Clopidogrel, prasugrel and ticagrelor for acute coronary syndrome[1]

EXTRACT

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Clopidogrel, Prasugrel, Ticagrelor, Acute Coronary Syndrome, Benefit Assessment, Systematic Review

Key statement

Research question

The objective of this investigation is to

comparatively assess the benefit of clopidogrel, prasugrel, and ticagrelor, each in combination with acetylsalicylic acid (ASA),

in the therapeutic indication of prasugrel-containing drugs, i.e. for the prevention of atherothrombotic events in adult patients with acute coronary syndrome (ACS) undergoing primary or delayed percutaneous coronary intervention (PCI) with regard to patient-relevant outcomes.

Conclusion

Because the manufacturer failed to submit the requested data on subpopulations of the TRITON-TIMI 38 and H7T-MC-TACE studies, the data pool for the comparison of prasugrel versus clopidogrel, each in combination with ASA, is incomplete for both patients with ST-segment elevation myocardial infarction (STEMI) + PCI and patients with non-ST-segment elevation myocardial infarction (NSTEMI)/unstable angina (UA) + PCI.

The 2 studies TRITON-TIMI 38 and H7T-MC-TACE represent the only identified evidence for the comparison of prasugrel versus clopidogrel, each in combination with ASA. A substantial part of the data is missing for both prasugrel and clopidogrel, particularly due to the lack of suitable data from the very large TRITON-TIMI 38 study. The analysis of the limited available data thus does not represent a valid basis for decision-making by the Federal Joint Committee (G-BA). From an exploratory examination of the available results, no clear advantage can be identified for any of the drugs of clopidogrel, prasugrel, or ticagrelor

Overall, no proof, indication, or hint of greater or lesser benefit or harm compared to the other drugs has been derived for the drugs of clopidogrel, ticagrelor, or prasugrel, each in combination with ASA.

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List of abbreviations

Abbreviation	Meaning
ACS	acute coronary syndrome
AP	angina pectoris
ASA	acetylsalicylic acid
CHD	coronary heart disease
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HR	hazard ratio
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
NMA	network metaanalysis
NSTE-ACS	acute coronary syndrome without ST-elevation
NSTEMI	non-ST-segment elevation myocardial infarction
PCI	percutaneous coronary intervention
RCT	randomized controlled trial
SPC	Summary of Product Characteristics
SR	systematic review
STEMI	ST-segment elevation myocardial infarction
TIA	transient ischaemic attack
UA	unstable angina
UFH	unfractionated heparin

1 Background

Coronary heart disease (CHD) is a permanent narrowing of the coronary arteries. It is a clinically relevant manifestation of atherosclerosis of the coronary vessels. The narrowing of the coronary vessels leads to a chronic undersupply of the myocardium, which results in an imbalance between oxygen demand and oxygen supply in the heart muscle. CHD usually manifests as chronic stable angina pectoris (AP), which can be triggered by physical or mental stress or other stimuli (e.g. cold) and manifests as paroxysmal retrosternal or thoracic pain. The pain is reproducible and disappears within a few minutes at rest or after administration of nitroglycerin. However, the overall clinical picture of chronic CHD is variable, ranging from asymptomatic (silent) courses to exercise-dependent stable AP [1,2].

Acute, immediately life-threatening episodes of CHD are distinguished from chronic forms of CHD and summarized under the term acute coronary syndrome (ACS). ACS represents crisis-onset myocardial ischaemia triggered by sudden atherothrombotic processes resulting from plaque rupture or erosion. Clinically, it takes the form of sudden cardiac death, acute myocardial infarction, or unstable AP. Due to different therapeutic concepts, acute myocardial infarction is categorized into non-ST-segment elevation myocardial infarction (NSTEMI) and ST-segment elevation myocardial infarction (STEMI) depending on the findings in the electrocardiogram (ECG). Common to both is an elevation in certain cardiac enzyme levels (e.g. troponin), which is, by definition, absent in unstable AP. Some sources also combine NSTEMI and unstable AP as ACS without ST-segment elevation (NSTE-ACS) [1,3-6].

Treatment for diagnosed STEMI consists of reperfusion of the infarcted vessel as soon as possible by primary percutaneous coronary intervention (PCI), usually in the form of angioplasty with stent implantation. If primary PCI is not feasible within 2 hours of STEMI diagnosis in patients with symptoms of ischemia of ≤ 12 hours duration, reperfusion should be achieved via fibrinolytic therapy followed by PCI unless contraindicated [7-9]. Regardless of the reperfusion strategy, the acute administration of acetylsalicylic acid (ASA) with an initial dose of 150 to 300 mg (orally) and a maintenance dose of 75 to 100 mg is an established treatment strategy. However, depending on the reperfusion strategy, the type and start of further supportive antithrombotic pretreatment or concomitant therapy (e.g. unfractionated heparin [UFH], enoxaparin, $P2Y_{12}$ inhibitors) differ.

Antithrombotic therapy is also mandatory in patients diagnosed with NSTE-ACS. In the choice and duration of treatment, both ischaemic and haemorrhagic complications must be taken into account equally, as they considerably influence the outcome of treatment [4,6]. As with STEMI, the standard therapy for patients with NSTE-ACS is immediate ASA administration [4,6,10]. In contrast to STEMI treatment, however, prompt PCI after diagnosis is not recommended as a standard procedure, but is recommended only for patients at very high or high risk of death or myocardial infarction (determined, e.g. by the Global Registry of Acute

Coronary Events [GRACE] risk score), within 2 hours (very high risk) or 24 hours (high risk). Patients usually receive additional parenteral anticoagulation with UFH. Routine pretreatment with a $P2Y_{12}$ inhibitor is not recommended in patients with NSTE-ACS (especially if the coronary anatomy is unknown and early invasive treatment is planned), but this treatment may be taken into consideration, e.g. in case of delayed PCI, provided the patient is not at increased risk of bleeding [4,6].

In general, all guidelines recommend up to 12 months of dual antiplatelet therapy (DAPT) consisting of an oral $P2Y_{12}$ inhibitor in addition to ASA as standard therapy for patients with ACS after PCI [4,6-11]. Ticagrelor is approved in combination with ASA for the treatment of patients with ACS (NSTE-ACS / STEMI), regardless of whether the patients are treated pharmacologically or have undergone PCI [12]. In combination with ASA, clopidogrel is approved for patients with pharmacologically treated ACS (NSTE-ACS / STEMI) as well as NSTE-ACS following PCI [13]. Prasugrel in combination with ASA is approved only for patients with ACS (NSTE-ACS / STEMI) following PCI [14].

The benefits and harms of clopidogrel, prasugrel, and ticagrelor, each in combination with ASA (hereafter + ASA), in patients with ACS have already been investigated in several assessments by the Institute for Quality and Efficiency in Health Care (IQWiG) [15-18].

For patients with NSTE-ACS, the overall evidence showed proof of benefit of clopidogrel + ASA in comparison with ASA monotherapy for a treatment period of up to 12 months. This was based, among other things, on an advantage in the myocardial infarction rate. This was offset by a disadvantage of clopidogrel + ASA in terms of increased bleeding complications. Studies where patients received primary PCI treatment were not found in the assessment [15]. The comparison of prasugrel + ASA versus clopidogrel + ASA showed an indication of added benefit of the former for patients with NSTE-ACS, including regarding nonfatal stroke (only in patients without pre-existing vascular disease) and nonfatal myocardial infarction. This is offset by an indication of greater harm of prasugrel + ASA due to more frequent major bleeding and a hint of greater harm due to more frequent neoplasia [16,17]. When comparing ticagrelor versus clopidogrel, both + ASA, there was overall proof of considerable added benefit of ticagrelor + ASA versus clopidogrel + ASA in patients with NSTE-ACS. This was based on benefits concerning all-cause mortality, cardiovascular mortality, and the number of myocardial infarctions. No greater or lesser harm was found [18].

For patients with STEMI following primary PCI, no studies comparing the drug combination (clopidogrel, prasugrel, or ticagrelor, each + ASA) with ASA monotherapy were found in any of the 3 assessments [15-18]. Accordingly, clopidogrel + ASA is not approved for the treatment of patients with STEMI following primary PCI [13]. In the comparison of ticagrelor + ASA versus prasugrel + ASA, an indirect comparison via the common comparator of clopidogrel + ASA for patients with STEMI following primary PCI showed no hint of added benefit [18].

Overall, especially in the therapeutic indication of prasugrel, i.e. in ACS following primary or delayed PCI, no conclusions can be drawn as to which $P2Y_{12}$ inhibitor (in combination with ASA) should primarily be used for the treatment of these patients. The present assessment therefore concerns the comparative benefit assessment of clopidogrel, prasugrel, and ticagrelor in the therapeutic indication of prasugrel.

2 Research question

The objective of this investigation is to

- comparatively assess the benefit of clopidogrel, prasugrel, and ticagrelor, each in combination with ASA,

in the therapeutic indication of prasugrel-containing drugs, i.e. for the prevention of atherothrombotic events in adult patients with acute coronary syndrome (ACS) undergoing primary or delayed percutaneous coronary intervention (PCI) with regard to patient-relevant outcomes.

3 Methods

The target population of the benefit assessment consists of patients with ACS (i.e. unstable angina pectoris, NSTEMI, or STEMI) undergoing primary or delayed PCI. For the treatment of ACS, the drugs clopidogrel, prasugrel, and ticagrelor, each in combination with ASA, were to be compared with each other and thus acted as both experimental and comparator interventions. The experimental and comparator interventions used in the studies had to be administered within the scope of the approval status valid for Germany [12-14,19].

The following patient-relevant outcomes were taken into account in the assessment:

- Mortality
  - all-cause mortality
- Morbidity
  - cardiovascular morbidity
  - cerebrovascular morbidity
  - vascular non-cardiovascular and non-cerebrovascular morbidity
- Health-related quality of life
- Side effects
  - severe adverse events (SAEs)
  - discontinuation due to adverse events (AEs)
  - haemorrhages

Only randomized controlled trials (RCTs) with a minimum duration of 3 months were included in the benefit assessment.

In parallel to the preparation of the project outline, a search for systematic reviews was conducted in the MEDLINE database (which includes the Cochrane Database of Systematic Reviews) and the Health Technology Assessment (HTA) database as well as on the websites of the National Institute for Health and Care Excellence (NICE) and the Agency for Healthcare Research and Quality (AHRQ).

It was ascertained whether at least 1 high-quality, current systematic review (SR) existed whose information retrieval was a suitable basis for the assessment (hereinafter: basic SR).

If that was the case, a 2nd step followed, where a supplementary search was conducted for studies for the time period not covered by the basic SR(s). Otherwise, the search for studies was carried out without time restriction.

The systematic search for studies was conducted in the databases MEDLINE, Embase, and Cochrane Central Register of Controlled Trials (CENTRAL).

In addition, the following information sources and search techniques were taken into account: study registries, manufacturer queries, publicly accessible documents from regulatory authorities, G-BA (Federal Joint Committee) and IQWiG websites as well as the screening of reference lists, and author queries.

Relevant studies were selected by 2 persons independently from one another. Any discrepancies were resolved by discussion between them.

Data were to be extracted into standardized tables. To assess the qualitative certainty of results, outcome-specific and study-level criteria for the risk of bias were to be assessed, and the risk of bias was rated as high or low in each case. The results of the individual studies were to be described organized by outcomes.

In addition to the comparison of the individual studies' results, metaanalyses and sensitivity analyses were to be conducted and effect modifiers investigated, provided that the methodological prerequisites had been met.

For each outcome, a conclusion was to be drawn regarding the evidence for (greater) benefit and (greater) harm, with 4 levels of certainty of conclusions: proof (highest certainty of conclusions), indication (moderate certainty of conclusions), hint (lowest certainty of conclusions), or neither of the above 3. The latter was to be the case if no data were available or the available data did not allow any of the other 3 conclusions to be drawn. In that case, the conclusion "There is no hint of (greater) benefit or (greater) harm" was to be drawn.

For the present benefit assessment, the interventions were to preferably be compared in the form of a network meta-analysis (NMA). Sufficient structural quality is the prerequisite for conducting and interpreting an NMA or indirect comparisons. It is present if the assumption of similarity, homogeneity, and consistency is met in each case.

To ensure sufficient similarity of the studies in the pool, one of the factors to be taken into account for testing the similarity assumption should be the proportion of patients with primary versus delayed (secondary) PCI. For the TRITON-TIMI 38 study, published subgroup analyses comparing patients undergoing primary PCI versus those undergoing secondary PCI show relevant effect modifications by PCI timing regarding several outcomes [20]. As a measure of study comparability with respect to the timing of PCI (primary versus secondary), the time from symptom onset to invasive treatment was therefore examined in more detail (see Section 4.1).

Separate analysis of patients with STEMI + PCI versus NSTEMI/UA + PCI

The present assessment should be conducted separately for patients with STEMI versus patients with NSTEMI/UA, each with primary or delayed PCI (hereafter referred to as STEMI + PCI or NSTEMI/UA + PCI). The rationale for distinguishing these groups is as follows:

- Clopidogrel approval status: clopidogrel, in combination with ASA, is therapeutically indicated in adult patients with non-ST-segment elevation ACS (NSTEMI or UA), including patients undergoing a stent placement following PCI, and in acute STEMI in medically treated patients eligible for thrombolytic therapy [13]. Accordingly, clopidogrel in combination with ASA is not approved for patients with STEMI who have undergone primary or delayed PCI. As described in benefit assessments A09-02 and A11-02, this assessment is based on a written enquiry from the G-BA to the European Medicines Agency [[17,18]]. In the present assessment, which is conducted within the therapeutic indication of prasugrel and thus exclusively examines patients with PCI, conclusions on clopidogrel can therefore be drawn only on patients with NSTEMI/UA undergoing PCI. (Regardless of this, a clopidogrel treatment group in STEMI + PCI may be used as a common comparator in an NMA comparing prasugrel versus ticagrelor).
- STEMI and NSTEMI/UA differ considerably: Separate European Society of Cardiology (ESC) guidelines [4,6,8,9] and American College of Cardiology (ACC) / American Heart Association (AHA) guidelines [3,7] are available for patients with STEMI versus patients with NSTEMI/UA. They show that patients with STEMI or NSTEMI/UA are treated differently and that the urgency of treatment differs as well. For example, patients with STEMI are treated immediately with ASA and a saturating dose of a $P2Y_{12}$ inhibitor, whereas pretreatment with a $P2Y_{12}$ inhibitor is not recommended for patients with NSTEMI or UA until the coronary anatomy is known. In addition, all patients with STEMI should receive immediate invasive treatment (primary PCI within 2 hours of initial medical contact). In the case of NSTEMI/UA, further treatment is carried out depending on certain patient risk factors and may be either pharmacological or invasive. In the case of invasive treatment, a distinction is made between immediate invasive (within 2 hours), early invasive (within 24 hours), and selective invasive treatment (later than 24 hours), depending on the risk.

4 Results

4.1 Results of the information retrieval

No systematic reviews were taken into account as basic SRs for the purpose of identifying primary studies.

Through the various search steps, a total of 20 suitable RCTs meeting the inclusion criteria were found. Of these, 11 studies were suitable for the benefit assessment. Nine studies were unsuitable for the benefit assessment. For 7 of the 9 studies, no analyses were available separately for the STEMI and NSTEMI/UA subpopulations, and none of the subpopulations comprised ≥ 80% of the total study population. Two of the 9 studies (CURE and Zhang 2019) examined the comparison of clopidogrel + ASA versus ASA. However, the comparator intervention of ASA does not represent a suitable common comparator in the study pool because no study comparing prasugrel + ASA or ticagrelor + ASA versus ASA was found. One ongoing study was found. Furthermore, 3 studies of unclear status and 2 completed studies without reported results were found.

The search strategies for bibliographic databases and trial registries are found in the appendix. The last search was conducted on 18 October 2021.

Table 1: Study pool of the benefit assessment (multipage table)

Study		**Available documents**			**Suitability for benefit assessment (yes/no)**
	Full publication (in scientific journals)	**Registry entry / result report from trial registries**	**Clinical study report from manufacturer documents (not publicly available)**	**Other documents**	
Prasugrel + ASS vs. Ticagrelor + ASS					
ISAR-REACT 5	Yes [21-33]	Yes [34-36] / no	No	Yes [34][a]	Yes[b]
Prasugrel + ASA vs. clopidogrel + ASA					
Dasbiswas 2013	Yes [37]	No/No	No	No	No[c]
Elderly ACS-2	Yes [38-42]	Yes [43,44] / no	No	No	No[c]
H7T-MC-TACE	Yes [45]	Yes [46] / yes [46]	Yes [47]	Yes [17]	Yes[d]
TRITON TIMI-38	Yes [20,48-81]	Yes [47,82] / yes [47,82]	Yes [83]	Yes [17,18]	Yes[d]
Ticagrelor + ASA vs. clopidogrel + ASA					
AFFECT EV	Yes [84,85]	Yes [86] / yes [86]	No	No	No[c]
HEALING-AMI	Yes [87,88]	Yes [89] / No	No	No	Yes[e]
Lu 2016	Yes [90]	No/No	No	No	No[c]
PHILO	Yes [91]	Yes [92,93] / yes [92]	Yes [94,95]	No	Yes[b]
PLATO	Yes [96-170]	Yes [171,172] / yes [171,172]	Yes [173,174]	Yes [18]	Yes[b]
PLEIO	Yes [175-177]	Yes [178] / yes [178]	No	No	No[c]
Qiu 2020	Yes [179]	No/No	No	No	Yes[f]
TAILOR-PCI	Yes [180-182]	Yes [183] / yes [183]	No	No	No[c]
Tang 2016	Yes [184]	No/No	No	No	Yes[e]
TICAKOREA	Yes [185]	Yes [186,187] / no	No	No	Yes[b]
Wu 2018	Yes [188]	No/No	No	No	Yes[g]
Yang 2018	Yes [189]	No/No	No	No	No[c]
Yang 2020	Yes [190]	No/No	No	No	Yes[h]
Clopidogrel + ASS vs. ASS					
CURE	Yes [191-215]	No/No	Yes [216]	Yes [15]	No[i]
Zhang 2019	Yes [217]	No/No	No	No	No[i]

Table 1: Study pool of the benefit assessment (multipage table)

Study		Available documents			Suitability for benefit assessment (yes/no)
	Full publication (in scientific journals)	Registry entry / result report from trial registries	Clinical study report from manufacturer documents (not publicly available)	Other documents	

a. Not publicly accessible.
b. Data are available for the study in patients with STEMI + PCI as well as those with NSTEMI/UA + PCI.
c. No data or analyses are available for the relevant subpopulations of STEMI + PCI or NSTEMI/UA + PCI (see Section 3), or none of the relevant subpopulations comprises ≥ 80% of the included patient population.
d. Manufacturer-sponsored study; data on subpopulations requested as part of manufacturer queries were not submitted. Therefore, the data pool for the benefit assessment is incomplete. The resulting consequences are explained in Section 4.1.
e. The study enrolled patients with STEMI who underwent PCI.
f. The study enrolled patients with UA who underwent PCI.
g. Of the enrolled patients, ≥ 80% had STEMI and underwent PCI.
h. Of the enrolled patients, ≥ 80% had NSTEMI/UA and underwent PCI.
i. The CURE and Zhang 2019 studies examined the comparison of clopidogrel + ASA versus ASA. However, the comparator intervention of ASA is not a suitable common comparator for the study pool because no other study conducting a comparison to ASA was found. The 2 studies are therefore disregarded for the assessment.

ASA: acetylsalicylic acid; NSTEMI: non-ST-segment elevation myocardial infarction; PCI: percutaneous coronary intervention; STEMI: ST-segment elevation myocardial infarction; UA: unstable angina

Four of the 11 suitable studies (PHILO, PLATO, TRITON-TIMI 38, and H7T-MC-TACE) were manufacturer-sponsored studies for which study reports were submitted in response to manufacturer queries. The remaining 7 studies are investigator-initiated trials (IITs). Due to its size, only the ISAR-REACT 5 study directly comparing ticagrelor + ASA versus prasugrel + ASA was subject to an author query (see below for justification). All 4 manufacturer-sponsored studies and the IIT ISAR-REACT 5 additionally required queries about subpopulations. This was due to (a) the approvals of the 3 drugs to be taken into account for the assessment – clopidogrel, prasugrel, and ticagrelor – and (b) the research question being divided into patients with STEMI + PCI versus patients with NSTEMI/UA + PCI. In addition, further information was requested to assess whether the patient populations were sufficiently similar for conducting a joint analysis in an NMA. The exact requests are presented in Section A6 of the full report.

Overall, however, relevant study results (TRITON-TIMI 38 and H7T-MC-TACE studies) were missing for the comparison of prasugrel versus clopidogrel, each in combination with ASA, because the manufacturer Daiichi Sankyo failed to provide data on the requested subpopulations. Because of the lack of data, it was therefore impossible to determine whether a closed network for an NMA can be formed, given that the 2 studies represent the only evidence found for the prasugrel versus clopidogrel edge, each in combination with ASA.

Hence, the data pool for the present benefit assessment is incomplete for all 3 comparisons because a significant part of the data potentially relevant for the NMA was not available for prasugrel + ASA as well as for clopidogrel + ASA. The evaluation of the available limited data would thus not be a valid basis for decision-making by the G-BA. On the basis of the available data, it is impossible to draw a conclusion on the benefit or harm of the drugs clopidogrel, ticagrelor, and prasugrel, each in combination with ASA, in comparison with each other. This is explained in detail below.

Data pool incomplete for the benefit assessment

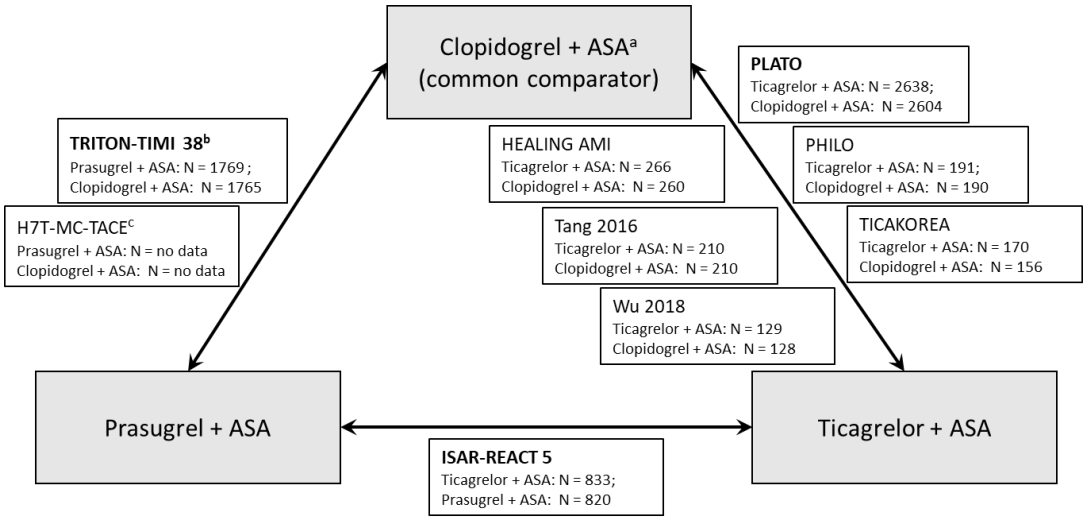
The information retrieval process identified a total of 11 relevant studies, which were distributed as follows between the individual comparisons of the drugs and the 2 questions:

- Prasugrel + ASA versus ticagrelor + ASA: 1 study (ISAR-REACT 5 [31]) with subpopulations on STEMI + PCI and NSTEMI/UA + PCI
- Prasugrel + ASA versus clopidogrel + ASA: 2 studies (TRITON-TIMI 38 [80] and H7T-MC-TACE [46]) with subpopulations on STEMI + PCI and NSTEMI/UA + PCI
- Ticagrelor + ASA versus clopidogrel + ASA: 8 studies
  - STEMI + PCI: HEALING-AMI [88], PHILO (subpopulation) [91], PLATO (subpopulation) [168], Tang 2016 [184], TICAKOREA (subpopulation) [185], Wu 2018 [188]
  - NSTEMI/UA + PCI: PHILO (subpopulation), PLATO (subpopulation), Qiu 2020 [179], TICAKOREA (subpopulation), Yang 2020 [190]

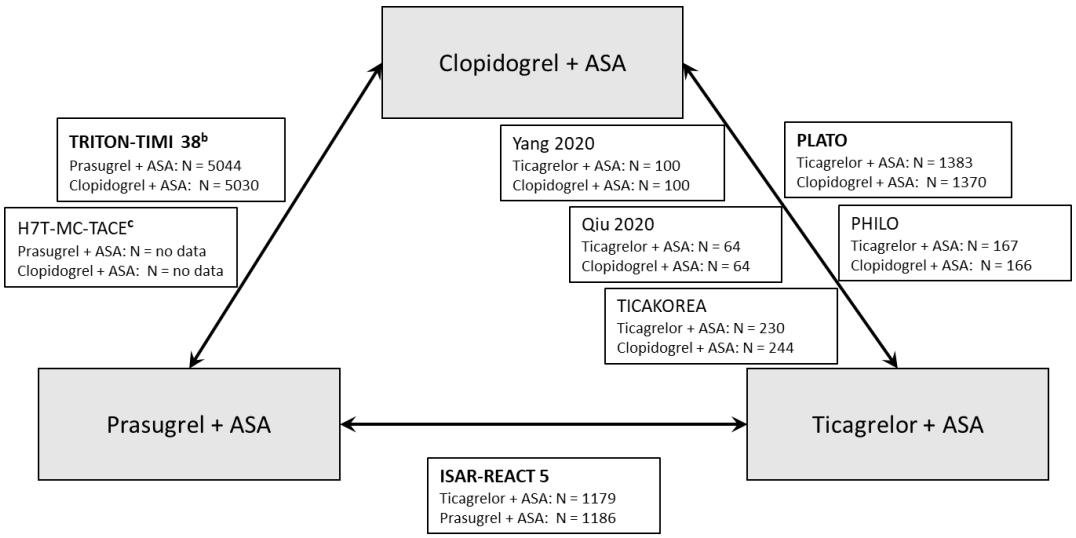
No smaller studies reporting additional, previously disregarded outcomes (e.g. health-related quality of life) were found (see Section A2.1.8 of the full report).

The following figures (see Figure 1) show the potential networks for the comparative benefit assessment for the patient populations STEMI + PCI and NSTEMI/UA + PCI, subject to a final relevance check of the requested subpopulations or verification of the similarity of the considered studies. The names of the studies for which sponsor queries were sent are printed in bold.

A. STEMI + PCI



B. NSTEMI/UA + PCI



a. Clopidogrel is not approved for patients with STEMI + PCI; nevertheless, the group of patients with STEMI + PCI who were treated with clopidogrel can be used as a common comparator in a network meta-analysis comparing prasugrel and ticagrelor.

b. All included patients underwent PCI; further specifications related to approvals and similarity of the patient population within the network were disregarded (see Section 4.1).

c. The arms potentially relevant to the assessment contained 149 patients with STEMI and 103 patients with NSTEMI/UA. The study documents provide data on the proportion of patients undergoing PCI only for the total ACS population, at 221 (88%) of patients undergoing PCI.

Figure 1: Potential networks for the comparative benefit assessment of clopidogrel, prasugrel, and ticagrelor, each in combination with ASA, for the patient populations

STEMI + PCI (Figure 1A) and NSTEMI/UA + PCI (Figure 1B), subject to final relevance testing of the requested subpopulations or verification of similarity of the incoming studies. The names of the studies for which sponsor queries were sent are printed in bold.

Section A3.2 of the full report presents the characteristics of the included studies. For each edge of the comparison of clopidogrel versus ticagrelor versus prasugrel, at least 1 large study (TRITON-TIMI 38, ISAR-REACT 5, and PLATO) with several thousand included patients was thus found.

Manufacturer queries were sent for the PHILO, PLATO, TRITON-TIMI 38, and H7T-MC-TACE studies (see Sections A3.1.2.1.3 and A6.1 of the full report). All other studies identified were IITs. Only the ISAR-REACT 5 study was subject to an author query because it was the only large study directly comparing prasugrel versus ticagrelor, each in combination with ASA (see Sections A3.1.2.2.4 and A6.2 of the full report). No other author queries were planned because the resulting information would presumably not have a relevant influence on the assessment due to the respective studies' limited sizes.

For both the manufacturer-sponsored studies and the ISAR-REACT 5 study, queries were made regarding specific subpopulations relevant to the benefit assessment. This was necessary, firstly, because of the separate analysis of the STEMI + PCI and NSTEMI/UA + PCI populations (see Section 3). Secondly, the assessment had to take into account the approvals of the 3 drugs, resulting in further specifications for data queries on patient populations. For the studies to be analysed together in a closed network, the similarity assumption must also be fulfilled. Due to the study designs differing widely in some cases, further adjustments of the patient populations were necessary, or additional data relevant for the similarity test were requested.

Rationale for the data requests for the studies ISAR-REACT 5, PHILO, PLATO, TRITON-TIMI 38, and H7T-MC-TACE

The benefit assessment primarily required subpopulations of patients with STEMI versus NSTEMI (see Section 3). The differing approvals of the 3 drugs as well as the different study designs, e.g. with regard to the inclusion of patients with delayed PCI (see below in this section), result in further specifications of the subpopulations to be analysed. The specifications made for the data query to the manufacturers (PHILO, PLATO, TRITON-TIMI 38, and H7T-MC-TACE) or the author (ISAR-REACT 5) are explained below. The data requests can be found in Section A6.1 and A6.2 of the full report.

Handling of prasugrel approval

As commissioned by the G-BA, the assessment is to be conducted in the therapeutic indication of prasugrel. Prasugrel is approved for patients with ACS who have undergone primary or

delayed PCI [14]. Due to the different study designs, some of the studies markedly differ in the proportions of patients with (primary or delayed) PCI, which in turn may vary between the STEMI and NSTEMI/UA subpopulations. Therefore, subpopulations were requested for all studies on patients with STEMI or NSTEMI/UA who, at the time of randomization, were to undergo primary PCI (≤ 24 hours between diagnosis and intervention) or delayed PCI (>24 hours between diagnosis and intervention). Because clopidogrel is not approved for patients with STEMI undergoing PCI, conclusions regarding this drug can be drawn only for patients with NSTEMI/UA + PCI. However, the group of STEMI + PCI patients treated with clopidogrel may be used as a common comparator in an NMA comparing prasugrel and ticagrelor.

Handling of patients ≥ 75 years of age and/or with a body weight < 60 kg

According to the Summary of Product Characteristics (SPC), patients ≥ 75 years of age and those with a body weight < 60 kg who are to be treated with prasugrel should receive a reduced maintenance dose of 5 mg once daily after a 60 mg loading dose, but the use of prasugrel is generally not recommended in patients ≥ 75 years of age [14]. This is because in the TRITON-TIMI 38 approval study, patients ≥ 75 years of age were at increased risk of bleeding when treated with a 10 mg maintenance dose of prasugrel [218].

In the TRITON-TIMI 38 study, patients ≥ 75 years of age and/or those with a body weight of < 60 kg were treated with a maintenance dose of 10 mg prasugrel once daily in deviation from approval. These patients were therefore excluded from the data query on the subpopulations. In this study, the proportion of patients ≥ 75 years of age was approximately 12% (STEMI + PCI) and 14% (NSTEMI + PCI), respectively. No data are available on the proportion of patients with a body weight < 60 kg in the TRITON-TIMI 38 study. In the overall study population, approximately 18% of patients had a body weight < 70 kg.

In the H7T-MC-TACE study, patients were randomized to different arms according to their age and body weight (≥ 75 years or body weight < 60 kg versus < 75 years and ≥ 60 kg body weight) and treated with prasugrel or clopidogrel (see Table 12 of the full report). Patients ≥ 75 years of age or with a body weight < 60 kg were treated with a maintenance dose of 5 mg prasugrel once daily in accordance with approval. In deviation from approval, however, prasugrel treatment was not initiated with a 30 mg loading dose. The arm was therefore disregarded in the data query on subpopulations.

In the ISAR-REACT 5 study, patients ≥ 75 years and/or with a body weight < 60 kg were treated with prasugrel (60 mg loading dose, 5 mg/day as maintenance dose) in compliance with approval. Therefore, no adjustment of the patient population was necessary.

In the PHILO and PLATO studies, patients ≥ 75 years or with a body weight < 60 kg were treated with ticagrelor or clopidogrel, respectively, in compliance with approval.

Handling of patients with a history of transient ischaemic attack or stroke

Prasugrel treatment is contraindicated in patients with a history of transient ischaemic attack (TIA) or stroke [14]. This is based on a subgroup analysis of the TRITON-TIMI 38 study, which analysed patients with versus those without a history of TIA or stroke. The analysis showed a disadvantage for prasugrel + ASA in comparison with clopidogrel + ASA for the outcome of major bleeding in patients with a history of TIA or stroke [80,218].

The H7T-MC-TACE and ISAR-REACT 5 studies excluded patients with a history of TIA or stroke (see Table 14 of the full report). Therefore, the patient populations of these studies did not need to be adjusted in this regard. In contrast, 1% to 3% of the total populations of the TRITON-TIMI 38, PHILO, and PLATO studies had a history of TIA, and 2% to 7% had a history of stroke. In the data request for the benefit assessment, these patients were therefore excluded from the defined subpopulation for the benefit assessment.

Handling of the ASA maintenance dose in the studies

The SPCs for prasugrel and clopidogrel specify an ASA dosage of 75 to 325 mg daily in combination therapy [13,14]. Ticagrelor, on the other hand, should be administered in combination with a low ASA maintenance dose of 75 to 150 mg daily [12]. Guidelines likewise recommend a low ASA maintenance dose (75 to 100 mg or 75 to 150 mg) for all 3 drugs [4,8,11].

The low recommended maintenance dose, particularly for ticagrelor, is due to the fact that the PLATO study showed an interaction between treatment effect and ASA maintenance dose for the primary composite outcome of major adverse cardiovascular events (MACE), consisting of cardiovascular death, myocardial infarction excluding silent infarctions, and stroke [140]. To this end, subgroup analyses comparing ticagrelor versus clopidogrel, each in combination with ASA, were conducted by region (United States versus rest of the world [non-U.S.]) and different categories of median ASA maintenance doses (≥ 300 mg versus > 100 to < 300 mg versus ≤ 100 mg) (see Figure 2). The analyses showed an advantage for clopidogrel at high median ASA maintenance doses (≥ 300 mg), which had been administered primarily in the United States, and an advantage for ticagrelor at low median ASA maintenance doses (≤ 100 mg), which had been used primarily in the rest of the world.

Region	ASA Dose (mg)	Ticagrelor N	Ticagrelor E	Clopidogrel N	Clopidogrel E	HR (95% CI)
US	≥300	324	40	352	27	1.62 (0.99, 2.64)
	>100–<300	22	2	16	2	*
	≤100	284	19	263	24	0.73 (0.40, 1.33)
Non-US	≥300	140	28	140	23	1.23 (0.71, 2.14)
	>100–<300	503	62	511	63	1.00 (0.71, 1.42)
	≤100	7449	546	7443	699	0.78 (0.69, 0.87)

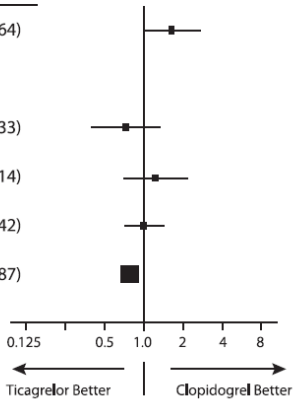


Figure 2: Comparison of ticagrelor versus clopidogrel for the PLATO study's primary composite efficacy outcome of MACE (cardiovascular death, myocardial infarction excluding silent infarctions, stroke) by region (United States versus rest of the world [non-U.S.]) and different median ASA maintenance dose categories
(≥ 300 mg versus > 100 to < 300 mg vs ≤ 100 mg) [140]

Accordingly, the TRITON-TIMI 38, H7T-MC-TACE, and ISAR-REACT 5 study participants had been treated with ASA in compliance with approval. The PHILO and PLATO studies, in contrast, allowed an ASA maintenance dose of up to 325 mg daily for up to 6 months after stent placement. Therefore, the data request for the PHILO and PLATO studies excluded patients with an ASA maintenance dose > 150 mg.

Similarities regarding PCI timing relative to symptom onset

Due to the different designs of the PHILO, PLATO, H7T-MC-TACE, TRITON-TIMI 38, and ISAR-REACT 5 studies, the timing of PCI relative to symptom onset differed markedly in some cases, necessitating further adjustments of the requested subpopulations or prompting further information requests in this regard to allow assessing the similarity of the patient populations with respect to this criterion. Below, this is described separately for the STEMI + PCI and NSTEMI + PCI populations.

STEMI + PCI: timing of PCI relative to symptom onset

In all 5 studies for which data requests were made regarding specific subpopulations, patients with STEMI were to undergo invasive treatment. In the PHILO, PLATO, and ISAR-REACT 5 studies, STEMI patients were to exhibit an onset of cardiac ischaemic symptoms within 24 hours before randomization. The TRITON-TIMI 38 and H7T-MC-TACE studies, in contrast, also allowed the enrolment of patients with STEMI who exhibited cardiac ischaemic symptoms within 14 days prior to randomization. Unlike the PHILO, PLATO, and ISAR-REACT 5 studies, the TRITON-TIMI 38 and H7T-MC-TACE studies therefore also enrolled patients with STEMI

who had secondary or delayed PCI (see Table 14 of the full report). According to the TRITON-TIMI 38 study design, patients who received PCI within 12 hours of symptom onset were assumed to have received primary PCI. Patients who received PCI between 12 hours and 14 days after symptom onset were deemed to have undergone secondary PCI [20].

A total of 3425 patients with STEMI + PCI were included in the TRITON-TIMI 38 study. According to the above categories of time between symptom onset and PCI, 2340 (68%) patients received primary PCI and 1085 (32%) underwent secondary (delayed) PCI [20]. This is significant in that published subgroup analyses comparing patients with primary PCI versus those with secondary PCI in the TRITON-TIMI 38 study showed relevant effect modifications by timing of PCI. For the outcomes of periprocedural myocardial infarctions and bleeding, in particular, the effect direction was even reversed at the end of the study (Month 15) (see Figure 3) [20,77]. This demonstrates that the timing of PCI relative to symptom onset substantially impacts outcomes. Therefore, this factor is important when testing the similarity of studies for an NMA.

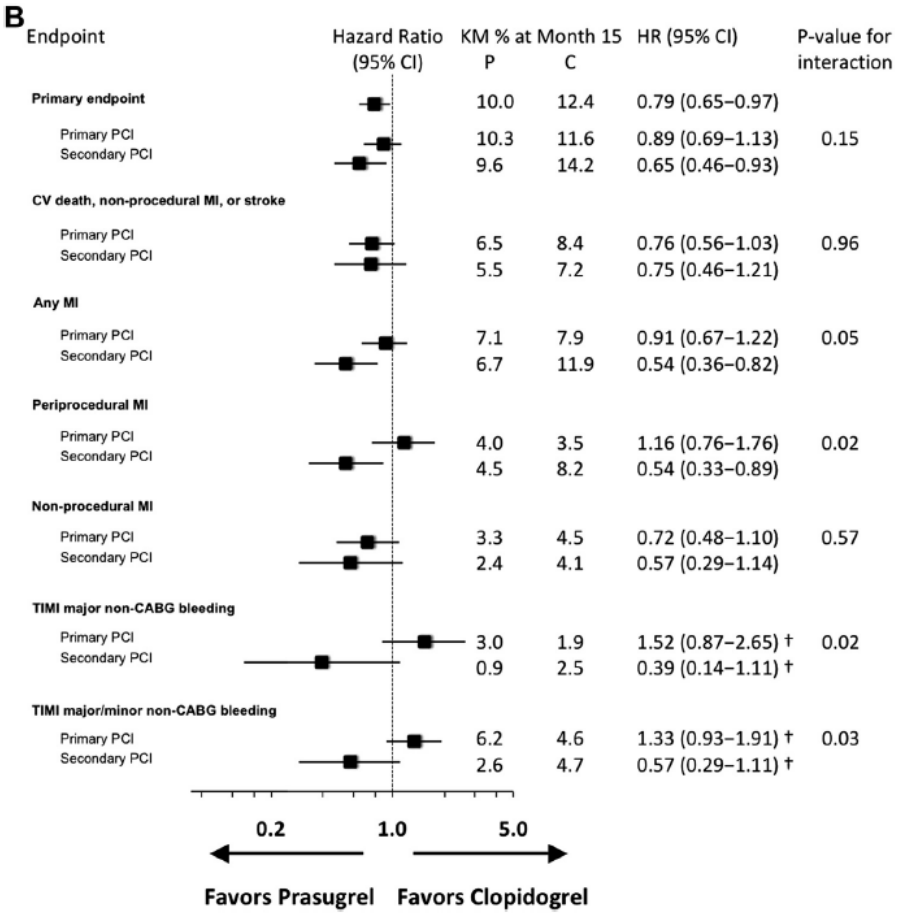


Figure 3: Forest plot comparing treatment effects in patients with STEMI with primary versus secondary PCI in the TRITON-TIMI 38 study at Month 15 [20]

As a measure of comparability between studies with respect to the timing of PCI (primary versus secondary), the time from symptom onset to invasive treatment was therefore analysed in more detail.

Table 2 shows the data on time from symptom onset to (invasive) treatment in patients with STEMI + PCI in the ISAR-REACT 5, PHILO, PLATO, TRITON-TIMI 38, and H7T-MC-TACE studies.

Table 2: STEMI + PCI – time from symptom onset to (invasive) treatment

Study	**ISAR-REACT 5**		**TRITON-TIMI 38**		**H7T-MC-TACE**		**PLATO**		**PHILO**	
	Ticagrelor + ASA	**Prasugrel + ASA**	**Prasugrel + ASA**	**Clopidogrel + ASA**	**Prasugrel + ASA**	**Clopidogrel + ASA**	**Ticagrelor + ASA**	**Clopidogrel + ASA**	**Ticagrelor + ASA**	**Clopidogrel + ASA**
	N[a] = 833	**N[a] = 820**	**N[a] = 1769**	**N[a] = 1765**	**N[a] = ND**	**N[a] = ND**	**N[a] = 2638**	**N[a] = 2604**	**N[a] = 191**	**N[a] = 190**
Time from symptom onset to PCI [hours], median [Q1; Q3]	ND	ND	6.8 [3.3; 29.2]	6.0 [3.1; 27.5]	ND	ND	4.7 [3.1; 8.5]	4.6 [3.0; 8.0]	5.4 [2.8; 13.3]	4.1 [2.5; 9.5]
Time from symptom onset to 1st dose [hours], median [Q1; Q3]	ND	ND	7.0 [3.7; 28.5]		ND	ND	4.3 [2.8; 7.8]	4.3 [2.8; 7.8]	5.4 [2.5; 12.0]	3.9 [2.3; 8.8]
Time from symptom onset to randomization [hours], median [Q1; Q3]	3.2 [1.8; 7.8][b]	3.0 [1.9; 8.7][b]	PCI total: 6.4 [2.9; 27.8]	5.6 [2.8; 26.9]	ND	ND	4.1 [2.6; 7.4]	4.0 [2.5; 7.1]	5.1 [2.2; 11.3]	3.7 [2.1; 8.8]
			Primary PCI: 3.8 [2.3; 6.6]							
			Secondary PCI: 46.9 [25.5; 86.2]							

a. Number of randomized patients. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
b. Data on time from symptom onset to hospital admission were missing for 120 patients in the ticagrelor arm and 111 patients in the prasugrel arm.

ASA: acetylsalicylic acid; N: number of randomized patients; ND: no data; PCI: percutaneous coronary intervention; Q1: 25% quartile; Q3: 75% quartile; STEMI: ST-segment elevation myocardial infarction

Data on time from symptom onset to PCI are available for the TRITON-TIMI 38, PLATO, and PHILO studies. The median time to PCI was markedly longer in TRITON-TIMI 38 participants than in PLATO participants, with the difference being particularly evident in the 3rd quartile (TRITON-TIMI 38: 27.5 and 29.2 hours, respectively; PLATO: 8.0 and 8.5 hours, respectively; PHILO: 9.5 and 13.3 hours, respectively). Hence, in a relevant proportion of TRITON-TIMI 38 participants, a long time elapsed between symptom onset and PCI. No data on time from symptom onset to PCI are available for the ISAR-REACT 5 study. Based on the data from the TRITON-TIMI 38, PLATO, and PHILO studies, the time from symptom onset to randomization can be used as an approximation of the time from symptom onset to PCI. On the latter, data from the ISAR-REACT 5 study are available. They show that the median time from symptom onset to randomization was almost twice as long in the TRITON-TIMI 38 study as in ISAR-REACT 5. Analysing the TRITON-TIMI 38 data separately for primary and secondary PCI reveals that these long periods were predominantly caused by patients undergoing secondary PCI. This raised the general question whether TRITON-TIMI 38 participants were sufficiently similar to the patient populations of the other studies (ISAR-REACT 5, PLATO, and PHILO) with respect to the criterion of time from symptom onset to PCI in order for these populations to be analysed together in an NMA.

When using the times from symptom onset to randomization as an approximation of time from symptom onset to PCI for TRITON-TIMI 38 participants with STEMI and primary PCI (median 3.8 hours), it becomes apparent that these times are comparable to those of the ISAR-REACT 5 (median 3.0 and 3.2 hours, respectively), PLATO (4.0 and 4.1 hours, respectively), and PHILO (3.7 and 5.1 hours, respectively) studies (see Table 1). To potentially enable the use of TRITON-TIMI 38 study data for patients with STEMI + PCI in the assessment after all, data on participants with STEMI who underwent primary PCI were requested from the manufacturer. For this purpose, primary PCI was defined as PCI within 24 hours after diagnosis in accordance with the current ESC guideline on STEMI [8,9].

The H7T-MC-TACE study is similar in design to the TRITON-TIMI 38 study. However, no information on the proportion of patients with primary or secondary PCI or on the time from symptom onset to PCI (or to randomization or 1st dose) is available from the H7T-MC-TACE study report. Therefore, it was unclear whether the included patients with STEMI + PCI were sufficiently similar to the other studies' patient populations with respect to this criterion. To allow an assessment of this, data on the proportion of patients with primary or secondary PCI and on the time from symptom onset to PCI (or randomization or 1st dose) were requested as part of the data query sent to the manufacturer (see Section A6.1.4 of the full report).

However, the requested data on the TRITON-TIMI 38 and H7T-MC-TACE studies were not sent by the manufacturer. Irrespective of this, it should be noted that, due to study size, the H7T-MC-TACE results would not have been able to call into question the results of TRITON-TIMI 38.

The arms of the H7T-MC-TACE study which were potentially relevant for the assessment included 149 patients with STEMI. Data on the proportion of patients with PCI are available in the study documents only for the total ACS population (N = 252 based on the full analysis set), with 88% (N = 221) of patients undergoing PCI. In the TRITON-TIMI 38 study, a total of 2340 patients with STEMI underwent primary PCI (defined as ≤ 12 hours from symptom onset to PCI). The relevant H7T-MC-TACE participants thus account for substantially less than 10% of the study pool for the comparison of prasugrel + ASA versus clopidogrel + ASA.

Due to the lack of data on the TRITON-TIMI 38 and H7T-MC-TACE studies, the data pool for the comparison of prasugrel versus ticagrelor via the common comparator of clopidogrel, each in combination with ASA, is incomplete, and no conclusions can be drawn regarding the 2 drugs' benefits or harms in comparison with each other for the STEMI + PCI patient population.

NSTEMI/UA + PCI: timing of PCI relative to symptom onset

Regarding the timing of PCI in patients with NSTEMI/UA + PCI, the study designs of the PHILO, PLATO, H7T-MC-TACE, TRITON-TIMI 38, and ISAR-REACT 5 studies differed as they did for the STEMI + PCI populations. The PHILO study's inclusion criteria specified for patients to undergo primary PCI. The PLATO study enrolled patients regardless of whether they were to undergo PCI, whereas the H7T-MC-TACE, TRITON-TIMI 38, and ISAR-REACT 5 studies specified for invasive treatment or PCI to be intended at baseline (see Table 14 of the full report). Inclusion criteria also differ with respect to the time from symptom onset to randomization. Patients were to have exhibited cardiac ischaemic symptoms within 48 hours before randomization in the ISAR-REACT 5 study, within 24 hours in the PLATO study, and within 72 hours in the TRITON-TIMI 38 and H7T-MC-TACE studies.

Table 3 shows the data on time from symptom onset to (invasive) treatment in patients with NSTEMI/UA + PCI in the ISAR-REACT 5, PHILO, PLATO, TRITON-TIMI 38, and H7T-MC-TACE studies.

Table 3: NSTEMI/UA + PCI – time from symptom onset to (invasive) treatment

Study	ISAR-REACT 5		TRITON-TIMI 38		H7T-MC-TACE		PLATO		PHILO	
	Ticagrelor + ASA	Prasugrel + ASA	Prasugrel + ASA	Clopidogrel + ASA	Prasugrel + ASA	Clopidogrel + ASA	Ticagrelor + ASA	Clopidogrel + ASA	Ticagrelor + ASA	Clopidogrel + ASA
	Na = 1179	Na = 1186	Na = 5044	Na = 5030	Na = ND	Na = ND	Na = 1383	Na = 1370	Na = 167	Na = 166
Time from symptom onset to PCI [hours], median [Q1; Q3]	ND	ND	ND	ND	ND	ND	16.7 [8.7; 23.8]	16.8 [9.3; 23.4]	12.5 [6.1; 22.8]	11.8 [5.0; 24.2]
Time from symptom onset to 1st dose [hours], median [Q1; Q3]	ND	ND	29.7 [17.4; 49.8]		ND	ND	13.4 [7.0; 19.8]	14.0 [7.7; 20.2]	9.0 [5.0; 15.3]	9.2 [4.6; 16.7]
Time from symptom onset to randomization [hours], median [Q1; Q3]	16.3 [8.0; 35.0][b]	16.0 [7.8; 34.6][b]	28.9 [16.6; 48.6]	29.0 [16.7; 49.0]	ND	ND	12.9 [6.7; 19.0]	13.4 [7.0; 19.3]	8.4 [4.2; 14.7]	8.2 [4.2; 15.6]

a. Number of randomized patients. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
b. Data on the time from symptom onset to hospital admission were missing for 279 patients in the ticagrelor arm and in 278 patients in the prasugrel arm.

ASA: acetylsalicylic acid; N: number of randomized patients; ND: no data; NSTEMI: non-ST-segment elevation myocardial infarction; PCI: percutaneous coronary intervention; Q1: 25% quartile; Q3: 75% quartile; UA: unstable angina

Data on time from symptom onset to PCI are available only for the PLATO and PHILO studies. When using time from symptom onset to randomization as a proxy for time from symptom onset to PCI, the NSTEMI/UA + PCI populations clearly differ between studies, as do the STEMI + PCI patient populations (see Table 2). In the TRITON-TIMI 38 study, the median time from symptom onset to randomization equals approximately 29 hours, which is substantially longer than that in the ISAR-REACT 5 (approximately 16 hours), PHILO (approximately 8 hours), and PLATO (approximately 13 hours) studies. For the H7T-MC-TACE study, the study documents included no data on this topic. Overall, even for patients with NSTEMI/UA + PCI, the question therefore arose whether TRITON-TIMI 38 and H7T-MC-TACE participants are sufficiently similar to the patient populations of the other studies (ISAR-REACT 5, PLATO, and PHILO) with regard to this criterion in order for them to be analysed together in an NMA.

While it is unclear whether the missing data on the timing of PCI relative to symptom onset is of comparable relevance in NSTEMI/UA + PCI as in STEMI + PCI (see above), information is needed to test the similarity of the included patient populations in terms of the proportion of patients with primary versus secondary PCI and the time from symptom onset to PCI in order to potentially identify a sufficiently similar subpopulation, particularly in the TRITON-TIMI 38 study. For this reason, further information on these criteria was requested from the manufacturers. However, because of the failure of Daiichi Sankyo to provide data on the TRITON-TIMI 38 and H7T-MC-TACE studies, insufficient information is available on the NSTEMI/UA + PCI patient population to assess whether it would be possible to form a subpopulation of TRITON-TIMI 38 or H7T-MC-TACE participants with NSTEMI/UA which is sufficiently similar to ISAR-REACT 5, PLATO, and PHILO participants. The data pool for the comparison of prasugrel versus clopidogrel versus ticagrelor, each in combination with ASA, is thus incomplete, and no conclusion can be drawn regarding the drugs' benefits or harms in comparison with each other in the NSTEMI/UA + PCI patient population.

Summary of the result of the data query on subpopulations of the relevant studies

The manufacturer responsible for the PHILO and PLATO studies and the author of the ISAR-REACT 5 study sent the required analyses of subpopulations of their studies. Due to the failure of Daiichi Sankyo to send data on the TRITON-TIMI 38 and H7T-MC-TACE studies for either STEMI + PCI or NSTEMI/UA + PCI, the available data were insufficient to examine the similarity of the patient populations in terms of the proportion of patients with primary versus delayed PCI or time from symptom onset to PCI, or to delineate a subpopulation with sufficient similarity to the other identified studies. Therefore, it remains unclear whether it would have been possible to analyse the patient populations jointly in an NMA. This is problematic given the size of the TRITON-TIMI 38 study and the fact that (a) the TRITON-TIMI 38 and H7T-MC-TACE studies are the only studies in the network comparing clopidogrel + ASA versus prasugrel + ASA in patients with NSTEMI/UA + PCI and (b) these studies account for a relevant proportion of the evidence on prasugrel + ASA in patients with STEMI + PCI.

Overall, the available data for the drugs clopidogrel, ticagrelor, and prasugrel, each in combination with ASA, do not allow drawing a conclusion regarding benefits or harms of the drugs in comparison with each other.

5 Discussion of the available results

The aim of this assessment was to compare the benefits or harms of the drugs clopidogrel, prasugrel, and ticagrelor in the therapeutic indication of prasugrel-containing drugs, i.e. for the prevention of atherothrombotic events in adult patients with ACS undergoing primary or delayed PCI, with regard to patient-relevant outcomes in the context of an NMA. As described in Section 4.1, this would have required, in particular, sufficiently similar data from the studies on patients who received PCI, distinguishing patients with STEMI versus NSTEMI/UA. The data pool for the assessment was incomplete because no data had been provided on the studies comparing prasugrel and clopidogrel, in particular from the TRITON-TIMI 38 study.

To nevertheless allow estimating whether it is possible to draw conclusions on benefit or harm for the comparison of clopidogrel versus prasugrel versus ticagrelor, this assessment used the available data from the 3 largest studies by far, TRITON-TIMI 38 (prasugrel + ASA versus clopidogrel + ASA, N = 13,608), PLATO (ticagrelor + ASA versus clopidogrel + ASA, N = 18,624), and ISAR-REACT 5 (ticagrelor + ASA versus prasugrel + ASA, N = 4018). Only the outcomes of all-cause mortality, major cardiovascular events (composite outcome of MACE), and major bleeding were entered into an exploratory analysis in the form of an NMA for different patient populations of the studies. The included data and results are discussed in detail below.

Data pool for the exploratory comparison of clopidogrel, prasugrel, and ticagrelor

Table 4 shows the patient populations included in the exploratory comparison of clopidogrel, prasugrel, and ticagrelor.

Table 4: Overview of patient populations used for exploratory NMAs

<table>
<tr><th></th><th>PLATO
(ticagrelor vs. clopidogrel)</th><th>ISAR-REACT 5
(ticagrelor vs. prasugrel)</th><th>TRITON-TIMI 38
(prasugrel vs. clopidogrel)</th></tr>
<tr><td>ACS</td><td rowspan="3">Study population
▪ Patient population not adjusted for the drugs' approval statuses
▪ 64% of patients underwent PCI</td><td rowspan="6">Study and approval population
▪ At randomization, all study participants were to receive invasive treatment (84% of patients underwent PCI)
▪ Adjustments of the populations to the approvals of the 3 drugs were not necessary; the study population thus corresponds to the approval population.</td><td rowspan="6">Study population
▪ At randomization, all participants were to receive invasive treatment (99% of patients underwent PCI).
▪ No further adjustments were made to match the approvals of the 3 drugs.
▪ Data requested from the manufacturer on the approval populations and on the restriction to patients with primary PCI (similarity aspect) were not received.</td></tr>
<tr><td>STEMI</td></tr>
<tr><td>NSTEMI/UA</td></tr>
<tr><td>ACS + PCI</td><td rowspan="3">Approval population
▪ At randomization, invasive treatment planned
▪ ≤ 150 mg ASA as a maintenance dose
▪ No history of stroke or TIA</td></tr>
<tr><td>STEMI + PCI</td></tr>
<tr><td>NSTEMI/UA + PCI</td></tr>
<tr><td colspan="4">ACS: acute coronary syndrome; ASA: acetylsalicylic acid; NSTEMI: non-ST-segment elevation myocardial infarction; PCI: percutaneous coronary intervention; STEMI: ST-segment elevation myocardial infarction; TIA: transient ischaemic attack; UA: unstable angina</td></tr>
</table>

To allow analysing the results for different constellations, different populations were used in the NMAs: the total population of patients with ACS (ACS population), the population of patients with STEMI (STEMI population), and the population of patients with NSTEMI/UA (NSTEMI/UA population). In addition, these 3 populations were analysed, restricted to patients who had undergone PCI (ACS + PCI, STEMI + PCI, and NSTEMI / IA + PCI). Thus, the NMAs were conducted for a total of 6 different populations.

For the ACS, STEMI, and NSTEMI/UA populations, the calculations were performed disregarding the specifications and differences in outcome operationalizations mentioned in the data requests. For the ACS + PCI, STEMI + PCI, and NSTEMI/UA + PCI populations in the PLATO and ISAR-REACT 5 studies, results from the data sent by manufacturers or authors in response to the queries were used to be in accordance with each drug's approval status. This applies in particular to the PLATO study because in its total population, the proportion of patients without PCI was 36%, and additionally, approximately 10% of participants received a high ASA maintenance dose (> 150 mg). For the ACS + PCI population, the results of the STEMI + PCI and NSTEMI/UA + PCI subpopulations were combined by way of metaanalysis (fixed-effect model). For the PLATO study, no results are available for the outcome of major bleeding in the respective approval populations (ACS + PCI, STEMI + PCI, or NSTEMI + PCI) because the manufacturer failed to submit the data (see Section A3.1.2.1.3 of the full report). Since Daiichi Sankyo failed to send any data for the TRITON-TIMI 38 study, no additional data were requested. Since Daiichi Sankyo did not send data, the results from the total population

of TRITON-TIMI 38 were used for all analysed populations. It should be noted that, at randomization, this study provided for all patients to undergo invasive treatment, and 99% of enrolled patients underwent PCI. Further adjustments of the patient population requested in the data query to the manufacturer were disregarded (see Section 4.1). In this context, it is important to note the difference in the proportion of TRITON-TIMI 38 participants undergoing secondary PCI and the associated effect modification (see Section 4.1, Figure 3). Furthermore, no final relevance test of the delivered subpopulations and no further similarity test of the patient populations and outcome operationalizations were conducted. This should be taken into account in the comparative interpretation of the results of the individual studies and the NMA.

Results of the exploratory NMAs for the drugs clopidogrel, prasugrel, and ticagrelor

The results of the direct comparisons of the PLATO, ISAR-REACT 5, and TRITON-TIMI 38 studies regarding the outcomes of all-cause mortality, MACE, and major bleeding are presented descriptively for the different patient populations in Section A8, Table 21 through Table 23 of the full report. Based on these results, exploratory NMAs were calculated for the respective patient populations (Section A8, Table 24 through Table 26 of the full report). Table 5 descriptively presents the effect estimates from the exploratory NMAs of the drugs clopidogrel, prasugrel, and ticagrelor for the comparison of the different study and approval populations. It should be noted that clopidogrel is not approved for patients with STEMI who underwent PCI (see Section 3).

Table 5: Descriptive presentation of effect estimates from the exploratory NMAs of the drug comparisons prasugrel versus clopidogrel versus ticagrelor

Outcome Comparison (each plus ASA)	ACS Effect estimate (HR)		STEMI Effect estimate (HR)		NSTEMI/UA Effect estimate (HR)	
	ACS population[a]	ACS + PCI population[b]	STEMI population[a]	STEMI + PCI population[b]	NSTEMI/UA population[a]	NSTEMI/UA + PCI population[b]
All-cause mortality						
Prasugrel vs. clopidogrel	0.84	0.92	*0.77*	*0.83*	0.86	0.89
Ticagrelor vs. clopidogrel	0.87	1.04	***0.82***	*1.01*	0.94	1.00
Ticagrelor vs. prasugrel	1.04	1.14	1.07	1.22	1.09	1.12
MACE						
Prasugrel vs. clopidogrel	**0.76**	**0.76**	***0.76***	***0.78***	**0.77**	0.72
Ticagrelor vs. clopidogrel	0.89	0.91	*0.89*	*0.95*	0.89	0.82
Ticagrelor vs. prasugrel	1.18	1.19	1.16	1.23	1.16	1.13
Severe bleeding events						
Prasugrel vs. clopidogrel	1.18	–[c]	*1.01*	–[c]	1.33	–[c]
Ticagrelor vs. clopidogrel	1.14	–[c]	*1.00*	–[c]	1.12	–[c]
Ticagrelor vs. prasugrel	0.96	–[c]	0.99	–[c]	0.84	–[c]

Italics: clopidogrel is not approved for patients with STEMI who underwent PCI.

Bold: statistically significant difference

a. Study populations: Patient populations of the ISAR-REACT 5, TRITON-TIMI 38, and PLATO studies included in the NMA were not adjusted to the drugs' approval; see Table 3.

b. Approval population: Patient populations of the PLATO study included in the NMA adjusted to the drugs' approval; for the ISAR-REACT 5 study, the approval population corresponds to the study population; for the TRITON-TIMI 38 study, the study populations were used due to missing data; see Table 3.

c. NMA not feasible for the PLATO study due to lack of data on major bleeding.

ACS: acute coronary syndrome; ASA: acetylsalicylic acid; HR: hazard ratio; MACE: major adverse cardiovascular event; NMA: network metaanalysis; NSTEMI: non-ST-segment elevation myocardial infarction; PCI: percutaneous coronary intervention; STEMI: ST-segment elevation myocardial infarction; UA: unstable angina

The calculations show that effect estimates differ depending on the patient population analysed (ACS versus STEMI versus NSTEMI/UA) and whether the drugs' approval is taken into account (study populations versus approval populations). The former was found, e.g. in the outcome of major bleeding for the comparison of prasugrel + ASA versus clopidogrel + ASA,

where a clear numerical disadvantage of clopidogrel + ASA versus prasugrel + ASA is seen for patients with NSTEMI/UA (hazard ratio [HR]: 1.33), whereas no difference (HR: 1.01) is found for patients with STEMI.

A difference between the study population versus the approval population is evident when comparing ticagrelor versus clopidogrel, each in combination with ASA, for the outcome of all-cause mortality. In patients with ACS, there are indications of a reversal of the effect direction: In the study population, there is an advantage of ticagrelor + ASA compared with clopidogrel + ASA for the outcome of all-cause mortality, whereas in the approval population, there is a disadvantage of ticagrelor + ASA compared with clopidogrel + ASA. A significant difference is also seen in the STEMI population when comparing ticagrelor + ASA versus prasugrel + ASA (HR of 1.07 for study population versus 1.22 for approval population). It should be noted, however, that the results of the TRITON-TIMI 38 study (prasugrel versus clopidogrel) were included in the NMA – regardless of whether primary or secondary PCI was performed in the study. As discussed in Section 4.1, the TRITON-TIMI 38 study showed an effect modification in multiple outcomes for patients treated with primary PCI versus secondary PCI. For the outcome of overall survival, no data on subgroup analyses for patients who underwent primary versus secondary PCI are available. Nevertheless, it is possible for the effect in the STEMI approval population (HR: 1.22) to have been overestimated in favour of prasugrel.

In summary, when answering the G-BA's research question, it is important to take into account both the separate analysis of the STEMI and NSTEMI/UA patient populations and the drugs' approvals. Even in the respective approval populations, however, conclusions on the comparison of clopidogrel, prasugrel, and ticagrelor can be drawn only to a very limited extent due to the data constellation as well as the failure to account for the (dis)similarity of study populations and outcome operationalizations. But overall, the available data show no clear advantage for any of the drugs of clopidogrel, prasugrel, or ticagrelor.

6 Conclusion

Because the manufacturer failed to submit the requested data on subpopulations of the TRITON-TIMI 38 and H7T-MC-TACE studies, the data pool for the comparison of prasugrel versus clopidogrel, each in combination with ASA, is incomplete for both patients with STEMI + PCI and patients with NSTEMI/UA + PCI.

The 2 studies TRITON-TIMI 38 and H7T-MC-TACE represent the only identified evidence for the comparison of prasugrel versus clopidogrel, each in combination with ASA. A substantial part of the data is missing for both prasugrel and clopidogrel, particularly due to the lack of suitable data from the very large TRITON-TIMI 38 study. The analysis of the limited available data thus does not represent a valid basis for decision-making by the G-BA. From an exploratory examination of the available results, no clear advantage can be identified for any of the drugs of clopidogrel, prasugrel, or ticagrelor

Overall, no proof, indication, or hint of greater or lesser benefit or harm compared to the other drugs has been derived for the drugs of clopidogrel, ticagrelor, or prasugrel, each in combination with ASA.

7 References for English extract

Please see full rapid report for full reference list.

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The full report (German version) is published under

https://www.iqwig.de/en/projects/a21-41.html

Appendix A Search strategies

A.1 Searches in bibliographic databases

Search for systematic reviews

1. MEDLINE

Search interface: Ovid

- Ovid MEDLINE(R) ALL <1946 to May 13, 2021>

The following filter was adopted:

- Systematic review: Wong [219] – High specificity strategy

#	Searches
1	(clopidogrel* or prasugrel* or ticagrelor* or ((p2y12 or "p2y(12)") adj3 (antagonist* or inhibitor*))).mp.
2	Acute Coronary Syndrome/ or exp Angina, Unstable/ or exp Myocardial Infarction/
3	(acute* adj1 coronar* adj1 syndrome*).ti,ab.
4	(angina* adj1 (unstable* or pectoris*)).ti,ab.
5	(myocardial* adj1 infarction*).ti,ab.
6	or/2-5
7	Cochrane database of systematic reviews.jn.
8	(search or MEDLINE or systematic review).tw.
9	meta analysis.pt.
10	or/7-9
11	10 not (exp animals/ not humans.sh.)
12	and/1,6,11
13	12 and (english or german).lg.
14	..l/ 13 yr=2016-Current

2. International HTA Database

Search interface: INAHTA

#	Searches
1	(clopidogrel* OR prasugrel* OR ticagrelor* OR ((p2y12 OR "p2y(12)") AND (antagonist* OR inhibitor*)))
2	"Acute Coronary Syndrome"[mh]
3	"Angina, Unstable"[mhe]
4	"Myocardial Infarction"[mhe]
5	((acute* AND coronar* AND syndrome*) OR (angina* AND (unstable* or pectoris*)) OR (myocardial* AND infarction*))
6	#5 OR #4 OR #3 OR #2
7	#6 AND #1
8	((((acute* AND coronar* AND syndrome*) OR (angina* AND (unstable* or pectoris*)) OR (myocardial* AND infarction*))) OR ("Myocardial Infarction"[mhe]) OR ("Angina, Unstable"[mhe]) OR ("Acute Coronary Syndrome"[mh])) AND ((clopidogrel* OR prasugrel* OR ticagrelor* OR ((p2y12 OR "p2y(12)") AND (antagonist* OR inhibitor*))))
9	(((((acute* AND coronar* AND syndrome*) OR (angina* AND (unstable* or pectoris*)) OR (myocardial* AND infarction*))) OR ("Myocardial Infarction"[mhe]) OR ("Angina, Unstable"[mhe]) OR ("Acute Coronary Syndrome"[mh])) AND ((clopidogrel* OR prasugrel* OR ticagrelor* OR ((p2y12 OR "p2y(12)") AND (antagonist* OR inhibitor*))))) FROM 2016 TO 2021

Search for primary studies

1. MEDLINE

Search interface: Ovid

- Ovid MEDLINE(R) 1946 to October 15, 2021

The following filter was adopted:

- RCT: Lefebvre [220] – Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity- and precision-maximizing version (2008 revision)

#	Searches
1	exp Myocardial Infarction/ or Acute Coronary Syndrome/
2	exp Percutaneous Coronary Intervention/
3	((acute adj1 coronary adj1 syndrome*) or (myocardial adj1 infarction)).ti,ab.
4	(percutaneous adj1 coronary adj1 intervention*).ti,ab.
5	or/1-4
6	(clopidogrel* or prasugrel* or ticagrelor*).mp.
7	randomized controlled trial.pt.
8	controlled clinical trial.pt.

#	Searches
9	(randomized or placebo or randomly).ab.
10	clinical trials as topic.sh.
11	trial.ti.
12	or/7-11
13	exp animals/ not humans.sh.
14	12 not 13
15	and/5-6,14
16	(animals/ not humans/) or comment/ or editorial/ or exp review/ or meta analysis/ or consensus/ or exp guideline/
17	hi.fs. or case report.mp.
18	or/16-17
19	15 not 18
20	19 and (english or german or multilingual or undetermined).lg.

Search interface: Ovid

- Ovid MEDLINE(R) Epub Ahead of Print and In-Process, In-Data-Review & Other Non-Indexed Citations October 15, 2021

#	Searches
1	((acute and coronary and syndrome*) or (myocardial and infarction)).ti,ab.
2	(percutaneous and coronary and intervention*).ti,ab.
3	or/1-2
4	(clopidogrel* or prasugrel* or ticagrelor*).mp.
5	(clinical trial* or random* or placebo).ti,ab.
6	trial.ti.
7	or/5-6
8	and/3-4,7
9	(animals/ not humans/) or comment/ or editorial/ or exp review/ or meta analysis/ or consensus/ or exp guideline/
10	hi.fs. or case report.mp.
11	or/9-10
12	8 not 11
13	12 and (english or german or multilingual or undetermined).lg.

2. Embase

Search interface: Ovid

- Embase 1974 to 2021 October 15

The following filter was adopted:

- RCT: Wong [219] – Strategy minimizing difference between sensitivity and specificity

#	Searches
1	exp acute coronary syndrome/
2	exp *heart infarction/
3	*percutaneous coronary intervention/
4	((acute adj1 coronary adj1 syndrome*) or (myocardial adj1 infarction)).ti,ab.
5	(percutaneous adj1 coronary adj1 intervention*).ti,ab.
6	or/1-5
7	*clopidogrel/ or *acetylsalicylic acid plus clopidogrel/ or *prasugrel/ or *ticagrelor/
8	(clopidogrel* or prasugrel* or ticagrelor*).ti,ab.
9	or/7-8
10	(random* or double-blind*).tw.
11	placebo*.mp.
12	or/10-11
13	6 and 9 and 12
14	13 not medline.cr.
15	14 not (exp animal/ not exp human/)
16	15 not (Conference Abstract or Conference Review or Editorial).pt.
17	16 not ((afrikaans or albanian or arabic or armenian or azerbaijani or basque or belorussian or bosnian or bulgarian or catalan or chinese or croatian or czech or danish or dutch or english or esperanto or estonian or finnish or french or gallegan or georgian or german or greek or hebrew or hindi or hungarian or icelandic or indonesian or irish gaelic or italian or japanese or korean or latvian or lithuanian or macedonian or malay or norwegian or persian or polish or polyglot or portuguese or pushto or romanian or russian or scottish gaelic or serbian or slovak or slovene or spanish or swedish or thai or turkish or ukrainian or urdu or uzbek or vietnamese) not (english or german)).lg.

3. The Cochrane Library

Search interface: Wiley

- Cochrane Central Register of Controlled Trials: Issue 10 of 12, October 2021

#	Searches
#1	[mh "Myocardial Infarction"] or [mh ^"Acute Coronary Syndrome"]
#2	[mh "Percutaneous Coronary Intervention"]
#3	((acute NEAR/1 coronary NEAR/1 syndrome*) or (myocardial NEAR/1 infarction)):ti,ab
#4	(percutaneous NEAR/1 coronary NEAR/1 intervention*):ti,ab
#5	#1 or #2 or #3 or #4
#6	(clopidogrel* or prasugrel* or ticagrelor*):ti,ab,kw
#7	#5 AND #6
#8	#7 not (*clinicaltrial*gov* or *who*trialsearch* or *clinicaltrialsregister*eu* or *anzctr*org*au* or *trialregister*nl* or *irct*ir* or *isrctn* or *controlled*trials*com* or *drks*de*):so
#9	#8 not ((language next (afr or ara or aze or bos or bul or car or cat or chi or cze or dan or dut or es or est or fin or fre or gre or heb or hrv or hun or ice or ira or ita or jpn or ko or kor or lit or nor or peo or per or pol or por or pt or rom or rum or rus or slo or slv or spa or srp or swe or tha or tur or ukr or urd or uzb)) not (language near/2 (en or eng or english or ger or german or mul or unknown)))
#10	#9 in Trials

A.2 Searches in study registries

1. ClinicalTrials.gov

Provider: U.S. National Institutes of Health

- URL: http://www.clinicaltrials.gov
- Type of search: Expert Search

Search strategy
(clopidogrel OR SC-25989C OR SC-25990C OR SR-25989 OR PCR-4099 OR prasugrel OR CS-747 OR LY-640315 OR ticagrelor OR AZD-6140) AND (acute coronary syndrome OR myocardial infarction)

2. EU Clinical Trials Register

Provider: European Medicines Agency

- URL: https://www.clinicaltrialsregister.eu/ctr-search/search
- Type of search: Basic Search

Search strategy
clopidogrel* OR SC-25989C OR SC25989C OR SC-25990C OR SC25990C OR SR-25989 OR SR25989 OR PCR-4099 OR PCR4099 OR prasugrel* OR CS-747 OR CS747 OR LY-640315 OR LY640315 OR ticagrelor* OR AZD-6140 OR AZD6140

3. International Clinical Trials Registry Platform Search Portal

Provider: World Health Organization

- URL: https://trialsearch.who.int
- Type of search: Standard Search

Search strategy
(clopidogrel OR SC-25989C OR SC25989C OR SC 25989C OR SC-25990C OR SC25990C OR SC 25990C OR SR-25989 OR SR25989 OR SR 25989 OR PCR-4099 OR PCR4099 OR PCR 4099 OR prasugrel OR CS-747 OR CS747 OR CS 747 OR LY-640315 OR LY640315 OR LY 640315 ticagrelor OR AZD-6140 OR AZD6140 OR AZD 6140) AND (acute coronary syndrome OR acute coronary syndrome OR acute coronary syndromes OR myocardial infarction OR myocardial infarctions)

A.3 Further information sources and search techniques

Regulatory agencies

EMA

URL: https://www.ema.europa.eu/en/medicines

Search terms
Clopidogrel
Prasugrel
Ticagrelor

FDA

URL: https://www.accessdata.fda.gov/scripts/cder/daf/

Search terms
Clopidogrel
Prasugrel
Ticagrelor

G-BA-Website und IQWiG-Website

G-BA

URL: https://www.g-ba.de/

Search terms
Clopidogrel
Prasugrel
Ticagrelor

IQWiG

URL: https://www.iqwig.de/

Search terms
Clopidogrel
Prasugrel
Ticagrelor