the managing physician, but it is preferred that the P2Y12 treatment continues at least until the end of study visit.

All outcomes (bleeding, death, MI, stroke, and stent thrombosis) will be collected at days 30, 90, 180, 270, and 360, and at a study visit 30 days after permanent cessation of study drug, either during or at the conclusion of the study.

**Genomic evaluation.** A pharmacogenomics sample for assessment of CYP2C19 metabolizer status will be obtained from all participants. The principal investigator will be informed of genotyping results for all subjects regardless of P2Y12 inhibitor choice (clopidogrel or ticagrelor) and any prior CYP2C19 genotype testing, and will inform subjects of the results. No instructions or guidelines will be provided from study leadership on how to interpret or use these results; however, investigators will be asked to prespecify what actions they expect to take with regard to P2Y12 inhibitor choice, and actual action will subsequently be tracked.

**End points**

The primary end point is Thrombolysis in Myocardial Infarction (TIMI) clinically significant bleeding (major, minor, or requiring medical attention). The primary exploratory efficacy determination will be a composite of cardiovascular death, MI, ischemic stroke, and stent thrombosis. All ischemic and bleeding outcomes after randomization will be adjudicated by an independent clinical events committee (Appendix A), blinded to treatment assignment, using previously published criteria and recommended event definitions. Bleeding events will be adjudicated based on TIMI, Bleeding Academic Research Consortium, Global Use of Strategies
to Open Occluded Coronary Arteries, and International Society on Thrombosis and Haemostasis criteria. Undetermined deaths will be categorized as cardiovascular deaths. Importantly, for this trial, all hemorrhagic deaths will be categorized as cardiovascular deaths. Event definitions are shown in Table IV.

Alterations in study treatment during conduct of the trial

Study treatment may be temporarily held if the patient:

a. undergoes PCI, CABG, or any other surgical procedure;
b. experiences a significant bleeding event;
c. develops a new neurologic deficit or alteration in mental status;
d. develops a platelet count <50,000/μL;
e. has an adverse event related to or exacerbated by study drug; or
f. requires anticoagulation or prohibited therapy on a temporary basis.

In these cases, study drug can be resumed when deemed safe by the investigator. If appropriate, open-label aspirin may be used during this period. Patients should discontinue treatment if they require open-label long-term anticoagulation, have a transient ischemic attack or stroke, become pregnant, develop renal insufficiency (CrCl <15 mL/min), or request to stop study drug.

In rare cases, it may be necessary to unblind treatment assignment to allow proper medical treatment to be administered (for instance, to dose other anticoagulants during urgent procedures or thrombolysis). In such cases, the investigator may contact the interactive Web response system vendor to determine individual patient assignments. It is recommended that the investigator contact the sponsor or its designee, if possible, to discuss the particular situation before breaking the blind, and the sponsor must be informed as soon as possible after unblinding has occurred. Investigators will not disclose treatment assignment to the subject whenever possible; subjects who have had their treatment assignment unblinded may continue on study drug if appropriate.

Concern over stent thrombosis and safety review

Dual antiplatelet therapy with aspirin and a P2Y12 inhibitor is the standard for prevention of acute thrombotic complications since a series of trials compared ticlopidine and aspirin with other anticoagulation strategies. Several developments have altered this landscape, including the development of novel oral anticoagulants which reach therapeutic levels within hours of administration and are not accompanied by an initial prothrombotic state. In addition, the development of more potent P2Y12 inhibitors, their routine earlier administration in the treatment for ACS patients, and newer less thrombogenic stent technologies have continued to impact post-PCI care since the completion of the ATLAS trials. GEMINI-ACS-1 differs from many trials in the early transition (1-10 days after presentation) to a dual-pathway strategy using a single antiplatelet agent post-ACS. Given that early cessation of DAPT has been associated with a significant risk of stent thrombosis, the safety of this approach has yet to be established, although it is reassuring that several studies incorporating similar strategies have either completed enrollment or are ongoing without evident safety concerns raised.

To monitor and protect patient safety, GEMINI-ACS-1 will actively engage and use an independent data
monitoring committee (DMC), coordinated out of Stanford University, including experts in clinical trials, interventional cardiology, thrombosis, and biostatistics. The DMC chairman will review each definite and probable stent thrombosis, death, and major bleeding event as they are reported. The DMC is scheduled to review data every 4 months throughout the enrollment period. In addition, a DMC meeting may be convened without notification of the sponsor or trial leadership.

### Table III. Key inclusion and exclusion criteria

**Inclusion criteria**

- Age $\geq$ 18 y
- ACS within 48 h of hospitalization or while hospitalized
- Receiving DAPT and plan to continue DAPT
- If age $<55$ y, must have diabetes or MI prior to index event

**Enrichment criteria**

A. STEMI

- ECG criteria (1 of the following):
  - ST-segment elevation $>0.1$ mV in 2 or more contiguous leads
  - New LBBB
  - ST-segment depression $>0.1$ mV in V1-V4 (posterior MI)
- Elevated cardiac biomarkers

B. NSTEMI

- Clinical symptoms of ACS + elevated cardiac biomarkers AND at least 1 of the following:
  1. ECG criteria
     - Transient ST-segment elevation $>0.1$ mV
     - New horizontal or down-sloping ST depression $>0.05$ mV
     - New T-wave inversions $>0.1$ mV in 2 leads with prominent R wave of t/s ratio $>1$
  2. Identification of a culprit lesion by angiography
  3. Unstable angina

- Clinical symptoms of ACS + elevated cardiac biomarkers AND at least 1 of the following:
  1. EKG criteria as listed above
  2. Revascularization for the index event AND
  3. TIMI risk score $\geq 4$

**Exclusion criteria**

- Prior stroke or TIA
- Contraindication to anticoagulation including:
  - Active bleeding
  - History of intracranial hemorrhage
  - Clinically significant GI bleeding within 12 mo
  - INR $>1.5$ or plt count $<90,000/\mu L$
- Use of abciximab within 8 h, or eptifibatide or tirofiban within 2 h
- Creatinine clearance $<20$ mL/min
- Severe concomitant disease, including HIV, liver disease, life-limiting conditions
- Fibrinolytic therapy precludes enrollment in the ticagrelor stratum
- Use of omeprazole or esomeprazole in the clopidogrel stratum
- Need for chronic anticoagulation
- Need for chronic nonsteroidal anti-inflammatory drug use
- Unwilling to take contraceptive measures to prevent pregnancy (both sexes)

**Abbreviations:** ECG, Electrocardiogram; GI, gastrointestinal; HIV, human immunodeficiency virus; INR, international normalized ratio; LBBB, left bundle-branch block; MI, MI, plt, platelet; TIA, transient ischemic attack.

### Table IV. Bleeding and ischemic end points

**Bleeding end points**

<table>
<thead>
<tr>
<th>TIMI Major</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\geq 5$ g/dL drop in Hgb</td>
</tr>
<tr>
<td>Intracranial hemorrhage</td>
</tr>
<tr>
<td>Fatal hemorrhage</td>
</tr>
</tbody>
</table>

**TIMI Minor**

- 3-4.9 g/dL drop in Hgb
- Requiring medical attention
- Medical or surgical treatment
- Life-threatening
- Fatal
- Need for IV inotropes
- Requires surgical intervention
- $\geq 4$ U transfusion
- Symptomatic intracranial

**ISTH**

**GUSTO**

**BARC**

**Ischemic end points**

<table>
<thead>
<tr>
<th>Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular</td>
</tr>
<tr>
<td>MI</td>
</tr>
<tr>
<td>Sudden cardiac death</td>
</tr>
<tr>
<td>Stroke</td>
</tr>
<tr>
<td>Heart failure</td>
</tr>
<tr>
<td>Cardiovascular procedure</td>
</tr>
<tr>
<td>Any hemorrhagic death</td>
</tr>
<tr>
<td>Other</td>
</tr>
<tr>
<td>Undetermined</td>
</tr>
<tr>
<td>Noncardiovascular</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>Focal neurologic deficit $&gt;24$ h</td>
</tr>
<tr>
<td>Nonlocalizing or transient symptoms with imaging evidence of stroke</td>
</tr>
<tr>
<td>Categorized as hemorrhagic, ischemic, or unknown</td>
</tr>
</tbody>
</table>

**MI (universal definition)**

**Stent thrombosis (ARC definition)**

**Abbreviations:** ARC, Academic Research Consortium; BARC, Bleeding Academic Research Consortium; GUSTO, Global Use of Strategies to Open Occluded Coronary Arteries; Hgb, hemoglobin; ISTH, International Society on Thrombosis and Haemostasis; IV, intravenous.

### Statistical considerations

The primary objective of the study is to estimate bleeding risk of rivaroxaban 2.5 mg twice daily compared with aspirin 100 mg daily when added to background of P2Y12 inhibition. A Cox proportional hazards model from time of randomization to the first non-CABG surgery-related TIMI clinically significant bleeding event will be used for the primary analysis. Bleeding rates were modeled based on the ATLAS ACS 2–TIMI 51 trial, assuming 85 primary events per stratum, an incidence rate of 4.5% at day 180 and 6.5% at day 360 in the aspirin (DAPT) arm, and a discontinuation rate of 10% by day
As a sensitivity analysis of the primary end point, a P2Y12-stratified Cox proportional hazards model will be conducted based on the intention-to-treat analysis set and on-treatment analysis phase across strata. Homogeneity of treatment effects between the clopidogrel and ticagrelor strata will be explored via a test for treatment-by-stratum interaction using the Cox proportional hazards model with treatment, stratum, and the treatment-by-stratum interaction as the covariates at a 2-sided significance level of .05. If there is a statistically significant interaction, clinical interpretations will be explored.

Additional post hoc analyses may be conducted to investigate unexpected results, including the impact of differential study drug discontinuations and/or differential discontinuation of P2Y12 between the 2 treatment groups and between the 2 strata.

Summary

GEMINI-ACS-1 will assess the bleeding risk of a dual antithrombotic therapy compared with conventional DAPT in an ACS population, a substantial proportion of which are expected to undergo PCI for their index event, while monitoring for concerning signals around ischemic events, specifically stent thrombosis.

Acknowledgment

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Disclosures


References

trial is a report of the American College of Cardiology/American Heart Association task force on clinical data standards (writing committee to develop cardiovascular endpoints data standards). J Am Coll Cardiol 2015;66:403-69.


