2. B008 Synopsis

Clinical Study Report Synopsis: Study H7T-MC-B008

Title of Study: Treatment Patterns and Bleeding Risks Comparison in Patients Treated with Clopidogrel and Prasugrel during the Index Hospitalisation in Germany

Number of Investigators: The exact number of investigators was not determined as this observational study was part of the Arbeitsgemeinschaft Leitender Kardiologischer Krankenhausaerzte – Percutaneous Coronary Intervention (ALKK-PCI) registry in Germany. The ALKK-PCI registry was based on an obligatory quality control program which requires all hospitals in Germany to document their coronary angiography and interventional procedures.

Study Centers: Data from 32 hospitals are included in this registry.

Publication Based on the Study: None at this time.

Length of Study:	**Phase of Development:** Observational Study
Date of first patient visit: 15 October 2009 Date of last patient visit: 28 February 2013	

Objectives:

The main B008 study objectives were as follows:

- To compare the incidence rates (cumulative incidence) of any non-CABG related bleeding (requiring any blood transfusion of whole blood or red blood cell concentrates [RBCs]) and/or intracranial hemorrhage (ICH) between prasugrel and clopidogrel patients treated for ACS-PCI (the indicated population for prasugrel) during the index hospitalisation.
- To compare the incidence rates (cumulative incidence) of any bleeding (requiring any blood transfusion of whole blood or RBCs) and/or ICH in:
  - ACS prasugrel and clopidogrel treated patients
  - identified subgroups of patients at increased risk for bleeding.
- To describe incidence rates of any bleeding in all ACS-PCI and ACS prasugrel and clopidogrel initiators
  - quantified by receiving any transfusion or not, and by number of units transfused
  - by anatomic bleeding location
- To describe the number, percentage, patient characteristics, and outcomes (for example, bleeding or death) in all prasugrel treated patients who
  - were not indicated (elective PCI, non-ACS)
  - were contraindicated (history of TIA/stroke, active pathological bleeding, known severe hepatic impairment)
  - received loading dose prior to coronary visualization
  - were treated with a 5 mg, 10 mg or other maintenance dose
  - were very elderly (≥75 years)
  - had a low body weight (<60 kg).

Study Design: The German Anwendungsbeobachtung zur **A**ntithrombozytären **T**herapie bei Patienten mit **ACS** und invasiver Diagnostik (ATACS) registry, also referrred to as Study H7T-MC-B008 (B008), was a prospective, observational, non-interventional, cohort study designed to assess bleeding risk in prasugrel-treated patients compared with clopidogrel-treated patients and the treatment patterns of prasugrel during the index hospitalisation in the ALKK-PCI registry in Germany. The ALKK-PCI registry is based on an obligatory quality control program which requires all hospitals in Germany to document their performed invasive coronary angiographic and interventional procedures. Cardiology centres belonging to the ALKK provided demographic and medical information on their consecutive patients who met inclusion criteria. Patients included in Study B008 were observed only during the index hospitalisation. This final report includes cumulative data that were collected between 15 October 2009 and 28 February 2013 describing baseline patient demographic and clinical characteristics, prasugrel/clopidogrel treatment patterns, PCI features, stent features, and bleeding incidence rates and characterization. Annual reports were previously submitted to CHMP for Study B008.

Number of Patients: This was an observational study.
Total number of patients: 11,201

Diagnosis and Main Criteria for Inclusion:
Patients who underwent an invasive cardiac diagnostic procedure in hospitals participating in the ALKK-PCI registry were considered for Study B008. The inclusion criteria were as follows:

- At least 18 years of age at study entry,
- Acute coronary syndrome (ACS) or treatment with prasugrel (with or without ACS),
- Prescribed clopidogrel or prasugrel during the index hospitalisation.

Patients were excluded from Study B008 for the following reason:

- Simultaneously participating in another study which includes an investigational drug at study entry.

The ideal ACS-PCI population was defined as follows:

- Prasugrel-treated patients:
  - without contraindication (history of transient ischemic attack [TIA]/stroke, active pathological bleeding, severe hepatic dysfunction), and
  - body weight ≥60 kg and age <75 years of age.
- Clopidogrel-treated patients:
  - without contraindication (active pathological bleeding).

Study Drug and Dose: Eligible patients were treated with prasugrel or clopidogrel at the discretion of the treating physicians. Treatment initiation or changes were solely at the discretion of the physician and the patient. Treatments for PCI were prescribed in the usual standard of care and were not provided by the study Sponsor.

Variables:
Data collected in the ATACS registry included the following:

- demography and some technicalities
- indication: prior revascularisation and important risk factors, initial assessment and presentation
- process: duration, patient's exposure and technical aspects of the procedure
- outcome: intra-procedural complications and adverse events during hospital stay
- cardiovascular history and comorbidities
- adjunctive antithrombotic medication
- treated lesions
- use of stents
- in-hospital events
- the timing of the LD of prasugrel and clopidogrel
- loading and maintenance doses of prasugrel and clopidogrel
- timing of the visualisation of the coronary arteries by angiography
- sites and date of bleeding (intracranial bleeding, retroperitoneal bleeding, GI bleeding, epistaxis, intraocular bleeding, haematuria, haemoptysis, puncture site, surgical site other than CABG- and PCI-related, haemopericardial, CABG-related bleeding, PCI-related bleeding)
- bleeding severity (blood transfusion ≥4 units of whole blood or RBCs versus blood transfusion <4 units of whole blood or RBCs)
- bleeding risk factors and contraindications for prasugrel

Statistical Methods:

Main Summary Measures: Descriptive summary measures are presented in tabular form for all relevant variables in the defined analysis populations and treatment groups. In addition to the total group, the calculations were done for the strata of patients with ST-segment elevation MI (STEMI), ACS without ST-segment elevation (NSTEMI or unstable angina [UA]), and patients without ACS if relevant. For binary variables, percentages and absolute counts of available cases and the category of interest are shown. For categorical variables with more than 2 categories the frequency of each category is shown. Metrically scaled variables are presented in suitably categorized form. The distribution of the key variables of age and body weight was additionally characterized by mean, standard deviation, median, quartiles, minimum, and maximum.

Main Statistical Methods: The clinical and procedural characteristics were compared between the 2 treatment groups calculating descriptive p-values. The Pearson chi-squared test was used for categorical variables, or Fisher's exact test in the case of dichotomous variables if at least one expected frequency in the contingency table was less than or equal to five. For the comparison of metrical variables, the Mann-Whitney-Wilcoxon test was applied.
The rates of defined endpoints were compared between treatment groups by using Fisher's exact test. Rates of bleeding events were shown in several analysis populations as well as in some known high-risk subgroups.

The associations of baseline characteristics and presumed risk factors with the specified outcomes were analysed in each treatment group separately, by comparing the distributions in patients with versus without the considered event. The metrical variables including age and weight were divided into categories. P-values and/or odds ratios (ORs) with 95% CI were reported for the test of association/treatment difference. In the case of multi-categorical factors, odds ratios (ORs) were calculated by logistic regression with respect to an appropriate reference category.

All CIs were 2-sided at the 95% confidence level and all tests of significance were performed at a 2-sided .05 significance level. No adjustment for multiple testing was made.

Propensity Scores: The propensity scores for the choice 'prasugrel treatment' were estimated from logistic regression models for the ACS population (Population i), the ACS-PCI population (Population c) and the "ideal" low-risk ACS population (Population j). The following indicators identifying basic patient groups were included: STEMI, performed PCI, and chronic pre-treatment with clopidogrel or prasugrel. Age, gender and body weight were included as known risk factors. Further potential predictors that showed different distributions in prasugrel and clopidogrel patients (univariate comparisons $p<0.01$), or were pre-specified as known risk factors, were considered for inclusion; these patient characteristics included diabetes, renal insufficiency, symptoms of heart failure, cardiogenic shock, previous MI, previous PCI, previous coronary angiography, previous CABG, history of stroke/TIA, peripheral vascular disease, arterial hypertension, severe hepatic dysfunction, smoking, and medical treatment with vitamin K antagonists, GP IIb/IIIa antagonists, aspirin, thrombolysis, and proton pump inhibitors, as well as radial access.

The significance of the covariates and their impact on the balance of patient characteristics was observed, especially those variables identified as associated with bleeding events. The achieved balance was assessed by comparison between treatment groups in quintiles of the propensity score and goodness of fit by the Hosmer-Lemeshow test. The functional form for age and weight was assessed using generalized additive models, and appropriate regression splines were calculated and entered in the model. The covariates were tested for interaction with type of ACS (NSTEMI/ UA or STEMI) and interaction terms were included for the relevant variables.

SUMMARY OF FINDINGS

Drug Usage Patterns in Prasugrel-Treated Patients

- A majority were ACS-PCI patients (Population c: the indicated population for prasugrel).
- A majority were <75 years of age and had body weight ≥60 kg.
    - Of those elderly and lower body weight patients who received a prasugrel maintenance dose (MD) during the index hospitalisation, the majority received 10 mg (≥75 years = 76.6%; <60 kg = 80.4%).
- Very few patients had contraindications such as TIA/stroke.
- The majority received a 60-mg LD (approximately 87%).

- A little more than half received the LD prior to coronary visualization; this percentage was highest in UA/NSTEMI in the all prasugrel (Population f: 70.4%), ACS prasugrel (Population i: 70.4%) and in the ACS-PCI prasugrel (Population c: 63.4%) populations.
- Fewer prasugrel-treated patients underwent emergency CABG after PCI than clopidogrel-treated patients (0.7% versus 1.5%; p<0.01). Data are not available indicating whether or not prasugrel was given prior to coronary visualization or indicating the specific LD used in patients who underwent CABG.

Results of Primary Analysis

The primary inferential analysis was non-CABG-related bleeding (requiring any transfusion of whole blood or RBCs) and/or ICH in patients with ACS undergoing PCI, the population indicated for prasugrel during the index hospitalisation. Adjustment of the comparison of bleeding endpoints was primarily done by stratification according to quintiles of the propensity score. This analysis was performed on the ACS-PCI population (Population c) and post hoc analyses were performed on the ACS population (Population i) and the ideal low-risk ACS population (Population j).

- There was not a statistically significant difference between prasugrel- and clopidogrel-treated patients in the non-CABG-related bleeding rate (requiring any transfusion of whole blood or RBCs) and/or ICH (adjusted for quintiles of the propensity score) in patients treated for ACS-PCI (Population c; the indicated population for prasugrel):
    - ACS-PCI population (Population c): (0.64% versus 0.76%; aOR [95% CI]: 1.48 [0.74-2.97], p=0.267)
- Post hoc analyses of the primary endpoint were also performed in the ACS population and in the ideal low-risk ACS population:
    - ACS population (Population i): 0.61% versus 0.71%; aOR [95% CI]: 1.39 [0.72-2.70], p=0.326
    - Ideal low-risk ACS population (Population j): 0.60% versus 0.35%; aOR [95% CI]: 2.36 [0.98-5.68], p=0.056).

Additional Analyses of Bleeding Rates Adjusted for Quintiles of the Propensity Score

- Rates of all bleeding (requiring any transfusion of whole blood or RBCs) and/or ICH (adjusted for quintiles of the propensity score) were very similar to results of the primary analysis:
    - Results for the ACS-PCI population (Population c) were identical for non-CABG and all bleeding events as there was no CABG-related bleeding in this population.
    - Compared with results of non-CABG analyses for the ACS population (Population i) and the ideal low-risk population (Population j), there were few additional events:
        - ACS population (Population i): 0.65% versus 0.71%; OR [95% CI]: 1.35 [0.72-2.55], p=0.352
        - Ideal low-risk ACS population (Population j): 0.65% versus 0.42%; OR [95% CI]: 2.15 [0.94-4.92], p=0.069
- Prasugrel-treated patients had significantly higher rates of any bleeding (adjusted for quintiles of the propensity score) compared with clopidogrel-treated patients in all 3 populations:
    - ACS-PCI population (Population c): (1.96% versus 1.82%; OR [95% CI]: 2.09 [1.37-3.18], p<0.001)
    - ACS population (Population i): 1.86% versus 1.82%; OR [95% CI]: 1.94 [1.30-2.90], p=0.001
    - Ideal low-risk ACS population (Population j): 1.91% versus 0.84%; OR [95% CI]: 3.03 [1.77-5.21], p<0.001).

Results of Bleeding Analyses

- No fatal bleeding was observed in prasugrel-treated patients.
- Forty-seven (1.7%) prasugrel-treated patients experienced any bleeding.
- The percentages of patients having any transfusion and median units for those with transfusions were low and similar for prasugrel- versus clopidogrel-treated patients in the ACS-PCI population (Population c):
    - Percentage of patients having any transfusion: 0.6% versus 0.6%, p=0.87
    - Median units for patients who received transfusions: 0 (0-1) versus 0 (0-2)

- Notable anatomic bleeding locations for prasugrel- and clopidogrel-treated patients in the ACS-PCI, respectively, were as follows:
    - Rates of ICH were low and similar between treatment groups: 0 versus 0.1%, p=0.68
    - Retroperitoneal bleeding was significantly higher for prasugrel- versus clopidogrel-treated patients: 0.2% versus 0%, p<0.01
    - GI bleeding was significantly lower for prasugrel- versus clopidogrel-treated UA/NSTEMI patients: 0% versus 0.5%, p<0.05

Bleeding Risk by Subgroups

Descriptive analyses of bleeding events in patients who received an LD of prasugrel by contraindication, timing of prasugrel LD, body weight, and age included the following findings:

- No bleeding events occurred in the 41 patients with a history of TIA/stroke who received a prasugrel LD.
- Of 5 patients with active pathological bleeding who received a prasugrel LD, 1 (20.0%) had any bleeding, but did not require any blood transfusion.
- Of 9 patients with known severe hepatic impairment who received a prasugrel LD, 1 (11.1%) had any bleeding which required blood transfusion of whole blood or RBCs and/or ICH.
- Of 269 non-ACS patients who underwent an elective PCI and received a prasugrel LD, 1 patient (0.4%) had any bleeding which required blood transfusion of whole blood or RBCs and/or ICH.
- Of 1329 patients who received a prasugrel LD prior to coronary visualization, 20 (1.5%) had any bleeding, with 9 requiring blood transfusion of whole blood or RBCs and/or ICH. Of 989 patients who received a prasugrel LD after coronary visualization, 20 (2.0%) had any bleeding, with 5 requiring blood transfusion of whole blood or RBCs and/or ICH.
- Of 158 patients ≥75 years of age who received a prasugrel LD, 4 (2.5%) had any bleeding requiring any blood transfusion of whole blood or RBCs and/or ICH.
    - Of the 121 patients ≥75 years of age who received a 10-mg MD of prasugrel during the index hospitalisation, 2 (1.7%) patients had any bleeding and none required blood transfusion.
- Of 56 prasugrel-treated patients with body weight <60 kg who received a prasugrel LD, 3 (5.4%) had any bleeding requiring any blood transfusion of whole blood or RBCs and/or ICH (all 3 received a 10-mg MD of prasugrel during the index hospitalisation).
    - Of the 45 patients with body weight <60 kg who received a 10-mg MD during the index hospitalisation; 3 (6.7%) of these patients had any bleeding requiring any blood transfusion of whole blood or RBCs and/or ICH.

Non-CABG and Any Bleeding Risk by Subgroups

Unadjusted analyses of non-CABG and any bleeding events for all prasugrel-treated patients were performed for subgroups including prasugrel indication (not indicated or contraindicated), LD prior to or after coronary visualization, prasugrel MD of 5 mg or 10 mg, age <75 or ≥75 years and body weight <60 kg or ≥60 kg.

- In results of non-CABG bleeding subgroup analyses, the treatment-by-subgroup interaction based on body weight was significant (interaction p=0.022). There were no other significant treatment-by-subgroup interactions observed for the remaining subgroups including prasugrel indication (contraindicated or not indicated [no ACS], LD prior to or after coronary visualization, prasugrel MD of 5 mg or 10 mg, or age ≥75 or <75 years.
    - In patients weighing <60 kg, prasugrel-treated patients had a significantly higher rate of non-CABG bleeding compared with clopidogrel-treated patients (5.56% versus 1.38%, p=0.037). There was not a significant between-treatment difference observed in patients ≥60 kg.
    - The rate of non-CABG-related bleeding in patients receiving LD prior to coronary visualization was similar to the rates of non-CABG bleeding in patients receiving LD after coronary visualization for both prasugrel- and clopidogrel-treated patients:
        - LD prior to coronary visualization for prasugrel versus clopidogrel: 0.62% (8/1300) versus 0.73% (28/3821); OR (95% CI): 0.84 (0.38-1.85); p=0.662
        - LD after coronary visualization for prasugrel versus clopidogrel: 0.51% (5/989) versus 0.66% (15/2264); OR (95% CI): 0.76 (0.28-2.10); p=0.598

- In results of subgroup analyses of any bleeding, no significant treatment-by-subgroup differences in rates of any bleeding were observed for prasugrel- versus clopidogrel-treated patients for any subgroup.
    - However, a significant between-treatment difference was observed for those age <75 with prasugrel-treated patients having a higher rate of any bleeding compared with clopidogrel-treated patients (1.85% versus 1.06%, p=0.008).

Conclusion

The main objective of Study B008 was to compare the incidence rates (cumulative incidence) of any non-CABG related bleeding (requiring any blood transfusion of whole blood or RBCs) and/ICH between prasugrel- and clopidogrel-treated patients treated in the ACS-PCI population (population c; the indicated population for prasugrel) during the index hospitalisation. There were no statistically significant differences between prasugrel- and clopidogrel-treated patients in the non-CABG-related bleeding rate (requiring any transfusion of whole blood or RBCs) and/or ICH (adjusted for quintiles of the propensity score) in the ACS-PCI population: (0.64% versus 0.76%; OR [95% CI]: 1.48 [0.74-2.97], p=0.267).

Study B008 was expected to address the CHMP concern with the possible risk of CABG-related bleeding associated with administration of a prasugrel LD prior to coronary angiography. More than half of prasugrel-treated patients received the approved 60-mg LD prior to coronary visualization in a real-world, in-hospital, registry setting. Prasugrel-treated subjects who underwent CABG had a very low rate of CABG-related bleeding. It is also notable that the unadjusted rates of non-CABG-related and "any" bleeding were not impacted by the timing of the prasugrel LD.

In conclusion, regarding results of the primary analysis, one possible reason for the similar event rate in prasugrel- and clopidogrel-treated patients may be that a majority of prasugrel-treated patients were <75 years of age (94.2%) and had a body weight ≥60 kg (97.6%). Thus, it appears that physicians from these 32 hospitals in the German registry are selecting a patient population for prasugrel use in which these serious bleeding events are of no greater concern than for clopidogrel-treated patients.

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2.2. Study Overview

The German Anwendungsbeobachtung zur **A**ntithrombozytären **T**herapie bei Patienten mit **ACS** und invasiver Diagnostik (ATACS) registry, also referrred to as Study H7T-MC-B008 (B008) was a prospective non-interventional cohort study designed to assess bleeding risk in prasugrel-treated patients compared with clopidogrel-treated patients and the treatment patterns of prasugrel during the index hospitalisation in the German Arbeitsgemeinschaft Leitender Kardiologischer Krankenhausaerzte – Percutaneous Coronary Intervention (ALKK-PCI) registry in Germany. Study B008 was expected to address the Committee for Medicinal Products for Human Use (CHMP) concern with possible coronary artery bypass graft-(CABG) related bleeding risk associated with the administration of a prasugrel loading dose (LD) prior to coronary angiography.

The ALKK-PCI registry is based on an obligatory quality control program which requires all hospitals in Germany to document their performed invasive coronary angiographic and interventional procedures. Altogether 32 hospitals participated in Study B008, among them 25 non-university hospitals and 7 university hospitals. The university hospitals are not regular members of the ALKK and contributed 17% of the enrolled cases. Cardiology centres belonging to the ALKK provided demographic and medical information on consecutive patients who met the inclusion criteria. Patients included in Study B008 were observed only during the index hospitalisation.

This final report includes cumulative data that have been collected between 15 October 2009 and 28 February 2013 describing baseline patient demographic and clinical characteristics, prasugrel/clopidogrel treatment patterns, PCI features, stent features, and bleeding incidence rates and characterization. Annual reports were previously submitted to CHMP from the ALKK-PCI registry.

2.3. Objectives

The main B008 study objectives were as follows:

- To compare the incidence rates (cumulative incidence) of any non-CABG related bleeding (requiring any blood transfusion of whole blood or red blood cell concentrates [RBCs]) and/or intracranial haemorrhage (ICH) between prasugrel and clopidogrel patients treated for ACS-PCI (the indicated population for prasugrel) during the index hospitalisation.
- To compare the incidence rates (cumulative incidence) of any bleeding (requiring any blood transfusion of whole blood or RBCs) and/or ICH in:
    - ACS prasugrel- and clopidogrel-treated patients
    - identified subgroups of patients at increased risk for bleeding.
- To describe incidence rates of any bleeding in all ACS-PCI and ACS prasugrel and clopidogrel initiators
    - quantified by receiving any transfusion or not, and by number of units transfused
    - by anatomic bleeding location
- To describe the number, percentage, patient characteristics, and outcomes (for example, bleeding or death) in all prasugrel-treated patients who
    - were not indicated (elective PCI, non-ACS)
    - were contraindicated (history of TIA/stroke, active pathological bleeding, known severe hepatic impairment)
    - received loading dose prior to coronary visualization
    - were treated with a 5 mg, 10 mg or other maintenance dose
    - were very elderly (≥75 years)
    - had a low body weight (<60 kg).

2.4. Populations for Analysis

2.4.1. Inclusion Criteria

Patients who underwent an invasive cardiac diagnostic procedure in hospitals participating in the Study B008 were considered for the study. The inclusion criteria were as follows:

- At least 18 years of age at study entry,
- Acute coronary syndrome (ACS) or treatment with prasugrel (with or without ACS),
- Prescribed clopidogrel or prasugrel during the index hospitalisation.

Patients were excluded from Study B008 for the following reason:

- Simultaneously participating in another study which includes an investigational drug at study entry.

The ideal ACS-PCI population (Population d) was defined as follows:

- Prasugrel-treated patients:
  - without contraindication (history of transient ischemic attack [TIA]/stroke, active pathological bleeding, severe hepatic dysfunction), and
  - body weight ≥60 kg and age <75 years of age.
- Clopidogrel-treated patients:
  - without contraindication (active pathological bleeding).

2.4.2. Analysis Populations

Patient characteristics, treatment patterns, and bleeding incidence were described for the following 10 study populations.

Analysis Population Definitions

a) ACS-PCI prasugrel- and clopidogrel-treated patients receiving an LD of either drug during the index hospitalisation but not on permanent therapy of either drug upon admission.

b) Ideal ACS-PCI prasugrel- and clopidogrel-treated patients receiving an LD of either drug during index hospitalisation but not on permanent therapy of either drug upon admission.

c) ACS-PCI prasugrel- and clopidogrel-treated patients receiving an LD of either drug during the index hospitalisation regardless of previous exposure of either drug (Population c).

d) Ideal ACS-PCI prasugrel- and clopidogrel-treated patients receiving an LD of either during index hospitalisation regardless of previous exposure of either drug. The ideal ACS-PCI population (Population d) was defined as follows:

   - Prasugrel-treated patients:
     - without contraindication (history of transient ischemic attack [TIA]/stroke, active pathological bleeding, severe hepatic dysfunction), and
     - body weight ≥60 kg and age <75 years of age.
   - Clopidogrel-treated patients:
     - without contraindication (active pathological bleeding).

e) All prasugrel- and ACS clopidogrel-treated patients receiving a LD of either drug during the index hospitalisation but not on permanent therapy of either drug upon admission.

f) All prasugrel- and ACS clopidogrel-treated patients receiving a LD of either drug during the index hospitalisation regardless of previous exposure of either drug (Population f).

g) All prasugrel- and ACS clopidogrel-treated patients who did not receive a loading dose of either drug, but only maintenance dose of either prasugrel or clopidogrel.

h) All patients who received an LD of both drugs during the index hospitalisation.

i) All ACS patients receiving an LD of either drug (that is, Population f excluding patients without ACS[Population i]).

j) an "ideal" low-risk ACS population (Population j) excluding patients with contraindications, or infrequent high-risk features defined as a subset of Population i by the following inclusion criteria:

- Age <75 years
- body weight ≥60 kg
- no history of stroke / TIA
- no active pathological bleeding
- no recent trauma or surgery
- no severe hepatic dysfunction
- no treatment with ticlopidine
- no prior thrombolysis

For populations a-g, treatment groups were defined by the type of thienopyridine received as an LD. Patients may have switched thienopyridines during the index hospitalisation. Patients who received LDs of both prasugrel and clopidogrel (population h) constituted a separate cohort and were excluded from the comparisons. The unadjusted bleeding risk comparison in this study report was based on the LD of thienopyridine during the index hospitalisation, using an intent-to-treat study design. Descriptive statistics were presented for the whole group, the ST segment elevation myocardial infarction (STEMI) and unstable angina (UA)/non-ST segment myocardial infarction (UA/NSTEMI) groups, respectively; non-ACS patients were described separately. Further details on the analyses are described in the statistical analysis plan. For population g, treatment groups were defined by the type of thienopyridine received as a maintenance dose in this Population during the index hospitalisation.

This report focuses on key results from the following populations:

- the all prasugrel and ACS clopidogrel population (Population f)
- the ACS population (Population i)
- the ACS-PCI population (Population c)

- the "ideal" ACS-PCI population (Population d)
- The "ideal low risk" ACS population (Population j).

The complete set of tables for the final report (Table 1a through Table 14c) can be found in Attachment 1.

2.5. General Considerations

2.5.1. Variables

The data collected in the ALKK-PCI registry consisted of several components corresponding to the structure of the registry.

For the official quality control program, information was obtained in order to construct suitable quality indicators for the following areas:

- demography and some technicalities
- indication: prior revascularisation and important risk factors, initial assessment and presentation
- process: duration, patient's exposure and technical aspects of the procedure
- outcome: intra-procedural complications and adverse events during hospital stay.

In addition, the ALKK-PCI registry asked for details about:

- cardiovascular history and comorbidities
- adjunctive antithrombotic medication
- treated lesions
- use of stents
- in-hospital events.

In order to collect study-specific information for the ALKK-PCI registry, additional data fields were incorporated in the case report form (CRF):

- the timing (date and time) of the loading dose of prasugrel and clopidogrel
- loading and maintenance doses of prasugrel and clopidogrel
- timing of the visualisation of the coronary arteries by angiography
- sites and date of bleeding (intracranial bleeding, retroperitoneal bleeding, GI bleeding, epistaxis, intraocular bleeding, haematuria, haemoptysis, puncture site, surgical site other than CABG- and PCI-related, haemopericardial, CABG-related bleeding, PCI-related bleeding)
- bleeding severity (blood transfusion ≥4 units of whole blood or RBCs versus blood transfusion <4 units of whole blood or RBCs)

- bleeding risk factors (for example, renal failure, recent trauma, recent surgery, concomitant usage of non-aspirin NSAIDs) and contraindications (for example, history of TIA, active pathological bleeding, or severe hepatic impairment) for prasugrel.

2.5.2. Data Sources and Measurement

The data were entered into an electronic CRF by the responsible personnel in the participating hospitals. A part of the data is identical to that collected for the official quality control program. The information was represented in the database as reported by the centres. Diagnoses and measurements were performed according to the standard protocol of each participating hospital.

2.5.3. Sample Size Considerations

Data collected from patients in the ALKK-PCI registry between 15 October 2009 and 28 February 2013 were used in Study B008. Sample size calculations for this study were based on the first objective of the study.

In TRITON-TIMI 38, 1.53% of prasugrel-treated patients in the All ACS population had non-CABG-related bleeding requiring transfusion within 7 days of randomisation compared to 1.27% of clopidogrel-treated patients (hazard ratio [HR]=1.21). To demonstrate that the relative increase (prasugrel versus clopidogrel) in bleeding risk as defined by non-CABG-related bleeding (requiring any transfusion of whole blood or RBCs) and/or ICH, is not substantially higher in real-world clinical practice than in TRITON-TIMI 38, a non-inferiority analysis was performed based on a 2-sided 95% confidence interval (CI) for the differences in proportions. A non-inferiority margin corresponding to 2.0 for the ratio of the proportion of prasugrel- to clopidogrel-treated patients, treated for PCI-ACS and experiencing non-CABG-related bleeding (requiring any transfusion of whole blood or RBCs) and/or ICH, was used. This margin of 2.0 was also used in the prasugrel Phase 2 dose-finding study, JUMBO-TIMI 26 (Wiviott et al. 2005), for TIMI bleeding during the index hospitalisation.

Assuming that 1.2% of clopidogrel-treated patients with ACS undergoing PCI (excluding patients with prior TIA/stroke) would have non-CABG-related bleeding (requiring any transfusion of whole blood or RBCs) and/or ICH during the index hospitalisation compared to 1.5% for prasugrel-treated patients, the number of patients required to have 90% power in this non-inferiority analysis (with a non-inferiority margin for the upper limit of the 2-sided 95% confidence interval of 2.4%) would depend on the ratio of prasugrel- to clopidogrel-treated patients in the ACS population as indicated in Table B008.2.1, which were obtained from n-query 7.0 based on the normal approximation to the binomial distribution.

Table B008.2.1. Sample Size Calculation

Ratio of clopidogrel- to prasugrel-treated patients	Patients treated with clopidogrel	Patients treated with prasugrel	Total patients
5:1	11,122	2,224	13,346
4:1	9,204	2,302	11,506
3:1	7,288	2,430	9,718
2:1	5,372	2,686	8,058
1:1	3,455	3,455	6,910

Approximately one year after the start of Study B008, the difference in event rates of any non-CABG-related bleeding events for prasugrel- and clopidogrel-treated patients and the ratio of the numbers of clopidogrel-treated to prasugrel-treated patients in this observational study were used to refine the sample size requirements. If the numbers were insufficient to adequately refine the sample size requirements at that time, additional re-estimation could occur with subsequent annual reports.

2.5.4. Derived Variables

The following derived variables were calculated from the collected parameters:

- Age, as the difference between date of admission and year of birth
- Prehospital time in STEMI patients, as difference between date and time of admission and date/time of symptom onset
- Door-to-balloon time, as difference between date/time of intervention and date/time of admission
- Glomerular filtration rate (GFR), calculated from age, sex and creatinine level according to the abbreviated MDRD formula (Levey et al. 2003)
- Length of stay after PCI, as number of days between date of intervention and date of discharge from hospital
- Time between loading dose of clopidogrel or prasugrel and start of invasive cardiac procedure, as difference between dates / date/times of start of first procedure and loading dose
- Switching from prasugrel to clopidogrel or vice versa, in the following situations:
    - clopidogrel LD to prasugrel LD: loading doses of both clopidogrel and prasugrel, date / date and time of prasugrel LD after clopidogrel LD.
    - prasugrel LD to clopidogrel LD: loading doses of both clopidogrel and prasugrel, date / date and time of clopidogrel LD after prasugrel LD.
    - clopidogrel LD to prasugrel maintenance dose (MD): LD of clopidogrel only and MD of prasugrel, date / date and time of clopidogrel LD not after stop of prasugrel MD.

  - prasugrel LD to clopidogrel MD: LD of prasugrel only and MD of clopidogrel, date / date and time of prasugrel LD not after stop of clopidogrel MD.
  - clopidogrel MD to prasugrel MD: MDs of both clopidogrel and prasugrel, date of stop of clopidogrel not after change or stop of prasugrel, no LD of prasugrel.
  - prasugrel MD to clopidogrel MD: maintenance doses of both clopidogrel and prasugrel, date of stop of prasugrel not after change or stop of clopidogrel, no LD of clopidogrel.
- Change of prasugrel or clopidogrel MD, if the date of change or a new MD was documented that differed from the previous one.
- Dichotomous variable non-CABG-related bleeding (requiring any transfusion of whole blood or RBCs) and/or ICH during the index hospitalisation (yes/no), primary endpoint
- Dichotomous variable any bleeding (requiring any transfusion of whole blood or RBCs) and/or ICH during the index hospitalisation (yes/no)
- Metric key variables were categorized in the following ways:
  - Age, dichotomized as age ≥75 versus <75 years (identified in TRITON-TIMI 38), and in decades (<35, 35 – 44, 45- 54, 55- 64, 65- 74, 75- 84, ≥85)
  - Body weight: dichotomized as <60 kg vs. ≥60 kg (identified in TRITON-TIMI 38)
  - GFR: categorized as ≥90, 60 - <90, 30 - <60, <30 ml/min per 1.73m²
  - Time from LD to start of invasive procedure dichotomized as: LD prior to coronary visualization versus receiving LD at/after coronary visualisation

2.6. Statistical Methods

The statistical analyses were performed at the Stiftung Institut für Herzinfarktforschung (IHF), Ludwigshafen, Germany. Dr. Matthias Hochadel from the IHF processed the data and prepared the analyses for the present report.

The statistical analysis system SAS release 9.2 (Cary, NC, U.S.A.) running on a personal computer was used for the statistical computations. This package is already in widespread use and is generally accepted as valid by national and international agencies.

2.6.1. Main Summary Measures

Descriptive summary measures are presented in tabular form for all relevant variables in the defined analysis populations and treatment groups. In addition to the total group, the calculations were done for the strata of patients with ST-segment elevation MI (STEMI), ACS without ST-segment elevation (NSTEMI or unstable angina [UA]), and patients without ACS if relevant. For binary variables, percentages and absolute counts of available cases and the category of interest are shown. For categorical variables with more than 2 categories, the frequency of each category is shown. Metrically scaled variables are presented in suitably

categorized form. The distribution of the key variables of age and body weight is additionally characterized by mean, standard deviation, median, quartiles, minimum and maximum.

2.6.2. Main Statistical Methods

The clinical and procedural characteristics were compared between the 2 treatment groups calculating descriptive p-values. The Pearson chi-squared test was used for categorical variables, or Fisher's exact test in the case of dichotomous variables if at least one expected frequency in the contingency table was less than or equal to five. For the comparison of metrical variables, the Mann-Whitney-Wilcoxon test was applied.

The rates of defined endpoints were compared between treatment groups by using Fisher's exact test. Rates of bleeding events were shown in several analysis populations as well as in some known high-risk subgroups.

The associations of baseline characteristics and presumed risk factors with the specified outcomes were analysed in each treatment group separately, by comparing the distributions in patients with versus without the considered event. The metrical variables including age and weight were divided into categories. P-values and/or odds ratios (ORs) with 95% CI were reported for the test of association/treatment difference. In the case of multi-categorical factors, ORs were calculated by logistic regression with respect to an appropriate reference category.

All CIs were 2-sided at the 95% confidence level and all tests of significance were performed at a 2-sided .05 significance level. No adjustment for multiple testing was made.

2.6.3. Bleeding Endpoint Analyses

The primary inferential analysis was non-CABG-related bleeding (requiring any transfusion of whole blood or RBCs) and/or ICH in patients with ACS undergoing PCI, the Population indicated for prasugrel during the index hospitalisation. This was based on propensity score methodology. Adjustment of the comparison of bleeding endpoints was primarily done by stratification according to quintiles of the propensity score. In each quintile defined by the propensity score, the comparison of the defined outcomes was performed as in the total group. The treatment difference in the bleeding rate was analysed using logistic regression with a model including the treatment arm, quintiles of propensity score as categorical variables and any unbalanced baseline factors after propensity score. Odds ratios and p-values of the Wald test were reported for the treatment difference.

Interactions were assessed using the Breslow-Day test for homogeneity of ORs based on comparisons of bleeding event rates for the following complementary high-risk and low-risk groups:

- Prasugrel contraindicated versus prasugrel not indicated (no ACS)
- LD prior to versus LD after coronary visualisation
- Prasugrel MD 5 mg versus 10 mg
- Age ≥75 years versus <75 years

- Body weight <60 kg versus ≥60 kg.

2.6.3.1. Propensity Scores

The propensity scores for the choice 'prasugrel treatment' were estimated from logistic regression models for the ACS population (Population i), the ACS-PCI population (Population c) and the "ideal" low-risk ACS population (Population j; Section 2.4.2). The following indicators identifying basic patient groups were included: STEMI, PCI performed, and chronic pre-treatment with clopidogrel or prasugrel. Age, gender and body weight were included as known risk factors. Further potential predictors that showed different distributions in prasugrel and clopidogrel patients (univariate comparisons $p<0.01$), or were pre-specified as known risk factors, were considered for inclusion; these patient characteristics included diabetes, renal insufficiency, symptoms of heart failure, cardiogenic shock, previous MI, previous PCI, previous coronary angiography, previous CABG, history of stroke/TIA, peripheral vascular disease, arterial hypertension, severe hepatic dysfunction, smoking, and medical treatment with vitamin K antagonists, GP IIb/IIIa antagonists, aspirin, thrombolysis, and proton pump inhibitors, as well as radial access.

The significance of the covariates and their impact on the balance of patient characteristics was observed, especially those variables identified as associated with bleeding events. The achieved balance was assessed by comparison between treatment groups in quintiles of the propensity score and goodness of fit by the Hosmer-Lemeshow test. The functional form for age and weight was assessed using generalized additive models, and appropriate regression splines were calculated and entered in the model. The covariates were tested for interaction with type of ACS (NSTEMI/ UA or STEMI) and interaction terms were included for the relevant variables.

2.6.4. Switching Analyses

The characteristics of patients switching between thienopyridines or not were compared for the following transitions: clopidogrel LD to prasugrel MD, prasugrel LD to clopidogrel MD, clopidogrel MD to prasugrel MD, and prasugrel MD to clopidogrel MD.

2.6.5. Missing Values

Descriptive statistics were generally calculated from the available cases. In the columns of total group in the tables, the number of observations with non-missing values is reported as denominator of proportions, as well as the number of cases in the category of interest in the numerator. The frequency of missing information is presented separately for age, weight, gender, and smoking habit.

If a patient had a missing value for a particular subgroup, that patient was not included in the subgroup analysis.

As the propensity score had to be calculated for all patients in the analysis population, a pattern mixture approach was used, resulting in the so-called generalized propensity score (Rosenbaum and Rubin; 1984). This involved classifying missing values as an additional category for some discrete covariates and applying a simpler model without weight as a covariate for patients whose body weight was not documented.

2.6.6. Sensitivity Analyses

In order to challenge the stability of the covariate adjustment, second line methods of applying the propensity score were used to analyse the overall bleeding comparison between prasugrel and clopidogrel treated patients:

- Direct standardization
- Final logistic regression models with the propensity score as a continuous variable.

Additionally, site effects were considered using a random effect model.

2.6.7. Quality Control

The data of the ALKK-PCI registry were collected via electronic case report forms (CRFs) or directly via the internet to the data coordinating centre (Galenus IT GmbH, Mannheim, and Stiftung Institut für Herzinfarktforschung, Ludwigshafen). The electronic and internet-based data collection forms contained a built-in consistency check tool. Because of participation in the obligatory quality control program, the documentation of all consecutive procedures and the completeness of a mandatory core dataset was checked by official institutions. In addition, all sites were informed and bound by contract that they could be selected for a randomized source data verification. Because of both aspects, high data quality can be presumed for the underlying ALKK-PCI registry.

Further plausibility checks were performed in SAS, and in case of substantial problems the centres were informed and asked for confirmation or correction. A few impossible values of body weight, height, creatinine level and date/times that had not been corrected by the centres were deleted. Missing values of body weight and high percentages of patients without LDs were 2 main issues requiring extensive queries in several sites.

In the framework of the ALKK-PCI registry, monitoring visits to 10 selected hospitals were arranged. The documented information was checked against the source data, with a focus on details of the antithrombotic therapy, indication for PCI and bleeding complications.

2.7. Changes to the Planned Analyses

2.7.1. Propensity Score Methodology

As described in Section 2.6.3, the primary inferential analysis was non-CABG-related bleeding (requiring any transfusion of whole blood or RBCs) and/or ICH in patients with ACS undergoing PCI, the Population indicated for prasugrel during the index hospitalisation; this analysis was based on propensity score methodology. This analysis was performed on the indicated ACS-PCI population (Population c) and was planned to be conducted on Population d, the ideal ACS-PCI population, which had different exclusion criteria for prasugrel and clopidogrel (Section 2.4.1). However, given the differences in Population d exclusion criteria for the 2 treatments (for example, those ≥75 years of age or those who weighed <60 kg were not included in the prasugrel group but were included in the clopidogrel group), it was not possible to use propensity score methodology on the ideal ACS-PCI population (Population d). Therefore, in addition to the

analysis of Population c, post hoc analyses were performed on 2 populations that were not originally included in the statistical analysis plan (SAP): the ACS population (Population i) and the ideal low-risk ACS population (Population j). Prasugrel- and clopidogrel-treated patients had identical exclusion criteria in the populations used for the primary analysis: populations c, i and j. The ACS population (Population i) excludes all non-ACS patients and the ideal low-risk ACS population (Population j) used the following inclusion criteria for both prasugrel- and clopidogrel-treated patients:

- age < 75 years
- body weight ≥60 kg
- no history of stroke / TIA
- no active pathological bleeding
- no recent trauma or surgery
- no severe hepatic dysfunction
- no treatment with ticlopidine
- no prior thrombolysis

2.7.2. Analyses of Risk Factors for Bleeding Event and Predictors for Switching Thienopyridines

As the numbers of bleeding events and of patients who switched between prasugrel and clopidogrel turned out to be too low to allow fitting large multiple logistic regression models, unadjusted comparisons for the single factors are presented. Descriptive statistics of risk factors for bleeding (tables 10 and 11) and determinants for switching (table 12) are shown in the patient groups with and without event, and p-values were calculated as described in sections 2.6.1 and 2.6.2. Odds ratios with 95% CIs were calculated using the most commonly presumed low-risk factors category as reference.

2.8. Results

2.8.1. Patient Population

Patients undergoing angiography or PCI in a real-life setting from 32 participating hospitals were included in Study B008; 11,201 patients with ACS and 10,133 patients with PCI were in the Study B008. Approximately 30% of the patients were treated with prasugrel.

Figure B008.2.1 presents the number of patients in each analysis population (key populations of interest are highlighted in the figure) and Table B008.2.2 presents the following key populations of interest, which are the focus of this report (see Section 2.4.2 for definitions of Population d and Population j):

- the all prasugrel and ACS clopidogrel population (Population f)
- the ACS population (Population i)
- the ACS-PCI population (Population c)
- the “ideal” ACS-PCI population (Population d)
- The “ideal low risk” ACS population (Population j).

Population f is the largest population and includes 2740 prasugrel-treated and 6500 ACS clopidogrel-treated patients (Figure B008.2.1). Approximately 75% of ACS-PCI patients (Population c) treated with prasugrel and almost all of the ACS-PCI patients (Population c) treated with clopidogrel belonged to the ideal ACS-PCI population (Population d; Section 2.4.2).

Approximately 74% of prasugrel-treated ACS patients and 48% of clopidogrel-treated ACS patients were in the "ideal low risk" population (Population j) which includes patients with either treatment who were <75 years, ≥60 kg, had no history of stroke/TIA, no active pathological bleeding, no recent trauma or surgery, no severe hepatic dysfunction, no treatment with ticlopidine, and no prior thrombolysis.

The full set of tables from the German ALKK-PCI registry (Table 1a through Table 14c) can be found in Attachment 1.

Table B008.2.2. Study B008 Key Patient Populations of Interest

Population Description	Analysis Population	Prasugrel (n)	ACS Clopidogrel (n)	Total (n)
One LD only	**f**	2740	6500	**9240**
STEMI		1373	1995	3368
UA/NSTEMI		1098	4481	5579
ACS	**i**	2471	6476	**8947**
ACS-PCI	**c**	2192	5549	**7741**
Ideal ACS-PCI	**d**	1653	5467	**7120**
Ideal low risk ACS	**j**	1838	3109	**4947**

Abbreviations: ACS = acute coronary syndromes, LD = loading dose, MD = maintenance dose, NSTEMI = non-ST-segment elevation myocardial infarction, PCI = percutaneous coronary intervention, UA = unstable angina.

Sources: Table 1f, Table 1i, Table 1c, Table 1d, Table 1j; Attachment 1

Analysis Population Definitions

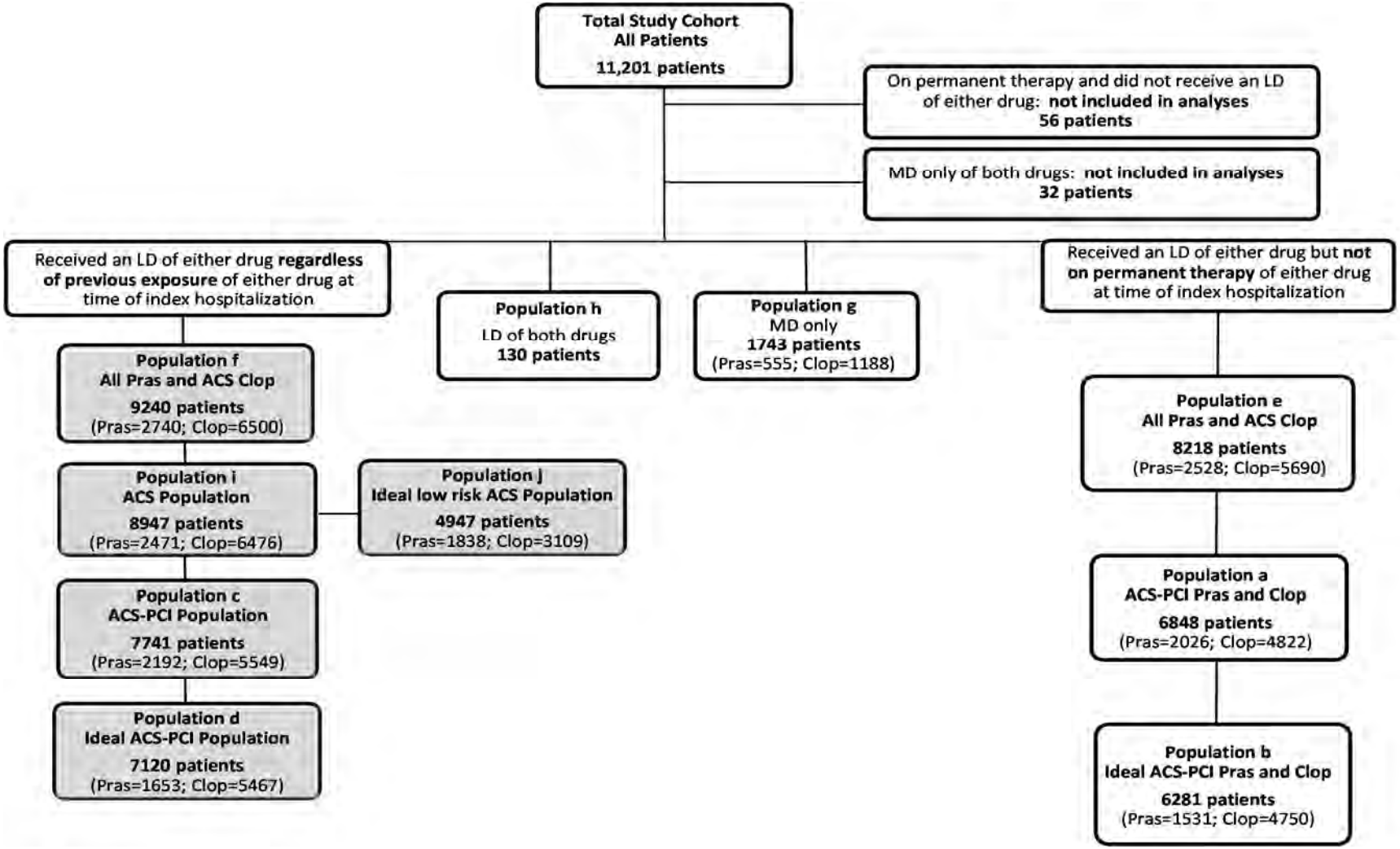
Population c: ACS-PCI prasugrel- and clopidogrel-treated patients receiving LD of either drug during the index hospitalisation regardless of previous exposure of either drug.

Population d: "Ideal" ACS-PCI prasugrel-treated (≥60 kg, <75 years, no history of TIA/stroke, no active pathological bleeding, no severe hepatic dysfunction) and clopidogrel-treated (no active pathological bleeding) patients receiving LD of either during index hospitalisation regardless of previous exposure of either drug.

Population f: All prasugrel- and ACS clopidogrel-treated patients receiving LD of either drug during the index hospitalisation regardless of previous exposure of either drug.

Population i: All ACS patients who received LD of either drug (i.e. Population f excluding patients without ACS)

Population j: "Ideal low risk" ACS population excluding patients with contraindications, or infrequent high-risk features (a subset of Population i) with the following inclusion criteria: age <75 years, body weight ≥60 kg, no history of stroke / TIA, no active pathological bleeding, no recent trauma or surgery, no severe hepatic dysfunction, no treatment with ticlopidine, no prior thrombolysis.



Abbreviations: ACS = acute coronary syndromes, clop = clopidogrel, LD = loading dose, MD = maintenance dose, PCI = percutaneous coronary intervention, pras = prasugrel.
Note: Grey-highlighted text boxes indicate the key populations of interest. Sources: Tables 1a through 1j.

Figure B008.2.1. Patient analysis populations in Study B008.

2.8.2. Baseline Demographic and Clinical Characteristics in Patients Receiving Only One LD of Prasugrel or Clopidogrel

Table B008.2.3 (from Table 1f, Attachment 1) presents demographics and medical history for all prasugrel and ACS clopidogrel patients who received an LD (Population f) during the recruitment period from 15 October 2009 to 28 February 2013.

Overall in Population f, prasugrel-treated patients were younger (94.2% <75 years) than the ACS clopidogrel-treated patients, more likely to be male, heavier (97.6% with body weight ≥60 kg), and more likely to be smokers. The percentage of prasugrel-treated patients ≥75 years of age in Population f was lower than in the ACS clopidogrel-treated group (5.8% versus 38.5%) (Table B008.2.3). Similar patterns of patient characteristics were observed in the STEMI and UA/NSTEMI subgroups and in other populations of interest (Tables 1i, 1c, 1d and 1j, Attachment 1).

The ALKK-PCI registry CRF collected 14 baseline medical conditions. The prevalence of those conditions was lower in prasugrel-treated versus clopidogrel-treated patients especially in terms of the following factors: the prevalence of previous PCI, previous coronary artery bypass graft (CABG), previous MI, diabetes, renal insufficiency, hypertension, hypercholesterolemia, peripheral vascular disease, previous TIA/stroke and active pathological bleeding. Prasugrel-treated patients who were STEMI or UA/NSTEMI also had a lower prevalence of the recorded co-morbidities than clopidogrel-treated patients; similar patterns were observed in the other key populations of interest (Tables 1i, 1c, 1d and 1j, Attachment 1).

Table B008.2.3. Demographic and Clinical Characteristics of all Prasugrel- and ACS Clopidogrel-Treated Patients Receiving an LD of Either Drug During the Index Hospitalisation Regardless of Previous Exposure of Either Drug (Population f)

	Total n=9240			STEMI n=3368			UA/NSTEMI n=5579			No ACS n=293	
	Pras n=2740	Clop n=6500	P-value	Pras n=1373	Clop n=1995	P-value	Pras n=1098	Clop n=4481	P-value	Pras n=289	Clop n=24
Demographics											
Age											
Mean±SD (yrs)	59.3 ± 10.6	69.5 ± 12.2		58.0 ± 10.7	67.0 ± 13.4		60.5 ± 10.5	70.6 ± 11.6		61.0 ± 9.9	67.5 ± 8.5
Median (yrs)	59.1	71.8	<0.0001	57.5	68.9	<0.0001	60.6	72.8	<0.0001	61.8	69.3
Interquartile range (years) (Q1-Q3)	51.5 - 67.6	60.8 - 78.7		50.4 - 66.0	56.4 - 77.6		52.7 - 69.1	63.3 - 79.1		54.0 - 68.3	59.5 - 73.4
Maximum	100.0	99.3		100.0	98.5		87.1	99.3		89.4	83.9
Minimum	23.0	19.1		23.0	19.1		26.2	27.3		35.6	50.3
Age categories			<0.0001			<0.0001			<0.0001		
<35 years	0.7 % (20/2740)	0.3 % (18/6500)		1.0 % (14/1373)	0.5 % (9/1995)		0.5 % (6/1098)	0.2 % (9/4481)		0.0 % (0/269)	0.0 % (0/24)
35-44	8.0 % (218/2740)	3.1 % (204/6500)		9.6 % (132/1373)	5.4 % (108/1995)		6.1 % (67/1098)	2.1 % (96/4481)		7.1 % (19/269)	0.0 % (0/24)
45-54	28.6 % (784/2740)	12.1 % (788/6500)		31.3 % (430/1373)	16.4 % (327/1995)		27.0 % (296/1098)	10.2 % (459/4481)		21.6 % (58/269)	8.3 % (2/24)
55-64	31.1 % (851/2740)	16.8 % (1089/6500)		31.3 % (430/1373)	19.9 % (398/1995)		30.3 % (333/1098)	15.3 % (685/4481)		32.7 % (88/269)	25.0 % (6/24)
65-74	25.9 % (709/2740)	29.2 % (1901/6500)		21.6 % (296/1373)	24.5 % (488/1995)		29.3 % (322/1098)	31.3 % (1402/4481)		33.8 % (91/269)	45.8 % (11/24)
75-84	5.4 % (147/2740)	31.2 % (2028/6500)		4.9 % (67/1373)	26.7 % (532/1995)		6.3 % (69/1098)	33.3 % (1491/4481)		4.1 % (11/269)	20.8 % (5/24)
≥85	0.4 % (11/2740)	7.3 % (472/6500)		0.3 % (4/1373)	6.7 % (133/1995)		0.5 % (5/1098)	7.6 % (339/4481)		0.7 % (2/269)	0.0 % (0/24)

	Total n=9240			STEMI n=3368			UA/NSTEMI n=5579			No ACS n=293	
	Pras n=2740	**Clop n=6500**	**P-value**	**Pras n=1373**	**Clop n=1995**	**P-value**	**Pras n=1098**	**Clop n=4481**	**P-value**	**Pras n=289**	**Clop n=24**
Age ≥75 vs <75 years			<0.0001			<0.0001			<0.0001		
≥75 years	5.8 % (158/2740)	38.5 % (2500/6500)		5.2 % (71/1373)	33.3 % (665/1995)		6.7 % (74/1098)	40.8 % (1830/4481)		4.8 % (13/269)	20.8 % (5/24)
<75 years	94.2 % (2582/2740)	61.5 % (4000/6500)		94.8 % (1302/1373)	66.7 % (1330/1995)		93.3 % (1024/1098)	59.2 % (2651/4481)		95.2 % (256/269)	79.2 % (19/24)
Age missing	0.0 % (0/2740)	0.0 % (0/6500)		0.0 % (0/1373)	0.0 % (0/1995)		0.0 % (0/1098)	0.0 % (0/4481)		0.0 % (0/269)	0.0 % (0/24)
Gender			<0.0001			<0.0001			<0.0001		
Male	78.7 % (2157/2740)	68.8 % (4473/6500)		79.4 % (1090/1373)	70.2 % (1401/1995)		77.6 % (852/1098)	68.1 % (3052/4481)		79.9 % (215/269)	83.3 % (20/24)
Female	21.3 % (583/2740)	31.2 % (2027/6500)		20.6 % (283/1373)	29.8 % (594/1995)		22.4 % (246/1098)	31.9 % (1429/4481)		20.1 % (54/269)	16.7 % (4/24)
Gender missing	0.0 % (0/2740)	0.0 % (0/6500)		0.0 % (0/1373)	0.0 % (0/1995)		0.0 % (0/1098)	0.0 % (0/4481)		0.0 % (0/269)	0.0 % (0/24)
Body weight											
Mean±SD in Kg	85.7 ± 16.0	81.2 ± 16.3		84.9 ± 15.7	80.9 ± 16.3		86.5 ± 16.2	81.2 ± 16.3		86.7 ± 15.9	89.4 ± 15.8
Median in Kg	84	80	<0.0001	84	80	<0.0001	85	80	<0.0001	84	88
Interquartile range [kg] (Q1-Q3)	75 - 95	70 - 90		75 - 93	70 - 90		75 - 95	70 - 90		76 - 95	79 - 102
Maximum	192	180		192	180		175	176		156	115
Minimum	41	27		41	34		46	27		55	59
Weight categories			<0.0001			<0.0001			<0.0001		
≥60 Kg	97.6 % (2231/2287)	93.9 % (5613/5976)		97.5 % (1137/1166)	93.8 % (1717/1830)		97.4 % (921/946)	94.0 % (3873/4122)		98.9 % (173/175)	95.8 % (23/24)
<60 Kg	2.4 % (56/2287)	6.1 % (363/5976)		2.5 % (29/1166)	6.2 % (113/1830)		2.6 % (25/946)	6.0 % (249/4122)		1.1 % (2/175)	4.2 % (1/24)
Body weight missing	16.5 % (453/2740)	8.1 % (524/6500)		15.1 % (207/1373)	8.3 % (165/1995)		13.8 % (152/1098)	8.0 % (359/4481)		34.9 % (94/269)	0.0 % (0/24)

	Total n=9240			STEMI n=3368			UA/NSTEMI n=5579			No ACS n=293	
	Pras n=2740	**Clop n=6500**	**P-value**	**Pras n=1373**	**Clop n=1995**	**P-value**	**Pras n=1098**	**Clop n=4481**	**P-value**	**Pras n=289**	**Clop n=24**
Smoker (n, %)											
Yes	64.9 % (1621/2498)	48.0 % (2757/5739)	<0.0001	70.5 % (853/1210)	53.7 % (889/1654)	<0.0001	59.8 % (614/1027)	45.7 % (1855/4061)	<0.0001	59.0 % (154/261)	54.2 % (13/24)
No	35.1 % (877/2498)	52.0 % (2982/5739)		29.5 % (357/1210)	46.3 % (765/1654)		40.2 % (413/1027)	54.3 % (2206/4061)		41.0 % (107/261)	45.8 % (11/24)
Smoker missing	8.8 % (242/2740)	11.7 % (761/6500)		11.9 % (163/1373)	17.1 % (341/1995)		6.5 % (71/1098)	9.4 % (420/4481)		3.0 % (8/269)	0.0 % (0/24)
Medical History (n, %)											
Previous diagnostic coronary angiography	27.2 % (727/2670)	35.6 % (2268/6375)	<0.0001	15.9 % (209/1318)	20.3 % (393/1940)	< 0.01	34.6 % (375/1084)	42.1 % (1858/4411)	<0.0001	53.4 % (143/268)	70.8 % (17/24)
Previous PCI	21.2 % (571/2692)	25.9 % (1651/6368)	<0.0001	12.9 % (173/1341)	14.9 % (290/1943)	0.10	27.3 % (297/1087)	30.6 % (1346/4401)	< 0.05	38.3 % (101/264)	62.5 % (15/24)
Previous CABG	5.3 % (145/2714)	11.2 % (723/6453)	<0.0001	2.3 % (31/1356)	4.2 % (83/1971)	< 0.01	7.4 % (81/1090)	14.2 % (635/4458)	<0.0001	12.3 % (33/268)	20.8 % (5/24)
Previous MI	20.3 % (545/2682)	24.7 % (1560/6305)	<0.0001	16.9 % (226/1335)	20.6 % (393/1910)	< 0.01	23.0 % (250/1086)	26.4 % (1153/4371)	< 0.05	26.4 % (69/261)	58.3 % (14/24)
Diabetes	23.8 % (632/2658)	31.0 % (1938/6257)	<0.0001	17.8 % (233/1311)	25.5 % (467/1831)	<0.0001	28.6 % (309/1079)	33.2 % (1463/4402)	< 0.01	33.6 % (90/268)	33.3 % (8/24)
Renal insufficiency	8.8 % (227/2584)	21.3 % (1334/6269)	<0.0001	6.8 % (85/1247)	14.3 % (264/1848)	<0.0001	11.6 % (124/1069)	24.2 % (1064/4397)	<0.0001	6.7 % (18/268)	25.0 % (6/24)
Hypertension	73.3 % (1882/2567)	82.5 % (5016/6083)	<0.0001	65.8 % (815/1239)	74.1 % (1287/1738)	<0.0001	78.7 % (835/1061)	85.8 % (3706/4321)	<0.0001	86.9 % (232/267)	95.8 % (23/24)
Hypercholester-olemia	51.9 % (1199/2310)	54.9 % (3037/5536)	< 0.05	47.0 % (500/1064)	46.8 % (715/1528)	0.92	55.3 % (546/988)	57.9 % (2307/3984)	0.13	59.3 % (153/258)	62.5 % (15/24)
Peripheral vascular disease	4.4 % (117/2655)	9.9 % (607/6156)	<0.0001	3.0 % (39/1305)	6.0 % (106/1761)	<0.0001	5.9 % (64/1083)	11.4 % (497/4371)	<0.0001	5.2 % (14/267)	16.7 % (4/24)
Previous stroke/TIA	1.5 % (41/2689)	8.1 % (502/6170)	<0.0001	1.5 % (20/1329)	6.4 % (114/1777)	<0.0001	1.5 % (16/1092)	8.9 % (388/4369)	<0.0001	1.9 % (5/268)	0.0 % (0/24)

	Total n=9240			STEMI n=3368			UA/NSTEMI n=5579			No ACS n=293	
	Pras n=2740	**Clop n=6500**	**P-value**	**Pras n=1373**	**Clop n=1995**	**P-value**	**Pras n=1098**	**Clop n=4481**	**P-value**	**Pras n=289**	**Clop n=24**
Active pathological bleeding	0.2 % (5/2725)	0.9 % (61/6431)	<0.0001	0.2 % (3/1364)	0.9 % (17/1959)	< 0.05	0.2 % (2/1092)	1.0 % (44/4448)	< 0.01	0.0 % (0/269)	0.0 % (0/24)
Known severe hepatic dysfunction	0.3 % (9/2703)	0.4 % (23/6405)	0.85	0.3 % (4/1346)	0.1 % (2/1950)	0.23	0.4 % (4/1089)	0.5 % (21/4432)	0.80	0.4 % (1/268)	0.0 % (0/23)
Recent trauma (<6 weeks)	0.9 % (24/2646)	1.3 % (83/6178)	0.09	1.5 % (20/1334)	1.8 % (34/1911)	0.54	0.4 % (4/1046)	1.2 % (49/4243)	< 0.05	0.0 % (0/266)	0.0 % (0/24)
Recent surgery (<6 weeks)	1.3 % (35/2642)	2.9 % (178/6165)	<0.0001	1.2 % (16/1336)	3.0 % (57/1902)	< 0.001	1.8 % (19/1040)	2.9 % (121/4239)	0.06	0.0 % (0/266)	0.0 % (0/24)
Medication usage											
Previous thrombolysis	1.6 % (42/2694)	1.1 % (72/6409)	0.09	2.7 % (37/1355)	2.0 % (40/1968)	0.19	0.5 % (5/1076)	0.7 % (31/4417)	0.39	0.0 % (0/263)	4.2 % (1/24)
Chronic therapy with NSAIDs	2.0 % (55/2696)	4.8 % (304/6321)	<0.0001	1.8 % (24/1351)	3.5 % (68/1921)	< 0.01	2.5 % (27/1082)	5.4 % (236/4376)	<0.0001	1.5 % (4/263)	0.0 % (0/24)
Estimated glomerular filtration rate (ml/min/1.73m²)			<0.0001			<0.0001			<0.0001		
<30	6.8 % (112/1650)	8.1 % (306/3766)		5.7 % (47/828)	6.8 % (77/1135)		9.5 % (64/674)	8.8 % (229/2609)		0.7 % (1/148)	0.0 % (0/22)
30-60	13.1 % (216/1650)	28.1 % (1058/3766)		11.7 % (97/828)	23.3 % (265/1135)		14.5 % (98/674)	30.1 % (785/2609)		14.2 % (21/148)	36.4 % (8/22)

	Total n=9240			STEMI n=3368			UA/NSTEMI n=5579			No ACS n=293	
	Pras n=2740	Clop n=6500	P-value	Pras n=1373	Clop n=1995	P-value	Pras n=1098	Clop n=4481	P-value	Pras n=289	Clop n=24
60-90	43.8 % (722/1650)	40.6 % (1530/3766)		44.7 % (370/828)	41.6 % (472/1135)		41.2 % (278/674)	40.2 % (1049/2609)		50.0 % (74/148)	40.9 % (9/22)
≥90	36.4 % (600/1650)	23.2 % (872/3766)		37.9 % (314/828)	28.3 % (321/1135)		34.7 % (234/674)	20.9 % (546/2609)		35.1 % (52/148)	22.7 % (5/22)
Results are based on number of patients. P-values are calculated by chi-squared, or Fisher's exact test for categorical variables, as appropriate, or Wilcoxon rank sum test for comparisons of continuous variables. Percentages are calculated from available cases. Variations in the denominators are due to missing information.											

Source: Table 1f, Attachment 1

2.8.3. Prasugrel Treatment Patterns

This section summarizes prasugrel treatment patterns from the following tables in this section and in Attachment 1 (see Section 2.4.2 for definitions of Population d and Population j):

- All prasugrel-treated patients receiving an LD during the index hospitalisation regardless of previous exposure of either drug (Population f, Table B008.2.4 [Table 2f]).
- ACS prasugrel-treated patients receiving an LD during the index hospitalisation regardless of previous exposure of either drug (Population i, Table 2i)
- ACS-PCI prasugrel-treated patients receiving an LD during the index hospitalisation regardless of previous exposure of either drug (Population c, Table 2c)
- Ideal ACS-PCI prasugrel-treated patients receiving an LD during the index hospitalisation regardless of previous exposure of either drug (Population d, Table 2d)
- Ideal low risk ACS prasugrel-treated patients receiving an LD during the index hospitalisation regardless of previous exposure (Population j, Table 2j)

In general, very few prasugrel-treated patients had contraindications to prasugrel. In addition, the majority of patients were <75 years of age, which may be a reflection of physicians in Germany adhering to the Summary of Product Characteristics (SPC) warning that using prasugrel in patients ≥75 years of age is generally not recommended. The majority of all prasugrel-treated and ACS clopidogrel-treated patients in Population f received a 60-mg LD (87.6%). Most were treatment naïve. A little more than half (52.2%) of the patients received the LD prior to coronary visualization. This percentage was higher in the UA/NSTEMI (70.4%) Population compared with the STEMI population (46.2%) (Table B008.2.4). A majority of prasugrel-treated patients were <75 years of age (94.2%), had body weight ≥60 kg (97.6%) (Table B008.2.3), and received a 10-mg maintenance dose. Of those elderly and lower weight patients who received a prasugrel MD, the majority received 10 mg (≥75 years = 76.6%; <60 kg = 80.4%). Switching between therapies was infrequent (Table B008.2.4).

Commonly used concomitant medications during the index hospitalisation were aspirin, glycoprotein (GP) IIb/IIIa antagonists, and proton pump inhibitors (Table B008.2.4).

Similar patterns were observed in the other key populations of interest with the main exception being that populations 2d and 2j did not include patients with contraindications (active pathological bleeding, history of TIA/stroke, or severe hepatic dysfunction) or patients who were ≥75 years of age or weighed <60 kg (Tables 2i, 2c, 2d and 2j, Attachment 1).

Table B008.2.4. Treatment Patterns During the Index Hospitalisation in all Prasugrel-Treated Patients Receiving an LD during the Index Hospitalisation Regardless of Previous Exposure of Either Drug (Population f)

	Prasugrel			
	Total n=2740	**STEMI n=1373**	**UA/NSTEMI n=1098**	**No ACS n=269**
Contraindication				
Active pathological bleeding	0.2 % (5/2725)	0.2 % (3/1364)	0.2 % (2/1092)	0.0 % (0/269)
History of TIA/Stroke	1.5 % (41/2689)	1.5 % (20/1329)	1.5 % (16/1092)	1.9 % (5/268)
Severe hepatic dysfunction	0.3 % (9/2703)	0.3 % (4/1346)	0.4 % (4/1089)	0.4 % (1/268)
Loading Dose				
30mg	1.0 % (28/2740)	0.5 % (7/1373)	1.5 % (16/1098)	1.9 % (5/269)
60 mg	87.6 % (2399/2740)	87.1 % (1196/1373)	85.9 % (943/1098)	96.7 % (260/269)
Other dose: 10 mg	2.8 % (77/2740)	3.1 % (42/1373)	2.9 % (32/1098)	1.1 % (3/269)
Other doses: unknown	8.1 % (223/2740)	9.0 % (123/1373)	9.1 % (100/1098)	0.0 % (0/269)
Other doses	0.5 % (13/2740)	0.4 % (5/1373)	0.6 % (7/1098)	0.4 % (1/269)
Already permanent therapy upon admission	6.4 % (176/2739)	5.5 % (76/1373)	6.6 % (72/1097)	10.4 % (28/269)
Timing of Loading dose and angiography†				
Loading dose prior to coronary visualization	52.2 % (1329/2548)	46.2 % (594/1286)	70.4 % (707/1004)	10.9 % (28/258)
Loading dose after coronary visualization	47.8 % (1219/2548)	53.8 % (692/1286)	29.6 % (297/1004)	89.1 % (230/258)
Maintenance doses by age				
≥75 years				
10mg	76.6 % (121/158)	87.3 % (62/71)	67.6 % (50/74)	69.2 % (9/13)
5 mg	13.3 % (21/158)	8.5 % (6/71)	16.2 % (12/74)	23.1 % (3/13)
No maintenance dose	8.2 % (13/158)	2.8 % (2/71)	13.5 % (10/74)	7.7 % (1/13)
<75 years				

	Prasugrel			
	Total n=2740	**STEMI n=1373**	**UA/NSTEMI n=1098**	**No ACS n=269**
10mg	94.3 % (2435/2582)	96.2 % (1253/1302)	91.3 % (935/1024)	96.5 % (247/256)
5 mg	0.3 % (9/2582)	0.4 % (5/1302)	0.3 % (3/1024)	0.4 % (1/256)
No maintenance dose	5.0 % (130/2582)	3.0 % (39/1302)	8.1 % (83/1024)	3.1 % (8/256)
Maintenance doses by body weight				
≥60 Kg				
10mg	92.4 % (2061/2231)	95.5 % (1086/1137)	88.2 % (812/921)	94.2 % (163/173)
5 mg	1.2 % (26/2231)	0.7 % (8/1137)	1.6 % (15/921)	1.7 % (3/173)
No maintenance dose	6.0 % (133/2231)	3.3 % (37/1137)	9.7 % (89/921)	4.0 % (7/173)
<60 Kg				
10mg	80.4 % (45/56)	79.3 % (23/29)	88.0 % (22/25)	0.0 % (0/2)
5 mg	5.4 % (3/56)	10.3 % (3/29)	0.0 % (0/25)	0.0 % (0/2)
No maintenance dose	14.3 % (8/56)	10.3 % (3/29)	12.0 % (3/25)	100.0 % (2/2)
Other maintenance dose	0.4 % (11/2740)	0.4 % (6/1373)	0.5 % (5/1098)	0.0 % (0/269)
Change of maintenance dose				
Yes	0.3 % (9/2597)	0.2 % (3/1332)	0.4 % (4/1005)	0.8 % (2/260)
No	99.7 % (2588/2597)	99.8 % (1329/1332)	99.6 % (1001/1005)	99.2 % (258/260)
Switching *				
From prasugrel LD to clopidogrel MD	3.1 % (86/2740)	2.6 % (36/1373)	3.8 % (42/1098)	3.0 % (8/269)
From clopidogrel LD to prasugrel MD	--- ---	--- ---	--- ---	--- ---
From clopidogrel MD to prasugrel MD	0.0 % (0/90)	0.0 % (0/38)	0.0 % (0/43)	0.0 % (0/9)
From prasugrel MD to clopidogrel MD	1.2 % (31/2597)	1.1 % (15/1332)	1.3 % (13/1005)	1.2 % (3/260)
From clopidogrel LD to prasugrel LD	--- ---	--- ---	--- ---	--- ---
From prasugrel LD to clopidogrel LD	0.0 % (0/2740)	0.0 % (0/1373)	0.0 % (0/1098)	0.0 % (0/269)

	Prasugrel			
	Total n=2740	**STEMI n=1373**	**UA/NSTEMI n=1098**	**No ACS n=269**
Concomitant medications				
Vit-K-antagonists	3.4 % (91/2715)	3.4 % (46/1360)	3.7 % (40/1090)	1.9 % (5/265)
NSAIDs	2.0 % (55/2696)	1.8 % (24/1351)	2.5 % (27/1082)	1.5 % (4/263)
Proton pump inhibitors	22.5 % (607/2699)	23.6 % (318/1349)	22.9 % (249/1086)	15.2 % (40/264)
Calcium channel blockers	11.8 % (318/2695)	9.7 % (130/1346)	15.0 % (163/1086)	9.5 % (25/263)
Gp IIb/IIIa antagonist	22.2 % (607/2740)	31.2 % (429/1373)	15.5 % (170/1098)	3.0 % (8/269)
Abciximab	35.3 % (214/607)	30.5 % (131/429)	46.5 % (79/170)	50.0 % (4/8)
Eptifibatide	28.7 % (174/607)	34.5 % (148/429)	14.7 % (25/170)	12.5 % (1/8)
Tirofiban	36.1 % (219/607)	35.0 % (150/429)	38.8 % (66/170)	37.5 % (3/8)
Aspirin	99.3 % (2721/2740)	99.3 % (1364/1373)	99.1 % (1088/1098)	100.0 % (269/269)
Oral	46.9 % (1275/2721)	31.0 % (423/1364)	58.5 % (636/1088)	80.3 % (216/269)
Intravenous	53.1 % (1446/2721)	69.0 % (941/1364)	41.5 % (452/1088)	19.7 % (53/269)

Results are based on number of patients. Variations in the denominators are due to missing information.

* Denominators include only patients who received the first-named treatment. Patients who switched after receiving LD and MD of the first drug are counted as switching from LD to MD as well as from MD to MD.

† This information could only be determined if time of loading dose and time of start of procedure was documented.

Source: Table 2f, Attachment 1

2.8.4. PCI Characteristics

This section summarizes PCI characteristics from the following tables in this section and in Attachment 1 (see Section 2.4.2 for definitions of Population d and Population j):

- All prasugrel-treated patients receiving an LD during the index hospitalisation regardless of previous exposure of either drug (Population f, Table B008.2.5).
- ACS prasugrel-treated patients receiving an LD during the index hospitalisation regardless of previous exposure of either drug (Population i, Table 4i)
- ACS-PCI prasugrel-treated patients receiving an LD during the index hospitalisation regardless of previous exposure of either drug (Population c, Table 4c)
- Ideal ACS-PCI prasugrel-treated patients receiving an LD during the index hospitalisation regardless of previous exposure of either drug (Population d, Table 4d)
- Ideal low risk ACS prasugrel-treated patients receiving an LD during the index hospitalisation regardless of previous exposure (Population j, Table 4j)

In the all prasugrel and ACS clopidogrel population (Population f), the majority of the STEMI patients received PCI/angiography within 6 hours after the onset of STEMI symptoms. Prasugrel-treated patients tended to receive PCI/angiography earlier than clopidogrel-treated patients. There were differences between prasugrel- and clopidogrel-treated patients in the treatments received during PCI; prasugrel patients received more bivalirudin and GPIIb/IIIa antagonists during PCI; clopidogrel patients received more aspirin, unfractionated heparin and low molecular weight heparin (Table B008.2.5).

During PCI, a higher percentage of patients with single-vessel disease in Population f were treated with prasugrel and a higher percentage of patients with double-vessel disease were treated with clopidogrel. Femoral access was most common. However, radial access was higher among patients treated with prasugrel than patients treated with clopidogrel (Table B008.2.5).

The percentages of patients requiring hemodynamic support during PCI were lower in prasugrel-treated patients than in clopidogrel-treated patients. Fewer prasugrel-treated patients underwent emergency CABG after PCI than clopidogrel-treated patients (0.7% [18/2592] versus 1.5% [87/5939]; $p<0.01$) (Table B008.2.5).

Patterns of PCI characteristics in the ACS-PCI population (Population c) and the ACS population (Population i), which were identical to each other in this analysis, were similar to patterns observed in Population f (Table 4c and Table 4i, Attachment 1). Patterns for the ideal ACS-PCI population (Population d) and the ideal low-risk ACS population (Population j) were also similar to Population f except that there was not a significant between-treatment difference in radial access in the Population d or Population j (Table 4d and Table 4j, Attachment 1).

Table B008.2.5. PCI in All Prasugrel- and ACS Clopidogrel-Treated Patients Receiving an LD of Either Drug during the Index Hospitalisation Regardless of Previous Exposure of Either Drug (Population f; Table 4f)

	Total n=8533			STEMI n=3495			UA/NSTEMI n=4753			No ACS n=285	
Treatment	**Prasugrel n=2594**	**Clopidogrel n=5939**	**P values**	**Prasugrel n=1433**	**Clopidogrel n=2062**	**P values**	**Prasugrel n=902**	**Clopidogrel n=3851**	**P values**	**Prasugrel n=259**	**Clopidogrel n=26**
Unfractioned heparin	90.6 % (2281/2519)	94.7 % (5382/5684)	< 0.0001	86.3 % (1202/1393)	94.2 % (1873/1989)	< 0.0001	95.1 % (829/872)	95.0 % (3485/3669)	0.92	98.4 % (250/254)	92.3 % (24/26)
LMW heparin	3.2 % (78/2415)	5.3 % (275/5174)	< 0.0001	2.6 % (35/1361)	2.6 % (49/1890)	0.97	4.7 % (38/806)	6.9 % (225/3258)	< 0.05	2.0 % (5/248)	3.8 % (1/26)
Enoxaparin	80.8 % (63/78)	88.7 % (244/275)	0.07	80.0 % (28/35)	91.8 % (45/49)	0.19	78.9 % (30/38)	88.0 % (198/225)	0.13	100.0 % (5/5)	100.0 % (1/1)
Other	19.2 % (15/78)	11.3 % (31/275)	0.07	20.0 % (7/35)	8.2 % (4/49)	0.19	21.1 % (8/38)	12.0 % (27/225)	0.13	0.0 % (0/5)	0.0 % (0/1)
Fondaparinux	5.5 % (134/2415)	4.3 % (220/5174)	< 0.05	1.5 % (21/1361)	1.2 % (23/1890)	0.43	13.6 % (110/806)	6.0 % (197/3258)	< 0.0001	1.2 % (3/248)	0.0 % (0/26)
Bivalirudin	15.4 % (372/2415)	3.5 % (179/5174)	< 0.0001	25.9 % (352/1361)	7.2 % (137/1890)	< 0.0001	2.5 % (20/806)	1.3 % (42/3258)	< 0.05	0.0 % (0/248)	0.0 % (0/26)
Gp IIb/IIIa antagonists during PCI	26.1 % (678/2593)	21.2 % (1257/5938)	< 0.0001	34.0 % (487/1433)	36.8 % (759/2062)	0.09	20.3 % (183/901)	12.9 % (496/3850)	< 0.0001	3.1 % (8/259)	7.7 % (2/26)
Abciximab	29.4 % (199/678)	23.9 % (301/1257)	< 0.01	29.0 % (141/487)	25.3 % (192/759)	0.15	29.5 % (54/183)	21.8 % (108/496)	< 0.05	50.0 % (4/8)	50.0 % (1/2)
Eptifibatide	35.7 % (242/678)	32.6 % (410/1257)	0.17	37.8 % (184/487)	29.4 % (223/759)	< 0.01	31.7 % (58/183)	37.7 % (187/496)	0.15	0.0 % (0/8)	0.0 % (0/2)
Tirofiban	35.0 % (237/678)	43.4 % (546/1257)	< 0.001	33.3 % (162/487)	45.3 % (344/759)	< 0.0001	38.8 % (71/183)	40.5 % (201/496)	0.68	50.0 % (4/8)	50.0 % (1/2)
Gp IIb/IIIa antagonist: upstream therapy	22.0 % (149/678)	19.2 % (241/1255)	0.15	20.7 % (101/487)	18.9 % (143/758)	0.42	25.1 % (46/183)	19.6 % (97/495)	0.12	25.0 % (2/8)	50.0 % (1/2)
ASA	92.3 % (2230/2415)	95.0 % (4917/5174)	< 0.0001	91.5 % (1245/1361)	94.6 % (1788/1890)	< 0.001	93.3 % (752/806)	95.3 % (3105/3258)	< 0.05	94.0 % (233/248)	92.3 % (24/26)
Oral	43.8 % (977/2230)	44.3 % (2176/4917)	0.73	27.5 % (342/1245)	25.8 % (461/1788)	0.30	59.2 % (445/752)	54.6 % (1695/3105)	< 0.05	81.5 % (190/233)	83.3 % (20/24)
Intravenous	56.2 % (1253/2230)	55.7 % (2741/4917)	0.73	72.5 % (903/1245)	74.2 % (1327/1788)	0.30	40.8 % (307/752)	45.4 % (1410/3105)	< 0.05	18.5 % (43/233)	16.7 % (4/24)

	Total n=8533			STEMI n=3495			UA/NSTEMI n=4753			No ACS n=285	
Treatment	**Prasugrel n=2594**	**Clopidogrel n=5939**	**P values**	**Prasugrel n=1433**	**Clopidogrel n=2062**	**P values**	**Prasugrel n=902**	**Clopidogrel n=3851**	**P values**	**Prasugrel n=259**	**Clopidogrel n=26**
PCI at											
Supply area of one vessel	93.3 % (2421/2594)	91.4 % (5427/5939)	< 0.01	93.9 % (1345/1433)	94.2 % (1942/2062)	0.69	92.4 % (833/902)	89.9 % (3461/3851)	< 0.05	93.8 % (243/259)	92.3 % (24/26)
Supply area of two vessels	6.1 % (159/2594)	8.3 % (490/5939)	< 0.001	5.8 % (83/1433)	5.5 % (114/2062)	0.74	6.8 % (61/902)	9.7 % (374/3851)	< 0.01	5.8 % (15/259)	7.7 % (2/26)
Supply area of three vessels	0.5 % (14/2594)	0.4 % (22/5939)	0.27	0.3 % (5/1433)	0.3 % (6/2062)	0.77	0.9 % (8/902)	0.4 % (16/3851)	0.11	0.4 % (1/259)	0.0 % (0/26)
Timing from STEMI symptom onset to PCI/ angiography (in hours)											
<2	93.3 % (2421/2594)	91.4 % (5427/5939)	< 0.01	93.9 % (1345/1433)	94.2 % (1942/2062)	0.69	92.4 % (833/902)	89.9 % (3461/3851)	< 0.05	93.8 % (243/259)	92.3 % (24/26)
2-6	6.1 % (159/2594)	8.3 % (490/5939)	< 0.001	5.8 % (83/1433)	5.5 % (114/2062)	0.74	6.8 % (61/902)	9.7 % (374/3851)	< 0.01	5.8 % (15/259)	7.7 % (2/26)
>6	0.5 % (14/2594)	0.4 % (22/5939)	0.27	0.3 % (5/1433)	0.3 % (6/2062)	0.77	0.9 % (8/902)	0.4 % (16/3851)	0.11	0.4 % (1/259)	0.0 % (0/26)
Access											
Femoral	71.2 % (1824/2563)	78.6 % (4626/5888)	< 0.0001	77.4 % (1094/1414)	84.7 % (1729/2041)	< 0.0001	73.7 % (660/895)	75.4 % (2881/3821)	0.30	27.6 % (70/254)	61.5 % (16/26)
Brachial	0.4 % (9/2563)	0.4 % (26/5888)	0.55	0.2 % (3/1414)	0.6 % (13/2041)	0.07	0.4 % (4/895)	0.3 % (13/3821)	0.55	0.8 % (2/254)	0.0 % (0/26)
Radial	28.4 % (728/2563)	21.0 % (1235/5888)	< 0.0001	22.3 % (316/1414)	14.6 % (298/2041)	< 0.0001	25.7 % (230/895)	24.3 % (927/3821)	0.37	71.7 % (182/254)	38.5 % (10/26)
Other	0.1 % (2/2563)	0.0 % (1/5888)	0.22	0.1 % (1/1414)	0.0 % (1/2041)	1.00	0.1 % (1/895)	0.0 % (0/3821)	0.19	0.0 % (0/254)	0.0 % (0/26)
Unknown	0.0 % (0/2563)	0.0 % (0/5888)		0.0 % (0/1414)	0.0 % (0/2041)		0.0 % (0/895)	0.0 % (0/3821)		0.0 % (0/254)	0.0 % (0/26)
Emergency CABG	0.7 % (18/2592)	1.5 % (87/5939)	< 0.01	0.9 % (13/1432)	1.6 % (33/2062)	0.08	0.6 % (5/901)	1.4 % (54/3851)	< 0.05	0.0 % (0/259)	0.0 % (0/26)
Hemodynamic support	9.8 % (254/2593)	14.8 % (879/5938)	< 0.0001	11.0 % (158/1433)	20.1 % (414/2062)	< 0.0001	10.0 % (90/901)	12.1 % (465/3850)	0.08	2.3 % (6/259)	0.0 % (0/26)
Results are based on number of PCI procedures. P-values are calculated by chi-squared, or Fisher's exact test, as appropriate. Percentages are calculated from available cases. Variations in the denominators are due to missing information.											

Source: Table 4f, Attachment 1

2.8.5. Stent Characteristics

This section summarizes stent characteristics from the following tables in this section and in Attachment 1 (see Section 2.4.2 for definitions of Population d and Population j):

- All prasugrel- versus ACS clopidogrel-treated patients receiving an LD of either drug during the index hospitalisation regardless of previous exposure of either drug (Population f, Table B008.2.6).
- ACS prasugrel- versus ACS clopidogrel-treated patients receiving an LD of either drug during the index hospitalisation regardless of previous exposure of either drug (Population i, Table 5i)
- ACS-PCI prasugrel- versus ACS-PCI clopidogrel-treated patients receiving an LD of either drug during the index hospitalisation regardless of previous exposure of either drug (Population c, Table 5c)
- Ideal ACS-PCI prasugrel-treated patients receiving an LD during the index hospitalisation regardless of previous exposure of either drug (Population d, Table 5d)
- Ideal low risk ACS prasugrel-treated patients receiving an LD during the index hospitalisation regardless of previous exposure (Population j, Table 5j).

Drug-eluting stents were used more frequently in ACS-PCI prasugrel-treated patients and bare metal stents were used more frequently ACS-PCI clopidogrel-treated patients (Table B008.2.6).

There were few clinical events during PCI in either treatment group. Nine ACS-PCI clopidogrel-treated patients died in the catheterization lab and 45 required resuscitation. There were no deaths among all prasugrel-treated patients in the catheterization lab; 16 patients required resuscitation. The occurrence of coronary occlusion, TIA/stroke, and cardiogenic shock during the stent procedure was similar between the 2 treatment groups in the ACS-PCI population (Table B008.2.6).

Similar stent characteristics were observed for the other key populations of interest (Table 5i, Table 5c, Table 5d, Table 5j, Attachment 1).

Table B008.2.6. Stent in All Prasugrel- and ACS Clopidogrel-Treated Patients Receiving an LD of Either Drug during the Index Hospitalisation Regardless of Previous Exposure of Either Drug

	Total n=8533			STEMI n=3495			UA/NSTEMI n=4753			No ACS n=285	
Treatment	**Prasugrel n=2594**	**Clopidogrel n=5939**	**P values**	**Prasugrel n=1433**	**Clopidogrel n=2062**	**P values**	**Prasugrel n=902**	**Clopidogrel n=3851**	**P values**	**Prasugrel n=259**	**Clopidogrel n=26**
Stent type (n, %)											
Bare-metal only	35.7 % (926/2594)	45.4 % (2694/5939)	< 0.0001	42.4 % (608/1433)	51.6 % (1065/2062)	< 0.0001	29.6 % (267/902)	42.2 % (1624/3851)	< 0.0001	19.7 % (51/259)	19.2 % (5/26)
Drug-eluting only	53.3 % (1383/2594)	42.8 % (2542/5939)	< 0.0001	47.0 % (674/1433)	37.4 % (772/2062)	< 0.0001	59.9 % (540/902)	45.5 % (1753/3851)	< 0.0001	65.3 % (169/259)	65.4 % (17/26)
Bare-metal and Drug eluting	2.5 % (66/2594)	2.4 % (142/5939)	0.67	2.3 % (33/1433)	2.2 % (45/2062)	0.81	1.7 % (15/902)	2.5 % (97/3851)	0.13	6.9 % (18/259)	0.0 % (0/26)
Other	0.7 % (19/2594)	1.1 % (63/5939)	0.15	0.6 % (9/1433)	1.4 % (29/2062)	< 0.05	0.6 % (5/902)	0.8 % (32/3851)	0.39	1.9 % (5/259)	7.7 % (2/26)
Unknown	2.0 % (51/2594)	1.9 % (115/5939)	0.93	2.0 % (28/1433)	2.1 % (44/2062)	0.71	2.4 % (22/902)	1.8 % (71/3851)	0.25	0.4 % (1/259)	0.0 % (0/26)
No Stent	5.7 % (149/2594)	6.4 % (383/5939)	0.22	5.7 % (81/1433)	5.2 % (107/2062)	0.55	5.9 % (53/902)	7.1 % (274/3851)	0.19	5.8 % (15/259)	7.7 % (2/26)
Events during procedure (n, %)											
Coronary occlusion	0.3 % (7/2594)	0.4 % (22/5939)	0.46	0.2 % (3/1433)	0.3 % (6/2062)	0.75	0.4 % (4/902)	0.4 % (16/3851)	0.78	0.0 % (0/259)	0.0 % (0/26)
TIA/stroke	0.0 % (1/2594)	0.0 % (2/5939)	1.00	0.0 % (0/1433)	0.0 % (1/2062)	1.00	0.1 % (1/902)	0.0 % (1/3851)	0.34	0.0 % (0/259)	0.0 % (0/26)
Resuscitation	0.6 % (16/2594)	0.8 % (45/5939)	0.48	1.0 % (14/1433)	1.5 % (31/2062)	0.17	0.1 % (1/902)	0.3 % (13/3851)	0.49	0.4 % (1/259)	3.8 % (1/26)
Cardiogenic shock [procedure related]	0.2 % (6/2594)	0.2 % (13/5939)	0.91	0.3 % (5/1433)	0.5 % (10/2062)	0.55	0.1 % (1/902)	0.1 % (3/3851)	0.57	0.0 % (0/259)	0.0 % (0/26)
Other	1.1 % (28/2594)	1.4 % (83/5939)	0.23	1.6 % (23/1433)	1.9 % (39/2062)	0.53	0.4 % (4/902)	1.1 % (44/3851)	0.06	0.4 % (1/259)	0.0 % (0/26)
Death in cath-lab	0.0 % (0/2594)	0.2 % (9/5939)	0.07	0.0 % (0/1433)	0.4 % (8/2062)	< 0.05	0.0 % (0/902)	0.0 % (1/3851)	1.00	0.0 % (0/259)	0.0 % (0/26)

	Total n=8533			STEMI n=3495			UA/NSTEMI n=4753			No ACS n=285	
Treatment	**Prasugrel n=2594**	**Clopidogrel n=5939**	**P values**	**Prasugrel n=1433**	**Clopidogrel n=2062**	**P values**	**Prasugrel n=902**	**Clopidogrel n=3851**	**P values**	**Prasugrel n=259**	**Clopidogrel n=26**
CABG											
No	94.9 % (2459/2592)	95.5 % (5672/5939)	0.20	95.1 % (1362/1432)	94.6 % (1951/2062)	0.52	93.2 % (840/901)	95.9 % (3695/3851)	< 0.001	99.2 % (257/259)	100.0 % (26/26)
Emergency	0.7 % (18/2592)	1.5 % (87/5939)	< 0.01	0.9 % (13/1432)	1.6 % (33/2062)	0.08	0.6 % (5/901)	1.4 % (54/3851)	< 0.05	0.0 % (0/259)	0.0 % (0/26)
Planned	0.0 % (1/2592)	0.3 % (19/5939)	< 0.05	0.0 % (0/1432)	0.3 % (6/2062)	0.09	0.1 % (1/901)	0.3 % (13/3851)	0.49	0.0 % (0/259)	0.0 % (0/26)
Unknown	4.4 % (114/2592)	2.7 % (161/5939)	< 0.0001	4.0 % (57/1432)	3.5 % (72/2062)	0.45	6.1 % (55/901)	2.3 % (89/3851)	< 0.0001	0.8 % (2/259)	0.0 % (0/26)
Results are based on number of PCI procedures. P-values are calculated by chi-squared, or Fisher's exact test, as appropriate. Percentages are calculated from available cases. Variations in the denominators are due to missing information.											

Source: Table 5f, Attachment 1

2.8.6. Bleeding Events

2.8.6.1. Primary Analysis of Bleeding Events

As described in Section 2.6.3, the primary inferential analysis was non-CABG-related bleeding (requiring any transfusion of whole blood or RBCs) and/or ICH in patients with ACS undergoing PCI, the population indicated for prasugrel during the index hospitalisation. Adjustment of the comparison of bleeding endpoints was primarily done by stratification according to quintiles of the propensity score.

As described in Section 2.7.1, this analysis was performed on the ACS-PCI population (Population c) and post hoc analyses were performed on the ACS population (Population i) and the ideal low-risk ACS population (Population j); see Section 2.4.2 for definition of Population j. Tables in this section present results of the following categories of bleeding analyses, unadjusted and adjusted for quintiles of the propensity score in all 3 populations:

- Non-CABG-related bleeding requiring any transfusion of whole blood or RBCs (Table B008.2.7)
- Bleeding requiring any transfusion of whole blood or RBCs (Table B008.2.8)
- Any bleeding (Table B008.2.9).

In results of the primary analysis (adjusted for quintiles of the propensity score) of non-CABG-related bleeding (requiring any transfusion of whole blood or RBCs) and/or ICH, there was no significant difference for prasugrel- versus clopidogrel-treated patients in the ACS-PCI population (0.64% versus 0.76%; aOR [95% CI]: 1.48 [0.74-2.97], p=0.267). Results of post hoc analyses in the ACS population were similar to those for the ACS-PCI population (0.61% versus 0.71%; adjusted odds ratio [aOR] [95% CI]: 1.39 [0.72-2.70], p=0.326). In results of post hoc analyses for the ideal low-risk ACS population, prasugrel-treated patients had a numerically higher event rate compared with clopidogrel-treated patients which approached statistical significance (0.60% versus 0.35%; aOR [95% CI]: 2.36 [0.98-5.68], p=0.056) (Table B008.2.7).

Results of unadjusted analyses were also reported in Table B008.2.7 and there were no statistically significant findings in any of the 3 populations.

Table B008.2.7. Non-CABG Bleeding (Requiring any Transfusion of Whole Blood or RBCs) and/or ICH in Prasugrel- and Clopidogrel-Treated Patients Receiving an LD of Either Drug during the Index Hospitalisation Regardless of Previous Exposure of Either Drug

	Prasugrel	Clopidogrel	Unadjusted			Adjusted for Quintiles of Propensity Score		
Population	**% (n/N)**	**% (n/N)**	**OR**	**95% CI**	**p-value**	**aOR**	**95% CI**	**p-value**
ACS Population (Population i)	0.61% (15/2470)	0.71% (46/6476)	0.85	0.48-1.53	0.597	1.39	0.72-2.70	0.326
ACS-PCI Population (Population c)	0.64% (14/2192)	0.76% (42/5549)	0.84	0.46-1.55	0.580	1.48	0.74-2.97	0.267
Ideal low-risk ACS Population (Population j)	0.60% (11/1837)	0.35% (11/3109)	1.70	0.73-3.92	0.211	2.36	0.98-5.68	0.056

Abbreviations: ACS = acute coronary syndrome; aOR = adjusted odds ratio; CI = confidence interval; OR = odds ratio; PCI = percutaneous coronary intervention

Sources: Table 13i-1, Table 13c-1, Table 13j-1; Attachment 1.

Unadjusted p-values are from Fisher's exact test.

Adjusted ORs, 95% CIs and p-values of the Wald test were reported for the treatment difference.

In comparing results of non-CABG and all bleeding requiring any transfusion of whole blood or RBCs and/or ICH, very similar results were observed for the ACS population (Population i) and the ideal low-risk population (Population j) with few additional events for "all bleeding" compared with non-CABG bleeding events. As expected, results for the ACS-PCI population (Population c) were identical for non-CABG and all bleeding events as there was no CABG-related bleeding in this population (Table B008.2.8).

Results of unadjusted analyses were also reported in Table B008.2.8 and there were no statistically significant findings in any of the 3 populations.

Table B008.2.8. All Bleeding (Requiring any Transfusion of Whole Blood or RBCs) and/or ICH in Prasugrel- and Clopidogrel-Treated Patients Receiving an LD of Either Drug during the Index Hospitalization Regardless of Previous Exposure of Either Drug

	Prasugrel	Clopidogrel	Unadjusted			Adjusted for Quintiles of Propensity Score		
Population	**% (n/N)**	**% (n/N)**	**OR**	**95% CI**	**p-value**	**aOR**	**95% CI**	**p-value**
ACS Population (Population i)	0.65% (16/2470)	0.71% (51/6476)	0.82	0.47-1.44	0.493	1.35	0.72-2.55	0.352
ACS-PCI Population (Population c)	0.64% (14/2192)	0.76% (42/5549)	0.84	0.46-1.55	0.580	1.48	0.74-2.97	0.267
Ideal low-risk ACS Population (Population j)	0.65% (12/1837)	0.42% (13/3109)	1.57	0.71-3.44	0.260	2.15	0.94-4.92	0.069

Abbreviations: ACS = acute coronary syndrome; aOR = adjusted OR; CI = confidence interval; OR = odds ratio; PCI = percutaneous coronary intervention

Sources: Table 13i-2, Table 13c-2, Table 13j-2; Attachment 1.

Unadjusted ORs, 95% CIs and p-values are from Fisher's exact test.

Adjusted ORs, 95% CIs and p-values of the Wald test were reported for the treatment difference.

The percentage of patients with any bleeding was similar for prasugrel- and clopidogrel-treated patients in the ACS population (population i) and in the ACS-PCI population (population c). The unadjusted treatment comparison showed no statistically significant between-treatment difference; however, the adjusted analysis showed statistically significant between-treatment differences with a slightly higher rate for prasugrel-treated patients (Table B008.2.9). The bleeding rate for clopidogrel-treated patients in the ideal low-risk ACS population (Population j) was much lower compared with the ACS (Population i) and the ACS-PCI population (Population c), whereas the bleeding rate for prasugrel-treated patients was consistent across the 3 populations. The prasugrel arm in the ideal low-risk ACS population (population j) had a significantly higher rate of any bleeding as both adjusted and unadjusted comparisons showed a statistically significant difference from the clopidogrel arm.

Table B008.2.9. Any Bleeding in Prasugrel- and Clopidogrel-Treated Patients Receiving an LD of Either Drug during the Index Hospitalization Regardless of Previous Exposure of Either Drug

Population	Prasugrel % (n/N)	Clopidogrel % (n/N)	Unadjusted OR	Unadjusted 95% CI	Unadjusted p-value	Adjusted for Quintiles of Propensity Score aOR	Adjusted for Quintiles of Propensity Score 95% CI	Adjusted for Quintiles of Propensity Score p-value
ACS Population (Population i)	1.86% (46/2470)	1.82% (118/6476)	1.02	0.73-1.44	0.899	1.94	1.30-2.90	0.001
ACS-PCI Population (Population c)	1.96% (43/2192)	1.82% (101/5549)	1.08	0.75-1.55	0.678	2.09	1.37-3.18	<0.001
Ideal low-risk ACS Population (Population j)	1.91% (31/1837)	0.84% (26/3109)	2.30	1.38-3.84	0.001	3.03	1.77-5.21	<0.001

Abbreviations: ACS = acute coronary syndrome; aOR = adjusted odds ratio; CI = confidence interval; OR = odds ratio; PCI = percutaneous coronary intervention

Sources: Table 13i-3, Table 13c-3, Table 13j-3; Attachment 1.

Unadjusted ORs, 95% CIs and p-values are from Fisher's exact test.

Adjusted ORs, 95% CIs and p-values of the Wald test were reported for the treatment difference.

2.8.6.1.1. Balance of Variables in Quintiles of Propensity Score during the Index Hospitalisation

Tables 9i, 9c and 9j (Attachment 1) present the balance of variables in quintiles of propensity score during the index hospitalisation; the propensity scores for the choice 'prasugrel treatment' were estimated from logistic regression models for the populations included in the primary analysis: the ACS-PCI population (Table 9c), the ACS population (Table 9i), and the ideal low-risk ACS population (Population j). The following indicators identifying basic patient groups were included: STEMI, performed PCI, chronic pre-treatment with clopidogrel or prasugrel. Age, gender and body weight were included as known risk factors.

Variables were generally well-balanced between treatment groups in each quintile (Tables 9i, 9c and 9j [Attachment 1]).

2.8.6.2. Incidence Rates of Bleeding and All-Cause Death

This section summarizes the incidence of bleeding and all cause death from the following tables in this section and in Attachment 1 (see Section 2.4.2 for definitions of Population d and Population j):

- All prasugrel- versus ACS clopidogrel-treated patients receiving an LD of either drug during the index hospitalisation regardless of previous exposure of either drug (Population f, Table B008.2.10).
- ACS prasugrel- versus ACS clopidogrel-treated patients receiving an LD of either drug during the index hospitalisation regardless of previous exposure of either drug (Population i, Table 6i)
- ACS-PCI prasugrel- versus ACS-PCI clopidogrel-treated patients receiving an LD of either drug during the index hospitalisation regardless of previous exposure of either drug (Population c, Table 6c)
- Ideal ACS-PCI prasugrel-treated patients receiving an LD during the index hospitalisation regardless of previous exposure of either drug (Population d, Table 6d)
- Ideal low risk ACS prasugrel-treated patients receiving an LD during the index hospitalisation regardless of previous exposure (Population j, Table 6j).

The incidence of any bleeding was low and similar for all prasugrel- versus ACS clopidogrel-treated patients (Population f): 1.7 % [47/2739] versus 1.8 % [118/6500], p=0.80). There was one intracranial bleed in the STEMI prasugrel-treated group. There were 6 clopidogrel-treated patients (4 STEMI and 2 UA/NSTEMI) that experienced an intracranial bleed. Both the severity of bleeding and the proportions of patients receiving transfusion were similar between all prasugrel-treated and ACS clopidogrel-treated patients (transfusion of whole blood or red blood concentrates: (16/2739) 0.6 % versus (45/6500) 0.7 %, p=0.67. The puncture site was the most common bleeding site among prasugrel-treated patients, followed by gastrointestinal and retroperitoneal bleeding and haematuria (Table B008.2.10).

The rates of retroperitoneal bleeding were significantly higher in prasugrel- versus clopidogrel-treated ACS-PCI patients for the total population (0.2% [5/2739] versus 0% [1/6500], $p<0.05$) and for the UA/NSTEMI population (0.3% [3/1097] versus 0% [0/4481], $p<0.01$. The rate of GI

bleeding was significantly lower for prasugrel- versus clopidogrel-treated ACS-PCI patients in the UA/NSTEMI population, with no events for prasugrel-treated patients (0% [0/1097] versus 0.4% [20/4481], $p<0.05$). The rate of major bleeding was similar for prasugrel- and clopidogrel-treated patients (0.3% [9/2739] versus 0.4% [25/6500], $p=0.85$) (Table B008.2.10).

Death at discharge was significantly lower in all prasugrel-treated patients than in all ACS clopidogrel-treated patients (1.4% [38/2740] versus 2.7% [174/6500], $p<0.0001$) and in STEMI patients treated with prasugrel (1.8% [25/1373] versus 4.6% [92/1995], $p<0.0001$) (Table B008.2.10).

Similar incidence rates of bleeding and all-cause death were observed for the other key populations of interest (Table 6i, Table 6c, Table 6d, Table 6j, Attachment 1).

Table B008.2.10. Incidence of Bleeding and All-Cause Death in all Prasugrel- and ACS Clopidogrel-Treated Patients Receiving an LD of Either Drug during the Index Hospitalisation Regardless of Previous Exposure of Either Drug (Population f)

	Total n=9240			STEMI n=3368			UA/NSTEMI n=5579			No ACS n=293	
	Prasugrel n=2740	Clopidogrel n=6500	P values	Prasugrel n=1373	Clopidogrel n=1995	P values	Prasugrel n=1098	Clopidogrel n=4481	P values	Prasugrel n=269	Clopidogrel n=24
Any bleeding	1.7 % (47/2739)	1.8 % (118/6500)	0.80	2.2 % (30/1373)	2.1 % (41/1995)	0.81	1.5 % (16/1097)	1.7 % (77/4481)	0.60	0.4 % (1/269)	0.0 % (0/24)
Site of bleeding											
01 = intracranial	0.0 % (1/2739)	0.1 % (6/6500)	0.68	0.1 % (1/1373)	0.2 % (4/1995)	0.65	0.0 % (0/1097)	0.0 % (2/4481)	1.00	0.0 % (0/269)	0.0 % (0/24)
02 = retroperitoneal	0.2 % (5/2739)	0.0 % (1/6500)	< 0.05	0.1 % (2/1373)	0.1 % (1/1995)	0.57	0.3 % (3/1097)	0.0 % (0/4481)	< 0.01	0.0 % (0/269)	0.0 % (0/24)
03 = gastrointestinal	0.2 % (6/2739)	0.4 % (28/6500)	0.14	0.4 % (5/1373)	0.4 % (8/1995)	1.00	0.0 % (0/1097)	0.4 % (20/4481)	< 0.05	0.4 % (1/269)	0.0 % (0/24)
04 = epistaxis	0.0 % (0/2739)	0.1 % (6/6500)	0.19	0.0 % (0/1373)	0.2 % (3/1995)	0.28	0.0 % (0/1097)	0.1 % (3/4481)	1.00	0.0 % (0/269)	0.0 % (0/24)
05 = intraocular	0.0 % (0/2739)	0.0 % (0/6500)		0.0 % (0/1373)	0.0 % (0/1995)		0.0 % (0/1097)	0.0 % (0/4481)		0.0 % (0/269)	0.0 % (0/24)
06 = haematuria	0.2 % (5/2739)	0.2 % (13/6500)	1.00	0.1 % (2/1373)	0.1 % (2/1995)	1.00	0.3 % (3/1097)	0.2 % (11/4481)	0.75	0.0 % (0/269)	0.0 % (0/24)
07 = haemoptysis	0.0 % (0/2739)	0.0 % (0/6500)		0.0 % (0/1373)	0.0 % (0/1995)		0.0 % (0/1097)	0.0 % (0/4481)		0.0 % (0/269)	0.0 % (0/24)
08 = puncture site	0.9 % (25/2739)	0.8 % (50/6500)	0.53	1.2 % (16/1373)	1.0 % (19/1995)	0.61	0.8 % (9/1097)	0.7 % (31/4481)	0.69	0.0 % (0/269)	0.0 % (0/24)
09 = surgical site other than CABG/PCI related	0.0 % (0/2739)	0.0 % (1/6500)	1.00	0.0 % (0/1373)	0.0 % (0/1995)		0.0 % (0/1097)	0.0 % (1/4481)	1.00	0.0 % (0/269)	0.0 % (0/24)
10 = haemopericardium	0.0 % (1/2739)	0.0 % (2/6500)	1.00	0.1 % (1/1373)	0.1 % (2/1995)	1.00	0.0 % (0/1097)	0.0 % (0/4481)		0.0 % (0/269)	0.0 % (0/24)
11 = CABG related	0.0 % (1/2739)	0.1 % (5/6500)	0.68	0.0 % (0/1373)	0.0 % (0/1995)		0.1 % (1/1097)	0.1 % (5/4481)	1.00	0.0 % (0/269)	0.0 % (0/24)
12 = PCI related	0.0 % (1/2739)	0.0 % (3/6500)	1.00	0.1 % (1/1373)	0.1 % (1/1995)	1.00	0.0 % (0/1097)	0.0 % (2/4481)	1.00	0.0 % (0/269)	0.0 % (0/24)
99 = other	0.2 % (5/2739)	0.1 % (4/6500)	0.14	0.4 % (5/1373)	0.1 % (1/1995)	< 0.05	0.0 % (0/1097)	0.1 % (3/4481)	1.00	0.0 % (0/269)	0.0 % (0/24)

	Total n=9240			STEMI n=3368			UA/NSTEMI n=5579			No ACS n=293	
	Prasugrel n=2740	**Clopidogrel n=6500**	**P values**	**Prasugrel n=1373**	**Clopidogrel n=1995**	**P values**	**Prasugrel n=1098**	**Clopidogrel n=4481**	**P values**	**Prasugrel n=269**	**Clopidogrel n=24**
Severity of most severe bleeding											
01 = major : intracranial or clinically overt and associated with fall in hemoglobin >5g/dl [fall in hematocrit >15%]	0.3 % (9/2739)	0.4 % (25/6500)	0.85	0.5 % (7/1373)	0.4 % (7/1995)	0.59	0.2 % (2/1097)	0.4 % (18/4481)	0.40	0.0 % (0/269)	0.0 % (0/24)
02 = minor: not intracranial but clinically overt with fall in hemoglobin of 3 to <=5g/dl [fall in hematocrit 9 to <=15%]	0.7 % (18/2739)	0.8 % (52/6500)	0.51	0.8 % (11/1373)	1.1 % (22/1995)	0.48	0.6 % (7/1097)	0.7 % (30/4481)	1.00	0.0 % (0/269)	0.0 % (0/24)
03 = minimal: not intracranial but clinically overt with fall in hemoglobin <3g/dl [fall in hematocrit <9%]	0.7 % (20/2739)	0.6 % (41/6500)	0.58	0.9 % (12/1373)	0.6 % (12/1995)	0.41	0.6 % (7/1097)	0.6 % (29/4481)	1.00	0.4 % (1/269)	0.0 % (0/24)
Transfusion of whole blood or red blood cell concentrates											
Yes	0.6 % (16/2739)	0.7 % (45/6500)	0.67	0.7 % (10/1373)	0.7 % (14/1995)	1.00	0.5 % (5/1097)	0.7 % (31/4481)	0.53	0.4 % (1/269)	0.0 % (0/24)
No	99.4 % (2723/2739)	99.3 % (6455/6500)		99.3 % (1363/1373)	99.3 % (1981/1995)		99.5 % (1092/1097)	99.3 % (4450/4481)		99.6 % (268/269)	100.0 % (24/24)
Transfusion of Thrombocyte concentrates											
Yes	0.1 % (2/2739)	0.1 % (5/6500)	1.00	0.1 % (2/1373)	0.1 % (1/1995)	0.57	0.0 % (0/1097)	0.1 % (4/4481)	1.00	0.0 % (0/269)	0.0 % (0/24)
No	99.9 % (2737/2739)	99.9 % (6495/6500)		99.9 % (1371/1373)	99.9 % (1994/1995)		100.0 % (1097/1097)	99.9 % (4477/4481)		100.0 % (269/269)	100.0 % (24/24)
Death at discharge	1.4 % (38/2740)	2.7 % (174/6500)	< 0.0001	1.8 % (25/1373)	4.6 % (92/1995)	< 0.0001	1.2 % (13/1098)	1.8 % (82/4481)	0.15	0.0 % (0/269)	0.0 % (0/24)

Source: Table 6f, Attachment 1

2.8.6.3. Characterization of Bleeding and Outcomes of Bleeding

Tables in this section and in Attachment 1 present characterization of bleeding and outcomes in patients who developed bleeding events during the index hospitalisation (see Section 2.4.2 for definitions of Population d and Population j):

- All prasugrel- versus ACS clopidogrel-treated patients receiving an LD of either drug during the index hospitalisation regardless of previous exposure of either drug (Population f, Table B008.2.11).
- ACS prasugrel- versus ACS clopidogrel-treated patients receiving an LD of either drug during the index hospitalisation regardless of previous exposure of either drug (Population i, Table 7i)
- ACS-PCI prasugrel- versus ACS-PCI clopidogrel-treated patients receiving an LD of either drug during the index hospitalisation regardless of previous exposure of either drug (Population c, Table 7c)
- Ideal ACS-PCI prasugrel-treated patients receiving an LD during the index hospitalisation regardless of previous exposure of either drug (Population d, Table 7d)
- Ideal low risk ACS prasugrel-treated patients receiving an LD during the index hospitalisation regardless of previous exposure (Population j, Table 7j).

Results were similar for all key populations of interest for prasugrel- and for clopidogrel-treated patients.

In prasugrel-treated patients, the majority of bleeding events occurred at only 1 site in (≥93.0%). All but 4 prasugrel-treated patients recovered from their bleeding events; 2 did not recover and the recovery status was unknown for 2 patients. There were no fatal bleeding events in prasugrel-treated patients (Table B008.2.11, Table 7i, Table 7c, Table 7d, Table 7j [Attachment 1]).

In subjects who received transfusions, the median (Q1-Q3) number of units transfused was (0 [0-1] versus 0 [0-2] (Table B008.2.11, Table 7i, Table 7c, Table 7d, Table 7j [Attachment 1]).

All but 1 clopidogrel-treated patient had bleeding at 1 site. Most clopidogrel patients also recovered (>80%); however, 7 clopidogrel patients had fatal bleeding, 3 patients did not recover and recovery status was unknown for 10 patients) (Table B008.2.11, Table 7i, Table 7c, Table 7d, Table 7j [Attachment 1]).

Table B008.2.11. Characterization of Bleeding and Outcomes in all Prasugrel- and ACS Clopidogrel-Treated Patients who Developed Bleeding Events during the Index Hospitalisation in Those Receiving an LD of Either Drug Regardless of Previous Exposure of Either Drug

	Total n=165		STEMI n=71		UA/NSTEMI n=93		No ACS n=1	
	Prasugrel n=47	Clopidogrel n=118	Prasugrel n=30	Clopidogrel n=41	Prasugrel n=16	Clopidogrel n=77	Prasugrel n=1	Clopidogrel n=0
Site of bleeding								
01 = intracranial	2.1 % (1/47)	5.1 % (6/118)	3.3 % (1/30)	9.8 % (4/41)	0.0 % (0/16)	2.6 % (2/77)	0.0 % (0/1)	
02 = retroperitoneal	10.6 % (5/47)	0.8 % (1/118)	6.7 % (2/30)	2.4 % (1/41)	18.8 % (3/16)	0.0 % (0/77)	0.0 % (0/1)	
03 = gastrointestinal	12.8 % (6/47)	23.7 % (28/118)	16.7 % (5/30)	19.5 % (8/41)	0.0 % (0/16)	26.0 % (20/77)	100.0 % (1/1)	
04 = epistaxis	0.0 % (0/47)	5.1 % (6/118)	0.0 % (0/30)	7.3 % (3/41)	0.0 % (0/16)	3.9 % (3/77)	0.0 % (0/1)	
05 = intraocular	0.0 % (0/47)	0.0 % (0/118)	0.0 % (0/30)	0.0 % (0/41)	0.0 % (0/16)	0.0 % (0/77)	0.0 % (0/1)	
06 = haematuria	10.6 % (5/47)	11.0 % (13/118)	6.7 % (2/30)	4.9 % (2/41)	18.8 % (3/16)	14.3 % (11/77)	0.0 % (0/1)	
07 = haemoptysis	0.0 % (0/47)	0.0 % (0/118)	0.0 % (0/30)	0.0 % (0/41)	0.0 % (0/16)	0.0 % (0/77)	0.0 % (0/1)	
08 = puncture site	53.2 % (25/47)	42.4 % (50/118)	53.3 % (16/30)	46.3 % (19/41)	56.3 % (9/16)	40.3 % (31/77)	0.0 % (0/1)	
09 = surgical site other than CABG/PCI related	0.0 % (0/47)	0.8 % (1/118)	0.0 % (0/30)	0.0 % (0/41)	0.0 % (0/16)	1.3 % (1/77)	0.0 % (0/1)	
10 = haemopericardium	2.1 % (1/47)	1.7 % (2/118)	3.3 % (1/30)	4.9 % (2/41)	0.0 % (0/16)	0.0 % (0/77)	0.0 % (0/1)	
11 = CABG related	2.1 % (1/47)	4.2 % (5/118)	0.0 % (0/30)	0.0 % (0/41)	6.3 % (1/16)	6.5 % (5/77)	0.0 % (0/1)	
12 = PCI related	2.1 % (1/47)	2.5 % (3/118)	3.3 % (1/30)	2.4 % (1/41)	0.0 % (0/16)	2.6 % (2/77)	0.0 % (0/1)	
99 = other	10.6 % (5/47)	3.4 % (4/118)	16.7 % (5/30)	2.4 % (1/41)	0.0 % (0/16)	3.9 % (3/77)	0.0 % (0/1)	
Numbers of bleeding sites								
1	93.6 % (44/47)	99.2 % (117/118)	90.0 % (27/30)	100.0 % (41/41)	100.0 % (16/16)	98.7 % (76/77)	100.0 % (1/1)	
2	6.4 % (3/47)	0.8 % (1/118)	10.0 % (3/30)	0.0 % (0/41)	0.0 % (0/16)	1.3 % (1/77)	0.0 % (0/1)	
3	0.0 % (0/47)	0.0 % (0/118)	0.0 % (0/30)	0.0 % (0/41)	0.0 % (0/16)	0.0 % (0/77)	0.0 % (0/1)	
≥4	0.0 % (0/47)	0.0 % (0/118)	0.0 % (0/30)	0.0 % (0/41)	0.0 % (0/16)	0.0 % (0/77)	0.0 % (0/1)	

	Total n=165		STEMI n=71		UA/NSTEMI n=93		No ACS n=1	
	Prasugrel n=47	**Clopidogrel n=118**	**Prasugrel n=30**	**Clopidogrel n=41**	**Prasugrel n=16**	**Clopidogrel n=77**	**Prasugrel n=1**	**Clopidogrel n=0**
Severity of most severe bleeding								
01 = major : intracranial or clinically overt and associated with fall in hemoglobin >5g/dl [fall in hematocrit >15%]	19.1 % (9/47)	21.2 % (25/118)	23.3 % (7/30)	17.1 % (7/41)	12.5 % (2/16)	23.4 % (18/77)	0.0 % (0/1)	
02 = minor: not intracranial but clinically overt with fall in hemoglobin of 3 to <=5g/dl [fall in hematocrit 9 to <=15%]	38.3 % (18/47)	44.1 % (52/118)	36.7 % (11/30)	53.7 % (22/41)	43.8 % (7/16)	39.0 % (30/77)	0.0 % (0/1)	
03 = minimal: not intracranial but clinically overt with fall in hemoglobin <3g/dl [fall in hematocrit <9%]	42.6 % (20/47)	34.7 % (41/118)	40.0 % (12/30)	29.3 % (12/41)	43.8 % (7/16)	37.7 % (29/77)	100.0 % (1/1)	
Transfusion of whole blood or red blood cell concentrates in units								
Mean ± SD in units	1.0 ± 1.9	1.1 ± 1.9	1.1 ± 2.1	0.6 ± 1.0	0.8 ± 1.7	1.4 ± 2.2	2.0	
Median (Q1-Q3)	0 (0-1)	0 (0-2)	0 (0-2)	0 (0-1)	0 (0-1)	0 (0-2)	2 (2-2)	
Transfusion of thrombocyte concentrates in units								
Mean ± SD in units	0.1 ± 0.4	0.2 ± 0.9	0.2 ± 0.5	0.1 ± 0.6	0.0 ± 0.0	0.2 ± 1.0	0.0	

	Total n=165		STEMI n=71		UA/NSTEMI n=93		No ACS n=1	
	Prasugrel n=47	**Clopidogrel n=118**	**Prasugrel n=30**	**Clopidogrel n=41**	**Prasugrel n=16**	**Clopidogrel n=77**	**Prasugrel n=1**	**Clopidogrel n=0**
Median (Q1-Q3)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	
Outcome of bleeding								
1 = recovered	91.5 % (43/47)	83.1 % (98/118)	93.3 % (28/30)	82.9 % (34/41)	87.5 % (14/16)	83.1 % (64/77)	100.0 % (1/1)	
2 = recovered with sequela	0.0 % (0/47)	0.8 % (1/118)	0.0 % (0/30)	0.0 % (0/41)	0.0 % (0/16)	1.3 % (1/77)	0.0 % (0/1)	
3 = not recovered	4.3 % (2/47)	2.5 % (3/118)	3.3 % (1/30)	4.9 % (2/41)	6.3 % (1/16)	1.3 % (1/77)	0.0 % (0/1)	
4 = fatal	0.0 % (0/47)	5.9 % (7/118)	0.0 % (0/30)	7.3 % (3/41)	0.0 % (0/16)	5.2 % (4/77)	0.0 % (0/1)	
5 = disability/incapacitated	0.0 % (0/47)	0.0 % (0/118)	0.0 % (0/30)	0.0 % (0/41)	0.0 % (0/16)	0.0 % (0/77)	0.0 % (0/1)	
6 = worsened	0.0 % (0/47)	0.0 % (0/118)	0.0 % (0/30)	0.0 % (0/41)	0.0 % (0/16)	0.0 % (0/77)	0.0 % (0/1)	
9 = unknown	4.3 % (2/47)	8.5 % (10/118)	3.3 % (1/30)	4.9 % (2/41)	6.3 % (1/16)	10.4 % (8/77)	0.0 % (0/1)	
Results are based on number of patients.								

Source: Table 7f, Attachment 1

2.8.6.4. Risk Factors for Bleeding in Prasugrel-Treated Patients

Table B008.2.12 (from Table 10f, Attachment 1) presents the risk factors for bleeding in all prasugrel-treated patients receiving an LD of either drug during the index hospitalisation regardless of previous exposure of either drug. As expected, risk factors for bleeding in prasugrel-treated patients included older age, female gender, and low body weight.

Risk factors associated with non-CABG-related bleeding requiring any blood transfusions of whole blood or RBC, or ICH in prasugrel-treated patients included:

- female gender
- low body weight
- known severe hepatic dysfunction
- use of a GPIIb/IIIa antagonist
- use of a proton pump inhibitor.

Risk factors for any bleeding requiring any blood transfusions of whole blood or RBC, or ICH in prasugrel-treated patients included:

- female gender
- low body weight
- known severe hepatic dysfunction
- use of a GPIIb/IIIa antagonist
- use of a proton pump inhibitor.

Risk factors for any bleeding in prasugrel-treated patients included:

- age 55 to 74 years
- active pathological bleeding
- known severe hepatic dysfunction
- symptoms of heart failure
- use of a GPIIb/IIIa antagonist
- use of a proton pump inhibitor.

Table B008.2.12 Risk Factors for Bleeding in all Prasugrel-Treated Patients Receiving an LD of Either Drug during the Index Hospitalisation Regardless of Previous Exposure of Either Drug

	Patients with bleeding	Patients without bleeding	P values	Odds ratio (95% CI)
Non-CABG-related bleeding requiring any blood transfusion of whole blood or red blood cell concentrates and/or intracranial hemorrhage				
PCI performed	93.8 % (15/16)	89.3 % (2433/2723)	0.57	1.79 (0.24-13.59)
No ACS	6.3 % (1/16)	9.8 % (268/2723)		1.02 (0.11-9.16)
NSTE-ACS	25.0 % (4/16)	40.1 % (1093/2723)		1 *
STEMI	68.8 % (11/16)	50.0 % (1362/2723)		2.21 (0.70-6.95)
Age	63.8 ± 8.3	59.2 ± 10.6	0.07	
<55 years	18.8 % (3/16)	37.4 % (1019/2723)		1 *
55 – 74 years	75.0 % (12/16)	56.8 % (1547/2723)		2.63 (0.74-9.36)
≥75 years	6.3 % (1/16)	5.8 % (157/2723)		2.16 (0.22-20.92)
Female gender	56.3 % (9/16)	21.1 % (574/2723)	< 0.001	4.81 (1.78-12.98)
Body weight	68.9 ± 11.4	85.8 ± 15.9	< 0.0001	
≥90 kg	0.0 % (0/15)	37.8 % (858/2271)		---
60 – 89 kg	80.0 % (12/15)	59.9 % (1360/2271)		1 *
< 60 kg	20.0 % (3/15)	2.3 % (53/2271)		6.42 (1.76-23.41)
History of stroke / TIA	0.0 % (0/16)	1.5 % (41/2672)	0.62	
Active pathological bleeding	0.0 % (0/16)	0.2 % (5/2708)	0.86	
Recent trauma	0.0 % (0/14)	0.9 % (24/2631)	0.72	
Recent surgery	0.0 % (0/14)	1.3 % (35/2627)	0.66	
Known severe hepatic dysfunction	6.3 % (1/16)	0.3 % (8/2686)	< 0.0001	22.32 (2.63-189.67)
Renal insufficiency	13.3 % (2/15)	8.7 % (224/2568)	0.53	1.61 (0.36-7.18)
Diabetes	40.0 % (6/15)	23.7 % (626/2642)	0.14	2.15 (0.76-6.06)
Symptoms of heart failure	18.8 % (3/16)	6.9 % (189/2723)	0.07	3.09 (0.87-10.95)
Cardiogenic shock at start of PCI	6.3 % (1/16)	2.4 % (65/2723)	0.32	2.73 (0.35-20.95)
Smoker	60.0 % (9/15)	64.9 % (1611/2482)	0.69	0.81 (0.29-2.29)
Radial access	7.1 % (1/14)	28.6 % (688/2406)	0.08	0.19 (0.03-1.47)
GP IIb/IIIa antagonists	56.3 % (9/16)	22.0 % (598/2723)	< 0.001	4.57 (1.69-12.32)
Vitamin K antagonists	0.0 % (0/16)	3.4 % (91/2698)	0.45	

	Patients with bleeding	Patients without bleeding	P values	Odds ratio (95% CI)
Proton pump inhibitors	62.5 % (10/16)	22.3 % (597/2682)	< 0.001	5.82 (2.11-16.08)
Thrombolysis < 24 h	0.0 % (0/16)	1.5 % (40/2676)	0.62	
Any bleeding requiring any blood transfusion of whole blood or red blood cell concentrates and/or intracranial hemorrhage				
PCI performed	88.2 % (15/17)	89.4 % (2433/2722)	0.88	0.89 (0.20-3.92)
No ACS	5.9 % (1/17)	9.8 % (268/2722)		0.81 (0.09-7.00)
NSTE-ACS	29.4 % (5/17)	40.1 % (1092/2722)		1 *
STEMI	64.7 % (11/17)	50.0 % (1362/2722)		1.76 (0.61-5.09)
Age	63.7 ± 8.0	59.2 ± 10.6	0.07	
<55 years	17.6 % (3/17)	37.4 % (1019/2722)		1 *
55 – 74 years	76.5 % (13/17)	56.8 % (1546/2722)		2.86 (0.81-10.04)
≥75 years	5.9 % (1/17)	5.8 % (157/2722)		2.16 (0.22-20.92)
Female gender	52.9 % (9/17)	21.1 % (574/2722)	< 0.01	4.21 (1.62-10.96)
Body weight	69.9 ± 11.7	85.8 ± 15.9	< 0.0001	
≥90 kg	0.0 % (0/16)	37.8 % (858/2270)		---
60 – 89 kg	81.3 % (13/16)	59.9 % (1359/2270)		1 *
<60 kg	18.8 % (3/16)	2.3 % (53/2270)		5.92 (1.64-21.39)
History of stroke / TIA	0.0 % (0/17)	1.5 % (41/2671)	0.61	
Active pathological bleeding	0.0 % (0/17)	0.2 % (5/2707)	0.86	
Recent trauma	0.0 % (0/15)	0.9 % (24/2630)	0.71	
Recent surgery	0.0 % (0/15)	1.3 % (35/2626)	0.65	
Known severe hepatic dysfunction	5.9 % (1/17)	0.3 % (8/2685)	< 0.0001	20.91 (2.47-177.08)
Renal insufficiency	18.8 % (3/16)	8.7 % (223/2567)	0.16	2.43 (0.69-8.58)
Diabetes	37.5 % (6/16)	23.7 % (626/2641)	0.20	1.93 (0.70-5.34)
Symptoms of heart failure	17.6 % (3/17)	6.9 % (189/2722)	0.08	2.87 (0.82-10.08)
Cardiogenic shock at start of PCI	5.9 % (1/17)	2.4 % (65/2722)	0.35	2.55 (0.33-19.55)
Smoker	62.5 % (10/16)	64.9 % (1610/2481)	0.84	0.90 (0.33-2.49)
Radial access	7.1 % (1/14)	28.6 % (688/2406)	0.08	0.19 (0.03-1.47)
GP IIb/IIIa antagonists	52.9 % (9/17)	22.0 % (598/2722)	< 0.01	4.00 (1.54-10.40)
Vitamin K antagonists	0.0 % (0/17)	3.4 % (91/2697)	0.44	
Proton pump inhibitors	58.8 % (10/17)	22.3 % (597/2681)	< 0.001	4.99 (1.89-13.16)

	Patients with bleeding	Patients without bleeding	P values	Odds ratio (95% CI)
Thrombolysis < 24 h	0.0 % (0/17)	1.5 % (40/2675)	0.61	
Any bleeding				
PCI performed	93.6 % (44/47)	89.3 % (2404/2692)	0.34	1.76 (0.54-5.69)
No ACS	2.1 % (1/47)	10.0 % (268/2692)		0.25 (0.03-1.91)
NSTE-ACS	34.0 % (16/47)	40.2 % (1081/2692)		1 *
STEMI	63.8 % (30/47)	49.9 % (1343/2692)		1.51 (0.82-2.78)
Age	62.9 ± 9.5	59.2 ± 10.6	< 0.05	
<55 years	19.1 % (9/47)	37.6 % (1013/2692)		1 *
55 – 74 years	72.3 % (34/47)	56.6 % (1525/2692)		2.51 (1.20-5.25)
≥75 years	8.5 % (4/47)	5.7 % (154/2692)		2.92 (0.89-9.61)
Female gender	29.8 % (14/47)	21.1 % (569/2692)	0.15	1.58 (0.84-2.98)
Body weight	76.1 ± 12.7	85.9 ± 16.0	< 0.0001	
≥90 kg	11.4 % (5/44)	38.0 % (853/2242)		0.22 (0.09-0.56)
60 – 89 kg	81.8 % (36/44)	59.6 % (1336/2242)		1 *
<60 kg	6.8 % (3/44)	2.4 % (53/2242)		2.10 (0.63-7.04)
History of stroke / TIA	0.0 % (0/47)	1.6 % (41/2641)	0.39	
Active pathological bleeding	2.1 % (1/47)	0.1 % (4/2677)	< 0.01	14.53 (1.59-132.51)
Recent trauma	0.0 % (0/45)	0.9 % (24/2600)	0.52	
Recent surgery	2.2 % (1/45)	1.3 % (34/2596)	0.60	1.71 (0.23-12.79)
Known severe hepatic dysfunction	2.2 % (1/46)	0.3 % (8/2656)	< 0.05	7.36 (0.90-60.05)
Renal insufficiency	16.3 % (7/43)	8.6 % (219/2540)	0.08	2.06 (0.91-4.69)
Diabetes	25.0 % (11/44)	23.8 % (621/2613)	0.85	1.07 (0.54-2.13)
Symptoms of heart failure	17.0 % (8/47)	6.8 % (184/2692)	< 0.01	2.80 (1.29-6.07)
Cardiogenic shock at start of PCI	6.4 % (3/47)	2.3 % (63/2692)	0.07	2.85 (0.86-9.41)
Smoker	61.4 % (27/44)	64.9 % (1593/2453)	0.62	0.86 (0.46-1.58)
Radial access	2.3 % (1/43)	28.9 % (688/2377)	< 0.001	0.06 (0.01-0.43)
GP IIb/IIIa antagonists	42.6 % (20/47)	21.8 % (587/2692)	< 0.001	2.66 (1.48-4.77)
Vitamin K antagonists	2.2 % (1/46)	3.4 % (90/2668)	0.65	0.64 (0.09-4.67)
Proton pump inhibitors	37.0 % (17/46)	22.2 % (590/2652)	< 0.05	2.05 (1.12-3.75)
Thrombolysis < 24 h	4.3 % (2/46)	1.4 % (38/2646)	0.11	3.12 (0.73-13.34)

Results are based on number of patients.

* reference category

Source: Table 10f, Attachment 1

2.8.6.5. Risk Factors for Bleeding in Clopidogrel-Treated Patients

Table B008.2.13 (from Table 11f, Attachment 1) presents risk factors for bleeding in all clopidogrel-treated patients receiving an LD of either drug during the index hospitalisation regardless of previous exposure of either drug. The following risk factors were observed consistently in the 3 categories of bleeding for clopidogrel-treated patients: older age, female gender, low body weight, active pathological bleeding, recent trauma, renal insufficiency, and cardiogenic shock.

Risk factors associated with non-CABG bleeding requiring any blood transfusions or ICH in clopidogrel-treated patients included:

- older age
- female gender
- low body weight
- active pathological bleeding
- recent trauma
- known severe hepatic dysfunction
- renal insufficiency
- symptoms of heart failure
- cardiogenic shock at start of PCI
- use of a proton pump inhibitor.

Patients risk factors for any bleeding requiring any blood transfusions or ICH in clopidogrel-treated patients included:

- older age
- female gender
- low body weight
- active pathological bleeding
- recent trauma
- known severe hepatic dysfunction
- renal insufficiency
- cardiogenic shock at start of PCI
- smoker
- use of a proton pump inhibitor.

Patients with risk factors for any bleeding in clopidogrel-treated patients included:

- older age
- female gender
- low body weight
- active pathological bleeding
- recent trauma
- renal insufficiency
- symptoms of heart failure
- cardiogenic shock at start of PCI

- smoker
- use of a proton pump inhibitor.

Table B008.2.13. Risk Factors for Bleeding in all ACS Clopidogrel-Treated Patients Receiving an LD of Either Drug During the Index Hospitalisation Regardless of Previous Exposure of Either Drug

	Patients with bleeding	Patients without bleeding	P values	Odds ratio (95% confidence interval)
Non-CABG-related bleeding requiring any blood transfusion of whole blood or red blood cell concentrates and/or intracranial hemorrhage				
PCI performed	91.3 % (42/46)	85.6 % (5507/6430)	0.27	1.76 (0.63-4.92)
STEMI	39.1 % (18/46)	30.7 % (1977/6430)	0.22	1.45 (0.80-2.62)
Age	75.9 ± 9.6	69.4 ± 12.3	< 0.001	
<55 years	2.2 % (1/46)	15.7 % (1007/6430)		1 *
55 – 74 years	37.0 % (17/46)	46.0 % (2956/6430)		5.79 (0.77-43.57)
≥75 years	60.9 % (28/46)	38.4 % (2467/6430)		11.43 (1.55-84.11)
Female gender	52.2 % (24/46)	31.1 % (1999/6430)	< 0.01	2.42 (1.35-4.32)
Body weight	74.2 ± 15.4	81.2 ± 16.3	< 0.01	
≥90 kg	22.2 % (10/45)	27.6 % (1630/5907)		0.80 (0.39-1.64)
60 – 89 kg	66.7 % (30/45)	66.4 % (3920/5907)		1 *
<60 kg	11.1 % (5/45)	6.0 % (357/5907)		1.83 (0.71-4.75)
History of stroke / TIA	4.8 % (2/42)	8.2 % (500/6104)	0.42	0.56 (0.14-2.33)
Active pathological bleeding	22.2 % (10/45)	0.8 % (51/6362)	< 0.0001	35.36 (16.62-75.21)
Recent trauma	9.8 % (4/41)	1.3 % (79/6113)	< 0.0001	8.26 (2.87-23.72)
Recent surgery	5.0 % (2/40)	2.9 % (176/6101)	0.43	1.77 (0.42-7.40)
Known severe hepatic dysfunction	2.2 % (1/45)	0.3 % (22/6337)	< 0.05	6.52 (0.86-49.47)
Renal insufficiency	40.5 % (17/42)	21.1 % (1311/6203)	< 0.01	2.54 (1.37-4.71)
Diabetes	34.9 % (15/43)	30.9 % (1915/6190)	0.58	1.20 (0.64-2.24)
Symptoms of heart failure	21.7 % (10/46)	11.2 % (717/6430)	< 0.05	2.21 (1.09-4.48)
Cardiogenic shock at start of PCI	8.7 % (4/46)	2.3 % (147/6430)	< 0.01	4.07 (1.44-11.50)
Smoker	28.6 % (10/35)	48.1 % (2734/5680)	< 0.05	0.43 (0.21-0.90)
Radial access	9.5 % (4/42)	21.1 % (1154/5464)	0.07	0.39 (0.14-1.10)
GP IIb/IIIa antagonists	21.7 % (10/46)	19.2 % (1237/6430)	0.67	1.17 (0.58-2.36)
Vitamin K antagonists	13.6 % (6/44)	9.3 % (588/6307)	0.33	1.54 (0.65-3.65)
Proton pump inhibitors	65.9 % (29/44)	35.4 % (2221/6282)	< 0.0001	3.54 (1.89-6.61)

	Patients with bleeding	Patients without bleeding	P values	Odds ratio (95% confidence interval)
Any bleeding requiring any blood transfusion of whole blood or red blood cell concentrates and/or intracranial hemorrhage				
Thrombolysis < 24 h	0.0 % (0/46)	1.1 % (67/6338)	0.48	
PCI performed	82.4 % (42/51)	85.7 % (5507/6425)	0.50	0.78 (0.38-1.60)
STEMI	35.3 % (18/51)	30.8 % (1977/6425)	0.49	1.23 (0.69-2.18)
Age	75.6 ± 9.7	69.4 ± 12.3	< 0.001	
<55 years	3.9 % (2/51)	15.7 % (1006/6425)		1 *
55 – 74 years	37.3 % (19/51)	46.0 % (2954/6425)		3.24 (0.75-13.91)
≥75 years	58.8 % (30/51)	38.4 % (2465/6425)		6.12 (1.46-25.66)
Female gender	51.0 % (26/51)	31.1 % (1997/6425)	< 0.01	2.31 (1.33-4.00)
Body weight	73.9 ± 15.2	81.2 ± 16.3	< 0.001	
≥90 kg	22.0 % (11/50)	27.6 % (1629/5902)		0.78 (0.39-1.54)
60 – 89 kg	68.0 % (34/50)	66.4 % (3916/5902)		1 *
<60 kg	10.0 % (5/50)	6.0 % (357/5902)		1.61 (0.63-4.15)
History of stroke / TIA	6.4 % (3/47)	8.2 % (499/6099)	0.65	0.77 (0.24-2.47)
Active pathological bleeding	20.4 % (10/49)	0.8 % (51/6358)	< 0.0001	31.71 (15.02-66.95)
Recent trauma	8.7 % (4/46)	1.3 % (79/6108)	< 0.0001	7.27 (2.55-20.76)
Recent surgery	4.4 % (2/45)	2.9 % (176/6096)	0.53	1.56 (0.38-6.51)
Known severe hepatic dysfunction	2.0 % (1/50)	0.3 % (22/6332)	0.05	5.85 (0.77-44.29)
Renal insufficiency	39.1 % (18/46)	21.1 % (1310/6199)	< 0.01	2.40 (1.32-4.35)
Diabetes	38.3 % (18/47)	30.9 % (1912/6186)	0.28	1.39 (0.77-2.50)
Symptoms of heart failure	19.6 % (10/51)	11.2 % (717/6425)	0.06	1.94 (0.97-3.89)
Cardiogenic shock at start of PCI	7.8 % (4/51)	2.3 % (147/6425)	< 0.01	3.63 (1.29-10.22)
Smoker	30.0 % (12/40)	48.1 % (2732/5675)	< 0.05	0.46 (0.23-0.91)
Radial access	9.5 % (4/42)	21.1 % (1154/5464)	0.07	0.39 (0.14-1.10)
GP IIb/IIIa antagonists	21.6 % (11/51)	19.2 % (1236/6425)	0.67	1.15 (0.59-2.26)
Vitamin K antagonists	12.2 % (6/49)	9.3 % (588/6302)	0.49	1.36 (0.57-3.20)
Proton pump inhibitors	67.3 % (33/49)	35.3 % (2217/6277)	< 0.0001	3.78 (2.07-6.88)
Thrombolysis < 24 h	0.0 % (0/51)	1.1 % (67/6333)	0.46	

	Patients with bleeding	Patients without bleeding	P values	Odds ratio (95% confidence interval)
Any bleeding				
PCI performed	85.6 % (101/118)	85.7 % (5448/6358)	0.98	0.99 (0.59-1.67)
Age	76.9 ± 9.4	69.3 ± 12.3	< 0.0001	
<55 years	2.5 % (3/118)	15.8 % (1005/6358)		1 *
55 – 74 years	33.1 % (39/118)	46.1 % (2934/6358)		4.45 (1.37-14.44)
≥75 years	64.4 % (76/118)	38.0 % (2419/6358)		10.52 (3.31-33.44)
Female gender	44.9 % (53/118)	31.0 % (1970/6358)	< 0.01	1.82 (1.26-2.62)
Body weight	74.8 ± 15.0	81.3 ± 16.3	< 0.0001	
≥90 kg	18.6 % (21/113)	27.7 % (1619/5839)		0.64 (0.39-1.04)
60 – 89 kg	69.0 % (78/113)	66.3 % (3872/5839)		1 *
<60 kg	12.4 % (14/113)	6.0 % (348/5839)		2.00 (1.12-3.57)
History of stroke / TIA	8.2 % (9/110)	8.2 % (493/6036)	1.00	1.00 (0.50-1.99)
Active pathological bleeding	16.4 % (19/116)	0.7 % (42/6291)	< 0.0001	29.14 (16.35-51.94)
Recent trauma	4.5 % (5/110)	1.3 % (78/6044)	< 0.01	3.64 (1.44-9.18)
Recent surgery	4.5 % (5/110)	2.9 % (173/6031)	0.30	1.61 (0.65-4.01)
Known severe hepatic dysfunction	0.9 % (1/117)	0.4 % (22/6265)	0.37	2.45 (0.33-18.30)
Renal insufficiency	32.4 % (36/111)	21.1 % (1292/6134)	< 0.01	1.80 (1.20-2.69)
Diabetes	33.6 % (38/113)	30.9 % (1892/6120)	0.54	1.13 (0.76-1.68)
Symptoms of heart failure	16.9 % (20/118)	11.1 % (707/6358)	< 0.05	1.63 (1.00-2.66)
Cardiogenic shock at start of PCI	5.1 % (6/118)	2.3 % (145/6358)	< 0.05	2.30 (0.99-5.30)
Smoker	35.6 % (36/101)	48.2 % (2708/5614)	< 0.05	0.59 (0.39-0.90)
Radial access	10.1 % (10/99)	21.2 % (1148/5407)	< 0.01	0.42 (0.22-0.80)
GP IIb/IIIa antagonists	21.2 % (25/118)	19.2 % (1222/6358)	0.59	1.13 (0.72-1.76)
Vitamin K antagonists	14.7 % (17/116)	9.3 % (577/6235)	< 0.05	1.68 (1.00-2.84)
Proton pump inhibitors	53.0 % (61/115)	35.2 % (2189/6211)	< 0.0001	2.08 (1.43-3.00)
Thrombolysis < 24 h	0.9 % (1/117)	1.1 % (66/6267)	0.83	0.81 (0.11-5.89)

Results are based on number of patients.
* reference category
Source: Table 11f, Attachment 1

2.8.6.6. Predictors for Switching from Clopidogrel to Prasugrel or from Prasugrel to Clopidogrel

Table B008.2.14 (from Table 12f, Attachment 1) presents predictors for switching in patients receiving an LD of either drug during the index hospitalisation regardless of previous exposure of either drug.

Switch from Clopidogrel LD to Prasugrel MD

Of 6500 patients who received a clopidogrel LD during the index hospitalisation, 266 switched to a prasugrel MD. As expected, patients with STEMI, and those who were younger, heavier, or smokers were more likely to switch. Also as expected, female patients, those with history of stroke/TIA, or were on a vitamin K antagonist were less likely to switch.

The following categories of patients were more likely to switch from a clopidogrel LD to a prasugrel MD:

- PCI performed in no ACS
- PCI performed in STEMI
- younger
- heavier
- smoker
- use of a GPIIb/IIIa antagonist

The following categories of patients were less likely to switch from a clopidogrel LD to a prasugrel MD:

- female gender
- hypertension
- hypercholesterolemia
- peripheral vascular disease
- history of stroke/TIA
- recent surgery
- renal insufficiency
- diabetes
- symptoms of heart failure
- cardiogenic shock at start of PCI
- vitamin K antagonist

Switch from Prasugrel LD to Clopidogrel MD:

Of 2740 patients who received a prasugrel LD during the index hospitalisation, 86 switched to a clopidogrel MD. As expected, patients who were older, had a history of stroke/TIA or were on vitamin K antagonists were more likely to switch. Also as expected, heavier patients were less likely to switch.

The following categories of patients were more likely to switch from a prasugrel LD to a clopidogrel MD:

- PCI performed in NSTE-ACS
- older
- peripheral vascular disease
- history stroke/TIA
- known severe hepatic dysfunction
- renal insufficiency
- diabetes
- vitamin K antagonists
- proton pump inhibitors
- NSAIDS

The following categories of patients were less likely to switch from a prasugrel LD to a clopidogrel MD:

- heavier

Switch from Clopidogrel MD to Prasugrel MD:

Of 6071 patients who were treated with a clopidogrel MD during the index hospitalisation, 47 switched to a prasugrel MD. As expected, patients who had a PCI performed for a STEMI, or were heavier more likely to switch. Also as expected, patients who were older, female or with a history of stroke/TIA were less likely to switch.

The following categories of patients were more likely to switch from a clopidogrel MD to a prasugrel MD:

- PCI performed in no ACS
- PCI performed in STEMI
- heavier

The following categories of patients were less likely to switch from a clopidogrel MD to a prasugrel MD:

- older
- female gender
- peripheral vascular disease
- history stroke/TIA

Switch from Prasugrel MD to Clopidogrel MD:

Of 2864 patients who were treated with a prasugrel MD during the index hospitalisation, 31 switched to a clopidogrel MD. As expected, patients who were older, had a history of stroke/TIA or were on vitamin K antagonists were more likely to switch.

The following categories of patients were more likely to switch from a prasugrel MD to a clopidogrel MD:

- older
- history stroke/TIA
- symptoms of heart failure
- vitamin K antagonists
- proton pump inhibitors.

Table B008.2.14. Predictors for Switching in Patients Receiving an LD of Either Drug during the Index Hospitalisation Regardless of Previous Exposure of Either Drug

	Switchers	Non-switchers	P values	Odds ratio (95% confidence interval)
Switching from clopidogrel LD to prasugrel MD				
PCI performed	98.5 % (262/266)	85.2 % (5311/6234)	< 0.0001	11.38 (4.23-30.63)
No ACS	8.6 % (23/266)	0.0 % (1/6234)		> 1000
NSTE-ACS	34.6 % (92/266)	70.4 % (4389/6234)		1*
STEMI	56.8 % (151/266)	29.6 % (1844/6234)		3.91 (3.00-5.09)
Age	60.5 ± 11.3	69.8 ± 12.1	< 0.0001	
<55 years	34.6 % (92/266)	14.7 % (918/6234)		1 *
55 – 74 years	55.3 % (147/266)	45.6 % (2843/6234)		0.52 (0.39-0.68)
≥75 years	10.2 % (27/266)	39.7 % (2473/6234)		0.11 (0.07-0.17)
Female gender	18.8 % (50/266)	31.7 % (1977/6234)	< 0.0001	0.50 (0.36-0.68)
Body weight	85.6 ± 14.8	81.0 ± 16.3	< 0.0001	
≥90 kg	36.6 % (96/262)	27.2 % (1555/5714)		1.44 (1.11-1.86)
60 – 89 kg	62.2 % (163/262)	66.5 % (3799/5714)		1 *
<60 kg	1.1 % (3/262)	6.3 % (360/5714)		0.19 (0.06-0.61)
Hypertension	72.7 % (184/253)	82.9 % (4832/5830)	< 0.0001	0.55 (0.41-0.73)
Hypercholesterolemia	40.0 % (96/240)	55.5 % (2941/5296)	< 0.0001	0.53 (0.41-0.70)
Peripheral vascular disease	5.7 % (15/262)	10.0 % (592/5894)	< 0.05	0.54 (0.32-0.92)
History of stroke / TIA	1.1 % (3/262)	8.4 % (499/5908)	< 0.0001	0.13 (0.04-0.39)
Active pathological bleeding	0.0 % (0/265)	1.0 % (61/6166)	0.10	
Recent trauma	0.0 % (0/264)	1.4 % (83/5914)	0.05	
Recent surgery	0.4 % (1/263)	3.0 % (177/5902)	< 0.05	0.12 (0.02-0.88)
Known severe hepatic dysfunction	0.0 % (0/264)	0.4 % (23/6141)	0.32	
Renal insufficiency	13.1 % (34/260)	21.6 % (1300/6009)	< 0.001	0.54 (0.38-0.79)
Diabetes	24.7 % (65/263)	31.2 % (1873/5994)	< 0.05	0.72 (0.54-0.96)
Symptoms of heart failure	5.6 % (15/266)	11.5 % (714/6234)	< 0.01	0.46 (0.27-0.78)
Cardiogenic shock at start of PCI	0.0 % (0/266)	2.4 % (151/6234)	< 0.05	
Smoker	63.9 % (161/252)	47.3 % (2596/5487)	< 0.0001	1.97 (1.52-2.56)
GP IIb/IIIa antagonists	35.7 % (95/266)	18.5 % (1155/6234)	< 0.0001	2.44 (1.89-3.16)
Vitamin K antagonists	4.5 % (12/265)	9.6 % (584/6110)	< 0.01	0.45 (0.25-0.81)
Proton pump inhibitors	33.6 % (89/265)	35.7 % (2170/6085)	0.49	0.91 (0.70-1.18)

	Switchers	Non-switchers	P values	Odds ratio (95% confidence interval)
NSAIDs	4.6 % (12/263)	4.8 % (292/6058)	0.85	0.94 (0.52-1.70)
Switching from prasugrel LD to clopidogrel MD				
PCI performed	82.6 % (71/86)	89.6 % (2377/2654)	< 0.05	0.55 (0.31-0.98)
No ACS	9.3 % (8/86)	9.8 % (261/2654)		0.77 (0.36-1.66)
NSTE-ACS	48.8 % (42/86)	39.8 % (1056/2654)		1 *
STEMI	41.9 % (36/86)	50.4 % (1337/2654)		0.68 (0.43-1.06)
Age	63.7 ± 11.6	59.1 ± 10.5	< 0.001	
<55 years	25.6 % (22/86)	37.7 % (1000/2654)		1 *
55 – 74 years	61.6 % (53/86)	56.8 % (1507/2654)		1.60 (0.97-2.64)
≥75 years	12.8 % (11/86)	5.5 % (147/2654)		3.40 (1.62-7.16)
Female gender	27.9 % (24/86)	21.1 % (559/2654)	0.13	1.45 (0.90-2.35)
Body weight	81.5 ± 14.5	85.9 ± 16.0	< 0.05	
≥90 kg	24.1 % (20/83)	38.0 % (838/2204)		0.53 (0.32-0.89)
60 – 89 kg	71.1 % (59/83)	59.6 % (1314/2204)		1 *
<60 kg	4.8 % (4/83)	2.4 % (52/2204)		1.71 (0.60-4.90)
Hypertension	74.7 % (59/79)	73.3 % (1823/2488)	0.78	1.08 (0.64-1.80)
Hypercholesterolemia	59.5 % (44/74)	51.7 % (1155/2236)	0.19	1.37 (0.86-2.20)
Peripheral vascular disease	9.9 % (8/81)	4.2 % (109/2574)	< 0.05	2.48 (1.17-5.27)
History of stroke / TIA	7.2 % (6/83)	1.3 % (35/2606)	< 0.0001	5.72 (2.34-14.01)
Active pathological bleeding	0.0 % (0/85)	0.2 % (5/2640)	0.69	
Recent trauma	2.4 % (2/82)	0.9 % (22/2564)	0.14	2.89 (0.67-12.50)
Recent surgery	3.7 % (3/82)	1.3 % (32/2560)	0.06	3.00 (0.90-10.00)
Known severe hepatic dysfunction	2.4 % (2/85)	0.3 % (7/2618)	< 0.01	8.99 (1.84-43.93)
Renal insufficiency	18.5 % (15/81)	8.5 % (212/2503)	< 0.01	2.46 (1.38-4.38)
Diabetes	35.4 % (29/82)	23.4 % (603/2576)	< 0.05	1.79 (1.13-2.84)
Symptoms of heart failure	11.6 % (10/86)	6.9 % (182/2654)	0.09	1.79 (0.91-3.51)
Cardiogenic shock at start of PCI	3.5 % (3/86)	2.4 % (63/2654)	0.51	1.49 (0.46-4.83)
Smoker	55.8 % (43/77)	65.2 % (1578/2421)	0.09	0.68 (0.43-1.07)
GP IIb/IIIa antagonists	20.9 % (18/86)	22.2 % (589/2654)	0.78	0.93 (0.55-1.57)
Vitamin K antagonists	9.3 % (8/86)	3.2 % (83/2629)	< 0.01	3.15 (1.47-6.73)
Proton pump inhibitors	34.9 % (30/86)	22.1 % (577/2613)	< 0.01	1.89 (1.20-2.97)

NSAIDs	7.0 % (6/86)	1.9 % (49/2610)	< 0.001	3.92 (1.63-9.42)
Switching from clopidogrel MD to prasugrel MD				
PCI performed	100.0 % (47/47)	87.7 % (5285/6024)	< 0.05	
No ACS	27.7 % (13/47)	0.2 % (10/6024)		303 (118-781)
NSTE-ACS	38.3 % (18/47)	69.7 % (4199/6024)		1 *
STEMI	34.0 % (16/47)	30.1 % (1815/6024)		2.06 (1.05-4.04)
Age	62.6 ± 10.9	69.8 ± 12.1	< 0.0001	
<55 years	29.8 % (14/47)	14.7 % (884/6024)		1 *
55 – 74 years	55.3 % (26/47)	45.8 % (2757/6024)		0.60 (0.31-1.15)
≥75 years	14.9 % (7/47)	39.6 % (2383/6024)		0.19 (0.07-0.46)
Female gender	12.8 % (6/47)	31.4 % (1890/6024)	< 0.01	0.32 (0.14-0.76)
Body weight	90.4 ± 14.8	80.9 ± 16.3	< 0.0001	
≥90 kg	48.9 % (23/47)	26.8 % (1485/5546)		2.50 (1.40-4.47)
60 – 89 kg	48.9 % (23/47)	67.0 % (3714/5546)		1 *
<60 kg	2.1 % (1/47)	6.3 % (347/5546)		0.47 (0.06-3.46)
Hypertension	78.3 % (36/46)	82.9 % (4662/5627)	0.41	0.75 (0.37-1.51)
Hypercholesterolemia	45.5 % (20/44)	55.6 % (2844/5116)	0.18	0.67 (0.37-1.21)
Peripheral vascular disease	0.0 % (0/47)	10.1 % (577/5686)	< 0.05	
History of stroke / TIA	0.0 % (0/47)	8.5 % (487/5705)	< 0.05	
Active pathological bleeding	0.0 % (0/47)	0.9 % (56/5960)	0.50	
Recent trauma	0.0 % (0/46)	1.4 % (78/5716)	0.43	
Recent surgery	0.0 % (0/46)	3.0 % (173/5704)	0.23	
Known severe hepatic dysfunction	0.0 % (0/46)	0.4 % (25/5935)	0.66	
Renal insufficiency	15.2 % (7/46)	21.8 % (1264/5803)	0.28	0.64 (0.29-1.44)
Diabetes	34.0 % (16/47)	31.5 % (1825/5790)	0.71	1.12 (0.61-2.06)
Symptoms of heart failure	4.3 % (2/47)	11.3 % (680/6024)	0.13	0.35 (0.08-1.44)
Cardiogenic shock at start of PCI	0.0 % (0/47)	2.3 % (141/6024)	0.29	
Smoker	47.8 % (22/46)	47.6 % (2519/5295)	0.97	1.01 (0.57-1.81)
GP IIb/IIIa antagonists	23.4 % (11/47)	19.0 % (1145/6024)	0.44	1.30 (0.66-2.57)
Vitamin K antagonists	4.3 % (2/47)	9.5 % (563/5909)	0.22	0.42 (0.10-1.74)
Proton pump inhibitors	34.0 % (16/47)	36.5 % (2147/5883)	0.73	0.90 (0.49-1.65)
NSAIDs	6.4 % (3/47)	4.8 % (281/5860)	0.61	1.35 (0.42-4.39)

Switching from prasugrel MD to clopidogrel MD				
PCI performed	83.9 % (26/31)	92.7 % (2627/2833)	0.06	0.41 (0.15-1.07)
No ACS	9.7 % (3/31)	9.9 % (280/2833)		0.89 (0.25-3.16)
NSTE-ACS	41.9 % (13/31)	38.3 % (1085/2833)		1 *
STEMI	48.4 % (15/31)	51.8 % (1468/2833)		0.85 (0.40-1.80)
Age	66.5 ± 12.0	59.3 ± 10.5	< 0.001	
<55 years	16.1 % (5/31)	37.5 % (1061/2833)		1 *
55 – 74 years	64.5 % (20/31)	56.7 % (1606/2833)		2.64 (0.99-7.06)
≥75 years	19.4 % (6/31)	5.9 % (166/2833)		7.67 (2.31-25.41)
Female gender	22.6 % (7/31)	20.9 % (591/2833)	0.81	1.11 (0.47-2.58)
Body weight	82.1 ± 8.7	85.9 ± 15.8	0.29	
≥90 kg	23.3 % (7/30)	37.8 % (899/2379)		0.48 (0.21-1.13)
60 – 89 kg	76.7 % (23/30)	60.1 % (1429/2379)		1 *
<60 kg	0.0 % (0/30)	2.1 % (51/2379)		---
Hypertension	67.9 % (19/28)	73.0 % (1942/2662)	0.55	0.78 (0.35-1.74)
Hypercholesterolemia	57.7 % (15/26)	50.3 % (1211/2408)	0.45	1.35 (0.62-2.95)
Peripheral vascular disease	10.3 % (3/29)	4.3 % (118/2753)	0.11	2.58 (0.77-8.63)
History of stroke / TIA	6.7 % (2/30)	1.3 % (35/2784)	< 0.01	5.61 (1.29-24.47)
Active pathological bleeding	0.0 % (0/30)	0.2 % (5/2818)	0.82	
Recent trauma	3.3 % (1/30)	0.8 % (22/2745)	0.13	4.27 (0.56-32.73)
Recent surgery	0.0 % (0/30)	1.2 % (32/2740)	0.55	
Known severe hepatic dysfunction	0.0 % (0/30)	0.3 % (7/2795)	0.78	
Renal insufficiency	14.3 % (4/28)	8.8 % (236/2683)	0.31	1.73 (0.59-5.02)
Diabetes	34.5 % (10/29)	23.4 % (645/2755)	0.16	1.72 (0.80-3.72)
Symptoms of heart failure	16.1 % (5/31)	6.7 % (191/2833)	< 0.05	2.66 (1.01-7.01)
Cardiogenic shock at start of PCI	0.0 % (0/31)	2.0 % (58/2833)	0.42	
Smoker	57.1 % (16/28)	65.4 % (1697/2594)	0.36	0.70 (0.33-1.50)
GP IIb/IIIa antagonists	25.8 % (8/31)	24.0 % (680/2833)	0.82	1.10 (0.49-2.47)
Vitamin K antagonists	12.9 % (4/31)	3.3 % (94/2808)	< 0.01	4.28 (1.47-12.47)
Proton pump inhibitors	41.9 % (13/31)	23.5 % (656/2792)	< 0.05	2.35 (1.15-4.83)
NSAIDs	6.5 % (2/31)	2.1 % (58/2789)	0.09	3.25 (0.76-13.93)

Results are based on number of patients.

* reference category

Source: Table 12f, Attachment 1

2.8.6.7. Subgroup Analyses

2.8.6.7.1. Characterization of Bleeding in Subgroups of Prasugrel-Treated Patients

Table B008.2.15 (from Table 8f, Attachment 1) characterizes bleeding in all patients who received an LD of prasugrel according to indication, contraindication, body weight, and age. Of 2739 prasugrel-treated patients who received an LD of prasugrel, 47 (1.7%) experienced any bleeding. No fatal bleeding was observed and there were no bleeding events in the 41 patients who had a history of TIA/stroke.

Of 158 patients who were ≥75 years of age, 4 (2.5%) had any bleeding requiring any blood transfusion of whole blood or RBCs and/or ICH. Of the 121 patients ≥75 years of age who received a 10-mg MD of prasugrel, 2 (1.7%) patients had any bleeding and none required blood transfusion.

Of 56 prasugrel-treated patients who weighed <60 kg, 45 received a 10-mg LD; 3 (6.7%) of these patients had any bleeding requiring any blood transfusion of whole blood or RBCs and/or ICH.

Of the 5 prasugrel-treated patients with active pathological bleeding, 1 (20.0%) had any bleeding, but did not require any blood transfusion. Of 9 patients with known severe hepatic impairment, 1 (11.1%) had any bleeding which required blood transfusion of whole blood or RBCs and/or ICH.

Of 269 non-ACS patients who underwent an elective PCI, 1 patient (0.4%) had any bleeding which required blood transfusion of whole blood or RBCs and/or ICH. Of 1329 patients who received a prasugrel LD prior to coronary visualization, 20 (1.5%) had any bleeding, with 9 of them requiring blood transfusion of whole blood or RBCs and/or ICH.

2.8.6.7.2. Bleeding Risk Comparisons by Subgroup

Table B008.2.16 and Table B008.2.17 (from Table 14f-1 and 14f-3, respectively, Attachment 1) present the unadjusted bleeding risk comparison between all prasugrel- and clopidogrel-treated patients receiving only 1 LD of either drug during the index hospitalisation for non-CABG bleeding and any bleeding, respectively.

Based on bleeding risk, subgroups with high bleeding risk were compared with subgroups with low bleeding risk factors. The following subgroups were included in the analyses:

- Prasugrel indication (contraindicated or not indicated [no ACS])
- LD prior to or after coronary visualization
- Prasugrel MD of 5 mg or 10 mg
- Age <75 or ≥75 years
- Body weight <60 kg or ≥60 kg

Overall, the unadjusted bleeding risk comparison shows that bleeding was low in both treatment groups.

Non-CABG Bleeding

The only significant treatment-by-subgroup interaction observed for the rate of non-CABG bleeding (requiring any transfusion of whole blood or RBC's) and /or ICH was based on body weight (interaction p=0.022). As expected in patients weighing <60 kg, prasugrel-treated patients had a significantly higher rate of non-CABG bleeding compared with clopidogrel-treated patients (5.56% [3/54] versus 1.38% [5/362], p=0.037). There was not a significant between-treatment difference observed in patients ≥60 kg (0.53% [11/2057] versus 0.72% [40/5590], p=0.389).

For non-CABG bleeding, there were no significant differences between treatment groups related to age (<75 years or ≥75 years) (Table B008.2.16).

The rate of non-CABG bleeding in patients receiving LD prior to coronary visualization was similar to the rate of non-CABG bleeding in patients receiving LD after coronary visualization for both prasugrel (0.62% versus 0.51%) and clopidogrel-treated (0.73% versus 0.66%) patients. The between-treatment risk of non-CABG bleeding was similar regardless of whether the LD was administered prior to coronary visualization (OR=0.84) or after coronary visualization (OR=0.76) (Table B008.2.16).

Any Bleeding

No significant treatment-by-subgroup differences in rates of any bleeding were observed for prasugrel- versus clopidogrel-treated patients for any subgroup. However, a significant between-treatment difference was observed for those age <75 years with prasugrel-treated patients having a higher rate of any bleeding compared with clopidogrel-treated patients (1.85% [43/2325] versus 1.06% [42/3981], p=0.008). No significant between-treatment difference was observed in subjects ≥75 years (Table B008.2.17).

The rate of any bleeding in patients receiving an LD prior to coronary visualization was slightly lower than the rate of any bleeding in patients receiving LD after coronary visualization for prasugrel-treated patients (1.54% versus 2.02%) but was similar for clopidogrel-treated patients (1.78% versus 1.99%). The between-treatment risk of any bleeding was similar regardless of whether the LD was administered prior to coronary visualization (OR=0.86) or after coronary visualization (OR=1.02) (Table B008.2.17).

Table B008.2.15. Characterization of Bleeding in All Prasugrel-Treated Patients Receiving an LD of Prasugrel Only Regardless of Previous Exposure to Either Clopidogrel or Prasugrel Upon Admission

	Total N=2739	are not indicated (elective PCI, non-ACS) (N,%) N=269	History of TIA/stroke (N,%) N=41	Known severe hepatic impairment (N,%) N=9	Active pathological bleeding (N,%) N=5	≥75 years receiving a 10-mg MD (N,%) N=121	<60 Kg receiving a 10 mg MD (N,%) N=45	Receive a loading dose prior to coronary visualization (N,%) N=1329	≥75 years (N,%) N=158	<60 Kg (N,%) N=56
Non-CABG-related bleeding requiring any blood transfusion of whole blood or red blood cell concentrates and/or intracranial hemorrhage	16 (0.6%)	1 (0.4%)	0 (0%)	1 (11.1%)	0 (0%)	0 (0%)	3 (6.7%)	8 (0.6%)	1 (0.6%)	3 (5.4%)
Any bleeding requiring any blood transfusion of whole blood or red blood cell concentrates and/or intracranial hemorrhage	17 (0.6%)	1 (0.4%)	0 (0%)	1 (11.1%)	0 (0%)	0 (0%)	3 (6.7%)	9 (0.7%)	1 (0.6%)	3 (5.4%)
Any bleeding	47 (1.7%)	1 (0.4%)	0 (0%)	1 (11.1%)	1 (20.0%)	2 (1.7%)	3 (6.7%)	20 (1.5%)	4 (2.5%)	3 (5.4%)
Fatal bleeding	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Results are based on number of patients.										

Source: Table 8f, Attachment 1

Table B008.2.16. Subgroup Analysis for Non-CABG Bleeding (Requiring any Transfusion of Whole Blood or RBCs) and/or ICH in Prasugrel- and Clopidogrel-Treated Patients Receiving an LD of Either Drug during the Index Hospitalisation Regardless of Previous Exposure of Either Drug

Subgroup variable	Prasugrel		Clopidogrel		Odds Ratio	95% CI of OR	p-value	Interaction p-value
	Estimated rate (N,n,%)	95% CI	Estimated rate (N,n,%)	95% CI				
Prasugrel contraindicated	0% (0/48)	---	2.08% (12/576)	0.92%-3.25%	---	---	0.313	---
Prasugrel not indicated	0.37% (1/269)	0.00%-1.10%	0% (0/24)	---	---	---	0.76	
LD prior to coronary visualisation	0.62% (8/1300)	0.19%-1.21%	0.73% (28/3821)	0.46%-1.00%	0.84	0.38-1.85	0.662	0.883
LD after coronary visualisation	0.51% (5/989)	0.06%-0.95%	0.66% (15/2264)	0.33%-1.00%	0.76	0.28-2.10	0.598	
Prasugrel MD 5 mg	0% (0/26)	---	---	---	---	---	---	---
Prasugrel MD 10 mg	0.61% (14/2299)	0.29%-0.93%	---	---	---	---	---	
Age ≥75 years	0% (0/145)	---	1.12% (28/2495)	0.71%-1.54%	---	---	0.200	0.132
Age <75 years	0.65% (15/2325)	0.32%-0.97%	0.45% (18/3981)	0.24%-0.66%	1.43	0.71-2.84	0.305	
Body weight <60 kg	5.56% (3/54)	0.00%-11.67%	1.38% (5/362)	0.18%-2.58%	4.20	0.97-18.11	0.037	0.022
Body weight ≥60 kg	0.53% (11/2057)	0.22%-0.85%	0.72% (40/5590)	0.49%-0.94%	0.75	0.38-1.46	0.389	

Note: odds ratios were not adjusted for quintiles of the propensity score.
Source: Table 14f-1, Attachment 1

Table B008.2.17. Subgroup Analysis for any Bleeding in Prasugrel- and Clopidogrel-Treated Patients Receiving an LD of either Drug during the Index Hospitalisation Regardless of Previous Exposure of Either Drug

Subgroup variable	Prasugrel		Clopidogrel		Odds Ratio	95% CI of OR	p-value	Interaction p-value
	Estimated rate (N,n,%)	95% CI	Estimated rate (N,n,%)	95% CI				
Prasugrel contraindicated	2.08% (1/48)	0.00%-6.12%	4.86% (28/576)	3.10%-6.62%	0.42	0.06-3.13	0.380	---
Prasugrel not indicated	0.37% (1/269)	0.00%-1.10%	0% (0/24)	---	---	---	0.76	
LD prior to coronary visualisation	1.54% (20/1300)	0.87%-2.21%	1.78% (68/3821)	1.36%-2.20%	0.86	0.52-1.43	0.563	0.657
LD after coronary visualisation	2.02% (20/989)	1.14%-2.90%	1.99% (45/2264)	1.41%-2.56%	1.02	0.60-1.73	0.948	
Prasugrel MD 5 mg	3.85% (1/26)	0.00%-11.24%	---	---	---	---	---	---
Prasugrel MD 10 mg	1.87% (43/2299)	1.32%-2.42%	---	---	---	---	---	
Age ≥75 years	2.07% (3/145)	0.00%-0.44%	3.05% (76/2495)	2.37%-3.72%	0.67	0.21-2.16	0.502	0.118
Age <75 years	1.85 % (43/2325)	1.30%-2.40%	1.06% (42/3981)	0.74%-1.37%	1.77	1.15-2.71	0.008	
Body weight <60 kg	5.56% (3/54)	0.00%-11.67%	3.87% (14/362)	1.18%-5.85%	1.46	0.41-5.26	0.559	0.675
Body weight ≥60 kg	1.94% (40/2057)	1.35%-2.54%	1.77% (99/5590)	1.43%-2.12%	1.10	0.76-1.59	0.614	

Note: odds ratios were not adjusted for quintiles of the propensity score.
Source: Table 14f-3, Attachment 1

2.9. Summary and Conclusions

2.9.1. Study Background

The pivotal study supporting prasugrel use in PCI was TRITON-TIMI 38, which demonstrated that a higher and more consistent level of platelet inhibition with prasugrel versus standard dose clopidogrel, on a background of low-dose aspirin, resulted in reduced ischemic events in moderate-to-high-risk ACS patients undergoing PCI (Wiviott et al. 2007). In the TRITON-TIMI 38 Study, superior efficacy of a more potent $P2Y_{12}$ inhibitor in attenuation of ischemic events was accompanied by a significant increase in TIMI major bleeding, including life-threatening and fatal bleeding. Three specific subgroups were identified as being at higher risk for bleeding: patients with a history of stroke or TIA, patients ≥75 years of age, and those with a body weight of less than 60 kg (Wiviott et al. 2007).

In order to optimise the benefit/risk balance of prasugrel treatment, prasugrel is contraindicated in patients with a history of TIA/stroke in the Summary of Product Characteristics (SPC). Furthermore, the use of prasugrel in the very elderly (age ≥75 years) is generally not recommended; if treatment is deemed appropriate after careful individual benefit/risk evaluation by the prescribing physician, then a lower 5 mg/day MD should be used. For patients <60 kg in body weight, the SPC specifies a lower maintenance daily dose of 5 mg.

In addition to the 3 specific subgroups identified as high risk in TRITON-TIMI 38, patients undergoing CABG had an increased risk of bleeding if the surgery was performed within 7 days after the last dose of prasugrel (Wiviott et al. 2007). Study B008 was expected to address the CHMP's concern with the possible CABG-related bleeding risk associated with LD administration of prasugrel prior to coronary angiography.

The main objective of Study B008 was to compare the incidence rates (cumulative incidence) of any non-CABG related bleeding (requiring any blood transfusion of whole blood or red blood cell concentrates [RBCs]) and/or intracranial haemorrhage (ICH) between prasugrel- and clopidogrel-treated patients treated in the ACS-PCI population (the indicated Population for prasugrel) during the index hospitalisation. Comparisons were also performed for event rates of any bleeding (including both non-CABG and CABG-related) requiring any blood transfusion of whole blood or RBCs) and/or ICH, and of any bleeding. In addition, analyses of any bleeding regardless of whether transfusion was required were performed.

An additional objective was to describe outcomes such as bleeding or death in various populations including patients who were: not indicated (elective PCI or non-ACS), contraindicated (for example, history of TIA/stroke), received an LD prior to coronary visualization, treated with a 5-mg, 10-mg or other dose, very elderly (≥75 years) and those with low body weight.

Altogether 32 hospitals participated in Study B008, among them 25 non-university hospitals and 7 university hospitals. The university hospitals are not regular members of the ALKK and contributed 17% of the enrolled cases. In general, the centers in the ALKK are representative of German community hospitals, although their participation might indicate somewhat more

ambitious efforts than in average clinical practice in German secondary care centres. As university hospitals account for not less than 10% of hospital beds in Germany, it seems plausible that the total data can be generalized to the situation in Germany as a whole. Due to different health care and referral systems, the profiles of patients admitted with ACS as well as the use of prasugrel may vary across European countries.

2.9.2. Limitations of Study

- Due to the observational nature of the study, the treatment groups differed with respect to patient characteristics and concomitant medications; therefore, the estimation of the effect of prasugrel versus clopidogrel on bleeding outcomes may be biased by confounding factors. In order to allow a thorough adjustment for potential confounders, information on the most important known risk factors for bleeding was obtained in this study. Propensity score methodology was employed to account for imbalances between the cohorts and to conduct the covariate adjustment (see Section 2.6.3.1). However, propensity score methodology does not help with confounders not collected in the registry.
- Data in Study B008 were limited to the 32 hospitals in the registry from which data were available. Thus, when interpreting data, caution should be taken when generalizing findings from this study.
- Bleeding rate assumptions at the time of the study design were based on the TRITON-TIMI 38 study; these assumptions were higher than those actually observed in Study B008. Power calculations were based on the assumption that the bleeding rate for clopidogrel patients would be approximately 1.2% and for prasugrel patients would be 1.5%. The actual bleeding rates in Study B008 were considerably lower which limited the power to detect a statistically significant difference between treatments.
- Prespecified subgroup analyses were conducted; however, the analysis of small subgroups yielded no meaningful results.
- The presence or absence of a diagnosis code in the database does not necessarily indicate the presence or absence of disease.
- General practitioners (GPs) were not required to record diagnoses in the database during patient consultations; thus, the prevalence of comorbidities and history of diseases could be underestimated.

2.9.3. Results

2.9.3.1. Patient Populations and Baseline Demographics

During the recruitment period between 15 October 2009 and 28 February 2013, Study B008 included 11, 201 patients. The current report focuses on 5 populations of interest: all prasugrel-treated and ACS clopidogrel-treated patients (Population f: 2740/6500), the ACS population

(Population i: 2471/6476), the ACS-PCI population (Population c: 2192/5549), the ideal ACS-PCI population (Population d: 1653/5467), and the ideal low-risk population (Population j: 1838/3109).

The "ideal" ACS-PCI population (Population d) had separate inclusion criteria for prasugrel (patients who were <75 years of age and weighed ≥60 kg with no history of TIA/stroke, or active pathological bleeding or severe hepatic dysfunction) and for clopidogrel-treated patients (no active pathological bleeding). The ideal low-risk population (Population j) included prasugrel- and clopidogrel-treated patients using the following inclusion criteria:

- age <75 years
- body weight ≥60 kg
- no history of stroke / TIA
- no active pathological bleeding
- no recent trauma or surgery
- no severe hepatic dysfunction
- no treatment with ticlopidine, no prior thrombolysis.

The primary analysis was performed on 3 of these populations including Population c, Population i, and Population j; Population d was not used for this analysis due to the different inclusion criteria for prasugrel- and clopidogrel-treated patients.

The data in this registry reflect real-world clinical practices and safety outcomes. Due to the observational nature of the study, the treatment groups differed with respect to patient characteristics and concomitant medications. Overall, the prasugrel-treated patients were younger, heavier, and more likely to be male than the clopidogrel-treated patients. The prevalence of relevant pre-existing medical conditions was higher among the patients treated with clopidogrel than among those treated with prasugrel. This difference was likely due to the older age of the clopidogrel-treated patients; approximately 6% of prasugrel-treated patients were over 75 years of age compared with approximately 39% of clopidogrel-treated patients. These differences could present confounding factors which may bias the estimate of the effect of prasugrel versus clopidogrel on bleeding outcomes. Propensity score methodology was employed to account for imbalances between the cohorts and to conduct the covariate adjustment (see Section 2.6.3.1).

Of the prasugrel patients and ACS clopidogrel patients in the registry who received a prasugrel LD (Population f), approximately 80% were in the indicated ACS-PCI population (Population c; 2192/2740; 80%). Very few ACS-PCI prasugrel-treated patients had contraindications; of those who received 1 LD of prasugrel, 1.5% had a history of TIA/stroke. The majority of the prasugrel ACS-PCI patients (Population c) belonged to the "ideal" Population d (1653/2192; 75%); Population d included prasugrel-treated patients ≥60 kg and <75 years old with no history of TIA/stroke, active pathological bleeding or severe hepatic dysfunction. Approximately 74% of prasugrel-treated ACS patients (Population i) and 48% of clopidogrel-treated ACS patients (Population i) were in the "ideal low risk" population (Population j).

2.9.3.2. Bleeding Rate Analyses

The bleeding rate comparison was performed after adjusting for quintiles of the propensity score. There was no significant difference for prasugrel- versus clopidogrel-treated patients in the primary inferential analysis of non-CABG-related bleeding (requiring any transfusion of whole blood or RBCs) and/or ICH in patients with ACS undergoing PCI (adjusted for quintiles of the propensity score) in the 3 populations analyzed: the ACS population (Population i), the ACS-PCI population (Population c), or in the ideal low-risk ACS population (Population j). Of note, however, there was a numerically higher event rate which approached statistical significance for prasugrel- versus clopidogrel-treated patients in Population j.

In the analysis that included all bleeding (requiring any transfusion of whole blood or RBCs) and/or ICH, very few additional events occurred compared with the non-CABG-related analysis; that is, there were very few CABG-related bleeding events and therefore results were similar to those for the primary non-CABG-related analysis.

In results of adjusted analyses of any bleeding, the significantly higher event rates observed for prasugrel-treated versus clopidogrel-treated patients were likely related to relatively minor events given the lack of significant difference observed for bleeding requiring any transfusion of whole blood or RBCs and/or ICH.

2.9.3.3. Overall Safety Results

In this real-world situation, there were very few clinical events (for example, emergency CABG or hemodynamic support) during PCI in ACS-PCI patients treated with prasugrel. Unadjusted rates of death at discharge were lower in all prasugrel-treated patients than in all ACS clopidogrel-treated patients (1.4% versus 2.7%, $p<0.0001$) and in STEMI patients treated with prasugrel versus clopidogrel (1.8% versus 4.6%, $p<0.0001$).

In Study B008, there were no fatal bleeding events in prasugrel-treated patients. Few patients with a contraindication were treated with prasugrel and very few of these patients had a bleeding event. Although the majority of patients ≥75 years of age who received a prasugrel LD were prescribed a 10-mg MD of prasugrel during the index hospitalisation (121/158: 76.6%), only 2 of 121 (1.7%) had any bleeding events; none of these required a blood transfusion of whole blood or RBCs or involved ICH. Similarly, a majority of patients with a body weight <60 kg who received a prasugrel LD were prescribed a 10-mg MD of prasugrel during the index hospitalisation (45/56: 80.4%); 3 (6.7%) of these patients had any bleeding requiring any blood transfusion of whole blood or RBCs and/or ICH.

Study B008 was expected to address the CHMP concern with possible CABG-related bleeding risk associated with the administration of a prasugrel LD prior to coronary angiography. However, a small number of prasugrel-treated subjects underwent emergency CABG during the index hospitalisation: of 2592 subjects in the largest prasugrel population (Population f), only 18 (0.7%) underwent emergency CABG. The CABG-related bleeding event rate was very low; of 47 prasugrel-treated subjects who developed a bleeding event during the index hospitalisation, only 1 event was CABG-related.

A little more than half (52.2%) of the patients received the LD prior to coronary visualization, with a higher percentage in the UA/NSTEMI (70.4%) versus the STEMI population (46.2%). There was not a significant difference based on timing of the LD given prior to versus after coronary visualisation in non-CABG-related bleeding requiring any transfusion of whole blood or RBCs and/or ICH (interaction p=0.883) or for any bleeding (interaction p=0.657); thus, these bleeding event rates were not statistically significantly different between patients who received an LD prior to versus after coronary visualization. Further, the between-treatment risk of non-CABG bleeding was similar regardless of whether the LD was administered prior to coronary visualization (OR=0.84) or after coronary visualization (OR=0.76).

One possible reason for the lower rates of bleeding observed in prasugrel-treated patients in Study B008 compared with the bleeding rates in TRITON may be that prescribers are using clinical judgment for individual patients, with consideration being given to risk minimization, based on the individual needs of the patient.

2.9.4. Summary

2.9.4.1. Drug Usage Patterns in Prasugrel-Treated Patients

- A majority were ACS-PCI patients (Population c: the indicated population for prasugrel).
- A majority were <75 years of age and had body weight ≥60 kg.
    - Of those elderly and lower body weight patients who received a prasugrel MD during the index hospitalisation, the majority received 10 mg (≥75 years = 76.6%; <60 kg = 80.4%).
- Very few patients had contraindications such as TIA/stroke.
- The majority received a 60-mg LD (approximately 87%).
- A little more than half received the LD prior to coronary visualization; this percentage was highest in UA/NSTEMI in the all prasugrel (Population f: 70.4%), ACS prasugrel (Population i: 70.4%) and in the ACS-PCI prasugrel (Population c: 63.4%) populations.
- Fewer prasugrel-treated patients underwent emergency CABG after PCI than clopidogrel-treated patients (0.7% versus 1.5%; p<0.01). Data are not available indicating whether or not prasugrel was given prior to coronary visualization or indicating the specific LD used in patients who underwent CABG.

2.9.4.2. Results of Primary Analysis

The primary inferential analysis was non-CABG-related bleeding (requiring any transfusion of whole blood or RBCs) and/or ICH in patients with ACS undergoing PCI, the population indicated for prasugrel during the index hospitalisation. Adjustment of the comparison of bleeding endpoints was primarily done by stratification according to quintiles of the propensity score. This analysis was performed on the ACS-PCI population (Population c) and post hoc analyses were performed on the ACS population (Population i) and the ideal low-risk ACS population (Population j).

- There was not a statistically significant difference between prasugrel- and clopidogrel-treated patients in the non-CABG-related bleeding rate (requiring any transfusion of

whole blood or RBCs) and/or ICH (adjusted for quintiles of the propensity score) in patients treated for ACS-PCI (Population c; the indicated population for prasugrel):
    - ACS-PCI population (Population c): (0.64% versus 0.76%; aOR [95% CI]: 1.48 [0.74-2.97], p=0.267)
- Post hoc analyses of the primary endpoint were also performed in the ACS population and in the ideal low-risk ACS population:
    - ACS population (Population i): 0.61% versus 0.71%; aOR [95% CI]: 1.39 [0.72-2.70], p=0.326
    - Ideal low-risk ACS population (Population j): 0.60% versus 0.35%; aOR [95% CI]: 2.36 [0.98-5.68], p=0.056).

2.9.4.2.1. Additional Analyses of Bleeding Rates Adjusted for Quintiles of the Propensity Score

- Rates of all bleeding (requiring any transfusion of whole blood or RBCs) and/or ICH (adjusted for quintiles of the propensity score) were very similar to results of the primary analysis:
    - Results for the ACS-PCI population (Population c) were identical for non-CABG and all bleeding events as there was no CABG-related bleeding in this population.
    - Compared with results of non-CABG analyses for the ACS population (Population i) and the ideal low-risk population (Population j), there were few additional events:
        - ACS population (Population i): 0.65% versus 0.71%; OR [95% CI]: 1.35 [0.72-2.55], p=0.352
        - Ideal low-risk ACS population (Population j): 0.65% versus 0.42%; OR [95% CI]: 2.15 [0.94-4.92], p=0.069
- Prasugrel-treated patients had significantly higher rates of any bleeding (adjusted for quintiles of the propensity score) compared with clopidogrel-treated patients in all 3 populations:
    - ACS-PCI population (Population c): 1.96% versus 1.82%; OR (95% CI): 2.09 (1.37-3.18), p<0.001
    - ACS population (Population i): 1.86% versus 1.82%; OR (95% CI): 1.94 (1.30-2.90), p=0.001
    - Ideal low-risk ACS population (Population j): 1.91% versus 0.84%; OR (95% CI): 3.03 (1.77-5.21), p<0.001.

2.9.4.3. Results of Bleeding Analyses

- No fatal bleeding was observed in prasugrel-treated patients.
- Forty-seven (1.7%) prasugrel-treated patients experienced any bleeding.
- The percentages of patients having any transfusion and median units for those with transfusions were low and similar for prasugrel- versus clopidogrel-treated patients in the ACS-PCI population (Population c):
    - Percentage of patients having any transfusion: 0.6% versus 0.6%, p=0.87

  - Median units for patients who received transfusions: 0 (0-1) versus 0 (0-2)

- Notable anatomic bleeding locations for prasugrel- and clopidogrel-treated patients in the ACS-PCI, respectively, were as follows:
  - Rates of ICH were low and similar between treatment groups: 0 versus 0.1%, p=0.68
  - Retroperitoneal bleeding was significantly higher for prasugrel- versus clopidogrel-treated patients: 0.2% versus 0%, p<0.01
  - GI bleeding was significantly lower for prasugrel- versus clopidogrel-treated UA/NSTEMI patients: 0% versus 0.5%, p<0.05

2.9.4.4. Bleeding Risk by Subgroups

Descriptive analyses of bleeding events in patients who received an LD of prasugrel by contraindication, timing of prasugrel LD, body weight, and age included the following findings:

- No bleeding events occurred in the 41 patients with a history of TIA/stroke who received a prasugrel LD.
- Of 5 patients with active pathological bleeding who received a prasugrel LD, 1 (20.0%) had any bleeding, but did not require any blood transfusion.
- Of 9 patients with known severe hepatic impairment who received a prasugrel LD, 1 (11.1%) had any bleeding which required blood transfusion of whole blood or RBCs and/or ICH.
- Of 269 non-ACS patients who underwent an elective PCI and received a prasugrel LD, 1 patient (0.4%) had any bleeding which required blood transfusion of whole blood or RBCs and/or ICH.
- Of 1329 patients who received a prasugrel LD prior to coronary visualization, 20 (1.5%) had any bleeding, with 9 requiring blood transfusion of whole blood or RBCs and/or ICH. Of 989 patients who received a prasugrel LD after coronary visualization, 20 (2.0%) had any bleeding, with 5 requiring blood transfusion of whole blood or RBCs and/or ICH.
- Of 158 patients ≥75 years of age who received a prasugrel LD, 4 (2.5%) had any bleeding requiring any blood transfusion of whole blood or RBCs and/or ICH.
  - Of the 121 patients ≥75 years of age who received a 10-mg MD of prasugrel during the index hospitalisation, 2 (1.7%) patients had any bleeding and none required blood transfusion.
- Of 56 prasugrel-treated patients with body weight <60 kg who received a prasugrel LD, 3 (5.4%) had any bleeding requiring any blood transfusion of whole blood or RBCs and/or ICH (all 3 received a 10-mg MD of prasugrel during the index hospitalisation).
  - Of the 45 patients with body weight <60 kg who received a 10-mg MD during the index hospitalisation; 3 (6.7%) of these patients had any bleeding requiring any blood transfusion of whole blood or RBCs and/or ICH.

2.9.4.4.1. Non-CABG and Any Bleeding Risk by Subgroups

Unadjusted analyses of non-CABG and any bleeding events for all prasugrel-treated patients were performed for subgroups including prasugrel indication (not indicated or contraindicated), LD prior to or after coronary visualization, prasugrel MD of 5 mg or 10 mg, age <75 or ≥75 years and body weight <60 kg or ≥60 kg.

- In results of non-CABG bleeding subgroup analyses, the treatment-by-subgroup interaction based on body weight was significant (interaction p=0.022). There were no other significant treatment-by-subgroup interactions observed for the remaining subgroups including prasugrel indication (contraindicated or not indicated [no ACS], LD prior to or after coronary visualization, prasugrel MD of 5 mg or 10 mg, or age ≥75 or <75 years.
    - In patients weighing <60 kg, prasugrel-treated patients had a significantly higher rate of non-CABG bleeding compared with clopidogrel-treated patients (5.56% versus 1.38%, p=0.037). There was not a significant between-treatment difference observed in patients ≥60 kg.
    - The rate of non-CABG-related bleeding in patients receiving LD prior to coronary visualization was similar to the rates of non-CABG bleeding in patients receiving LD after coronary visualization for both prasugrel- and clopidogrel-treated patients:
        - LD prior to coronary visualization for prasugrel versus clopidogrel: 0.62% (8/1300) versus 0.73% (28/3821); OR (95% CI): 0.84 (0.38-1.85); p=0.662
        - LD after coronary visualization for prasugrel versus clopidogrel: 0.51% (5/989) versus 0.66% (15/2264); OR (95% CI): 0.76 (0.28-2.10); p=0.598
- In results of subgroup analyses of any bleeding, no significant treatment-by-subgroup differences in rates of any bleeding were observed for prasugrel- versus clopidogrel-treated patients for any subgroup.
    - However, a significant between-treatment difference was observed for those age <75 with prasugrel-treated patients having a higher rate of any bleeding compared with clopidogrel-treated patients (1.85% versus 1.06%, p=0.008).

2.9.5. Discussion

Results of Study B008 demonstrated that physicians from the 32 hospitals included in the German registry were less likely to prescribe prasugrel than clopidogrel, respectively, to specific subgroups previously identified as being at higher risk for bleeding with prasugrel, including patients with a history of stroke or TIA (1.5% versus 8.1%), patients ≥75 years of age (5.8% versus 38.5%), and those with a body weight of <60 kg (2.4% versus 6.1%). This may be a reflection of physicians in Germany adhering to the prasugrel SPC which states that prasugrel is contraindicated in patients with a history of stroke or TIA, warns that using prasugrel in patients ≥75 years of age is generally not recommended, and advises that physicians may consider prasugrel treatment of patients <60 kg only after a careful individual benefit/risk evaluation.

It is less clear, however, why patients at higher risk for bleeding more often received a 10-mg MD rather than the recommended 5-mg dose of prasugrel. For example, of the small number of higher risk patients who received a prasugrel MD prescription, only 13.3% of patients ≥75 years of age and only 5.4% of those who weighed <60 kg were prescribed a 5-mg MD of prasugrel. One possible explanation is that patients may have received a 10-mg prescription with the understanding that they were to cut the 10-mg tablet in half, thus actually taking only a 5-mg daily dose. It may also be due to a hesitation on the part of physicians to prescribe a prasugrel 5-mg MD as, until recently, the SPC stated that the evidence for the 5-mg dose was based only on pharmacodynamics/pharmacokinetic analyses and no clinical data was available on the safety of this dose in patients ≥75 years. Further, the SPC previously stated that efficacy and safety of the prasugrel 5-mg dose had not been prospectively assessed in patients weighing <60 kg. As of 30 May 2013, this information has been updated in the SPC based on results of 3 studies (H7T-MC-TADI, H7T-MC-TACY, and H7T-MC-TABY), and now states that these clinical studies have demonstrated that a 5-mg prasugrel MD in patients ≥75 years or who weigh <60 kg is effective and safe.

Although the higher risk patients were more likely to be treated with a 10-mg MD than the recommended 5-mg MD, the study demonstrated low rates of bleeding in these subgroups. None of the patients ≥75 years treated with a prasugrel 10-mg MD had fatal bleeding, bleeding requiring transfusion of whole blood or RBCs, or had an ICH; only 2 patients (1.7%) had any bleeding. Only 3 (6.7%) patients with body weight <60 kg who received a prasugrel 10-mg MD had non-CABG-related bleeding requiring transfusion of whole blood or RBCs or had an ICH; there was no fatal bleeding in this subgroup. Thus, in the rare event that higher risk subgroups were treated with prasugrel, the incidence of any bleeding was low and there was no fatal bleeding.

Over half of prasugrel-treated patients and over 60% of clopidogrel-treated patients received the LD prior to coronary visualization. Bleeding rates were not significantly different between those who received an LD of either drug prior to versus after coronary visualization. Likewise, there were no between-treatment differences for those who were pretreated or those who received a prasugrel LD after coronary visualization. For both prasugrel- and clopidogrel-treated subjects who received pretreatment, the rate of non-CABG bleeding requiring any transfusion of whole blood or RBCs and/or with an ICH was <1% and the rate of any bleeding was <2%. Thus, rates of non-CABG and any bleeding were low and similar in patients who received prasugrel or clopidogrel as pretreatment.

2.9.6. Conclusions

The main objective of Study B008 was to compare the incidence rates (cumulative incidence) of any non-CABG related bleeding (requiring any blood transfusion of whole blood or RBCs) and/ICH between prasugrel- and clopidogrel-treated patients treated in the ACS-PCI population (population c; the indicated population for prasugrel) during the index hospitalisation. There were no statistically significant differences between prasugrel- and clopidogrel-treated patients in the non-CABG-related bleeding rate (requiring any transfusion of whole blood or RBCs) and/or

ICH (adjusted for quintiles of the propensity score) in the ACS-PCI population: (0.64% versus 0.76%; OR [95% CI]: 1.48 [0.74-2.97], p=0.267).

Study B008 was expected to address the CHMP concern with the possible risk of CABG-related bleeding associated with administration of a prasugrel LD prior to coronary angiography. More than half of prasugrel-treated patients received the approved 60-mg LD prior to coronary visualization in a real-world, in-hospital, registry setting. Prasugrel-treated subjects who underwent CABG had a very low rate of CABG-related bleeding. It is also notable that the unadjusted rates of non-CABG-related and "any" bleeding were not impacted by the timing of the prasugrel LD.

In conclusion, regarding results of the primary analysis, one possible reason for the similar event rate in prasugrel- and clopidogrel-treated patients may be that a majority of prasugrel-treated patients were <75 years of age (94.2%) and had a body weight ≥60 kg (97.6%). Thus, it appears that physicians from these 32 hospitals in the German registry are selecting a patient population for prasugrel use in which these serious bleeding events are of no greater concern than for clopidogrel-treated patients.

2.10. References

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