2. B011 Synopsis

Approval Date: 09-Apr-2013 GMT

Clinical Study Report Synopsis: Study H7T-MC-B011

<table>
<tr><td colspan="2">Title of Study: Prasugrel Treatment Patterns in Outpatient Settings in Germany, the United Kingdom, and France</td></tr>
<tr><td colspan="2">Number of Investigators: Not applicable.</td></tr>
<tr><td colspan="2">Study Centers: Not applicable.</td></tr>
<tr><td colspan="2">Publications Based on the Study: None at this time.</td></tr>
<tr><td>Length of Study: Data include all prasugrel initiators in the following databases for the following time periods:
All prasugrel initiators in the IMS Disease Analyzer France from January 2010 to October 2012.
All prasugrel initiators in the IMS Disease Analyzer United Kingdom (UK) and the Clinical Practice Research Datalink (CPRD) from July 2009 to October 2012.
All prasugrel initiators in the IMS Disease Analyzer Germany from April 2009 to October 2011.</td><td>Phase of Development: Retrospective observational study</td></tr>
<tr><td colspan="2">Objectives: The objective of the study is to provide descriptive statistics on patterns of prasugrel usage in outpatient settings in France, the UK, and Germany, as outlined below:
Use in the contraindicated population of patients with a history of transient ischemic attack (TIA) or stroke
Prasugrel maintenance doses stratified by age (≥75 years versus <75 years)
Prasugrel maintenance doses stratified by body weight (≥60 kg and <60 kg, in countries where body weight is available)
Indications for prescription of prasugrel
Co-prescriptions (other thienopyridines, other anti-platelet agents, oral anticoagulants, aspirin, non-steroidal anti-inflammatory drugs [NSAIDs], proton pump inhibitors [PPIs], etc.)
Patterns of drug usage (for example, duration and medication possession ratio)
Patient characteristics (for example, demographics)
Co-morbid health conditions and medical history (for example, diabetes).</td></tr>
<tr><td colspan="2">Study Design: H7T-MC-B011 was an observational, retrospective, non-interventional cohort study aimed to describe the treatment patterns of prasugrel in outpatient settings in France and Germany using the IMS Disease Analyzer and in the UK using the IMS Disease Analyzer and the CPRD, from launch to 3 years post-launch. One previous annual report for Germany and two previous annual reports including data from France, the UK and Germany were generated from the study prior to this final report.

The study population consisted of patients who had the first prescription records of prasugrel, also referred to as prasugrel initiators, in the IMS Disease Analyzer and CPRD after prasugrel launch in France, the UK, and Germany. The date of the first prasugrel prescription for each individual patient that was recorded in the databases was defined as the index date. All prasugrel initiators in the IMS Disease Analyzer (France, the UK, and Germany) and CPRD were included. The prasugrel initiators were followed from the index date until death, transfer out of the practice, or the end of the study, whichever came first.
Eligible patients were treated with prasugrel at the discretion of the treating physicians. Treatment initiation or changes were solely at the discretion of the physician and the patient.</td></tr>
</table>

Number of Patients:

Planned: This was a descriptive study. Of note, analyses were to be initiated and reports were to be generated after the numbers of patients in respective countries reached at least 100.

Total number of prasugrel initiators (patients): France: 1052; UK: 1580; Germany: 1474

Diagnosis and Main Criteria for Inclusion: The study population consisted of patients who had the first prescription records of prasugrel, also referred to as prasugrel initiators, in the IMS Disease Analyzer and CPRD after prasugrel launch in France, the UK, and Germany.

Dose: Patients were treated with prasugrel at the discretion of the treating physicians. Treatment initiation or changes were solely at the discretion of the physician and the patient.

Treatment Pattern Analyses:

Descriptive statistics, including count, percentages, and 95% confidence intervals (CIs) were used to describe the treatment patterns in patients who received prasugrel prescriptions in France and Germany using the IMS Disease Analyzer and in the UK using the IMS Disease Analyzer and the CPRD databases.

History of TIA or stroke was defined as a diagnostic code for TIA or stroke recorded any time prior to the date of the first prasugrel prescription. Dosages recorded in the therapy file were stratified by age (≥75 years versus <75 years) and by the most recent record of body weight (≥60 kg and <60 kg, in countries where this measure was available). Counts, percentages, and CIs were provided for the proportions of prasugrel initiators with a history of TIA or stroke and for dosages by age and body weight.

The indications for prasugrel prescriptions were obtained by the links between indications and prescriptions in countries where the linkage was available. Comorbid health conditions were also categorised.

Co-prescriptions of prasugrel with other drugs (for example, other thienopyridines, other antiplatelets, oral anticoagulants, and PPIs) were counted if the drugs were prescribed on the same day as prasugrel or within 30 days prior to or after the date of any prasugrel prescription.

Treatment duration and medication possession ratio (MPR) were assessed for patients who had at least a 12-month follow-up period in the IMS Disease Analyzer and CPRD after the cohort entry date. The permissible gap between two consecutive prasugrel prescriptions was 30 days plus the days of supply. Patients were considered to have discontinued prasugrel if the period between two prescriptions exceeded the permissible gap. The duration of prasugrel treatment was defined as the days from the date of the first prescription to the time of the discontinuation. Medication possession ratio was estimated as the day's supply of prasugrel during the 12-month follow up divided by the numbers of days from the first prescription to the end of the follow up. The numbers of treatment interruptions were summarised.

Details of the proposed analyses are documented in a statistical analysis plan.

SUMMARY

Patient Characteristics

- The majority of patients did not have a history of TIA/stroke, were <75 years of age, and had a body weight ≥60 kg in France, the UK, and Germany, respectively:
    - No history of TIA/stroke: 99.8%, 96.0%, and 98.2%
    - <75 years of age: 94.3%, 89.7%, and 90.8%
    - Percentage of patients with known body weight who weighed ≥60 kg: 95.0%, 94.3%, and 94.3%.

- In prasugrel-treated patients with a known diagnosis linked to a prasugrel prescription, the majority were consistent with acute CHD, including ACS, in all 3 countries.

- The most prevalent comorbidities (≥20%) in each country included:
    - France: hyperlipidemia = 97.1%; CHD = 52.3%; ACS = 30.4%, hypertensive diseases = 24.9%, diabetes = 23.8%, and previous MI = 23.7%
    - UK: CHD = 94.2%, ACS = 85.9%, previous MI = 79.6%, hypertensive diseases = 35.3%
    - Germany: hyperlipidemia = 84.9%, CHD = 64.5%, hypertension = 52.7%, ACS = 25.3%, diabetes = 22.3%.

- As expected, the most commonly prescribed concomitant medications in all 3 countries included platelet inhibitors, lipid-lowering agents, beta blockers, and ACE inhibitors.
    - Of note, anti-ulcerants, including PPIs and H2 blockers, were prescribed in 55.1% of prausgrel-treated patients in France, 45.5% of those in the UK, and 27.2% of those in Germany.

Patterns of Drug Usage

- The majority of prasugrel prescriptions in France (99.8%), the UK (91.4%) and Germany (93.7%) were for the 10-mg dose. Of note, the 5-mg dose is not marketed in France.
- The percentage of prasugrel-treated patients who switched from another thienopyridine (primarily clopidogrel) to prasugrel was 13.7% in France, 23.2% in the UK, and 21.5% in Germany.
- The MPR reflects the amount of time an individual remains on chronic drug therapy. An MPR of 80% is considered a reasonable threshold for persistence. The following MPRs suggested a lack of persistence of prasugrel treatment over the period of 6 months or 12 months in France, the UK, and Germany, respectively:
    - 6-month follow-up: 60.7%, 75.5%, and 68.6%, respectively
    - 12-month follow-up: 63.2%, 76.9%, and 58.8%, respectively.

Prasugrel Contraindication of Prior Stroke/TIA

Very few patients with the prasugrel contraindication of prior TIA or stroke are being treated with prasugrel (0.2% in France, 4.0% in the UK, and 1.8% in Germany).

Body Weight <60 kg

Of the patients with known body weight, few patients with body weight <60 kg are being treated with prasugrel.

- France
    - Of 1052 total patients, body weight was unknown for the majority (n=555; 52.8%)
    - A total of 25 patients (2.4%) had a recorded body weight <60 kg
    - No patients (0/25) with a recorded body weight <60 kg were prescribed a 5-mg dose
- United Kingdom
    - Of 1580 total patients, body weight was unknown for only 75 patients (4.7%)
    - A total of 86 patients (5.4%) had a recorded body weight of <60 kg.
    - 29.1% (25/86) of those with a recorded body weight <60 kg were prescribed a 5-mg dose
- Germany
    - Of 1474 total patients, body weight was unknown for the majority (n=994; 67.4%)
    - A total of 10 patients (0.7%) had a recorded body weight <60 kg

- No patients with recorded body weight <60 kg were prescribed a 5-mg dose

Age ≥75 Years

Few patients ≥75 years of age, for whom the use of prasugrel is generally not recommended, are being treated with prasugrel.

- France
  - 5.4% (57/1052) of patients treated with prasugrel were ≥75 years of age.
  - The majority of patients in France were treated with a 10-mg dose, including those ≥75 years of whom 3.5% (2/57) were prescribed a 5-mg dose. (As noted, the 5-mg prasugrel tablet is not marketed in France.)
- United Kingdom
  - 10.3% (163/1580) of patients treated with prasugrel were ≥75 years of age.
  - 44.8% (73/163) of those ≥75 years receiving prasugrel were treated with a 5-mg dose.
- Germany
  - 9.2% (136/1474) of patients treated with prasugrel were ≥75 years of age.
  - 29.4% (40/136) of those ≥75 years receiving prasugrel were treated with a 5-mg dose.

Where body weight was available, patients ≥75 years of age treated with the 10-mg tablet had a higher mean body weight than those prescribed a 5-mg dose.

- France
  - As only 2 of 57 very elderly patients were treated with a 5-mg dose, and weight was unknown for 1 of the 2 patients, this data is not meaningful.
- United Kingdom
  - Of patients ≥75 years, mean body weight was 78 kg for those receiving a 10-mg dose and was 69 kg for those receiving a 5-mg dose; body weight was unknown for only 3 of 163 patients.
- Germany
  - Of patients ≥75 years, mean body weight was 82 kg for those receiving a 10-mg dose and was 76 kg for those receiving a 5-mg dose; body weight was unknown for only 1 of 136 patients.

CONCLUSION

Based on data describing patients who had at least 1 prasugrel prescription record in France from January 2010 to October 2012, in Germany from April 2009 to October 2011 using the IMS Disease Analyzer, and in the UK from July 2009 to October 2012 using the IMS Disease Analyzer and the CPRD, the majority of prasugrel prescriptions were for patients <75 years of age and ≥60 kg. This is consistent with data observed in the ALKK-PCI registry in which patients ≥75 years and patients <60 kg were less likely to receive prasugrel than clopidogrel. It is also notable that very few patients with the prasugrel contraindication of prior TIA or stroke were treated with prasugrel. When prasugrel is used in the very elderly or lower body weight populations, it appears that the 10-mg dose is being prescribed. Overall, however, the low percentages of prasugrel prescriptions recorded for patients ≥75 years of age, <60 kg, or prior TIA or stroke, may indicate that guidance from the SPC is being considered by prescribing physicians.

2.1. Table of Contents

Section **Page**

Table of Contents

Table **Page**

Table of Contents

Attachment **Page**

2.2. Study Overview

Study H7T-MC-B011 was a retrospective, nonintervention cohort study aimed at describing the treatment patterns of prasugrel in outpatient practices in Germany and France using the IMS Disease Analyzer and in the United Kingdom (UK) using the IMS Disease Analyzer and the Clinical Practice Research Datalink (CPRD), formerly known as General Practice Research Database (GPRD), starting from launch to 3 years postlaunch. Descriptive analyses were to be initiated once the numbers of unique prasugrel prescription records reached at least 100 in respective countries. One previous annual report for Germany and two previous annual reports including data from France, the UK and Germany were generated from the study prior to this final report.

This document provides the key findings from the final annual analysis report in Germany that was also provided in the 17 April 2012 annual report, and summarizes the third and final annual analysis report in France, and the third and final annual analysis report in the UK.

2.3. Objectives

The objectives of the study were to provide descriptive statistics for the contraindication of TIA/stroke, maintenance dose, indication, patient characteristics, co-morbidities, co-prescriptions, and patterns of drug usage in outpatient practices in France, the UK, and Germany, as outlined below:

- The contraindication of history of transient ischemic attack (TIA) or stroke
- Prasugrel maintenance doses stratified by age (≥75 years versus <75 years)
- Prasugrel maintenance doses stratified by body weight (≥60 kg and <60kg, in countries where body weight is available)
- Indications for prescription of prasugrel
- Co-prescriptions (other thienopyridines, other anti-platelet agents, oral anticoagulants, aspirin, NSAIDs, proton pump inhibitors, etc.)
- Patterns of drug usage (for example, duration and medication possession ratio)
- Patient characteristics (for example, demographics)
- Co-morbid health conditions and medical history (for example, diabetes).

2.4. Methods

2.4.1. Summary of Analytical Methods

The study population consisted of patients who had at least 1 prescription record of prasugrel in France and Germany using the IMS Disease Analyzer and in the UK using the IMS Disease Analyzer and the CPRD. The date of the first prasugrel prescription recorded in the databases was defined as the index date. The patients were followed from the index date until death, transfer out of the practice, or the end of the study, whichever came first. Descriptive statistics

(that is, mean [SD], median, and quartile ranges for quantitative variables, and frequencies and percentages for qualitative variables) were provided for the contraindication of TIA/stroke, maintenance doses, body weight, patient demographic characteristics, co-morbidities, co-prescriptions, and patterns of drug usage in outpatient practices in respective countries. More details on the analyses are shown in the SAP.

2.5. Integrated Demographics across Countries

The following is a summary of prasugrel-treated patients by history of TIA/stroke and age group in France from January 2010 to October 2012, the UK from July 2009 to October 2012, and in Germany from April 2009 to October 2011 (Table B011.2.1; adapted from Tables 5b in the respective countries; see Attachment 1, Attachment 2, and Attachment 3).

Table B011.2.1. Summary of Prasugrel Prescriptions in the IMS and CPRD Databases

		FRANCE		UNITED KINGDOM		GERMANY	
		Total receiving prasugrel MD N (%)	**Initiating 5 mg MD (n)**	**Total receiving prasugrel MD N (%)**	**Initiating 5 mg MD (n)**	**Total receiving prasugrel MD N (%)**	**Initiating 5 mg MD (n)**
TOTAL PATIENTS		1052 (100)	2	1580 (100)	135	1474 (100)	93
History of TIA/Stroke	Yes	2 (0.0)	0	63 (4.0)	16	27 (1.8)	4
	No	1050 (99.8)	2	1517 (96.0)	119	1447 (98.2)	89
Weight	<60 kg	25 (2.4)	0	86 (5.4)	25 (29.1% [a])	10 (0.7)	0
	≥60 kg	472 (44.9)	1	1419 (89.8)	108	470 (31.9)	33
	Unknown	555 (52.8)	1	75 (4.7)	2	994 (67.4)	60
Age Group	<75 years old	992 (94.3)	0	1417 (89.7)	62	1338 (90.8)	53
	≥75 years old	57 (5.4)	2 (3.5% [b])	163 (10.3)	73 (44.8% [b])	136 (9.2)	40 (29.4% [b])

Abbreviations: CPRD = General Practice Research Datalink; MD = maintenance dose; N = total number of patients; n = number of patients; TIA = transient ischemic attack.

[a] Percentage of prasugrel-treated patients with body weight <60 kg receiving a 5-mg dose.

[b] Percentage of prasugrel-treated patients ≥75 years receiving a 5-mg dose.

Sources: Tables 5b in Attachment 1, Attachment 2, and Attachment 3.

2.6. Results from the IMS Disease Analyzer France

This is the third and final annual analysis report from the IMS Disease Analyzer France. The descriptive analyses were conducted using outpatient general practice data from January 2010 to October 2012. Details of the statistical methods and relevant definitions used to generate Table B011.2.2 through Table B011.2.11 are described in the Methods Section 2.4 and the Appendices of the full analysis report (Attachment 1). The key findings and the summary text are presented below.

It is notable that, unlike in the UK and Germany, the 5-mg dose of prasugrel is not marketed in France.

2.6.1. Characteristics for Patients Treated with Prasugrel

In the October 2012 update of the IMS Disease Analyzer, France recorded 1052 patients with at least 1 prasugrel prescription. As shown in Table B011.2.2, the majority of the patients were male (male 85.0% vs. female 15.0%). Two male patients (0.2%) had a history of TIA or stroke. The overall mean age was 58, with 5.4% of the patients 75 years of age or older and 94.3% under 75 years of age (age was unknown for 0.3%). The mean age was 60 for females and 57 for males. In patients with body weight recorded in the database (47.2%), the mean body weight was 85 kg for males and 72 kg for females; 2.4% of all patients had body weight <60 kg.

Table B011.2.2. All Prasugrel Patients, Distribution by Risk Segment from IMS Disease Analyzer France

		Total patients		Males		Females	
TOTAL PATIENTS	Row percentages based on Total patients	**1052**	**100.0%**	**894**	**85.0%**	**158**	**15.0%**
Prior TIA/Stroke - n %	Yes	2	0.2%	2	0.2%	0	0.0%
	No	1050	99.8%	892	99.8%	158	100.0%
Age Group* - n %	0 - 17 years old	3	0.3%	2	0.2%	1	0.6%
	18 - 34 years old	13	1.2%	11	1.2%	2	1.3%
	35 - 44 years old	90	8.6%	81	9.1%	9	5.7%
	45 - 54 years old	313	29.8%	271	30.3%	42	26.6%
	55 - 64 years old	336	31.9%	294	32.9%	42	26.6%
	65 - 74 years old	237	22.5%	189	21.1%	48	30.4%
	75 - 84 years old	52	4.9%	40	4.5%	12	7.6%
	<75 years old	992	94.3%	847	94.7%	144	91.1%
	≥75 years old	57	5.4%	44	4.9%	13	8.2%
	≥85 years old	5	0.5%	4	0.4%	1	0.6%
	Unknown	3	0.3%	2	0.2%	1	0.6%
Age - Statistics	Mean (±SD) in years	58 (46.9, 68.6)		57 (46.7, 68.0)		60 (48.0, 71.6)	
	Median in years	58		57		61	
	Interquartile range in years (Q1, Q3)	(50.0, 65.0)		(50.0, 65.0)		(52.0, 68.0)	
Weight† - n %	<60 kg	25	2.4%	7	0.8%	18	11.4%
	≥60 kg	472	44.9%	397	44.4%	75	47.5%
	Unknown	555	52.8%	490	54.8%	65	41.1%
Weight† - Statistics	Mean (±SD) in kg	83 (66.9, 98.2)		85 (70.5, 99.6)		72 (56.1, 87.3)	
	Median in kg	81		82		70	
	Interquartile range in kg (Q1, Q3)	(72.0, 91.0)		(74.6, 94.0)		(61.0, 81.0)	

Abbreviations: SD = standard deviation; TIA = transient ischemic attack.
* at first prasugrel
† where available
Percentages are based on the corresponding column total. Source: Table 1, Attachment 1.

2.6.2. Diagnoses and Co-Morbidities

2.6.2.1. Diagnoses for Which Prasugrel was First Prescribed

The diagnoses for which prasugrel was first prescribed are displayed in Table B011.2.3. The data in Table B011.2.3 were generated using only diagnoses that were linked to the first prasugrel prescription. In France, the linked diagnoses are not required for health care providers to complete when writing a prescription. As a result, the linked diagnoses were missing in 31% of the patients; furthermore, some of the linked diagnoses are not actual clinical diagnoses, such as ISSUE REP PRESCRIPT (Table B011.2.3). Due to the large number of missing or uninformative linked diagnoses, additional analyses were conducted to search the database for a record of predefined International Statistical Classification of Diseases and Health Related Problems 10th Revision (ICD-10) codes of relevant coronary heart diseases (acute coronary syndrome, coronary heart disease (CHD), and previous myocardial infarction [MI]) for each patient at the following time points: on the same date of the first prasugrel prescriptions or 30 days, 60 days, 90 days, and any time prior to the first prasugrel prescriptions (intermediate steps shown in Table 2, Attachment 1). The final analysis (Table B011.2.4) showed that 52% of the patients prescribed with prasugrel had relevant diagnoses of heart disease any time prior to or on the same date of the first prasugrel prescription; relevant coronary heart disease diagnoses were missing in 48% of patients.

Table B011.2.3. Diagnoses for Which Prasugrel Was First Prescribed IMS Disease Analyzer France

Original table using only diagnoses linked to prasugrel		Number of patients	% of total patients
TOTAL PATIENTS		1052	100.0%
Z760	ISSUE REP PRESCRIPT	346	32.9%
I219	AC MYOCARD INFARCT UNSP	114	10.8%
I251	ATHEROSCL HEART DIS	71	6.7%
I259	CHR ISCHAEM HRT DIS UNSP	48	4.6%
I252	OLD MYOCARD INFARCT	26	2.5%
I248	O/FORMS AC ISCH HRT DIS	19	1.8%
I258	O/FRM CHR ISCH HRT DIS	18	1.7%
Z768	PER ENC HLTH SER SPC CIR	18	1.7%
Z955	CORO ANGIOPL IMPL/GRAFT	17	1.6%
I209	ANGINA PECTORIS UNSP	10	1.0%
I100	ESSENTIAL (PRIM) HYPERT	7	0.7%
I210	AC TRANSMUR MI ANT WALL	7	0.7%
I255	ISCHAEMIC CARDIOMYOPATHY	7	0.7%
I211	AC TRANSMUR MI INF WALL	3	0.3%
I519	HEART DISEASE UNSP	3	0.3%
I429	CARDIOMYOPATHY UNSP	2	0.2%
I509	HEART FAILURE UNSP	2	0.2%
I776	ARTERITIS UNSPECIFIED	2	0.2%
I990	OTH/UNSP DIS CIRC SYST	2	0.2%
J068	O/AC UP RESP INF MULT ST	2	0.2%
Z298	OTH SPEC PROPHY MEASURE	2	0.2%
Z959	CARD/VAS IMP/GRFT UNP	2	0.2%
M255	PAIN IN JOINT	1	0.1%
Diagnosis missing		**323**	**31%**

Source: Table 2, Attachment 1.

Table B011.2.4. Relevant Coronary Heart Disease at Any Time Prior to Index Date IMS Disease Analyzer France

Step 6: Search all other diagnosis fields for acceptable diagnoses ever† in the database.		Number of patients	% of total patients
TOTAL PATIENTS		**1052**	**100.0%**
I219	AC MYOCARD INFARCT UNSP	185	17.6%
I251	ATHEROSCL HEART DIS	104	9.9%
I259	CHR ISCHAEM HRT DIS UNSP	75	7.1%
I209	ANGINA PECTORIS UNSP	39	3.7%
I252	OLD MYOCARD INFARCT	39	3.7%
I248	O/FORMS AC ISCH HRT DIS	27	2.6%
I258	O/FRM CHR ISCH HRT DIS	20	1.9%
I208	OTH FORMS ANGINA PECTOR	14	1.3%
I255	ISCHAEMIC CARDIOMYOPATHY	14	1.3%
I210	AC TRANSMUR MI ANT WALL	10	1.0%
I200	UNSTABLE ANGINA	9	0.9%
I211	AC TRANSMUR MI INF WALL	7	0.7%
Diagnosis missing		**509**	**48%**

† Number of Days From Most Recent Acceptable Diagnosis to First Prasugrel Rx: there are no additional patients given a diagnosis via the algorithm between 90 days and ever (Appendix 3, Attachment 1).

Source: Table 2, Attachment 1.

2.6.2.2. Previous Diagnoses at the First Prasugrel Script

Table B011.2.5 lists the most common previous diagnoses recorded any time prior to or on the date of the first prescription of prasugrel. The full list of the diagnoses can be found in Attachment 1, Table 3a. Some of the most prevalent conditions include essential hypertension, non-insulin-dependent diabetes mellitus (NIDDM), and atherosclerotic heart disease.

Table B011.2.5. Previous Diagnoses at First Recorded Prasugrel IMS Disease Analyzer France

		Number of patients	% of total patients
TOTAL PATIENTS		**1052**	**100.0%**
Z760	ISSUE REP PRESCRIPT	773	73.5%
Z768	PER ENC HLTH SER SPC CIR	307	29.2%
I100	ESSENTIAL (PRIM) HYPERT	259	24.6%
J000	AC NASOPHARYNGITIS	238	22.6%
I219	AC MYOCARD INFARCT UNSP	236	22.4%
J400	BRONCH NOT SPEC AC/CHR	236	22.4%
M545	LOW BACK PAIN	218	20.7%
I251	ATHEROSCL HEART DIS	174	16.5%
Z027	ISSUE MEDICAL CERT	156	14.8%
A090	DIARR & GASTRO PRES INF	133	12.6%
M255	PAIN IN JOINT	133	12.6%
J029	ACUTE PHARYNGITIS UNSP	132	12.5%
R050	COUGH	132	12.5%
I259	CHR ISCHAEM HRT DIS UNSP	128	12.2%
Z018	OTH SPEC SPECIAL EXAMS	124	11.8%
J111	INFL+O/RESP MAN-VIR UNID	122	11.6%
E780	PURE HYPERCHOLESTEROLAEM	113	10.7%
R530	MALAISE AND FATIGUE	109	10.4%
Z000	GENERAL MEDICAL EXAM	107	10.2%
J209	ACUTE BRONCHITIS UNSP	95	9.0%
Z251	NEED IMMUNOZ INFLUENZA	94	8.9%
K219	GAS/OES RF DIS WO OESOPH	89	8.5%
J068	O/AC UP RESP INF MULT ST	84	8.0%
I252	OLD MYOCARD INFARCT	83	7.9%
Z017	LABORATORY EXAMINATION	82	7.8%

Source: Table 3a, Attachment 1.

2.6.2.3. Relevant Comorbidities

For a better understanding of the comorbidities of prasugrel patients, Table B011.2.6 shows the prevalence of relevant conditions that were recorded in the database within the 12 months prior to or on the date of the first prasugrel prescription. Of note, 97.1% of the patients had a history of hyperlipidemia, 52.3% a history of CHD, 30.4% acute coronary syndrome (ACS), 24.9% hypertensive diseases, 23.8% diabetes, and 23.7% previous MI. The ICD-10 codes used to define the conditions are included in Appendix 1 of Attachment 1.

Table B011.2.6. Relevant Comorbidities in Patients Treated with Prasugrel IMS Disease Analyzer France

	Number of patients	% of total patients
TOTAL PATIENTS	**1052**	**100.0%**
Hyperlipidemia	1022	97.1%
Coronary heart disease	550	52.3%
ACS - Acute coronary syndrome	320	30.4%
Hypertensive diseases	262	24.9%
Diabetes	250	23.8%
Previous myocardial infarction	249	23.7%
Peripheral artery disease	28	2.7%
Heart failure	23	2.2%
Atrial fibrillation and flutter	12	1.1%
Renal disease	6	0.6%
Peptic ulcer	5	0.5%

Note: A comorbidity is defined as any diagnosis recorded in the 12 months prior to or on the index date (date of the first recorded prasugrel prescription). ICD-10 code groupings were defined by Lilly.
Source: Table 3b, Attachment 1 contains a full list of relevant comorbidities.

2.6.3. Concomitant Medications

2.6.3.1. Concomitant Medications by Drug Class

Table B011.2.7 lists the most common concomitant medications by drug class in prasugrel-treated patients. Concomitant medications are defined as medications prescribed 30 days before or after the date of the first prasugrel prescription. As would be expected for this patient population, the most commonly prescribed concomitant medications include platelet inhibitors, lipid lowering agents, beta blockers, angiotensin-converting-enzyme (ACE)-inhibitors, non-narcotic analgesics, tranquilisers, nitrates, and antidiabetic agents. Of note, anti-ulcerants, which include proton pump inhibitors (PPIs) and H2 blockers, were prescribed in 55.1% of the patients. The full list of the concomitant medication by class is included in Attachment 1, Table 4a.

Table B011.2.7. Concomitant Medications by Drug Class in Patients Treated with Prasugrel
IMS Disease Analyzer France

		Number of patients	% of total patients
TOTAL PATIENTS		**1052**	**100.0%**
ATC3 code	ATC3 text		
B01C	PLATELET AGGREG INHIBITRS	1052	100.0%
C10A	CHOLEST&TRIGLY.REGULATOR	948	90.1%
C07A	BETA BLOCKING AGENT PLAIN	881	83.7%
C09A	ACE INHIBITORS PLAIN	654	62.2%
A02B	ANTIULCERANTS	580	55.1%
N02B	NON-NARCOTIC ANALGESICS	233	22.1%
N05C	TRANQUILLISERS	174	16.5%
C01E	NITRITES AND NITRATES	139	13.2%
C03A	DIURETICS	138	13.1%
A10J	BIGUANIDE ANTIDIABETICS	126	12.0%
C08A	CALCIUM ANTAGONISTS PLAIN	103	9.8%
C01D	CORON THER EX CA/ANT/NIT	101	9.6%
C10B	ANTI-ATHEROMA NATRL ORIG	97	9.2%
C09C	ANGIOTENSN-II ANTAG,PLAIN	96	9.1%
N05B	HYPNOTICS & SEDATIVES	91	8.7%
N06A	ANTIDEPRESS.& MOOD STAB.	84	8.0%
R01A	TOPICAL NASAL PREPS	74	7.0%
C09D	ANGIOTENSIN-II ANTAG,COMB	59	5.6%
A10H	SULPHONYLUREA A-DIABS	57	5.4%
R06A	ANTIHISTAMINES SYSTEMIC	57	5.4%
A10C	HUMAN INSULIN+ANALOGUES	56	5.3%
R05D	COUGH SEDATIVES	50	4.8%
T02D	DIABETES TESTS	49	4.7%
G04C	BPH PRODUCTS	48	4.6%
M02A	TOP A-RHEUMATICS & ANALG	45	4.3%
M04A	ANTI-GOUT PREPARATIONS	44	4.2%
A10N	DPP-IV INHIBITOR A-DIABS	41	3.9%
C10C	LIP.REG.CO.W.OTH.LIP.REG	41	3.9%
C09B	ACE INHIBITORS COMBINAT	37	3.5%
J01C	BROAD SPECTRUM PENICILLIN	37	3.5%

Note: Concomitant medications defined as medications prescribed 30 days before or after the date of the first prasugrel prescription.

Source: Table 4a, Attachment 1.

2.6.3.2. Concomitant Medications by Specific Generic Drugs

Table B011.2.8 lists the concomitant medications by generic names in prasugrel-treated patients. Concomitant medications are defined as medication prescribed 30 days before or after the date of the first prasugrel prescription. As expected from this patient population, the most commonly prescribed concomitant medications were aspirin, statins, beta blockers, ACE-inhibitors, PPIs, and antidiabetic agents. The full list of the concomitant medication by generic names is included in Table 4b in Attachment 1.

**Table B011.2.8. Concomitant Medications by Specific Generic Drugs in Patients Treated with Prasugrel
IMS Disease Analyzer France**

	Number of patients	% of total patients
TOTAL PATIENTS	**1052**	**100.0%**
ACETYLSALICYLIC ACID	986	93.7%
ATORVASTATIN	547	52.0%
BISOPROLOL	487	46.3%
ROSUVASTATIN	345	32.8%
RAMIPRIL	329	31.3%
PERINDOPRIL	298	28.3%
ESOMEPRAZOLE	239	22.7%
ATENOLOL	183	17.4%
PANTOPRAZOLE	167	15.9%
PARACETAMOL	162	15.4%
NITROGLYCERIN	130	12.4%
METFORMIN	124	11.8%
DOCOSAHEXANOIC ACID+ETHYL-EICOSAPENT	93	8.8%
ACEBUTOLOL	91	8.7%
FUROSEMIDE	85	8.1%
OMEPRAZOLE	77	7.3%
NEBIVOLOL	73	6.9%
RABEPRAZOLE	72	6.8%
IVABRADINE	66	6.3%
BROMAZEPAM	58	5.5%
ALPRAZOLAM	56	5.3%
GLUCOSE, BLOOD TESTS	53	5.0%
AMLODIPINE	52	4.9%
EPLERENONE	41	3.9%
SIMVASTATIN+EZETIMIBE	41	3.9%
ZOPICLONE	41	3.9%

Source: Table 4b, Attachment 1.

2.6.4. Characteristics of Initial Daily Dose

2.6.4.1. Patient and Dose Characteristics

Table B011.2.9 describes the initial daily dose by history of TIA/stroke, age groups, and body weight strata. The analyses were performed in 2 ways: 1) based on the daily dose prescribed on the date of the first prasugrel prescription, and 2) assuming that the dosage instruction was once daily in cases where the daily dosing instructions were missing. The full analyses using both methods are included in Attachment 1. Only the results based on the second analysis method are presented below (Table B011.2.9, from Table 5b, Attachment 1).

Of the 1052 prasugrel-treated patients, 1050 patients (99.8 %) received an initial prescribed daily maintenance dose (MD) of 10 mg and 2 patients (0.2%) an initial daily MD of 5 mg. Of note, even though the 5-mg prasugrel tablet is not marketed in France, it is possible for patients to be prescribed half of a 10-mg daily dose. Two patients (0.2%) with history of TIA/stroke received a 10-mg prescription. Of the 57 patients who were ≥75 years of age, 2 received the 5-mg prescription and the other 55 received the 10-mg prescription. Of the patients with body weight recorded in the database, 472 were ≥60 kg and 25 patients were <60 kg. All but 1 of the patients ≥60 kg were prescribed 10 mg, while all 25 patients <60 kg were prescribed 10 mg (Table B011.2.9 from Table 5b, Attachment 1).

Additional analyses were performed in the 57 patients aged ≥75 years: 18 patients had history of diabetes, 5 had history of MI, 26 had unknown body weight information, and 28 were ≥60 kg. Of the 55 patients on the 10-mg MD, 17 had history of diabetes and 5 had history of MI. Of the 2 patients on the 5-mg MD, 1 patient was diabetic (Table B011.2.10).

Table B011.2.9. Characteristics by Initial Daily Dose - Dosage Assumed to be Once Daily
IMS Disease Analyzer France

		TOTAL PATIENTS		Initial dose 5 mg		Initial dose 10 mg	
		Number of patients	% of TOTAL PATIENTS	Number of patients	% of row totals (with 95% CI)	Number of patients	% of row totals (with 95% CI)
TOTAL PATIENTS		1052	100%	2	0.2% (0.0, 0.7)	1050	99.8% (99.3, 100)
History of TIA/Stroke	Yes	2	0%	0	-	2	100% (15.8, 100)
	No	1050	100%	2	0.2% (0.0, 0.7)	1048	99.8% (99.3, 100)
Age Group*	<75 years old	992	94%	0	-	992	100% (99.6, 100)
	≥75 years old	57	5%	2	3.5% (0.4, 12.1)	55	96.5% (87.9, 99.6)
	Unknown	3	0%	0	-	3	100% (29.2, 100)
Weight†	<60 kg	25	2%	0	-	25	100% (86.3, 100)
	≥60 kg	472	45%	1	0.2% (0.0, 1.2)	471	99.8% (98.8, 100)
	Unknown	555	53%	1	0.2% (0.0, 1.0)	554	99.8% (99.0, 100)
Weight - Statistics	Mean (+/- SD) in kg	83 (66.9, 98.2)		95 (95, 95)		83 (66.9, 98.1)	
	Median in kg	81		95		81	

Abbreviations: CI = confidence interval; SD = standard deviation; TIA = transient ischemic attack.
* at first prasugrel
† where available
For Total Patients, an additional column showing percentages based on the total number of patients is displayed.
All other percentages and confidence intervals are based on the corresponding row total.
Where daily dose was missing, the dosage instruction was assumed to be once daily and the strength in mg was used to populate the field.
Note that although a 5-mg dose was not marketed in France, it is possible for patients to be prescribed half a 10-mg pill once daily.
Source: Table 5b, Attachment 1.

Table B011.2.10. Dosage Assumed to be Once Daily, Breakdown of Patients ≥75 Years IMS Disease Analyzer France

		TOTAL PATIENTS		Initial dose 5 mg		Initial dose 10 mg	
		Number of patients	% of TOTAL PATIENTS	Number of patients	% of row totals	Number of patients	% of row totals
TOTAL PATIENTS ≥75 YEARS		57	100%	2	3.5% (0.4, 12.1)	55	96.5% (87.9, 99.6)
History of Diabetes	Yes	18	32%	1	5.6% (0.1, 27.3)	17	94.4% (72.7, 99.9)
	No	39	68%	1	2.6% (0.1, 13.5)	38	97.4% (86.5, 99.9)
History of MI	Yes	5	9%	0	-	5	100% (47.8, 100)
	No	52	91%	2	3.9% (0.5, 13.2)	50	96.2% (86.8, 99.5)
Weight†	<60 kg	3	5%	0	-	3	100% (29.2, 100)
	≥60 kg	28	49%	1	3.6% (0.1, 18.4)	27	96.4% (81.7, 99.9)
	Unknown	26	46%	1	3.9% (0.1, 19.6)	25	96.2% (80.4, 99.9)
Weight - Statistics	Mean (+/- SD) in kg	77 (61.6, 91.5)		95 (95, 95)		76 (61.2, 90.7)	
	Median in kg	75		95		75	

Abbreviations: MI = myocardial infarction; SD = standard deviation.

† where available.

Note: For Total Patients, an additional column showing percentages based on the total number of patients is displayed. All other percentages and confidence intervals are based on the corresponding row total. Where daily dose was missing, the dosage instruction was assumed to be once daily and the strength in mg was used to populate the field. Note that although a 5-mg dose was not marketed in France, it is possible for patients to be prescribed half a 10-mg pill once daily.

Source: Table 5b, Attachment 1.

2.6.4.2. Switching from Other Thienopyridines

Table B011.2.11 (from Table 6, Attachment 1) summarizes the patients who were new to prasugrel and the switching to prasugrel from another thienopyridine that occurred at the first prasugrel prescription.

Of 1052 prasugrel-treated patients, most were newly prescribed to a thienopyridine consisting of prasugrel only (N=905), with an additional 3 receiving prescriptions for both prasugrel and clopidogrel on the same day. A total of 144 patients (13.7%) switched from another thienopyridine (3 from ticlopidine and 141 from clopidogrel) to prasugrel.

Table B011.2.11. Switching to Prasugrel from Another Thienopyridine
IMS Disease Analyzer France

	Number of patients	% of total patients
TOTAL PATIENTS	**1052**	**100.0%**
Total number of new patients	908	86.3%
- New with prasugrel only	905	86.0%
- New with prasugrel plus ticlopidine (same day coprescription)	0	0.0%
- New with prasugrel plus clopidogrel (same day coprescription)	3	0.3%
Total number of patients who switched from other thienopyridine*	144	13.7%
- Switch from ticlopidine	3	0.3%
- Switch from clopidogrel	141	13.4%

NOTE: A switch is defined as any patient who has ever had a prescription for clopidogrel, ticlopidine, or both recorded in the database prior to initiation of prasugrel. Note that it is possible for patients to have previously been prescribed both clopidogrel and ticlopidine, so double counting may occur.
Source: Table 6, Attachment 1.

2.6.5. Prasugrel Maintenance Dose Usage over Time

Table 7 in Attachment 1 describes the usage of the 5-mg and 10-mg MDs over a 12-month period, broken down by 3-month intervals and by history of TIA/stroke, age groups, and body weight. Of note, the 5-mg dose of prasugrel is not marketed in France. The 2 patients who started with the 5-mg MD stayed on the initial prescribed dose during the 12-month period. The rest of the patients (n=1050) started on the 10-mg MD. The majority of these patients (60.2%) stayed on the initial prescribed dose through the first 3 months after the first prasugrel prescription; 1 patient who started on the 10-mg MD switched to the 5-mg MD during the first 3 months. The percentage of patients receiving a prasugrel prescription decreased over each successive 3-month period. Approximately 17% of patients had a prasugrel prescription at the end of 12 months.

2.6.6. Medication Possession Ratio for Prasugrel

Table 8 in Attachment 1 presents the persistence of prasugrel treatment over 6-month and 12-month intervals using the medication possession ratio (MPR). The MPR reflects the amount of time an individual remains on chronic drug therapy. An MPR of 80% is considered a reasonable threshold for persistence. Overall, the MPR was 60.7% in patients with at least 6-month follow-up after the first prasugrel prescription and 63.2% in patients with at least 12-month follow-up, suggesting a lack of persistence of prasugrel treatment over the period of 6 months or 12 months.

2.7. Results from the IMS Disease Analyzer UK and CPRD

This is the third annual analysis report in the UK. The descriptive analyses were conducted using outpatient general practice data from July 2009 to October 2012 in both databases. Details of the statistical methods and relevant definitions used to generate Table B011.2.12 through Table B011.2.23 are described in the Methods Section 2.4 and in the Appendices of the full report (Attachment 2). The key findings and the summary text are presented below.

2.7.1. Characteristics for Patients Treated with Prasugrel

The October 2012 final annual report of the IMS Disease Analyzer UK and CPRD recorded 1580 patients with at least 1 prasugrel prescription.

As shown in Table B011.2.12 (from Table 1, Attachment 2), the majority of the patients were male. Few patients had a history of TIA or stroke. The overall mean age was 60, with 163 (10.3%) of the patients 75 years of age or older. Among patients with body weight recorded in the database (95.3%), 86 patients (5.4%) had body weight <60 kg.

Table B011.2.12. All Prasugrel Patients, Distribution by Risk Segment
IMS Disease Analyzer UK and CPRD

		Total patients		Males		Females	
TOTAL PATIENTS	**Row percentages based on Total patients**	**1580**	**100.0%**	**1218**	**77.1%**	**362**	**22.9%**
Prior TIA/Stroke - n %	Yes	63	4.0%	42	3.4%	20	5.5%
	No	1517	96.0%	1176	96.6%	342	94.5%
Age Group* - n %	0 - 17 years old	0	0.0%	0	0.0%	0	0.0%
	18 - 34 years old	15	0.9%	11	0.9%	4	1.1%
	35 - 44 years old	117	7.4%	100	8.2%	17	4.7%
	45 - 54 years old	348	22.0%	282	23.2%	66	18.2%
	55 - 64 years old	514	32.5%	417	34.2%	97	26.8%
	65 - 74 years old	423	26.8%	311	25.5%	112	30.9%
	75 - 84 years old	146	9.2%	87	7.1%	59	16.3%
	<75 years old	1417	89.7%	1121	92.0%	296	81.8%
	≥75 years old	163	10.3%	97	8.0%	66	18.2%
	≥85 years old	17	1.1%	10	0.8%	7	1.9%
	Unknown	0	0.0%	0	0.0%	0	0.0%
Age - Statistics	Mean (±SD) in years	60 (49.3, 71.5)		60 (48.8, 70.3)		63 (51.4, 74.7)	
	Median in years	61		60		64	
	Interquartile range in years (Q1, Q3)	(53.0, 68.0)		(52.0, 67.0)		(55.0, 72.0)	
Weight† - n %	<60 kg	86	5.4%	26	2.1%	60	16.6%
	≥60 kg	1419	89.8%	1126	92.4%	293	80.9%
	Unknown	75	4.7%	66	5.4%	9	2.5%
Weight† - Statistics	Mean (±SD) in kg	84 (66.8, 101.0)		87 (70.6, 103.2)		74 (58.2, 89.8)	
	Median in kg	83		86		72	
	Interquartile range in kg (Q1, Q3)	(72.0, 94.0)		(75.9, 95.2)		(63.9, 82.6)	

Abbreviations: SD = standard deviation; TIA = transient ischemic attack.
* at first prasugrel † where available Percentages are based on the corresponding column total. Source: from Table 1, Attachment 2.

2.7.2. Diagnoses and Comorbidities

2.7.2.1. Diagnoses for Which Prasugrel was First Prescribed

The most common diagnoses for which prasugrel was first prescribed are displayed in Table B011.2.13. The data were generated using only diagnoses (both ICD-10 and READ codes) that were linked to the first prasugrel prescription. Due to the structure of CPRD data, no diagnoses are linked to prescriptions, and therefore the listed diagnoses are those that appear in a patient's medical records on the day that prasugrel was prescribed. With the large number of missing or uninformative linked diagnoses, additional analyses were conducted to search the database for a record of predefined ICD-10 codes of relevant coronary heart diseases (ACS, CHD, and previous MI) for each patient at the following time points: on the same date of the first prasugrel prescriptions, or 30 days, 60 days, 90 days, and any time prior to the first prasugrel prescriptions (intermediate steps shown in Table 2, Attachment 2). The final analysis (Table B011.2.14, from Table 2, Step 6, Attachment 2) showed that 94% of the patients prescribed with prasugrel had relevant diagnoses of heart diseases any time prior to the first prasugrel prescription; relevant coronary heart disease diagnoses were missing in 6% of patients.

Table B011.2.13. Diagnosis for Which Prasugrel Was First Prescribed IMS Disease Analyzer UK and CPRD

Original table using only diagnoses linked to prasugrel		Number of patients	% of total patients
TOTAL PATIENTS		**1580**	**100.0%**
I219	AC MYOCARD INFARCT UNSP	154	9.7%
I259	CHR ISCHAEM HRT DIS UNSP	95	6.0%
I213	AC TRANSMUR MI UNSP SITE	76	4.8%
Z518	OTH SPEC MEDICAL CARE	39	2.5%
Z408	OTH PROPHYLACTIC SURGERY	32	2.0%
Z519	MEDICAL CARE UNSP	17	1.1%
R698	ILL DEFINED DIAG	15	0.9%
I214	AC SUBENDOCARD MI	12	0.8%
I211	AC TRANSMUR MI INF WALL	11	0.7%
I100	ESSENTIAL (PRIM) HYPERT	8	0.5%
I200	UNSTABLE ANGINA	8	0.5%
I209	ANGINA PECTORIS UNSP	8	0.5%
R694	DIOC ADMIN CODES	8	0.5%
I990	OTH/UNSP DIS CIRC SYST	7	0.4%
R098	O/SP SYM/SGN CIRC/RESP	7	0.4%
Z136	SPEC SCR CARDIOVASC DIS	7	0.4%
Z760	ISSUE REP PRESCRIPT	7	0.4%
I210	AC TRANSMUR MI ANT WALL	6	0.4%
I516	CARDIOVASCULAR DIS UNSP	6	0.4%
I251	ATHEROSCL HEART DIS	5	0.3%
Z027	ISSUE MEDICAL CERT	5	0.3%
F411	GENERALIZED ANXIETY DIS	4	0.3%
M796	PAIN IN LIMB	4	0.3%
R074	CHEST PAIN UNSPECIFIED	4	0.3%
E119	NIDDM WITHOUT COMP	3	0.2%

Source: Table 2, Attachment 2

Table B011.2.14. Relevant Coronary Heart Disease at Any Time Prior to Index Date IMS Disease Analyzer UK and CPRD

Step 6: Search all other diagnosis fields for acceptable diagnoses ever† in the database.		Number of patients	% of total patients
TOTAL PATIENTS		**1580**	**100.0%**
I219	AC MYOCARD INFARCT UNSP	539	34.1%
I213	AC TRANSMUR MI UNSP SITE	370	23.4%
I259	CHR ISCHAEM HRT DIS UNSP	212	13.4%
I214	AC SUBENDOCARD MI	112	7.1%
I209	ANGINA PECTORIS UNSP	77	4.9%
I200	UNSTABLE ANGINA	62	3.9%
I211	AC TRANSMUR MI INF WALL	37	2.3%
I210	AC TRANSMUR MI ANT WALL	35	2.2%
I251	ATHEROSCL HEART DIS	32	2.0%
I212	AC TRANSMUR MI OTH SITES	5	0.3%
I208	OTH FORMS ANGINA PECTOR	3	0.2%
I252	OLD MYOCARD INFARCT	2	0.1%
I229	SUBSEQUENT MI UNSP SITE	1	0.1%
I241	DRESSLER'S SYNDROME	1	0.1%
I250	ATHEROSCL CARDIOVASC DIS	1	0.1%
Diagnosis missing		**91**	**6%**

† Number of Days From Most Recent Acceptable Diagnosis to First Prasugrel Rx: there are no additional patients given a diagnosis via the algorithm between 90 days and ever (Appendix 3, Attachment 2).

Source: Table 2, Step 6, Attachment 2

2.7.2.2. Previous Diagnoses at the First Prasugrel Prescription

Table B011.2.15 and Table B011.2.16 list the most common previous diagnoses (in both ICD-10 codes and READ codes) recorded any time prior to or on the date of the first prescription of prasugrel. The full list of the diagnoses can be found in Attachment 2, Table 3a. Some of the most prevalent conditions include acute MI, essential hypertension, NIDDM, and angina pectoris.

Table B011.2.15. Previous Diagnoses at Any Time Prior to the Index Date IMS Disease Analyzer UK and CPRD

IMS Disease Analyzer using the ICD-10 codes

		Number of patients	% of total patients
TOTAL PATIENTS		**1580**	**100.0%**
Z408	OTH PROPHYLACTIC SURGERY	1195	75.6%
R694	DIOC ADMIN CODES	1018	64.4%
I219	AC MYOCARD INFARCT UNSP	740	46.8%
Z518	OTH SPEC MEDICAL CARE	625	39.6%
M796	PAIN IN LIMB	590	37.3%
I100	ESSENTIAL (PRIM) HYPERT	556	35.2%
J220	UNSP AC LOW RESP INFECT	505	32.0%
I259	CHR ISCHAEM HRT DIS UNSP	475	30.1%
I213	AC TRANSMUR MI UNSP SITE	470	29.7%
M255	PAIN IN JOINT	413	26.1%
J069	AC UPP RESP INFECT UNSP	407	25.8%
M545	LOW BACK PAIN	320	20.3%
K300	DYSPEPSIA	271	17.2%
M542	CERVICALGIA	264	16.7%
F329	DEPRESSIVE EPISODE UNSP	259	16.4%
E119	NIDDM WITHOUT COMP	255	16.1%
I209	ANGINA PECTORIS UNSP	253	16.0%
T149	INJURY UNSPECIFIED	251	15.9%
Z136	SPEC SCR CARDIOVASC DIS	251	15.9%
M199	ARTHROSIS UNSPECIFIED	239	15.1%
Z519	MEDICAL CARE UNSP	228	14.4%
J019	ACUTE SINUSITIS UNSP	213	13.5%
R698	ILL DEFINED DIAG	211	13.4%
H103	AC CONJUNCTIVITIS UNSP	204	12.9%
F522	FAILURE GENITAL RESPONSE	203	12.8%

Source: Table 3a, Attachment 2.

Table B011.2.16. Previous Diagnoses at Any Time Prior to the Index Date IMS Disease Analyzer UK and CPRD

READ Codes

		Number of patients	% of total patients
TOTAL PATIENTS		**1580**	**100.0%**
0....	Occupations	719	45.5%
G30..	Acute myocardial infarction	697	44.1%
N245.	Pain in limb	495	31.3%
G30X0	Acute ST segment elevation mi	470	29.7%
G3...	Ischaemic heart disease	452	28.6%
H06z0	Chest infection NOS	419	26.5%
G20..	Essential hypertension	411	26.0%
H05z.	Upper respiratory infect.NOS	391	24.7%
N142.	Pain in lumbar spine	309	19.6%
J16y4	Dyspepsia	267	16.9%
N131.	Cervicalgia - pain in neck	264	16.7%
8B314	Medication review	262	16.6%
C10F.	Type 2 diabetes mellitus	248	15.7%
G33..	Angina pectoris	244	15.4%
8B311	Medication given	226	14.3%
G2...	Hypertensive disease	221	14.0%
73050	Irrig ext aud canal remov wax	213	13.5%
79294	Insert coronary artery stent	212	13.4%
H01..	Acute sinusitis	203	12.8%
N143.	Sciatica	203	12.8%
E2273	Impotence	202	12.8%
793G.	Perc tran bal ang sten cor art	201	12.7%
7L172	Blood withdrawal for testing	201	12.7%
F4C0.	Acute conjunctivitis	199	12.6%
7L17.	Blood withdrawal	198	12.5%

Source: Table 3a, Attachment 2.

2.7.2.3. Relevant Comorbidities

For a better understanding of the comorbidities of prasugrel patients, Table B011.2.17 (from Table 3b, Attachment 2) shows the prevalence of relevant conditions that were recorded in the database within the 12 months prior to or on the date of the first prasugrel prescription. Of note, 94.2% of the patients had a history of CHD, 85.9% ACS, 79.6% previous MI, and 35.3% hypertensive diseases. The ICD-10 codes used to define the conditions are included in Attachment 2.

Table B011.2.17. Relevant Comorbidities in Patients Treated with Prasugrel IMS Disease Analyzer UK and CPRD

ICD-10 Codes

	Number of patients	% of total patients
TOTAL PATIENTS	**1580**	**100.0%**
Coronary heart disease	1489	94.2%
ACS - Acute coronary syndrome	1357	85.9%
Previous myocardial infarction	1258	79.6%
Hypertensive diseases	557	35.3%
Diabetes	289	18.3%
Hyperlipidemia	278	17.6%
Heart failure	138	8.7%
Peripheral artery disease	81	5.1%
Atrial fibrillation and flutter	71	4.5%
Peptic ulcer	50	3.2%
Renal disease	23	1.5%

Note: A comorbidity is defined as any diagnosis recorded in the 12 months prior to or on the index date (date of the first recorded prasugrel prescription). ICD-10 code groupings were defined by Lilly.
Source: Table 3b, Attachment 2 contains a full list of relevant comorbidities.

2.7.3. Concomitant Medications

2.7.3.1. Concomitant Medications by Drug Class

Table B011.2.18 and Table B011.2.19 list the most common concomitant medications by drug class in prasugrel-treated patients in the Disease Analyzer UK and CPRD, respectively. Concomitant medications were defined as medications prescribed 30 days before or after the date of the first prasugrel prescription. As would be expected for this patient population, the most commonly prescribed concomitant medications included platelet inhibitors, lipid-lowering agents, beta blockers and ACE-inhibitors, nitrates, and diuretics. Of note, anti-ulcerants, which include PPIs and H2 blockers, were prescribed in 45.5% of the patients in the Disease Analyzer UK. In the CPRD database, there were 28 patients out of 1244 (2.3%) prescribed oral anticoagulants; the full list of the concomitant medications by class is attached in Attachment 2, Table 4a.

Table B011.2.18. Concomitant Medications by Drug Class in Patients Treated with Prasugrel
IMS Disease Analyzer UK

ATC3 Codes - Disease Analyzer Only

		Number of patients	% of total patients
TOTAL PATIENTS		**336**	**100.0%**
ATC3 code	**ATC3 text**		
B01C	PLATELET AGGREG INHIBITRS	336	100.0%
C10A	CHOLEST&TRIGLY.REGULATOR	321	95.5%
C07A	BETA BLOCKING AGENT PLAIN	293	87.2%
C09A	ACE INHIBITORS PLAIN	269	80.1%
A02B	ANTIULCERANTS	153	45.5%
C01E	NITRITES AND NITRATES	133	39.6%
N02B	NON-NARCOTIC ANALGESICS	89	26.5%
C03A	DIURETICS	76	22.6%
C10B	ANTI-ATHEROMA NATRL ORIG	69	20.5%
C08A	CALCIUM ANTAGONISTS PLAIN	46	13.7%
N07B	ANTISMOKING PRODUCTS	40	11.9%
N06A	ANTIDEPRESS.& MOOD STAB.	38	11.3%
C09C	ANGIOTENSN-II ANTAG,PLAIN	34	10.1%
T02D	DIABETES TESTS	31	9.2%
R03A	B2-STIMULANTS	29	8.6%
A06A	LAXATIVES	25	7.4%
A10J	BIGUANIDE ANTIDIABETICS	23	6.8%
M01A	ANTIRHEUMATIC NON-STEROID	21	6.3%
A10C	HUMAN INSULIN+ANALOGUES	19	5.7%
Y21A	DIABETIC INJECTION DEVICE	19	5.7%
J01C	BROAD SPECTRUM PENICILLIN	18	5.4%
A10H	SULPHONYLUREA A-DIABS	15	4.5%
C01D	CORON THER EX CA/ANT/NIT	14	4.2%
D02A	EMOLLIENTS & PROTECTIVES	14	4.2%
N02A	NARCOTIC ANALGESICS	14	4.2%

Source: Table 4a, Attachment 2.

Table B011.2.19. Concomitant Medications by Drug Class in Patients Treated with Prasugrel

CPRD only

BNF Chapter text - CPRD only		
	Number of	% of total
TOTAL PATIENTS	**1244**	**100.0%**
BNF Chapter		
Antiplatelet drugs	1242	99.8%
Statins	1159	93.2%
Antiplatelet drugs/Non-opioid analgesics/Non-steroidal anti-inflammatory drugs	1096	88.1%
Beta-adrenoceptor blocking drugs	1078	86.7%
Angiotensin-converting enzyme inhibitors	993	79.8%
Nitrates	541	43.5%
Proton pump inhibitors	541	43.5%
Omega-3 fatty acid compounds	246	19.8%
Loop diuretics	166	13.3%
Calcium channel blockers	151	12.1%
Non-opioid analgesics	147	11.8%
Angiotensin-II receptor antagonists	134	10.8%
Potassium-sparing diuretics and aldosterone antagonists	130	10.5%
Biguanides	120	9.6%
Non-opioid analgesics/Opioid analgesics	119	9.6%
Selective serotonin re-uptake inhibitors	110	8.8%
Cigarette smoking	109	8.8%
Opioid analgesics	93	7.5%
Diagnostic & monitoring agents for diabetes mellitus/Meter read strip	84	6.8%
Other antianginal drugs	74	5.9%
Selective beta-2-agonists	70	5.6%
Emollient skin preparations	69	5.5%
Broad-spectrum penicillins/Urinary-tract infections	68	5.5%
Intermediate- and long-acting insulins	67	5.4%
Thiazides and related diuretics	66	5.3%

Abbreviations: BNF = British National Formulary; CPRD = Clinical Practice Research Datalink.
Note that drugs may fall into multiple BNF chapters depending on the diagnosis for which they were prescribed.
Source: Table 4a, Attachment 2.

2.7.3.2. Concomitant Medications by Specific Generic Drugs

Table B011.2.20 lists the most common concomitant medications by generic names in prasugrel-treated patients in Disease Analyzer UK and CPRD combined. Concomitant medications are defined as medication prescribed 30 days before or after the date of the first prasugrel prescription. As expected from this patient population, the most commonly prescribed concomitant medications were ACE-inhibitors, aspirin, beta blockers, statins, nitrates, PPIs, and diuretics. Clopidogrel was prescribed in 10.8% of the patients. The full list of the concomitant medication by generic names is attached in Attachment 2, Table 4b.

Table B011.2.20. Concomitant Medications by Specific Generic Drugs in Patients Treated with Prasugrel IMS Disease Analyzer UK and CPRD

	Number of patients	Percentage of total patients (%)
TOTAL PATIENTS	**1580**	**100.0%**
RAMIPRIL	1133	71.4
ASPIRIN	1096	69.4
BISOPROLOL FUMARATE	980	62.0
ATORVASTATIN CALCIUM	836	52.9
GLYCERYL TRINITRATE	477	30.2
SIMVASTATIN	444	28.1
OMEPRAZOLE	346	21.9
LANSOPRAZOLE	327	20.7
ACETYLSALICYLIC ACID	288	18.2
BISOPROLOL	275	17.4
EICOSAPENTAENOIC ACID + DOCOSAHEXAENOIC ACID	245	15.5
ATORVASTATIN	202	12.8
PARACETAMOL	194	12.3
FUROSEMIDE	185	11.7
CLOPIDOGREL	170	10.8
NONE KNOWN	143	9.1
ISOSORBIDE MONONITRATE	136	8.6
NICOTINE	131	8.3
AMLODIPINE	127	8.0
METFORMIN HYDROCHLORIDE	120	7.6
NITROGLYCERIN	118	7.5
EPLERENONE	114	7.2
CODEINE PHOSPHATE + PARACETAMOL	97	6.1
LEVOTHYROXINE SODIUM	75	4.7
ATENOLOL	73	4.7

Note: Concomitant medications defined as medication prescribed 30 days before or after the date of the first prasugrel prescriptions.

Source: The full list of the concomitant medication by generic names is attached in Attachment 2, Table 4b.

2.7.4. Characteristics of Initial Daily Dose

2.7.4.1. Patient and Dose Characteristics

Table B011.2.21 and Table B011.2.22 describe the initial daily dose by history of TIA/stroke, age groups, and body weight strata. The analyses were performed in two ways: 1) based on the daily dose prescribed on the date of the first prasugrel script, and 2) assuming that the dosage instruction was once daily in cases where the daily dosing instructions were missing. The full analyses using both methods are presented in Attachment 2. Only the results based on the second method are shown below (Table B011.2.21 and Table B011.2.22).

The majority of patients (91.4%) received an initial prescribed maintenance dose of 10 mg. Of the patients with history of TIA/stroke, 16 received a 5-mg prescription and 47 a 10-mg prescription. Of the patients ≥75 years of age, 73 (44.8%) received a 5-mg prescription and 90 (55.2%) a 10-mg prescription. Among the patients with body weight recorded in the database, 86 (5.4%) were <60 kg (25 prescribed with 5 mg, and 61 with 10 mg (Table B011.2.21), from Table 5b, Attachment 2).

Additional analyses were for the 163 very elderly (age ≥75 years) patients. Of the 90 very elderly patients on the 10-mg MD, 22 had a history of diabetes and 78 had a history of MI. Of the 73 very elderly patients on the 5-mg MD, 15 had a history of diabetes, and 54 had a history of MI. Among the 163 very elderly patients with body weight recorded, 27 weighed <60 kg; 10 of these patients were prescribed the 10-mg MD. Of note, the body weight of the very elderly patients on the 10-mg MD was higher than that of the patients on the 5-mg MD (mean body weight 78 kg versus 69 kg) (Table B011.2.22, from Table 5b, Attachment 2).

Table B011.2.21. Characteristics by Initial Daily Dose - Dosage Assumed to be Once Daily IMS Analyzer UK and CPRD

		TOTAL PATIENTS		Initial dose 5mg		Initial dose 10mg	
		Number of patients	% of TOTAL PATIENTS	Number of patients	% of row totals (with 95% CI)	Number of patients	% of row totals (with 95% CI)
TOTAL PATIENTS		**1580**	**100.0%**	**135**	**8.6% (7.2, 10.1)**	**1445**	**91.4% (90.0, 92.8)**
History of TIA/Stroke	Yes	63	4.0%	16	25.8% (15.5, 38.5)	47	74.2% (61.5, 84.5)
	No	1517	96.0%	119	7.9% (6.6, 9.3)	1399	92.1% (90.7, 93.4)
Age Group*	<75 years old	1417	89.7%	62	4.4% (3.4, 5.6)	1355	95.6% (94.4, 96.6)
	≥75 years old	163	10.3%	73	44.8% (37.0, 52.8)	90	55.2% (47.2, 63.0)
Weight†	<60 kg	86	5.4%	25	29.1% (19.8, 39.9)	61	70.9% (60.1, 80.2)
	≥60 kg	1419	89.8%	108	7.6% (6.3, 9.2)	1306	92.4% (90.9, 93.7)
	Unknown	75	4.7%	2	2.7% (0.3, 9.3)	73	97.3% (90.7, 99.7)
Weight - Statistics	Mean (+/- SD) in kg	84 (66.8, 101.0)		73 (60.2, 86.7)		85 (68.6, 101.2)	
	Median in kg	83		73		85	

Abbreviations: CI = confidence interval; SD = standard deviation; TIA = transient ischemic attack.

* at first prasugrel † where available For Total Patients, an additional column showing percentages based on the total number of patients is displayed. All other percentages and confidence intervals are based on the corresponding row total. Where daily dose was missing, the dosage instruction was assumed to be once daily and the strength in mg was used to populate the field.

Source: Table 5b, Attachment 2.

Table B011.2.22. Dosage Assumed to be Once Daily- Breakdown of Patients ≥75 years

		TOTAL PATIENTS		Initial dose 5mg		Initial dose 10mg	
		Number of patients	% of TOTAL PATIENTS	Number of patients	% of row totals	Number of patients	% of row totals
TOTAL PATIENTS ≥75 YEARS		**163**	**100.0%**	**73**	**44.8% (37.0, 52.8)**	**90**	**55.2% (47.2, 63.0)**
History of Diabetes	Yes	37	22.7%	15	40.5% (24.8, 57.9)	22	59.5% (42.1, 75.3)
	No	126	77.3%	58	46.0% (37.1, 55.1)	68	54.0% (44.9, 62.9)
History of MI	Yes	132	81.0%	54	40.9% (32.4, 49.8)	78	59.1% (50.2, 67.6)
	No	31	19.0%	19	61.3% (42.2, 78.2)	12	38.7% (21.9, 57.8)
Weight†	<60 kg	27	16.6%	17	63.0% (42.4, 80.6)	10	37.0% (19.4, 57.6)
	≥60 kg	133	81.6%	55	41.4% (32.9, 50.2)	78	58.7% (49.8, 67.1)
	Unknown	3	1.8%	1	33.3% (0.8, 90.6)	2	66.7% (9.4, 99.2)
Weight - Statistics	Mean (+/- SD) in kg	75 (62.7, 87.5)		69 (56.7, 80.7)		78 (65.9, 89.4)	
	Median in kg	73		67		74	

Abbreviations: MI = myocardial infarction; SD = standard deviation.

Note: For Total Patients, an additional column showing percentages based on the total number of patients is displayed. All other percentages and confidence intervals are based on the corresponding row total. Where daily dose was missing, the dosage instruction was assumed to be once daily and the strength in mg was used to populate the field.

* at first prasugrel.

† where available.

Source: Table 5b, Attachment 2.

2.7.4.2. Switching from Other Thienopyridines

Table B011.2.23 summarizes the switching to prasugrel from another thienopyridine that occurred at the first prasugrel prescription. Most patients were newly prescribed to prasugrel only. All of the patients who did switch treatments were previously on clopidogrel. Thirteen patients (0.8%) received prasugrel and clopidogrel prescriptions on the same date.

Of 1580 prasugrel-treated patients, most were newly prescribed to a thienopyridine consisting of prasugrel only (N=1200), with an additional 13 receiving prescriptions for both prasugrel and clopidogrel on the same day. A total of 367 patients (23.2%) switched from clopidogrel to prasugrel.

Table B011.2.23. Switching to Prasugrel from Another Thienopyridine IMS Disease Analyzer UK and CPRD

	Number of patients	% of total patients
TOTAL PATIENTS	**1580**	**100.0%**
Total number of new patients	**1213**	**76.8%**
- New with prasugrel only	1200	75.9%
- New with prasugrel plus ticlopidine (same day coprescription)	0	0.0%
- New with prasugrel plus clopidogrel (same day coprescription)	13	0.8%
Total number of patients who switched from other thienopyridine*	**367**	**23.2%**
- Switch from ticlopidine	0	0.0%
- Switch from clopidogrel	367	23.2%

Note: A switch is defined as any patient who has ever had a prescription for clopidogrel, ticlopidine or both recorded in the database prior to initiation of prasugrel.

*Note that it is possible for patients to have previously been prescribed both clopidogrel and ticlopidine, so double counting may occur.

Source: Table 6, Attachment 2.

2.7.5. Prasugrel Maintenance Dose Usage over Time

Table 7 in Attachment 2 describes the usage of the 5-mg and 10-mg maintenance doses over a 12-month period, broken down by 3-month intervals and by history of TIA/stroke, age groups, and body weight. The majority of patients stayed on the initial prescribed prasugrel dose for a mean duration of 59.2 days for the 5-mg dose and 59.3 days for the 10-mg dose. The percentage of patients receiving a prasugrel prescription decreased over each successive 3-month period. Approximately 28% of patients had a prasugrel prescription at the end of 12 months.

Very few patients who started with the 5-mg maintenance dose switched to the 10-mg maintenance dose over the 12-month period. The same pattern was observed for patients who started with the 10-mg maintenance dose.

2.7.6. Medication Possession Ratio for Prasugrel

Table 8 in Attachment 2 presents the persistence of prasugrel treatment over 6-month and 12-month intervals using the MPR. The MPR reflects the amount of time an individual remains on chronic drug therapy. An MPR of 80% is considered a reasonable threshold for persistence. Overall, the MPR is 75.5% in patients with at least a 6-month follow up after the first prasugrel prescription, and 76.9% in patients with at least a 12-month follow up, suggesting some degree of lack of persistence of prasugrel treatment over the period of 6 months or 12 months.

2.8. Results from the IMS Disease Analyzer Germany

This is the final study report from the IMS Disease Analyzer Germany. Details of the statistical methods and relevant definitions used to generate Table B011.2.24 through Table B011.2.32 are described in the full analysis report (Attachment 3). The descriptive analyses for this report were conducted using the cumulative data from April 2009 to October 2011 in the database. The key findings and the summary texts are presented below.

2.8.1. Characteristics for Patients Treated with Prasugrel

In the October 2011 Germany IMS Disease Analyzer data update, 1474 patients with at least one prasugrel prescription were recorded. As shown in Table B011.2.24, the majority of the patients were male. Few patients had a history of TIA or stroke. The overall mean age was 60, with 9.2% of the patients over 75 years of age. Only 32.6% of the patients had body weight recorded in the database; of those, 10 (0.7%) were <60 kg in weight.

Table B011.2.24. Characteristics of All Prasugrel Treated Patients by History of TIA/Stroke, Age, and Body Weight IMS Disease Analyzer Germany

		Total patients		Males		Females	
TOTAL PATIENTS	**Row percentages based on Total patients**	**1474**	**100.0%**	**1141**	**77.4%**	**333**	**22.6%**
Prior TIA/Stroke - n %	Yes	27	1.8%	21	1.8%	6	1.8%
	No	1447	98.2%	1120	98.2%	327	98.2%
Age Group* - n %	0 - 17 years old		0.0%		0.0%		0.0%
	18 - 34 years old	8	0.5%	7	0.6%	1	0.3%
	35 - 44 years old	94	6.4%	78	6.8%	16	4.8%
	45 - 54 years old	362	24.6%	291	25.5%	71	21.3%
	55 - 64 years old	443	30.1%	358	31.4%	85	25.5%
	65 - 74 years old	431	29.2%	314	27.5%	117	35.1%
	75 - 84 years old	126	8.5%	88	7.7%	38	11.4%
	<75 years old	1338	90.8%	1048	91.8%	290	87.1%
	≥75 years old	136	9.2%	93	8.2%	43	12.9%
	≥85 years old	10	0.7%	5	0.4%	5	1.5%
	Unknown	0	0.0%	0	0.0%	0	0.0%
Age - Statistics	Mean (±SD) in years	60 (49.5, 71.3)		60 (49.0, 70.5)		63 (51.4, 73.9)	
	Median in years	60		60		64	
	Interquartile range in years (Q1, Q3)	(52.0, 69.0)		(51.0, 69.0)		(54.0, 71.0)	
Weight† - n %	<60 kg	10	0.7%	4	0.4%	6	1.8%
	≥60 kg	470	31.9%	369	32.3%	101	30.3%
	Unknown	994	67.4%	768	67.3%	226	67.9%
Weight† - Statistics	Mean (±SD) in kg	86 (70.2, 102.7)		89 (72.7, 104.8)		78 (64.2, 92.3)	
	Median in kg	85		86		76	
	Interquartile range in kg (Q1, Q3)	(75.5, 95.0)		(78.0, 96.0)		(68.0, 88.0)	

Abbreviations: SD = standard deviation; TIA = transient ischemic attack.
Note: Percentages are based on the corresponding column total.
* at first prasugrel
† where available
Source: Table 1; Attachment 3.

2.8.2. Diagnoses and Comorbidities

2.8.2.1. Diagnoses for Which Prasugrel was First Prescribed

The diagnoses for which prasugrel was first prescribed are displayed in Table B011.2.25 and Table B011.2.26. The data in Table B011.2.25 were generated using only diagnoses that were linked to the first prasugrel prescription. In Germany, the linked diagnoses are not required for health care providers to complete when writing a prescription. As a result, the linked diagnoses were missing in 50% of the patients; furthermore, some of the linked diagnoses are uninformative, such as "Harmful use-tobacco." Due to the large number of missing or uninformative linked diagnoses, additional analyses were conducted to search the database for a record of predefined ICD-10 codes of relevant coronary heart diseases (ACS, CHD, and previous MI) for each patient at the following time points: on the same date of the first prasugrel prescriptions or 30 days, 60 days, 90 days, and any time prior to the first prasugrel prescriptions (intermediate steps shown in Table 2, Attachment 3). The final analysis (Table B011.2.26) showed that 55% of the patients prescribed prasugrel had relevant diagnoses of heart diseases any time prior to the first prasugrel prescription; relevant coronary heart disease diagnoses were missing in 45% of patients.

Table B011.2.25. Diagnosis for Which Prasugrel Was First Prescribed IMS Disease Analyzer Germany

Original table using only diagnoses linked to prasugrel		Number of patients	% of total patients
TOTAL PATIENTS		**1474**	**100.0%**
I259	CHR ISCHAEM HRT DIS UNSP	157	10.7%
I251	ATHEROSCL HEART DIS	99	6.7%
Z955	CORO ANGIOPL IMPL/GRAFT	92	6.2%
I219	AC MYOCARD INFARCT UNSP	58	3.9%
I100	ESSENTIAL (PRIM) HYPERT	51	3.5%
I252	OLD MYOCARD INFARCT	49	3.3%
I210	AC TRANSMUR MI ANT WALL	24	1.6%
I211	AC TRANSMUR MI INF WALL	24	1.6%
E785	HYPERLIPIDAEMIA UNSP	14	0.9%
I209	ANGINA PECTORIS UNSP	12	0.8%
I480	ATRIAL FIBRILLAT/FLUTTER	8	0.5%
I509	HEART FAILURE UNSP	8	0.5%
Z951	AORTOCORO BYPASS GRAFT	8	0.5%
I200	UNSTABLE ANGINA	6	0.4%
I214	AC SUBENDOCARD MI	6	0.4%
M541	RADICULOPATHY	5	0.3%
I248	O/FORMS AC ISCH HRT DIS	4	0.3%
I249	AC ISCHAEM HRT DIS UNSP	4	0.3%
I340	MITRAL (VALVE) INSUFF	4	0.3%
I971	O/FUNC DIST AFT CARDSURG	4	0.3%
Z958	OTH CARD/VASC IMPL/GRAFT	4	0.3%
Z959	CARD/VAS IMP/GRFT UNP	4	0.3%
I119	HYPRTN HRT DIS WO HRT FL	3	0.2%
I212	AC TRANSMUR MI OTH SITES	3	0.2%
I258	O/FRM CHR ISCH HRT DIS	3	0.2%
I499	CARDIAC ARRHYTHMIA UNSP	3	0.2%
I739	PERIPH VASCULAR DIS UNSP	3	0.2%
Z090	F/U EXM PST SRG OTH CON	3	0.2%
E119	NIDDM WITHOUT COMP	2	0.1%
E149	UNSP D.MELL WO COMP	2	0.1%
E780	PURE HYPERCHOLESTEROLAEM	2	0.1%
F171	HARMFUL USE-TOBACCO	2	0.1%
I208	OTH FORMS ANGINA PECTOR	2	0.1%
I250	ATHEROSCL CARDIOVASC DIS	2	0.1%
I409	ACUTE MYOCARDITIS UNSP	2	0.1%
I749	EMBOL & THROMB UNSP ART	2	0.1%

(continued)

Table B011.2.25. Diagnosis for Which Prasugrel Was First Prescribed IMS Disease Analyzer Germany (continued)

I872	VEN INSUFF (CHR)(PERIPH)	2	0.1%
J449	CHR OBST PULM DIS UNSP	2	0.1%
K210	GAS/OES REF DIS+OESOPHAG	2	0.1%
M069	RHEUM ARTHRIT UNSP	2	0.1%
M796	PAIN IN LIMB	2	0.1%
T887	UNSP ADVER EFF DRG/MED	2	0.1%
Z018	OTH SPEC SPECIAL EXAMS	2	0.1%
Z921	P/H LNG TERM ANTICOAG	2	0.1%
Z950	CARDIAC PACEMAKER	2	0.1%
C730	CA OF THYROID GLAND	1	0.1%
D688	O/SPEC COAGULAT DEFECTS	1	0.1%
E139	OTH SPEC D.MELL WO COMP	1	0.1%
E788	OTH DIS LIPOPROT METAB	1	0.1%
E889	METABOLIC DISORDER UNSP	1	0.1%
F106	AMNESIC SYND-ALCOHOL	1	0.1%
F339	RECURR DEPRSV DIS UNSP	1	0.1%
F410	PANIC DIS	1	0.1%
F439	REACT TO SVRE STRES UNSP	1	0.1%
G459	TRANS CER ISCH ATTK UNSP	1	0.1%
I213	AC TRANSMUR MI UNSP SITE	1	0.1%
I255	ISCHAEMIC CARDIOMYOPATHY	1	0.1%
I420	DILATED CARDIOMYOPATHY	1	0.1%
I441	ATRIOVENT BLOCK SEC DEG	1	0.1%
I443	OTH/UNSP ATRIOVENTR BLCK	1	0.1%
I447	LT BUNDLE BRANCH BL UNSP	1	0.1%
I472	VENTRICULAR TACHYCARDIA	1	0.1%
I479	PAROXYS TACHYCARD UNSP	1	0.1%
I490	VENTRIC FIBRILLAT/FLUTT	1	0.1%
I501	LEFT VENTRICULAR FAILURE	1	0.1%
I701	ATHEROSCLEROSIS REN ART	1	0.1%
I702	ATHEROSCLER ART EXTREM	1	0.1%
I719	AORT ANEUR UNS ST N/RUPT	1	0.1%
I729	ANEURYSM OF UNSP SITE	1	0.1%
I978	O/POSTPROC DIS CIRC SYST	1	0.1%
J069	AC UPP RESP INFECT UNSP	1	0.1%
J158	OTHER BACT PNEUMONIA	1	0.1%
J208	AC BRONCH-O/SPEC ORGISMS	1	0.1%
J209	ACUTE BRONCHITIS UNSP	1	0.1%
J329	CHRONIC SINUSITIS UNSP	1	0.1%
K295	CHRONIC GASTRITIS UNSP	1	0.1%
K297	GASTRITIS UNSPECIFIED	1	0.1%
L309	DERMATITIS UNSPECIFIED	1	0.1%

(continued)

Table B011.2.25. Diagnosis for Which Prasugrel Was First Prescribed IMS Disease Analyzer Germany (concluded)

L400	PSORIASIS VULGARIS	1	0.1%
L409	PSORIASIS UNSPECIFIED	1	0.1%
M539	DORSOPATHY UNSPECIFIED	1	0.1%
M542	CERVICALGIA	1	0.1%
M754	IMPINGE SYND SHOULDER	1	0.1%
M766	ACHILLES TENDINITIS	1	0.1%
R570	CARDIOGENIC SHOCK	1	0.1%
R695	INCOMPLETE DIAGNOSIS	1	0.1%
T828	O/CMP CD/VSC PRSTH DVC	1	0.1%
Z251	NEED IMMUNOZ INFLUENZA	1	0.1%
Z298	OTH SPEC PROPHY MEASURE	1	0.1%
Z299	PROPHY MEASURE UNSP	1	0.1%
Diagnosis missing		**731**	**50%**

Source: Table 2, Attachment 3

Table B011.2.26. Relevant Coronary Heart Disease at Any Time Prior to Index Date IMS Disease Analyzer Germany

Step 6: Search all other diagnosis fields for acceptable diagnoses ever† in the database.		Number of patients	% of total patients
TOTAL PATIENTS		**1474**	**100.0%**
I259	CHR ISCHAEM HRT DIS UNSP	336	22.8%
I251	ATHEROSCL HEART DIS	165	11.2%
I219	AC MYOCARD INFARCT UNSP	93	6.3%
I252	OLD MYOCARD INFARCT	68	4.6%
I211	AC TRANSMUR MI INF WALL	40	2.7%
I210	AC TRANSMUR MI ANT WALL	36	2.4%
I209	ANGINA PECTORIS UNSP	33	2.2%
I208	OTH FORMS ANGINA PECTOR	9	0.6%
I214	AC SUBENDOCARD MI	9	0.6%
I200	UNSTABLE ANGINA	7	0.5%
I248	O/FORMS AC ISCH HRT DIS	5	0.3%
I212	AC TRANSMUR MI OTH SITES	4	0.3%
I249	AC ISCHAEM HRT DIS UNSP	4	0.3%
I258	O/FRM CHR ISCH HRT DIS	3	0.2%
I213	AC TRANSMUR MI UNSP SITE	2	0.1%
I250	ATHEROSCL CARDIOVASC DIS	2	0.1%
I255	ISCHAEMIC CARDIOMYOPATHY	1	0.1%
Diagnosis missing		**657**	**45%**

† For timescale between most recent acceptable diagnosis and prasugrel rx, see Attachment 3.
Source: Table 2, Step 6, Attachment 3

2.8.2.2. Relevant Comorbidities

For a better understanding of the comorbidities of prasugrel patients, Table B011.2.27 shows the prevalence of relevant conditions that were recorded in the database within the 12 months prior to or on the index date in patients treated with prasugrel. Of note, 84.9% of the patients had a history of hyperlipidemia, 64.5% CHD, 52.7% hypertensive diseases, 25.3% ACS, and 22.3% diabetes. The ICD-10 codes used to define the conditions are presented in Attachment 3.

Table B011.2.27. Relevant Comorbidities in Patients Treated with Prasugrel IMS Disease Analyzer Germany

ICD-10 codes		
	Number of patients	% of total patients
TOTAL PATIENTS	**1474**	**100.0%**
Hyperlipidemia	1251	84.9%
Coronary heart disease	951	64.5%
Hypertensive diseases	777	52.7%
ACS - Acute coronary syndrome	373	25.3%
Diabetes	328	22.3%
Previous myocardial infarction	290	19.7%
Heart failure	130	8.8%
Atrial fibrillation and flutter	79	5.4%
Peripheral artery disease	69	4.7%
Peptic ulcer	39	2.6%
Renal disease	19	1.3%

Note: A comorbidity is defined as any diagnosis recorded in the 12 months prior to or on the index date (date of the first recorded prasugrel prescription). ICD-10 code groupings were defined by Lilly. For full list of relevant comorbidities, see Appendix 4 of the full analysis report (Attachment 3).

Source: Table 3b, Attachment 3

2.8.3. Concomitant Medications

2.8.3.1. Concomitant Medications by Drug Class

Table B011.2.28 lists the most common concomitant medications by drug class in prasugrel-treated patients. Concomitant medications are defined as medication prescribed 30 days before or after the date of the first prasugrel prescription. As would be expected for this patient population, the most commonly prescribed concomitant medications included anti-platelet agents, lipid-lowering agents, anti-hypertensive agents, diuretics, nitrates, and anti-diabetic agents. Of note, anti-ulcerants, which include PPIs, were prescribed in 27.2% of the patients treated with prasugrel. Heparins were used in 3.2% of the patients. The full list of concomitant medications by class is presented in Attachment 3.

Table B011.2.28. Concomitant Medications by Drug Class in Patients Treated with Prasugrel

		Number of patients	% of total patients
TOTAL PATIENTS		**1474**	**100.0%**
ATC3 code	ATC3 text		
B01C	PLATELET AGGREG INHIBITRS	1474	100.0%
C10A	CHOLEST&TRIGLY.REGULATOR	882	59.8%
C07A	BETA BLOCKING AGENT PLAIN	871	59.1%
C09A	ACE INHIBITORS PLAIN	710	48.2%
A02B	ANTIULCERANTS	401	27.2%
C03A	DIURETICS	309	21.0%
C01E	NITRITES AND NITRATES	182	12.3%
C08A	CALCIUM ANTAGONISTS PLAIN	137	9.3%
C09C	ANGIOTENSN-II ANTAG,PLAIN	105	7.1%
N02B	NON-NARCOTIC ANALGESICS	100	6.8%
A10J	BIGUANIDE ANTIDIABETICS	97	6.6%
C09B	ACE INHIBITORS COMBINAT	92	6.2%
M01A	ANTIRHEUMATIC NON-STEROID	81	5.5%
C09D	ANGIOTENSIN-II ANTAG,COMB	68	4.6%
T02D	DIABETES TESTS	67	4.5%
H03A	THYROID PREPARATIONS	65	4.4%
N06A	ANTIDEPRESS.& MOOD STAB.	63	4.3%
A10C	HUMAN INSULIN+ANALOGUES	60	4.1%
C01D	CORON THER EX CA/ANT/NIT	58	3.9%
C10C	LIP.REG.CO.W.OTH.LIP.REG	57	3.9%
M04A	ANTI-GOUT PREPARATIONS	52	3.5%
B01B	HEPARINS	47	3.2%
N05B	HYPNOTICS & SEDATIVES	37	2.5%
N03A	ANTI-EPILEPTICS	34	2.3%
C02A	ANTIHYPERTENS(NON HERB)PL	33	2.2%

Source: Table 4a, Attachment 3

2.8.3.2. Concomitant Medications by Specific Generic Drugs

Table B011.2.29 (Table 4b, Attachment 3) lists the most common concomitant medications by generic names in prasugrel-treated patients. Concomitant medicationswere defined as medication prescribed 30 days before or after the date of the first prasugrel prescription. Although the indication for prasugrel is that it be taken with aspirin, concomitant aspirin use was recorded for only 55.8% of the patients. This may be because patients took aspirin as an over-the-counter medication, so its use was not recorded as a prescription in the database. Clopidogrel was prescribed as a concomitant medication in 5.7% of the prasugrel-treated patients, which may be due to switching from one drug to another. The full list of concomitant medications by generic names is presented in Attachment 3.

Table B011.2.29. Concomitant Medications by Specific Generic Drugs in Patients Treated with Prasugrel IMS Disease Analyzer Germany

	Number of patients	% of total patients
TOTAL PATIENTS	**1474**	**100.0%**
ACETYLSALICYLIC ACID	822	55.8%
SIMVASTATIN	774	52.5%
RAMIPRIL	631	42.8%
METOPROLOL	446	30.3%
BISOPROLOL	372	25.2%
PANTOPRAZOLE	281	19.1%
TORASEMIDE	141	9.6%
NITROGLYCERIN	102	6.9%
METFORMIN	97	6.6%
AMLODIPINE	95	6.4%
EPLERENONE	85	5.8%
CLOPIDOGREL	84	5.7%
HYDROCHLOROTHIAZIDE + RAMIPRIL	77	5.2%
OMEPRAZOLE	68	4.6%
PENTAERYTHRITYL TETRANITRATE	68	4.6%
GLUCOSE, BLOOD TESTS	65	4.4%
HYDROCHLOROTHIAZIDE	57	3.9%
LEVOTHYROXINE SODIUM	57	3.9%
SIMVASTATIN + EZETIMIBE	57	3.9%
METAMIZOLE SODIUM	56	3.8%
CANDESARTAN CILEXETIL	53	3.6%
RANITIDINE	53	3.6%
ALLOPURINOL	50	3.4%
SPIRONOLACTONE	46	3.1%
DICLOFENAC	42	2.8%

Source: Table 4b, Attachment 3

2.8.4. Characteristics of Initial Daily Dose

2.8.4.1. Patient and Dose Characteristics

Table B011.2.30 describes the initial daily dose by history of TIA/stroke, age groups, and body weight strata. The analyses were performed in two ways: 1) based on the daily dose prescribed on the date of the first prasugrel script, and 2) assuming that the dosage instruction was once daily in cases where the daily dosing instructions were missing. The full analyses using both methods are attached in Attachment 3. Only the results based on the assumption of daily dose are presented below (Table B011.2.30 and Table B011.2.31, from Table 5b, Attachment 3).

Most of the patients received an initial prescribed maintenance dose of 10 mg. Few patients had a history of TIA/stroke or were very elderly (≥75 years of age). Many of the very elderly patients were prescribed the 10-mg MD. Among the patients with body weight recorded in the database, most were ≥60kg. All 10 of the patients with body weight <60 kg were prescribed the 10-mg MD.

Table B011.2.31 presents characteristics of the 136 patients aged ≥75 years. Only 26 of these patients had body weight information and 25 were <60 kg. The percentage of very elderly patients with a history of diabetes or MI was lower in the 5-mg MD group than in the 10-mg MD group.

In Germany, the data collected in the IMS database was largely from internists but also includes data collected from cardiologists.

Table B011.2.30. Characteristics by Initial Daily Dose - Dosage Assumed to be Once Daily IMS Disease Analyzer Germany

		TOTAL PATIENTS		Initial dose 5mg		Initial dose 10mg	
		Number of patients	% of TOTAL PATIENTS	Number of patients	% of row totals (with 95% CI)	Number of patients	% of row totals (with 95% CI)
TOTAL PATIENTS		**1474**	**100.0%**	**93**	**6.3% (5.1, 7.7)**	**1381**	**93.7% (92.3, 94.9)**
History of TIA/Stroke	Yes	27	1.8%	4	14.8% (4.2, 33.7)	23	85.2% (66.3, 95.8)
	No	1447	98.2%	89	6.2% (5.0, 7.5)	1358	93.9% (92.5, 95.0)
Age Group*	<75 years old	1338	90.8%	53	4.0% (3.0, 5.2)	1285	96.0% (94.9, 97.0)
	≥75 years old	136	9.2%	40	29.4% (21.9, 37.8)	96	70.6% (62.2, 78.1)
Weight†	<60 kg	10	0.7%	0		10	100% (69.2, 100)
	≥60 kg	470	31.9%	33	7.0% (4.9, 9.7)	437	93.0% (90.3, 95.1)
	Unknown	994	67.4%	60	6.0% (4.6, 7.7)	934	94.0% (92.3, 95.4)
Weight - Statistics	Mean (+/- SD) in kg	86 (70.2, 102.7)		83 (68.6, 98.3)		87 (70.4, 103.0)	
	Median in kg	85		80		85	

Abbreviations: CI = confidence interval; SD = standard deviation; TIA = transient ischemic attack.
Source: Table 5b, Attachment 3

Table B011.2.31. Breakdown of Patients ≥75 years - Dosage Assumed to be Once Daily IMS Disease Analyzer Germany

		TOTAL PATIENTS		Initial dose 5mg		Initial dose 10mg	
		Number of patients	% of TOTAL PATIENTS	Number of patients	% of row totals	Number of patients	% of row totals
TOTAL PATIENTS ≥ 75 YEARS		**136**	**100.0%**	**40**	**29.4% (21.9, 37.8)**	**96**	**70.6% (62.2, 78.1)**
History of Diabetes	Yes	47	34.6%	12	25.5% (13.9, 40.4)	35	74.5% (59.7, 86.1)
	No	89	65.4%	28	31.5% (22.0, 42.2)	61	68.5% (57.8, 78.0)
History of MI	Yes	13	9.6%	4	30.8% (9.1, 61.4)	9	69.2% (38.6, 90.9)
	No	123	90.4%	36	29.3% (21.4, 38.2)	87	70.7% (61.9, 78.6)
Prasugrel prescribed by	Internists/GPs		0.0%				
	Gastroenterologist	42	30.9%	18	42.9% (27.7, 59.0)	24	57.1% (41.0, 72.3)
	Cardiologist	94	69.1%	22	23.4% (15.3, 33.3)	72	76.6% (66.7, 84.7)
	Pneumologist	108	79.4%	35	32.4% (23.7, 42.1)	73	67.6% (57.9, 76.3)
	Psychiatrist	1	0.7%			1	100% (2.5, 100)
Weight†	<60 kg	25	18.4%	4	16.0% (4.5, 36.1)	21	84.0% (63.9, 95.5)
	≥60 kg	1	0.7%	-		1	100% (2.5, 100)
	Unknown	1	0.7%	1	100% (2.5, 100)		
Weight - Statistics	Mean (+/- SD) in kg	79 (68.7, 90.0)		76 (68.8, 83.7)		82 (69.5, 93.8)	
	Median in kg	80		80		80	

Note: For Total Patients, an additional column showing percentages based on the total number of patients is displayed. All other percentages and confidence intervals are based on the corresponding row total. Where daily dose was missing, the dosage instruction was assumed to be once daily and the strength in mg was used to populate the field.

* at first prasugrel.

† where available.

Source: Table 5b, Attachment 3

2.8.4.2. Switching from Other Thienopyridines

Table B011.2.32 summarizes the switching to prasugrel from another thienopyridine that occurred at the first prasugrel prescription. Most of the patients were newly prescribed to prasugrel only. Seven patients received prasugrel and clopidogrel prescriptions on the same date. Approximately 21% of the patients switched from clopidogrel to prasugrel but very few switched from ticlopidine to prasugrel.

Table B011.2.32. Patients New to Prasugrel: New Versus Switched from Other Thienopyridine
IMS Disease Analyzer Germany

	Number of patients	% of total patients
TOTAL PATIENTS	**1474**	**100.0%**
Total number of new patients	1157	78.5%
- New with prasugrel only	1150	78.0%
- New with prasugrel plus ticlopidine (same day coprescription)	0	0.0%
- New with prasugrel plus clopidogrel (same day coprescription)	7	0.5%
Total number of patients who switched from other thienopyridine*	317	21.5%
- Switch from ticlopidine	11	0.7%
- Switch from clopidogrel	309	21.0%

Note: A switch is defined as any patient who has ever had a prescription for clopidogrel, ticlopidine or both recorded in the database prior to initiation of prasugrel.

*Note that it is possible for patients to have been previously prescribed both clopidogrel and ticlopidine, so double counting may occur.

Source: Table 6, Attachment 3

2.8.5. Prasugrel Maintenance Dose Usage over Time

Table 7 in Attachment 3 describes the usage of the 5-mg and 10-mg maintenance doses over a 12-month period, broken down by 3-month intervals and by history of TIA/stroke, age groups, and body weight. The majority of the patients stayed on the initial prescribed dose through the first 3 months after the first prasugrel prescription. The percentage of the patients receiving a prasugrel prescription decreased over each successive 3-month period. Overall, less than 20% of patients on the 5-mg dose had a prasugrel prescription at the end of 12 months. The mean duration from first prasugrel prescription to first therapy interruption or discontinuation was longer for patients receiving an initial 5-mg daily dose than for patients receiving an initial 10-mg daily dose.

Approximately 12.9% of the patients who started with the 5-mg MD switched to the 10-mg MD over the 12-month period. However, very few patients starting with a 10-mg daily dose switched to 5-mg at the end of each time interval.

2.8.6. Medication Possession Ratio for Prasugrel

Table 8 in Attachment 3 presents the persistence of prasugrel treatment over 6-month and 12-month intervals using the MPR. The MPR reflects the amount of time an individual remains on chronic drug therapy. An MPR of 80% is considered a reasonable threshold for persistence. Overall, the MPR was 68.6% in patients with at least 6-month follow up after the first prasugrel prescription, and 58.8% in patients with at least 12-month follow up, suggesting a lack of persistence of prasugrel treatment over the period of 6 months or 12 months.

2.9. Summary and Conclusions

2.9.1. Study Rationale

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 their assessment of the prasugrel Risk Management Plan (RMP), the Committee for Medicinal Products for Human Use (CHMP) had the following specific request for post-marketing observational studies: "The applicant is asked to present proposals to measure off-label use using drug utilisation methods." Study B011 was a post-marketing observational study designed to describe real-world treatment patterns of prasugrel in outpatient practices in France and Germany using the IMS Disease Analyzer and in the United Kingdom (UK) using the IMS Disease Analyzer and the Clinical Practice Research Datalink (CPRD), from launch to 3 years postlaunch.

The objectives of Study B011 were to provide descriptive statistics for the contraindication of a history of TIA or stroke, as well as for maintenance doses by age (<75 years and ≥75 years) and body weight (≥60 kg and <60 kg). Additional objectives were to provide data describing indications for prasugrel prescriptions, co-prescriptions, patterns of drug usage including duration, and patient characteristics including medical history.

2.9.2. Limitations of Study

- As outpatient physicians receive information related to diagnoses from in-hospital physicians, outpatient physicians may not always receive complete information regarding diagnoses related to treatment of relevant coronary heart disease. If patients received prasugrel prescriptions outside the IMS Disease Analyzer or CPRD network of physicians, those prescriptions were not captured by the 2 databases.
- The presence of a prescription record for a filled prescription does not indicate that the medication was consumed or that it was taken as prescribed.
- Over-the-counter drugs (for example, aspirin) were not captured by the IMS Disease Analyzer or CPRD.
- The presence or absence of a diagnosis code in the database does not necessarily indicate the presence or absence of the disease.
- In France and Germany, patients may receive prescriptions from both office-based cardiologists and GPs. If the prescriptions from the cardiologists outside the network were not recorded in the database, the estimates of study duration, discontinuation, and switching would be biased. Furthermore, if patients visited both a GP and a cardiologist within the network, a patient's medical history could have been counted twice.
- If the diagnoses were not recorded by the GPs during the consultation, the prevalence of comorbidity and disease history would be underestimated.
- Due to the limitations of the databases, it was not possible to study the contraindications of active pathological bleeding and severe hepatic impairment.
- Body weight values were missing in the majority of patients in databases from France and Germany.
- There were assumptions that all doses were daily because of incomplete information on the initial daily doses. It is possible that physicians could have prescribed a 5-mg dose of prasugrel by suggesting use of ½ of a 10-mg tablet or by taking a 10-mg tablet every other day.

2.9.3. Discussion

According to data from the IMS Disease Analyzer in France and Germany and both the IMS Disease Analyzer and the CPRD in the UK, the number of patients who had at least 1 prescription record of prasugrel from outpatient practices was 1052 in France from January 2010 to October 2012, 1580 in the UK from July 2009 to October 2012, and 1474 from April 2009 to October 2011 in Germany.

In all 3 countries, the majority of patients were male, and few had a history of TIA/stroke, were ≥75 years of age, or had body weight <60 kg. In patients ≥75 years of age, for whom the use of prasugrel is generally not recommended, few were treated with prasugrel. In France, the majority of patients were prescribed an initial 10-mg daily dose, including those ≥75 years of age (of note, the 5-mg dose is not marketed in France). In the UK 45% and in Germany 29% of those aged ≥75 years were prescribed the 5-mg MD. For patients with recorded body weight in the UK and Germany, patients ≥75 years of age treated with the 10-mg tablet had a higher mean body weight than those prescribed a 5-mg dose. In France, mean weight was higher for those

≥75 years of age who received a 5-mg versus a 10-mg dose; however, there were only 2 patients who were ≥75 years who received the 5-mg dose.

In patients for whom body weight was recorded in a database, few with body weight <60 kg were treated with prasugrel. In France and Germany, no prasugrel-treated patients with a recorded body weight <60 kg received the recommended 5-mg dose as specified in the SPC; however, the number of patients with a recorded body weight <60 kg was very low in both countries (2.4% [25/1052] and 0.7% [10/1474], respectively). In the UK where the majority of the patients had body weight recorded in the database, 5.4% (86/1580) had a body weight <60 kg, of whom 29.1% (25/86) were prescribed the 5-mg dose.

These findings are consistent with initial data from a recently concluded observational, in-hospital registry study from the German Arbeitsgemeinschaft Leitende Kardiologische Krankenhausärzte-Percutaneuous Coronary Intervention (ALKK-PCI) registry in which ACS PCI patients in high-risk categories were less likely to be treated with prasugrel than clopidogrel (≥75 years: 6.0% versus 38.8%; <60 kg: 2.4% versus 5.8%). In the ALKK-PCI registry, 76.6% of patients ≥75 received a 10-mg dose, 13.3% received a 5-mg dose and 8.2% did not receive an MD. In patients who weighed <60 kg, 94.3% received a 10-mg dose, 0.3% received a 5-mg dose and 5.0% did not receive an MD. The final ALKK study report is in progress.

Of all patients with prasugrel prescriptions in France and Germany, over 50% had relevant coronary heart disease diagnoses; whereas 94% of patients in the UK had relevant coronary heart disease diagnoses. Of prasugrel-treated patients with known diagnoses, the majority had diagnoses consistent with acute CHD (including ACS) in outpatient settings in France, the UK, and Germany.

As expected in this patient population, relevant comorbidities occurring within 12 months prior to or on the date of the first prasugrel prescription with a prevalence of at least 20% of prasugrel-treated patients in all 3 countries included CHD, ACS, and hypertension. Also as expected, the most commonly prescribed concomitant medications in all 3 countries included platelet inhibitors, lipid-lowering agents, beta blockers and ACE inhibitors. Of note, anti-ulcerants, which include PPIs and H2 blockers, were prescribed in 55.1% of prasugrel-treated patients in France, 45.5% of those in the UK, and 27.2% of those in Germany.

In Germany, the data collected in the IMS database was largely from internists but also included data collected from cardiologists. Based on these data, similar prescribing practices were observed in both groups of physicians. However, treatment patterns varied across the countries.

The MPR reflects the amount of time an individual remains on chronic drug therapy. An MPR of 80% is considered a reasonable threshold for persistence. In France, the UK, and Germany, the MPRs suggested a lack of persistence of prasugrel treatment over the period of 6 months or 12 months.

2.9.4. Summary

Patient Characteristics

- The majority of patients did not have a history of TIA/stroke, were <75 years of age, and had a body weight ≥60 kg in France, the UK, and Germany, respectively:
    - No history of TIA/stroke: 99.8%, 96.0%, and 98.2%
    - <75 years of age: 94.3%, 89.7%, and 90.8%
    - Percentage of patients with known body weight who weighed ≥60 kg: 95.0%, 94.3%, and 94.3%.

- In prasugrel-treated patients with a known diagnosis linked to a prasugrel prescription, the majority were consistent with acute CHD, including ACS, in all 3 countries.

- The most prevalent comorbidities (≥20%) in each country included:
    - France: hyperlipidemia = 97.1%; CHD = 52.3%; ACS = 30.4%, hypertensive diseases = 24.9%, diabetes = 23.8%, and previous MI = 23.7%
    - UK: CHD = 94.2%, ACS = 85.9%, previous MI = 79.6%, hypertensive diseases = 35.3%
    - Germany: hyperlipidemia = 84.9%, CHD = 64.5%, hypertension = 52.7%, ACS = 25.3%, diabetes = 22.3%.

- As expected, the most commonly prescribed concomitant medications in all 3 countries included platelet inhibitors, lipid-lowering agents, beta blockers, and ACE inhibitors.
    - Of note, anti-ulcerants, including PPIs and H2 blockers, were prescribed in 55.1% of prausgrel-treated patients in France, 45.5% of those in the UK, and 27.2% of those in Germany.

Patterns of Drug Usage

- The majority of prasugrel prescriptions in France (99.8%), the UK (91.4%) and Germany (93.7%) were for the 10-mg dose. Of note, the 5-mg dose is not marketed in France.
- The percentage of prasugrel-treated patients who switched from another thienopyridine (primarily clopidogrel) to prasugrel was 13.7% in France, 23.2% in the UK, and 21.5% in Germany.
- The MPR reflects the amount of time an individual remains on chronic drug therapy. An MPR of 80% is considered a reasonable threshold for persistence. The following MPRs suggested a lack of persistence of prasugrel treatment over the period of 6 months or 12 months in France, the UK, and Germany, respectively:
    - 6-month follow-up: 60.7%, 75.5%, and 68.6%, respectively
    - 12-month follow-up: 63.2%, 76.9%, and 58.8%, respectively.

Prasugrel Contraindication of Prior Stroke/TIA

Very few patients with the prasugrel contraindication of prior TIA or stroke are being treated with prasugrel (0.2% in France, 4.0% in the UK, and 1.8% in Germany).

Body Weight <60 kg

Of the patients with known body weight, few patients with body weight <60 kg are being treated with prasugrel.

- France
  - Of 1052 total patients, body weight was unknown for the majority (n=555; 52.8%)
  - A total of 25 patients (2.4%) had a recorded body weight <60 kg
  - No patients (0/25) with a recorded body weight <60 kg were prescribed a 5-mg dose
- United Kingdom
  - Of 1580 total patients, body weight was unknown for only 75 patients (4.7%)
  - A total of 86 patients (5.4%) had a recorded body weight of <60 kg.
  - 29.1% (25/86) of those with a recorded body weight <60 kg were prescribed a 5-mg dose
- Germany
  - Of 1474 total patients, body weight was unknown for the majority (n=994; 67.4%)
  - A total of 10 patients (0.7%) had a recorded body weight <60 kg
  - No patients with recorded body weight <60 kg were prescribed a 5-mg dose

Age ≥75 Years

Few patients ≥75 years of age, for whom the use of prasugrel is generally not recommended, are being treated with prasugrel.

- France
  - 5.4% (57/1052) of patients treated with prasugrel were ≥75 years of age.
  - The majority of patients in France were treated with a 10-mg dose, including those ≥75 years of whom 3.5% (2/57) were prescribed a 5-mg dose. (As noted, the 5-mg prasugrel tablet is not marketed in France.)
- United Kingdom
  - 10.3% (163/1580) of patients treated with prasugrel were ≥75 years of age.
  - 44.8% (73/163) of those ≥75 years receiving prasugrel were treated with a 5-mg dose.
- Germany

- 9.2% (136/1474) of patients treated with prasugrel were ≥75 years of age.
- 29.4% (40/136) of those ≥75 years receiving prasugrel were treated with a 5-mg dose.

Where body weight was available, patients ≥75 years of age treated with the 10-mg tablet had a higher mean body weight than those prescribed a 5-mg dose.

- France
  - As only 2 of 57 very elderly patients were treated with a 5-mg dose, and weight was unknown for 1 of the 2 patients, this data is not meaningful.
- United Kingdom
  - Of patients ≥75 years, mean body weight was 78 kg for those receiving a 10-mg dose and was 69 kg for those receiving a 5-mg dose; body weight was unknown for only 3 of 163 patients.
- Germany
  - Of patients ≥75 years, mean body weight was 82 kg for those receiving a 10-mg dose and was 76 kg for those receiving a 5-mg dose; body weight was unknown for only 1 of 136 patients.

2.9.5. Conclusion

Based on data describing patients who had at least 1 prasugrel prescription record in France from January 2010 to October 2012, in Germany from April 2009 to October 2011 using the IMS Disease Analyzer, and in the UK from July 2009 to October 2012 using the IMS Disease Analyzer and the CPRD, the majority of prasugrel prescriptions were for patients <75 years of age and ≥60 kg. This is consistent with data observed in the ALKK-PCI registry in which patients ≥75 years and patients <60 kg were less likely to receive prasugrel than clopidogrel. It is also notable that very few patients with the prasugrel contraindication of prior TIA or stroke were treated with prasugrel. When prasugrel is used in the very elderly or lower body weight populations, it appears that the 10-mg dose is being prescribed. Overall, however, the low percentages of prasugrel prescriptions recorded for patients ≥75 years of age, <60 kg, or prior TIA or stroke, may indicate that guidance from the SPC is being considered by prescribing physicians.

2.10. Reference

Wiviott SD, Braunwald E, McCabe CH, Montalescot G, Ruzyllo W, Gottlieb S, Neumann FJ, Ardissino D, De SS, Murphy SA, Riesmeyer J, Weerakkody G, Gibson CM, Antman EM; TRITON-TIMI 38. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *New Engl J Me*d. 2007b;357(20):2001-2015.