



# Coronary revascularisation: Cangrelor

Evidence summary

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[www.nice.org.uk/guidance/esnm63](http://www.nice.org.uk/guidance/esnm63)

## Key points from the evidence

The content of this evidence summary was up-to-date in November 2015. See [summaries of product characteristics \(SPCs\)](#), [British national formulary \(BNF\)](#) or the [MHRA](#) or [NICE](#) websites for up-to-date information.

## Summary

Cangrelor statistically significantly reduced the risk of periprocedural ischaemic events compared with clopidogrel in a large RCT of people receiving periprocedural aspirin who underwent percutaneous coronary intervention (PCI) for mixed indications without P2Y12 inhibitor pre-treatment, with a number needed to treat of 84 at 48 hours. However, it did not statistically significantly reduce mortality and clinical benefits were described by the European Medicines Agency as modest. Bleeding and dyspnoea events were more frequent in the cangrelor group (numbers needed to harm of 26 and 142 at 48 hours for mild bleeding and dyspnoea respectively).

There are no published studies comparing cangrelor with other oral antiplatelet agents for people undergoing PCI. In the pivotal study, the treatment pathway differed from usual UK practice regarding choice of oral antiplatelet drug and this limits the applicability of the evidence to UK practice where prasugrel and ticagrelor have superseded clopidogrel as the standard of care for people with unstable angina, non-ST-segment-elevation myocardial infarction and myocardial infarction with ST-segment-elevation. Cangrelor, co-administered with aspirin, is therefore a second-line treatment option for use in people with coronary artery disease undergoing PCI for whom oral therapy with P2Y12 inhibitors is not feasible or desirable.

Cangrelor was considered appropriate for a NICE technology appraisal but NICE is unable to make a recommendation about the use in the NHS of cangrelor for the licensed indication because no evidence submission was received from the manufacturer of the technology.

**Regulatory status:** Cangrelor received a European marketing authorisation in March 2015 and was launched in the UK in July 2015.

Effectiveness	Safety
<ul style="list-style-type: none"> <li>In 1 double-blind, double-dummy RCT in people with non-ST-segment-elevation myocardial infarction (NSTEMI), ST-segment-elevation myocardial infarction (STEMI) or stable angina undergoing PCI (n=11,145) and receiving aspirin, cangrelor bolus plus infusion followed by transition to a loading dose of clopidogrel statistically significantly reduced the risk of a composite outcome of death from any cause, myocardial infarction (MI), ischaemia-driven revascularisation or stent thrombosis at 48 hours compared with a single loading dose of clopidogrel (number needed to treat [NNT] 84, p=0.005).</li> <li>The <a href="#">European public assessment report for cangrelor</a> states that the results of the pivotal study were driven by the statistically significantly lower incidence of MI and stent thrombosis; there was no statistically significant reduction in mortality.</li> </ul>	<ul style="list-style-type: none"> <li>In a pooled analysis of 3 RCTs of similar design to the efficacy study (n=25,107), the incidence of GUSTO-defined severe bleeding at 48 hours was not statistically significantly increased in the cangrelor group compared with the clopidogrel group. There was a statistically significant increase in the risk of ACUITY-defined major bleeding at 48 hours (number needed to harm [NNH] 71). The NNH for GUSTO-defined mild bleeding at 48 hours was 26. The NNH for dyspnoea was 142.</li> <li>Cangrelor is contraindicated in people with active bleeding or at increased risk of bleeding, and in people with a history of stroke or transient ischaemic attack. It should be used with caution in people with severe renal impairment (creatinine clearance 15–30 mL/minute) because of a risk of worsening of renal function and increased risk of bleeding.</li> </ul>

Patient factors	Resource implications
<ul style="list-style-type: none"> <li>• Cangrelor is administered intravenously over 2 to 4 hours during PCI procedures.</li> <li>• There are no comparative data with either prasugrel or ticagrelor during PCI procedures.</li> <li>• The <a href="#">summary of product characteristics</a> for cangrelor states that when clopidogrel is administered during infusion of cangrelor, the expected inhibitory effect of clopidogrel on platelets is not achieved. For transition, a loading dose of oral P2Y12 therapy (clopidogrel, ticagrelor or prasugrel) should be administered immediately following discontinuation of cangrelor infusion.</li> </ul>	<ul style="list-style-type: none"> <li>• The cost of cangrelor 50 mg powder for injection is £250 per vial (excluding VAT; prices taken from <a href="#">MIMS</a> October 2015). This equates to £250 to £500 per PCI procedure (for an average 70 kg person)</li> <li>• PCI periprocedural costs for other oral antiplatelet agents range from 26p to £10.19 (excluding VAT; prices taken from <a href="#">Drug Tariff</a> October 2015).</li> </ul>
<p>Abbreviations:</p> <p>GUSTO: Global Utilisation of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries</p> <p>ACUITY: Acute Catheterization and Urgent Intervention Triage strategy</p>	

## Introduction and current guidance

Coronary revascularisation (widening of blocked or narrowed coronary arteries) is undertaken using a procedure called coronary angioplasty where a balloon catheter is used to dilate the artery from within. Most modern angioplasty procedures also involve inserting a permanent stent into the artery during the procedure to improve blood flow. This procedure is called percutaneous coronary intervention (PCI).

NICE guidance on [stable angina](#) recommends that coronary revascularisation is an option for people whose symptoms are not satisfactorily controlled with optimal medical treatment. In such circumstances, PCI is usually a pre-planned (elective) process. NICE guidance on the [acute management of myocardial infarction with ST-segment-elevation \(STEMI\)](#) and NICE guidance on [unstable angina and non-ST-segment-elevation myocardial infarction \(NSTEMI\)](#) recommend that people with unstable angina, NSTEMI or STEMI

usually require PCI more urgently. For all people undergoing PCI, there is an increased risk of periprocedural ischaemic events. The full NICE guideline on [unstable angina and NSTEMI](#) explains that antithrombotic therapy reduces this and subsequent risk. NICE guidance recommends oral antiplatelet agents in addition to aspirin for people undergoing PCI.

The NICE pathways [stable angina](#) and [acute coronary syndromes](#) bring together all related NICE guidance and associated products on these conditions in a set of interactive topic-based diagrams.

Full text of [introduction and current guidance](#).

## Product overview

Cangrelor ([Kengrexal](#)) is licensed for reducing the risk of thrombotic cardiovascular events in adults with coronary artery disease undergoing PCI who have not received an oral P2Y12 inhibitor prior to the PCI procedure and in whom oral therapy with P2Y12 inhibitors is not feasible or desirable. It is licensed only for co-administration with aspirin. Oral P2Y12 inhibitors include clopidogrel, prasugrel and ticagrelor.

Cangrelor is administered intravenously and provides reversible, rapid-onset but short-acting P2Y12 platelet receptor inhibition. The recommended dose of cangrelor is a 30 micrograms/kg intravenous bolus followed immediately by 4 micrograms/kg per minute intravenous infusion. The bolus and infusion should be initiated prior to the PCI procedure and continued for at least 2 hours or for the duration of the procedure, whichever is longer. At the discretion of the physician, the infusion may be continued for a total duration of 4 hours. For continuation of long-term treatment, people should be changed onto oral antiplatelet therapy, such as clopidogrel, prasugrel or ticagrelor, post-procedure.

Cangrelor was considered appropriate for a NICE technology appraisal. NICE is unable to make a recommendation about the use in the NHS of cangrelor for reducing atherothrombotic events in people with coronary artery disease undergoing PCI (or in people awaiting surgery requiring interruption of antiplatelet therapy) because no evidence submission was received from the manufacturer of the technology ([terminated appraisal 351](#)).

Full text of [product overview](#).

## Evidence review

- The efficacy and safety of cangrelor in its licensed indication have been studied in 3 large double-blind, phase III, randomised controlled trials (RCTs) conducted as part of the CHAMPION programme. These have all been published in full.
- CHAMPION PHOENIX (Bhatt et al. 2013) provides the best available evidence for the efficacy of cangrelor in its licensed indication. Two earlier RCTs of a very similar design, CHAMPION PLATFORM (Bhatt et al. 2009, n= 5362) and CHAMPION PCI (Harrington et al. 2009, n= 8877) were stopped early as interim analysis showed that the primary outcome would not be achieved. The definition of myocardial infarction (MI) used in CHAMPION PHOENIX was amended from that used in the earlier CHAMPION studies, to avoid confounding periprocedural MIs with evolving preprocedural MIs. CHAMPION PLATFORM and CHAMPION PCI are not discussed in detail but combined pooled data from all 3 RCTs (Steg et al. 2013) provide the main body of safety data for cangrelor and are discussed in the safety section.
- CHAMPION PHOENIX (Bhatt et al. 2013) had a double-blind, double-dummy design and recruited people with stable angina, NSTEMI or STEMI who were undergoing either urgent or elective PCI. Participants in the cangrelor group received oral placebo plus cangrelor as a bolus (30 microgram/kg) followed immediately by infusion at 4 microgram/kg per minute for at least 2 hours or until the end of the procedure, whichever was the longer. At the discretion of the treating physician, the infusion could be continued for a total duration of 4 hours. At the end of the infusion, participants in this group received a 600 mg dose of clopidogrel orally. Participants in the clopidogrel group received placebo bolus and infusion and a single oral dose of either 300 mg or 600 mg clopidogrel immediately before or immediately after PCI (dose and time at the discretion of the treating physician), with oral placebo at the end of the placebo infusion.

- In CHAMPION PHOENIX the rate of the primary composite outcome of periprocedural ischaemic events (all-cause death, MI, ischaemia-driven revascularisation, or stent thrombosis at 48 hours) was statistically significantly lower in the cangrelor group compared with the clopidogrel group (4.7% compared with 5.9%, odds ratio [OR] 0.78, 95% confidence interval [CI] 0.66 to 0.93, p=0.005). A statistically significant reduction in the rate of periprocedural MI accounted for most of the benefit (3.8% compared with 4.7%, OR 0.80, 95% CI 0.67 to 0.97, p=0.02). The incidence of stent thrombosis at 48 hours also was statistically significantly lower in the cangrelor group. The European public assessment report for cangrelor (EPAR) describes these benefits as modest.
- In the pooled analysis of the 3 CHAMPION studies (Steg et al. 2013) there was no statistically significant difference in the rate of GUSTO-defined severe non-CABG-related bleeding at 48 hours (p=0.49). However, there was a statistically significant increase in ACUITY-defined major bleeding in the cangrelor group (4.2% compared with 2.8%, OR 1.53, 95% CI 1.34 to 1.76, p<0.0001). This was due in part to the increased number of large haematomas in the cangrelor group but persisted after excluding these. Cangrelor was also associated with an increased rate of less severe bleeding events compared with clopidogrel such as GUSTO mild bleeding (absolute risk reduction [ARR] 3.8%, OR 1.35, 95% CI 1.26 to 1.45, p<0.0001). Transient dyspnoea was reported more frequently with cangrelor than with clopidogrel (1.1% compared with 0.4%, p<0.0001). Serious adverse events were reported at the same frequency in both the cangrelor and comparator groups (2.2%).
- The Kengrexal summary of product characteristics (SPC) states that in pivotal studies conducted in patients undergoing PCI, there were more intracranial bleeds, including fatal bleeds, at 30 days with cangrelor (0.07%) than with clopidogrel (0.02%), and a higher rate of cardiac tamponades at 30 days with cangrelor (0.12%) than with clopidogrel (0.02%). In patients with severe renal impairment (creatinine clearance 15–30 mL/min) a higher rate of worsening in renal function (3.2%) was reported with cangrelor compared to clopidogrel (1.4%) and a higher rate of GUSTO moderate bleeding was reported with cangrelor (6.7%) compared to clopidogrel (1.4%).

- The [EPAR](#) states that the study design of CHAMPION PHOENIX was not optimal and may have favoured cangrelor, although it was accepted as reliable and representative of the diversity of current EU clinical practice. The [EPAR](#) notes inclusion in the study population of 3 subsets of people with different diagnoses but states that the size of the effect of cangrelor appeared consistent irrespective of the initial presentation and that the results can be generalised to all 3 patient groups. Nevertheless, the [EPAR](#) also states that the exclusion of people with a history of prior stroke limits the validity of the study to clinical practice. Furthermore, in the control arm the loading dose of clopidogrel was either 300 mg or 600 mg and could be given at the beginning or end of PCI, although the [EPAR](#) states that the effect of cangrelor seemed consistent irrespective of the timing of clopidogrel administration.
- In addition to these issues with the study design, the treatment pathway in CHAMPION PHOENIX ([Bhatt et al. 2013](#)) differs from usual UK practice regarding choice of antiplatelet drug. Specialists involved the production of this evidence summary advise that in UK practice prasugrel and ticagrelor have superseded clopidogrel as the standard of care for people with unstable angina, NSTEMI and STEMI. This limits the applicability to UK practice of evidence from CHAMPION PHOENIX and the wider CHAMPION programme. The [EPAR](#) states that prasugrel and ticagrelor may have been more valid comparators.

Full text of [evidence review](#).

## Context

The P2Y12 inhibitors clopidogrel, prasugrel and ticagrelor are licensed for use, in combination with aspirin, for the prevention of thrombotic events in people with acute coronary syndrome or STEMI, including those people undergoing PCI (see [summaries of product characteristics](#) for specific licensed indications). NICE guidance and European guidelines recommend the use of these oral antiplatelet agents as treatment options for people with coronary artery disease undergoing PCI (in specified circumstances). Cangrelor is licensed for use only if it is co-administered with aspirin and only in people undergoing PCI who have not received an oral P2Y12 inhibitor prior to the PCI procedure and in whom oral therapy with P2Y12 inhibitors is not feasible or desirable.

Full text of [context](#).



## Estimated impact for the NHS

Based on the evidence and licensed indication, cangrelor is a second-line treatment option. It should be considered only when treatment with oral antiplatelet agents is not feasible or desirable. During assessment of the marketing authorisation application for cangrelor, the Committee for medicinal products for human use (CHMP) stated that the benefit of cangrelor was modest but noted that intravenous administration of an antiplatelet agent with a fast offset of action can be useful in selected people undergoing PCI ([CHMP meeting minutes, January 2015](#)).

Two further caveats apply to the use of cangrelor. Firstly, in CHAMPION PHOENIX ([Bhatt et al. 2013](#)) almost all participants received periprocedural aspirin and this is reflected in the [licensed indication](#). Only oral forms of aspirin are available as licensed products in the UK, thus the person would usually be conscious and able to take aspirin orally (or have taken it that day) and have no contraindications to its use. Administering cangrelor without periprocedural aspirin would be an off-label use of the drug (note that prasugrel and ticagrelor are also both licensed for use only when co-administered with aspirin).

Secondly, the [SPC](#) states that when clopidogrel is administered during infusion of cangrelor, the expected inhibitory effect of clopidogrel on platelets is not achieved. Consequently, it is important that the loading dose of clopidogrel is delayed until the infusion finishes. The SPC states that no clinically relevant interruption of P2Y12 inhibition was observed in phase III studies when 600 mg clopidogrel was administered immediately after discontinuation of the cangrelor infusion, but this is an unlicensed dose of clopidogrel.

Any potential clinical benefits must be considered in the context of potential harms and RCT data show an increased risk of bleeding events and transient breathlessness with cangrelor compared with clopidogrel.

As well as efficacy, safety and individual user factors, local decision makers will need to take cost into account when considering the likely place in therapy of cangrelor. Costs for oral antiplatelet agents used periprocedurally range from 26p to £10.19 per procedure, whereas the estimated average cost of cangrelor per procedure is £250 to £500.

Full text of [estimated impact for the NHS](#).

### About this evidence summary

'Evidence summaries: new medicines' provide summaries of key evidence for selected new medicines, or for existing medicines with new indications or formulations, that are considered to be of significance to the NHS. The strengths and weaknesses of the relevant evidence are critically reviewed within this summary to provide useful information for those working on the managed entry of new medicines for the NHS, **but this summary is not NICE guidance.**

## Full evidence summary

### Introduction and current guidance

Coronary revascularisation (widening of blocked or narrowed coronary arteries) is undertaken using a procedure called percutaneous transluminal coronary angioplasty, usually referred to as percutaneous coronary intervention (PCI). A balloon catheter is used to dilate the artery from within. Most PCI procedures also involve inserting a short wire-mesh tube, called a stent, into the artery during the procedure. The stent is left in place permanently to allow blood to flow more freely. PCI is an alternative coronary revascularisation technique to coronary artery bypass grafting (CABG) for treating coronary artery disease. PCI is recommended as an option within NICE guidance in 3 clinical situations: stable angina, myocardial infarction with ST-segment-elevation (STEMI), and unstable angina and non-ST-segment-elevation myocardial infarction (NSTEMI).

NICE guidance on [stable angina](#) recommends that coronary revascularisation (CABG or PCI) is an option for people whose symptoms are not satisfactorily controlled with optimal medical treatment. In these circumstances, PCI is usually a pre-planned (elective) process.

NICE guidance on the [acute management of STEMI](#) recommends that coronary reperfusion therapy should be delivered as quickly as possible for people with acute STEMI. Coronary angiography (with follow-on PCI if indicated) is NICE's preferred coronary reperfusion strategy if the person presents within 12 hours of onset of symptoms and primary PCI can be delivered within 120 minutes of the time when fibrinolysis could have been given.

NICE guidance on [unstable angina and NSTEMI](#) recommends offering coronary

angiography (with follow-on PCI if indicated) to people who have no contraindications to angiography and an intermediate or higher risk of adverse cardiovascular events or have ischaemia. It should be performed as soon as possible for people who are clinically unstable or at high ischaemic risk.

The full NICE guideline on [unstable angina and NSTEMI](#) explains that, for all people undergoing PCI, there is an increased risk of platelet aggregation and thrombus formation which may lead to periprocedural ischaemic events such MI or stent thrombosis. Antithrombotic therapy reduces this and subsequent risk. NICE recommends the following antiplatelet drugs as options in PCI, in combination with aspirin (300 mg loading dose, followed by 75 mg daily):

- [Clopidogrel](#) (300 mg loading dose and then 75 mg daily continued for up to 12 months) is a treatment option in people who have had an NSTEMI regardless of treatment and in people who have had a STEMI and have received a stent: see NICE guidance on [unstable angina and NSTEMI](#) and on [secondary prevention of MI](#).
- [Prasugrel](#) (60 mg loading dose and then 10 mg daily continued for up to 12 months) is a treatment option in adults with STEMI, unstable angina or NSTEMI, who are having primary or delayed PCI: see NICE [guidance on prasugrel with PCI](#).
- [Ticagrelor](#) (180 mg loading dose and then 90 mg twice daily continued for up to 12 months) is a treatment option in adults with STEMI who are to receive PCI, unstable angina or NSTEMI: see NICE guidance on [ticagrelor](#).

European Society of Cardiology (ESC) clinical practice guidelines on [myocardial revascularisation](#) state that because clopidogrel is a prodrug with a slower onset of action and a larger variability in oral bioavailability, the faster-acting antiplatelet agents prasugrel or ticagrelor are recommended in preference to clopidogrel for use in people with unstable angina, NSTEMI or STEMI who are undergoing PCI. If these are contraindicated or unavailable, the European [guidelines](#) recommend a 600 mg clopidogrel loading dose is used. The European [guidelines](#) also recommend pre-treatment with clopidogrel 600 mg for people undergoing elective PCI, preferably 2 hours or more before the procedure. This dose is higher than the 300 mg clopidogrel licensed in Europe for these indications but it is acknowledged in the [European public assessment report for cangrelor \(Kengrexal, EPAR\)](#) that 600 mg clopidogrel is more effective. Specialists involved in the production of this evidence summary advise that in UK practice prasugrel and ticagrelor have superseded clopidogrel as the standard of care for people with unstable angina, NSTEMI and STEMI.

The NICE pathways on [acute coronary syndromes](#) and [stable angina](#) bring together all related NICE guidance and associated products on these conditions in a set of interactive topic-based diagrams.

## Product overview

### Drug action

Cangrelor is an intravenous, direct P2Y<sub>12</sub> platelet receptor inhibitor that blocks adenosine diphosphate (ADP)-induced platelet activation and aggregation. Cangrelor provides rapid-onset P2Y<sub>12</sub> inhibition (within a few minutes) with reversible binding and has a half-life of 3 to 6 minutes.

### Licensed therapeutic indication

Cangrelor ([Kengrexal](#)) is licensed for reducing the risk of thrombotic cardiovascular events in adults with coronary artery disease undergoing PCI who have not received an oral P2Y<sub>12</sub> inhibitor prior to the PCI procedure and in whom oral therapy with P2Y<sub>12</sub> inhibitors is not feasible or desirable. It is licensed only for co-administration with aspirin. Oral P2Y<sub>12</sub> inhibitors include clopidogrel, prasugrel and ticagrelor.

### Course and cost

The [Kengrexal summary of product characteristics](#) (SPC) states that the recommended dose of cangrelor is a 30 micrograms/kg intravenous bolus followed immediately by 4 micrograms/kg per minute intravenous infusion. The bolus and infusion should be initiated prior to the procedure and continued for at least 2 hours or for the duration of the procedure, whichever is longer. At the discretion of the physician, the infusion may be continued for a total duration of 4 hours. For continuation of long-term treatment, people should be changed onto oral P2Y<sub>12</sub> therapy post-procedure. For transition to this, a loading dose of oral P2Y<sub>12</sub> therapy (clopidogrel, prasugrel or ticagrelor) should be administered immediately following discontinuation of cangrelor infusion. Alternatively, a loading dose of ticagrelor or prasugrel, but not clopidogrel, may be administered up to 30 minutes before the end of the infusion. No dose adjustment of cangrelor is required in people aged 75 years or older or in people with renal or hepatic impairment, but caution is advised when administering cangrelor to people with severe renal impairment (creatinine clearance 15–30 mL/minute).

Cangrelor is available as a 50 mg powder for concentrate for solution for infusion and costs £250 per vial.

## Evidence review

Cangrelor was considered appropriate for a NICE technology appraisal. NICE is unable to make a recommendation about the use in the NHS of cangrelor for reducing atherothrombotic events in people with coronary artery disease undergoing PCI (or in people awaiting surgery requiring interruption of antiplatelet therapy) because no evidence submission was received from the manufacturer of the technology ([terminated appraisal 351](#)).

The efficacy and safety of cangrelor in its licensed indication have been studied in 3 large double-[blind](#), phase III, randomised controlled trials (RCTs) conducted as part of the CHAMPION programme. These 3 studies were undertaken by the same group of investigators, had similar trial designs and protocols and were all published individually. CHAMPION PLATFORM ([Bhatt et al. 2009](#)) and CHAMPION PCI ([Harrington et al. 2009](#)) were stopped early following interim analysis which identified that the primary end point in both studies was unlikely to be achieved. This summary of the evidence for efficacy of cangrelor is therefore based on CHAMPION PHOENIX ([Bhatt et al. 2013](#)) because this is the only published RCT that achieved its primary objective. A pooled analysis of all 3 of the CHAMPION RCTs ([Steg et al. 2013](#)) provides the main body of safety data and is discussed in the safety section of this evidence summary. Information from the [EPAR](#) has been used to clarify and supplement data from the published RCTs included in this evidence summary.

### **Effect of cangrelor on periprocedural outcomes in percutaneous coronary interventions: CHAMPION PHOENIX** [Bhatt et al. 2013](#)

- Design: CHAMPION PHOENIX ([Bhatt et al. 2013](#)) was a randomised (1:1 ratio), controlled, double-blind, double-dummy trial conducted in 153 centres (40% of patients were enrolled in Europe, none in the UK). [Allocation was concealed](#).

- Population: 11,145 participants were enrolled. The modified intention-to-treat (mITT) population, (n=10,942) included all participants who underwent PCI and received at least 1 dose of the study drug (median age 64 years, 28% female). Eligible patients were those with coronary atherosclerosis who required PCI for stable angina (56% of the mITT population), NSTEMI-ACS (26% of the mITT population) or STEMI (18% of the mITT population). Exclusion criteria included prior stroke, receipt of a P2Y12 inhibitor or abciximab during the 7 days before randomisation or fibrinolytic therapy or a glycoprotein IIb/IIIa inhibitor in the 12 hours before randomisation. Baseline demographics and characteristics (including previous cardiovascular disease) were similar and distributed evenly across the 2 treatment groups. Unless contraindicated, all participants received aspirin starting any time on the day of the PCI and continuing for at least 30 days after the procedure; in fact nearly all patients in the mITT population (94%) received periprocedural aspirin (75–325 mg). In addition, 92% of them received periprocedural fractionated or unfractionated heparin, 23% received bivalirudin and 3% received fondaparinux. Although similar numbers of participants in both groups received each of these treatments, they were all administered according to the treating physician's discretion and no published data on doses, timing or duration of treatment are available. Bailout use of glycoprotein IIb/IIIa inhibitors was permitted and occurred in 2.3% of cangrelor participants and 3.5% of clopidogrel participants in the mITT population. A total of 56% of participants received drug-eluting stents and 42% received bare-metal stents.

- Intervention and comparator: Randomisation occurred once suitability for PCI had been confirmed by angiography or STEMI diagnosis. Intravenous therapy was commenced as soon as possible after randomisation in people with STEMI and no more than 30 minutes before guide wire insertion in other patients. Participants randomised to the cangrelor group received cangrelor as a bolus (30 microgram/kg) followed immediately by infusion at 4 microgram/kg per minute for at least 2 hours or until the end of the procedure, whichever was the longer. At the discretion of the treating physician, the infusion could be continued for a total duration of 4 hours. These patients also received oral placebo immediately before or immediately after PCI and 600 mg clopidogrel orally at the end of the infusion. Participants randomised to the clopidogrel group received placebo bolus and infusion and a single oral dose of either 300 mg or 600 mg clopidogrel administered either immediately before or immediately after PCI, with oral placebo at the end of the placebo infusion. The dose and timing of the periprocedural clopidogrel was at the discretion of the treating physician: 74% of patients received 600 mg and 63% received it before PCI. Patients in both groups received clopidogrel 75 mg within the first 48 hours after the procedure; thereafter, clopidogrel or another P2Y12 inhibitor could be administered at the discretion of the treating physician, according to local guidelines.
- Outcomes: The primary outcome was a composite of all-cause death, myocardial infarction (MI), ischaemia-driven revascularisation, or stent thrombosis at 48 hours. Secondary outcomes included stent thrombosis at 48 hours and events of death, MI, ischemia-driven revascularisation and stent thrombosis that occurred during the first 30 days after randomisation. The primary efficacy analysis was conducted in the mITT population excluding people lost to follow-up or who withdrew consent (n=3 at 48 hours and a further 20 at 30 days).

CHAMPION PCI ([Harrington et al. 2009](#), n=8667) and CHAMPION PLATFORM ([Bhatt et al. 2009](#), n=5362) also compared cangrelor with clopidogrel in patients receiving PCI, with similar study designs. CHAMPION PCI recruited people with stable angina, NSTEMI or STEMI. CHAMPION PLATFORM recruited people with stable angina or NSTEMI. In both studies cangrelor was administered at the same dosage and duration as in CHAMPION PHOENIX and was followed by clopidogrel 600 mg at the end of the infusion. Participants in the control arms of both studies received a placebo bolus and infusion plus a single 600 mg dose of clopidogrel administered either at the start of the infusion (in CHAMPION PCI) or at the end of the PCI procedure (in CHAMPION PLATFORM). The primary endpoints in CHAMPION PCI and CHAMPION PLATFORM were identical and were similar to that in CHAMPION PHOENIX (a composite of all-cause death, MI, or ischaemia-driven revascularisation within 48 hours after PCI). However, the definition of MI in CHAMPION

PHOENIX, the Universal Definition of MI, was amended from that used in the earlier CHAMPION studies to avoid confounding periprocedural MIs with evolving preprocedural MIs. The primary composite outcome in the earlier CHAMPION studies did not include stent thrombosis.

The primary safety outcome in CHAMPION PHOENIX was severe bleeding not related to CABG, as defined by the Global Utilisation of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) criteria, at 48 hours after PCI. Secondary safety outcomes included Thrombolysis in Myocardial Infarction (TIMI) and Acute Catheterization and Urgent Intervention Triage strategy (ACUITY) defined bleeding (Bhatt et al. 2013). Data relating to the same bleeding outcomes were collected in the other 2 CHAMPION RCTs (although no specific primary safety outcome was defined in these: Steg et al. 2013). Data relating to adverse events were also collated and analysed in all 3 RCTs.

**Table 1 Summary of CHAMPION PHOENIX (Bhatt et al. 2013)**

	Cangrelor plus clopidogrel	Clopidogrel	Analysis
Randomised	n=5581	n=5564	
<b>Efficacy<sup>a</sup></b>	n=5472	n=5470	
Primary outcome: composite of death from any cause, MI, Ischaemia-driven revascularisation, or stent thrombosis at 48 hours	4.7% (257/5470)	5.9% (322/5469)	adjusted OR <sup>b</sup> 0.78, 95% CI 0.66 to 0.93 p=0.005
Selected secondary outcomes:			
Incidence of stent thrombosis at 48 hours	0.8% (46/5470)	1.4% (74/5469)	adjusted OR <sup>b</sup> 0.62, 95% CI 0.43 to 0.90 p=0.01
Incidence of MI at 48 hours	3.8% (207/5470)	4.7% (255/5469)	adjusted OR <sup>b</sup> 0.80, 95% CI 0.67 to 0.97 p=0.02



Death from any cause	0.3% (18/5470)	0.3% (18/5469)	adjusted OR <sup>b</sup> 1.00, 95% CI 0.52 to 1.92 p>0.999
Composite of death from any cause, MI, Ischaemia-driven revascularisation, or stent thrombosis at 30 days	6.0%	7.0%	adjusted OR <sup>b</sup> 0.85 95% CI 0.73 to 0.99 p=0.03
Abbreviations: OR, <u>odds ratio</u> ; CI, <u>confidence interval</u> ; MI, myocardial infarction; p, <u>p value</u> ;			
<sup>a</sup> Modified <u>intention-to-treat population</u> : all participants who underwent PCI and received study drug. Two people were lost to follow-up in the cangrelor group and 1 person in the clopidogrel group withdrew consent post-procedure by 48 hours, and between 48 hours and 30 days a further 8 people in the cangrelor group and 9 people in the clopidogrel group were lost to follow up, and 3 people in the clopidogrel group withdrew their consent. These people were not included in analyses.			
<sup>b</sup> Prespecified logistic-regression analysis, which adjusted for baseline status and clopidogrel loading dose.			

**Table 2 Safety data from a combined pooled analysis of patient level data of the 3 CHAMPION studies (Steg et al. 2013)**

	Cangrelor plus clopidogrel	Clopidogrel <sup>b</sup>	Analysis
<b>Randomised</b>	n=12,604	n=12,564	
<b>Safety<sup>a</sup></b>	n=12,565	n=12,542	
GUSTO severe non-CABG-related bleeding at 48 hours	0.2% (28/12,565)	0.2% (23/12,542)	OR 1.22, 95% CI 0.70 to 2.11, p=0.49
Any GUSTO non-CABG-related bleeding at 48 hours <sup>c</sup>	17.5% (2196/12,565)	13.5% (1696/12,542)	OR 1.35, 95% CI 1.26 to 1.45, p=0.0001
TIMI major bleeding	0.3% (32/12,565)	0.2% (28/12,542)	OR 1.14, 95% CI 0.69 to 1.90, p=0.61

TIMI major or minor bleeding	0.9% (109/ 12,565)	0.6% (79/ 12,542)	OR 1.38, 95% CI 1.03 to 1.85, p=0.029
ACUITY major bleeding	4.2% (534/ 12,565)	2.8% 353/ 12,542)	OR 1.53, 95% CI 1.34 to 1.76, p<0.0001
ACUITY major or minor bleeding	17.5% (2196/ 12,565)	13.5% (1696/ 12,542)	OR 1.35, 95% CI 1.26 to 1.45, p<0.0001
Any adverse event	23.1% (2900/12,565)	21.9% (2745/ 12,542)	p=0.024
Serious adverse events	2.2% (281/12,565)	2.2% (270/ 12,542)	p=0.65
Discontinuations due to adverse events	0.6% (74/ 12,565)	0.4% (51/ 12,542)	p=0.04
Dyspnoea	1.1% (143/12,565)	0.4% (48/12,542)	p<0.0001
Abbreviations: OR, <u>odds ratio</u> ; CI, <u>confidence interval</u> ; p, <u>p value</u>			
<sup>a</sup> Safety population: all participants who underwent randomisation and received at least 1 dose of study drug.			
<sup>b</sup> Pooled comparator data for placebo and clopidogrel.			

## Clinical effectiveness

Cangrelor bolus plus infusion followed by transition to a loading dose of clopidogrel statistically significantly reduced the risk of periprocedural ischaemic events compared with a single loading dose of clopidogrel in a large RCT of people receiving periprocedural aspirin who underwent PCI for mixed indications without P2Y12 inhibitor pre-treatment. It did not statistically significantly reduce mortality, and the positive results were mainly driven by a reduction in the rate of acute periprocedural MI and stent thrombosis. The number needed to treat for the primary outcome of death from any cause, MI, ischaemia-driven revascularisation or stent thrombosis at 48 hours was 84 (Bhatt et al. 2013). The incidence of MI and of stent thrombosis at 48 hours was also statistically

significantly lower in the cangrelor group compared with the clopidogrel group (absolute risk reduction [ARR] 0.9%,  $p=0.02$  and 0.6%,  $p=0.01$ , respectively, see table 1, [Bhatt et al. 2013](#)). Benefits for people in the cangrelor group compared with clopidogrel, in terms of reduction in the odds of ischaemic events following PCI, were maintained at 30 days (see table 1, [Bhatt et al. 2013](#)).

The first 2 studies in the phase III clinical evaluation of the efficacy of cangrelor, CHAMPION PLATFORM ([Bhatt et al. 2009](#)) and CHAMPION PCI ([Harrington et al. 2009](#)) were terminated early as interim analysis showed that cangrelor did not statistically significantly reduce the primary outcome of periprocedural events in PCI (a composite of death from any cause, MI or ischaemia-driven revascularisation at 48 hours). The third, larger RCT, CHAMPION PHOENIX ([Bhatt et al. 2013](#)) used a narrower definition of MI. The authors state that this increased the sensitivity of the analysis to discriminate between events occurring before and after randomisation. They suggest that this is why the clinical benefits of cangrelor in the 2 previous studies were limited to secondary outcomes (primarily stent thrombosis at 48 hours), whereas in CHAMPION PHOENIX cangrelor was statistically significantly superior to clopidogrel for the primary composite outcome (see table 1 above).

## Safety and tolerability

The safety population from the pooled analysis ([Steg et al. 2013](#)) provides data for a large number of people ( $n=25,107$ ) approximately half of whom were exposed to cangrelor (see table 2). All participants in the safety population were followed up for 30 days and more than half were followed up for up to 1 year. The [EPAR](#) states that the safety database is adequate for the licensed indication and the maximum duration (4 hours) of treatment.

The CHAMPION studies evaluated bleeding events according to 3 definitions: GUSTO, TIMI and ACUITY. GUSTO and TIMI criteria have been used for several decades and were initially used to identify significant bleeding in the setting of fibrinolytic therapy for STEMI. ACUITY criteria have been developed by adapting the components of TIMI major and GUSTO severe/moderate bleeding that are relevant to patients undergoing PCI ([Mehran et al, 2011](#)).

The [EPAR](#) states that the results from the CHAMPION studies show that there was a statistically significant higher bleeding risk associated with cangrelor (17.5%) compared with clopidogrel (13.5%) at 48 hours (see table 2). There was no statistically significant difference in the rate of GUSTO severe non-CABG-related bleeding at 48 hours (see

table 2). However, there was a statistically significant increase in ACUITY major bleeding in the cangrelor group (4.2% compared with 2.8%, absolute risk difference 1.4%, OR 1.53, 95% CI 1.34 to 1.76,  $p < 0.0001$ ). This was in part due to an increased number of haematomas at the puncture site that were 5 cm or larger, but persisted after exclusion of these haematomas (1.3% compared with 1.0%, OR 1.38, 95% CI 1.09 to 1.74,  $p = 0.007$ ). The number needed to harm for ACUITY major bleeding at 48 hours was 71, and for ACUITY major bleeding at 48 hours excluding puncture site haematomas 5 cm or larger it was 333.

There was no statistically significant difference in GUSTO moderate bleeding, in TIMI major bleeding, or in the rate of transfusions. Cangrelor did increase the rate of less severe bleeding events such as GUSTO mild bleeding (ARR 3.8%, OR 1.35, 95% CI 1.26 to 1.45,  $p < 0.0001$ ), TIMI minor bleeding or ACUITY minor bleeding compared with clopidogrel. In the pooled analysis (Steg et al. 2013) the number needed to harm for GUSTO mild bleeding at 48 hours was 26. Fatal bleeding occurred in 0.1% of participants in each group.

Transient dyspnoea was also reported more frequently with cangrelor compared with clopidogrel (1.1% compared with 0.4%,  $p < 0.0001$ ). The EPAR states that the higher incidence of breathlessness reported with cangrelor than with clopidogrel is a class effect for direct P2Y<sub>12</sub> inhibitors and has been previously reported with ticagrelor. Serious adverse events were infrequent and reported at the same frequency in both the cangrelor and comparator groups (2.2%).

The SPC states that in pivotal studies conducted in patients undergoing PCI, there were more intracranial bleeds, including fatal bleeds, at 30 days with cangrelor (0.07%) than with clopidogrel (0.02%), and a higher rate of cardiac tamponades at 30 days with cangrelor (0.12%) than with clopidogrel (0.02%). In patients with severe renal impairment (creatinine clearance 15–30 mL/min) a higher rate of worsening in renal function (3.2%) was reported with cangrelor compared to clopidogrel (1.4%) and a higher rate of GUSTO moderate bleeding was reported with cangrelor group (6.7%) compared to clopidogrel (1.4%).

Cangrelor is contraindicated in people with active bleeding or increased risk of bleeding and in people with any history of stroke or transient ischaemic attack. The SPC advises that cangrelor should be used with caution in people with severe renal impairment (creatinine clearance 15–30 mL/min). The SPC gives further information on contraindications, potential interactions and adverse effects of cangrelor.

## Evidence strengths and limitations

The large phase III RCT CHAMPION PHOENIX, ([Bhatt et al. 2013](#)) provides patient orientated outcome data suggesting clinical benefit for some people undergoing PCI receiving cangrelor bolus plus infusion followed by transition to a loading dose of clopidogrel compared with a single loading dose of clopidogrel. This benefit was described as modest by the Committee for medicinal products for human use (CHMP, [CHMP meeting minutes, January 2015](#)). Treatment with cangrelor did not increase the risk of severe bleeding events according to 1 definition (GUSTO), but rates of severe bleeding were increased according to a different definition that is particularly intended for use in people undergoing PCI (ACUITY). Mild and moderate bleeding and transient breathlessness were more common in people receiving cangrelor compared with clopidogrel or placebo.

The [EPAR](#) states that the study design of CHAMPION PHOENIX was not optimal and may have favoured cangrelor, although it was accepted as reliable and representative of the diversity of current EU clinical practice. The EPAR notes that inclusion in the study population of 3 subsets of people with differential diagnosis is questionable due to the different risk factors and standard of care for each condition. It states that the results for the composite outcome were only statistically significantly superior with cangrelor for the people with stable angina. However, CHAMPION PHOENIX was not powered to show superiority for all 3 main subsets of participants: the [EPAR](#) states that the size of the effect of cangrelor appeared consistent irrespective of the initial presentation and that the results can be generalised to all 3 patient groups. Nevertheless, the [EPAR](#) also states that the exclusion of people with a history of stroke limits the validity of the study to clinical practice.

Furthermore, the loading dose of clopidogrel in the control arm was either 300 mg or 600 mg at the discretion of the site investigator, but a fixed 600 mg was given in the cangrelor group. Clopidogrel 300 mg is the licensed loading dose however the [EPAR](#) states that a higher, 600 mg dose has been shown to be more effective and this is advocated in [ESC guidelines](#). Specialists involved in the production of this evidence summary advise that in UK clinical settings a loading dose of clopidogrel 600 mg is common practice when this drug is used. Moreover, in CHAMPION PHOENIX the clopidogrel loading dose was given at the end of the PCI procedure in 30% of people in the control arm. According to [Steg et al. 2013](#), deferred administration of clopidogrel at the end of the PCI procedure could have magnified the difference in platelet inhibition between the study arms, although the [EPAR](#) states that the effect of cangrelor seemed consistent irrespective of the dose or timing of clopidogrel administration.

In addition to these issues with the study design, the treatment pathway in CHAMPION PHOENIX (Bhatt et al. 2013) differs from usual UK practice regarding choice of antiplatelet drug. Specialists involved in the production of this evidence summary advise that in UK practice prasugrel and ticagrelor have superseded clopidogrel as the standard of care for people with unstable angina, NSTEMI and STEMI. This limits the applicability to UK practice of evidence from CHAMPION PHOENIX and the wider CHAMPION programme. Prasugrel and ticagrelor have positive NICE technology appraisals and their use is advocated in [ESC guidelines](#) as the standard of care in people at higher risk of ischaemic events, requiring immediate PCI. An [editorial](#) (Mehta 2013) accompanying the pooled analysis (Steg et al. 2013) points out that there are no data for how cangrelor compares with either prasugrel or ticagrelor and the [EPAR](#) states that these may have been more valid comparators.

## Context

### Alternative treatments

Cangrelor, co-administered with aspirin, is indicated for the reduction of thrombotic cardiovascular events in adults with coronary artery disease undergoing PCI who have not received an oral P2Y12 inhibitor prior to the PCI procedure and in whom oral therapy with P2Y12 inhibitors is not feasible or desirable.

The oral P2Y12 inhibitors clopidogrel, prasugrel and ticagrelor are licensed for use, in combination with aspirin, for the prevention of atherothrombotic events in people with NSTEMI-ACS and STEMI including those undergoing PCI (see [summaries of product characteristics](#) for specific licensed indications). Price comparisons with these agents are included for context although cangrelor is an option only when use of these agents is not feasible or desirable.

### Costs of alternative treatments

Drug	Licensed dosage <sup>a</sup>	Cost excluding VAT <sup>b</sup>

Cangrelor 50 mg powder for concentrate for solution for injection or infusion	30 micrograms/kg intravenous bolus followed immediately by 4 micrograms/kg per minute intravenous infusion for 2–4 hours	£250 to £500 <sup>c</sup>
Clopidogrel 75 mg tablets	300 mg <sup>d</sup>	26p <sup>e</sup>
Clopidogrel 300 mg tablets	300 mg <sup>d</sup>	£4.75 <sup>e</sup>
Prasugrel 10 mg tablets	60 mg	£10.19 <sup>e</sup>
Ticagrelor 90 mg tablets	180 mg	£1.95 <sup>e</sup>

<sup>a</sup> The doses shown are taken from the relevant summary of product characteristics, in relation to loading doses for use in PCI. They do not imply therapeutic equivalence.

<sup>b</sup> Costs have therefore been calculated on the basis of cost per PCI procedure for medication administered periprocedurally for an average 70 kg adult and do not include the cost of aspirin. Prices quoted are the lowest NHS costs based on availability of different strengths and pack sizes. Costs may vary locally depending on local procurement arrangements.

<sup>c</sup> Price excludes VAT, taken from [MIMS](#) (October 2015).

<sup>d</sup> The licensed dose of clopidogrel is 300 mg but usual practice is to administer a dose of 600 mg.

<sup>e</sup> Prices are excluding VAT, taken from [Drug Tariff](#) October 2015.

## Estimated impact for the NHS

### Likely place in therapy

During assessment of the marketing authorisation application for cangrelor, CHMP stated that cangrelor is a suitable alternative for the existing antiplatelet agents, especially in situations where an ad hoc PCI would be considered in people who have not yet received dual antiplatelet therapy. CHMP stated that the intravenous administration of cangrelor and its fast offset of action can be useful in selected people. The benefit of cangrelor was considered modest by the CHMP, mainly a reduction of periprocedural MI and stent thrombosis with an acceptable bleeding risk. CHMP agreed that, for people already pre-treated with an oral P2Y<sub>12</sub> inhibitor, cangrelor was unsuitable ([CHMP meeting minutes, January 2015](#)). Any potential clinical benefits must be considered in the context of potential harms and results from the 3 CHAMPION RCTs show an increased risk of bleeding and breathlessness with cangrelor compared with clopidogrel. Specialists

involved in the production of this evidence summary advise that cangrelor, co-administered with aspirin, maybe an alternative option for some people undergoing PCI and for whom oral P2Y12 inhibitors are not feasible or desirable (as required within the licensed indication). For example:

- People with acute coronary syndromes who may experience reduced bioavailability as a consequence of nausea, use of opiates or impaired gastrointestinal absorption.
- People with an unclear coronary anatomy and where early administration of a long acting P2Y12 inhibitor may increase clinical risk (for example, aortic dissection or rupture, oesophageal tear, pericarditis).
- People in an unconscious state undergoing emergency PCI in whom bleeding risk is deemed to be low.

Two further caveats apply to the use of cangrelor. Firstly, in CHAMPION PHOENIX ([Bhatt et al. 2013](#)) almost all participants received periprocedural aspirin and this is reflected in the [licensed indication](#). Only oral forms of aspirin are available as licensed products in the UK, thus the person would usually be conscious and able to take aspirin orally (or have taken it that day) and have no contraindications to its use. Administering cangrelor without periprocedural aspirin would be an off-label use of the drug. (Note that prasugrel and ticagrelor are also both licensed only for use when co-administered with aspirin).

Secondly, the [SPC](#) states that when clopidogrel is administered during infusion of cangrelor, the expected inhibitory effect of clopidogrel on platelets is not achieved. Consequently it is important that the loading dose of clopidogrel is delayed until the infusion finishes. The [SPC](#) states that no clinically relevant interruption of P2Y12 inhibition was observed in phase III studies when 600 mg clopidogrel was administered immediately after discontinuation of the cangrelor infusion, but this is an unlicensed dose of clopidogrel.

As well as efficacy, safety and individual user factors, local decision makers will need to take cost into account when considering the likely place in therapy of cangrelor.

No estimate of the current UK use of oral antiplatelets specifically for use during PCI procedures was available at the time this evidence summary was prepared. In research conducted with 45 UK interventional cardiologists by The Medicines Company in 2014, 14–17% of ACS patients were documented as "oral antiplatelet therapy not feasible or desirable" and therefore not likely to receive an oral platelet inhibitor. According to the



British Cardiovascular Intervention Society [audit](#), there were 92,589 PCIs in 2013, 65.6% of which were acute (n=60,738); 14 to 17% of these would result in a potential population of 8,503 to 10,325 people who may undergo treatment with cangrelor over a 12-month period (personal communication, The Medicines Company June 2015).

## Relevance to NICE guidance programmes

Cangrelor was considered appropriate for a NICE technology appraisal. However, NICE is unable to make a recommendation about the use in the NHS of cangrelor for reducing atherothrombotic events in people with coronary heart disease undergoing percutaneous coronary intervention (or in people awaiting surgery requiring interruption of antiplatelet therapy) because no evidence submission was received from The Medicines Company for the technology ([terminated appraisal 351](#)).

NICE has issued guidelines on the [acute management of myocardial infarction with STEMI](#) (published July 2013), [unstable angina and NSTEMI](#) (published March 2010) and [management of stable angina](#) (published July 2011). All 3 guidelines are scheduled to be reviewed in 2015 to see if they need updating.

NICE guidance also exists for:

- [MI – secondary prevention: Secondary prevention in primary and secondary care for patients following a myocardial infarction](#) (2013) NICE guideline CG172
- [Drug-eluting stents for the treatment of coronary artery disease](#) (2008) NICE technology appraisal guidance 152
- [Prasugrel with percutaneous coronary intervention for treating acute coronary syndromes](#) (2014) NICE technology appraisal guidance 317
- [Ticagrelor for the treatment of acute coronary syndromes](#) (2011) NICE technology appraisal guidance 236

Additional NICE products include:

- NICE pathway on [stable angina](#) [last updated March 2015]
- NICE pathway on [acute coronary syndromes](#) [last updated June 2015].

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## Development of this evidence summary

The [integrated process statement](#) sets out the process NICE uses to select topics for the evidence summaries: new medicines and how the summaries are developed, quality assured and approved for publication.

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## Declarations of interest

Sotiris Antoniou has acted as an advisor and received honoraria from the following companies: AstraZeneca, Eli Lilly / Daiichi Sankyo, Correvio, Bayer and Boehringer Ingelheim

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Rajdeep Khattar has no interests to declare

### About this evidence summary

'Evidence summaries: new medicines' provide summaries of key evidence for selected new medicines, or for existing medicines with new indications or formulations, that are considered to be of significance to the NHS. The strengths and weaknesses of the relevant evidence are critically reviewed within this summary to provide useful information for those working on the managed entry of new medicines for the NHS, **but this summary is not NICE guidance.**

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