Occurrence of Bleeding and Thrombosis during Antiplatelet therapy In Non-cardiac surgery
A prospective observational study

OBTAIN Study

Statistical Analysis Plan of Final Analysis

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1.0 BACKGROUND

OBTAiN is an international study to compare the use of aspirin alone with dual antiplatelet therapy (i.e. aspirin and clopidogrel) in patients presenting for elective non-cardiac surgery who have undergone PCI with either bare metal stent or drug eluting stent placement in the four years prior to surgery. It is an observational study conducted between March 2011 and December 2013 in 41 hospitals across 12 European nations. The target sample size is x 1400 patients. All patients older than 16 years admitted to participating hospitals for elective or non-elective surgery were eligible for inclusion.

This document describes the proposed statistical analysis for the OBTAiN study. The purpose is i) to clarify primary analyses ii) to avoid any potentially spurious interpretations that would arise from post-hoc analyses. Thus the statistical plan has been drawn up in advance of looking at the outcome data.

2.0 OBJECTIVE

This study will compare dual antiplatelet therapy with aspirin and clopidogrel to aspirin monotherapy in the perioperative period. The study population will be patients undergoing non-cardiac surgery within four years of PCI with a bare metal stent or drug eluting stent. Studies reviewed in the introduction (above) lead us to expect that dual antiplatelet therapy will be associated with a decreased risk of major adverse cardiac events in the perioperative period but with an increased risk of bleeding. The question that will be addressed by this study is whether the benefit of dual antiplatelet therapy in reducing MACE outweighs the hazard posed by clinically significant bleeding and clopidogrel outweighs the hazards of this treatment. The following two research questions will be addressed by the study.

1) What is the absolute risk reduction for in-hospital MACE associated with the use of dual antiplatelet therapy as compared with aspirin alone in this population?

2) What is the absolute risk increase for clinically significant bleeding during the same period associated with the use of dual antiplatelet therapy as compared with aspirin alone in this population?

3.0 DESCRIPTIVES

3.1 Study Profile

The flow of study participants will be displayed in diagram patient flow diagram as recommended in strengthening the Reporting of Observational Studies in Epidemiology (STROBE). The number of patients who fulfilled study inclusion criteria, and the number of patients included in the primary and secondary analyses as well as reasons for exclusion will be reported. Frequency of missing or inconsistent data will also be reported.
3.2 Antiplatelet use

Preoperative antiplatelet use (aspirin, clopidogrel or other antiplatelet agent) is defined as antiplatelet therapy taken 7 days or less before surgery.

Mono therapy is defined as having aspirin and dual antiplatelet therapy as aspirin in combination with clopidogrel or other antiplatelet agent.

Working definition preoperative aspirin use:

- Aspirin use started before or on admission (ASP_E3_C3=1 or ASP_E3_C3=2)
- If aspirin discontinued, and time between date of discontinuation and date of surgery is 7 days or less, preoperative aspirin use is yes. (ASPDISC_E3_C3=1 & ASPSRDT_E3_C3, SURGDAT_E2_C2)
- If aspirin discontinued, and time between date of discontinuation and date of surgery is more than 7 days, preoperative aspirin use is no. (ASPDISC_E3_C3=1 & ASPSRDT_E3_C3, SURGDAT_E2_C2)

Working definition preoperative clopidogrel use:

- Clopidogrel use started before or on admission (CLP_E3_C3=1 or CLP_E3_C3=2)
- If clopidogrel discontinued, and time between date of discontinuation and date of surgery is 7 days or less, preoperative clopidogrel use is yes. (CLPDISC_E3_C3=1 & CLPSRDT_E3_C3, SURGDAT_E2_C2)
- If aspirin discontinued, and time between date of discontinuation and date of surgery is more than 7 days, preoperative clopidogrel use is no. (CLPDISC_E3_C3=1 & CLPSRDT_E3_C3, SURGDAT_E2_C2)

Working definition preoperative other antiplatelet agent use:

- Other antiplatelet use started before or on admission (OTHIE_E3_C3=2 or OTHIE_E3_C3=3)
- If other antiplatelet agent discontinued, and time between date of discontinuation and date of surgery is 7 days or less, preoperative other antiplatelet agent use is yes. (extra data query round 3)
- If other antiplatelet agent discontinued, and time between date of discontinuation and date of surgery is more than 7 days, preoperative other antiplatelet agent use is no. (extra data query round 3)

Working definition mono and dual antiplatelet use:

- Mono antiplatelet therapy: only preoperative aspirin (as defined above)
- Dual antiplatelet therapy: preoperative use of aspirin (as defined above) in combination with clopidogrel (as defined above) or other antiplatelet agent (as defined above).

### 3.3 Baseline characteristics

Baseline demographics and clinical data for patients who were given dual antiplatelet therapy compared to those with single antiplatelet therapy. The following baseline characteristics will be compared before and after propensity score matching:

- **Demographic:** Age, gender
- **ASA score, Urgency of surgery, grade of surgery, surgical speciality (type of surgery), and comorbid disorders.**
- **Details of most recent PCI:** time between PCI and non-cardiac surgery, number of stents deployed, type of stents used (if both drug eluting and bare metal the patient with be considered to have drug eluting stents in situ).
- **Risk factors for stent thrombosis:** Advanced age (>79 years), ejection fraction (%), stent placed for acute coronary syndrome, multiple stents, diabetes, renal impairment.
- **Risk factors for major adverse cardiac events:** Previous myocardial infarctions, previous cerebrovascular accidents, previous episodes of acute heart failure, angina, ECG or echocardiographic evidence of left ventricular hypertrophy, limited exercise tolerance (unable to climb one flight of 10-12 stairs without stopping), history of smoking, left ventricular ejection fraction.

Number (%), means (SD), or medians (IQR) as appropriate will be given in each category.

### 3.4 Clinical Management

Clinical management for antiplatelet groups will be summarised and subject to statistical testing. The following characteristics will be compared:

- **Anaesthetic technique**
- **Medication use**
- **Transfusion**

Number (%), means (SD), or medians (IQR) as appropriate will be given in each category. P values will be quoted to analyse if there is any association between these factors and antiplatelet therapy.

### 3.5 Outcome

This study will record and analyse in-hospital major adverse cardiac events and clinically significant bleeding.

**Major Adverse Cardiac Events (MACE)** will be defined as a composite of:
1. Myocardial infarction as defined by the Universal Definition of Myocardial Infarction (including cardiac arrest and cardiac death as described in this definition) 2007;[1] i.e. troponin above URL together with ischemia symptoms/ ECG changes (ST+LBBB)/ Q waves/ NWMA and sudden unexpected cardiac death (including cardiac arrest)

2. PCI for a cardiac event occurring following surgery.

**Working Definition MACE:**

1. Peak postoperative troponin above URL (PPTRPVAL_E2_C2>=TRPUPPL_E2_C2)
   
   Combined with one of the following:
   
   A. Postoperative chest pain suspected to be cardiac (CHPAIN_E2_C2=1)
   
   B. New postoperative conduction defect on ECG and nature conduction defect is LBB
      (ECGDEFCNT_E2_C2=1 & ECGCNDNT_E2_C2=2)
   
   C. New postoperative ST depression or elevation greater than 1 mm on ECG
      (STDPELV_E2_C2=1)
   
   D. New postoperative Q-waves (ECGQWV_E2_C2=1)
   
   E. New wall motion abnormality (CRIMGMOT_E2_C2=1))

2. Postoperative cardiac arrest (PCIAST_E2_C2=1)

3. In-hospital death with cardiovascular cause (HDTCAU_E2_C2=1)

4. Postoperative coronary angio with new changes (evidence of new in stent coronary thrombosis/stenosis; or evidence of coronary thrombosis/stenosis not in stent)
   (CORANGIO_E2_C2=1 & (ANGIOEVI_E2_C2=3 | ANGIOEVI_E2_C2=4))

**Clinically Significant Bleeding Events** will be defined as:

1. Reoperation for bleeding

2. Gastrointestinal haemorrhage

3. Intracranial haemorrhage/Haemorrhagic stroke

4. Spinal/epidural haematoma

**Working definition Clinically Significant Bleeding**
1. Reoperation for bleeding (REOPBLD_E2_C2=1)
2. Haemorrhagic stroke (POGSHMR_E2_C2=1)
3. Spinal or epidural haematoma (POSPHMT_E2_C2=1)
4. Haemorrhagic stroke (POGSHSTR_E2_C2=1)

The transfusion of blood and blood products will also be recorded and compared between patients on dual antiplatelet therapy and aspirin alone.

4.0 PRIMARY ANALYSES

4.1 Outcome
The primary endpoint of the study is in-hospital MACE and bleeding in patients who receive dual versus single antiplatelet therapy. Outcome will be compared between the two groups using chi-squared test and Fisher’s exact test. P values will be reported and significance will be set to p<0.05.

Binary logistic regression model will be used to conduct univariable and multivariable analysis to explore the effect of antiplatelet therapy on outcomes. Potential confounders are: age, gender, lower ejection fraction, PCI for ACS, diabetes, multiple stents, and PCI within one year of surgery. The results of the logistic regression model will be reported as an adjusted odds ratio with 95% confidence interval. The unadjusted odds ratio will be presented for comparison.

Complete case analysis will be undertaken provided that missingness of key covariates is less than 5%. See also Section 6.0 for sensitivity analyses.

4.2 Propensity matching
The analysis of data from this study will be based on the use of propensity scoring to mimic some of the characteristics of a randomised controlled trial of mono vs. dual antiplatelet therapy in patients undergoing non-cardiac surgery.

1. Propensity score matching. A propensity score will be developed using logistic regression to model for the propensity of patients to be prescribed dual antiplatelet therapy. Factors that may affect the choice of antiplatelet therapy are the risk factors which may predispose to stent thrombosis and the cardiovascular risk factors listed under 3.2 (i.e. Advanced age (>79 years), ejection fraction (%), stent placed for acute coronary syndrome, multiple stents, diabetes, renal impairment, previous myocardial infarctions, previous cerebrovascular accidents, previous episodes of acute heart failure, angina, ECG or echocardiographic evidence of left ventricular hypertrophy, limited exercise tolerance (unable to climb one flight of 10-12 stairs without stopping), history of smoking, left ventricular ejection fraction). Age, sex, operative risk, type of stent and timing between PCI and non-cardiac surgery will also be included in the model. Centre will be fitted as a random effect to take the clustering of the patients within the centres into account. Patients will be matched by propensity to receive dual antiplatelet therapy. During propensity scoring, covariate balancing will be sought so that the subsequent results will be robust against mis-specification of the propensity model. We will
aim to balance on a subset of variables: age, sex, diabetes, type of stent, timing between PCI and non-cardiac surgery, surgical risk.

2. MACE and clinically significant bleeding will be compared between the two matched groups.
3. The absolute risk reduction for MACE and the absolute risk increase for bleeding associated with dual antiplatelet therapy will be derived.

From the absolute risk reduction and increase values derived in (3) above the NNT for reduction in MACE and the NNH for the increase in clinically significant bleeding will be derived. From the comparison of these figures we will draw conclusions regarding the relative risk and benefit of dual antiplatelet therapy in this setting.

5.0 SENSITIVITY ANALYSES
The impact on the interpretation of the findings due to missing or inconsistent values will be explored by imputation. Should the rate of missingness and inconsistent values be less than 2%, then extreme values of the covariates will be substituted, covariate by covariate, to assess the extreme impacts on the model and consequent interpretations. If the rate of missingness and inconsistent data be greater than 2% then multiple imputation techniques will be implemented to assess the impact on findings should the data be regarded as missing at random.
Appendix 1: Dummy tables and figures

Figure 1: STROBE patient flow diagram

XXXXX patients who underwent surgery

Reason for exclusion

XXXXX with data available for inclusion/analysis

Reason for further exclusion (if any)

XXXXXX included in analysis

Number not matched

Xxxx included in propensity matched analysis
Table 1: Antiplatelet therapy at presentation and at surgery

<table>
<thead>
<tr>
<th></th>
<th>At Presentation</th>
<th>At Surgery (within 7 days)</th>
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<tbody>
<tr>
<td>None</td>
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</tr>
<tr>
<td>Single</td>
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<tr>
<td>Dual</td>
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<tr>
<td>TOTAL</td>
<td></td>
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</tr>
</tbody>
</table>
Table 2: Baseline Characteristics (before+after matching)

<table>
<thead>
<tr>
<th>Antiplatelet Therapy</th>
<th>None n=</th>
<th>Single n=</th>
<th>Dual n=</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt;80</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
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<td></td>
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<tr>
<td>Renal impairment</td>
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<td></td>
<td></td>
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<tr>
<td>Multiple stents</td>
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<tr>
<td>Previous MI</td>
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<td></td>
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<tr>
<td>Angina</td>
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<tr>
<td>Previous CABG</td>
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<tr>
<td>LVH</td>
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### Table 3: MACE

<table>
<thead>
<tr>
<th>Antiplatelet Treatment</th>
<th>No Event</th>
<th>MACE</th>
<th>Odds Ratio</th>
</tr>
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<tbody>
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<td>None</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dual</td>
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### Table 4: Perioperative Bleeding

<table>
<thead>
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<th>Antiplatelet Treatment</th>
<th>No Event</th>
<th>Bleeding</th>
<th>Odds Ratio</th>
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</thead>
<tbody>
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<td>None</td>
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</tr>
<tr>
<td>Single</td>
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<tr>
<td>Dual</td>
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