A contemporary platelet inhibitor for PCI: the role for IV KENGREAL® (cangrelor)

Indication

KENGREAL® (cangrelor) for Injection is a $P2Y_{12}$ platelet inhibitor indicated as an adjunct to percutaneous coronary intervention (PCI) to reduce the risk of periprocedural myocardial infarction (MI), repeat coronary revascularization, and stent thrombosis (ST) in patients who have not been treated with a $P2Y_{12}$ platelet inhibitor and are not being given a glycoprotein IIb/IIIa inhibitor.

Important Safety Information

KENGREAL® (cangrelor) for Injection is contraindicated in patients with significant active bleeding.

Please see additional Important Safety Information throughout and Full Prescribing Information.

KENGREAL®
(cangrelor) for injection

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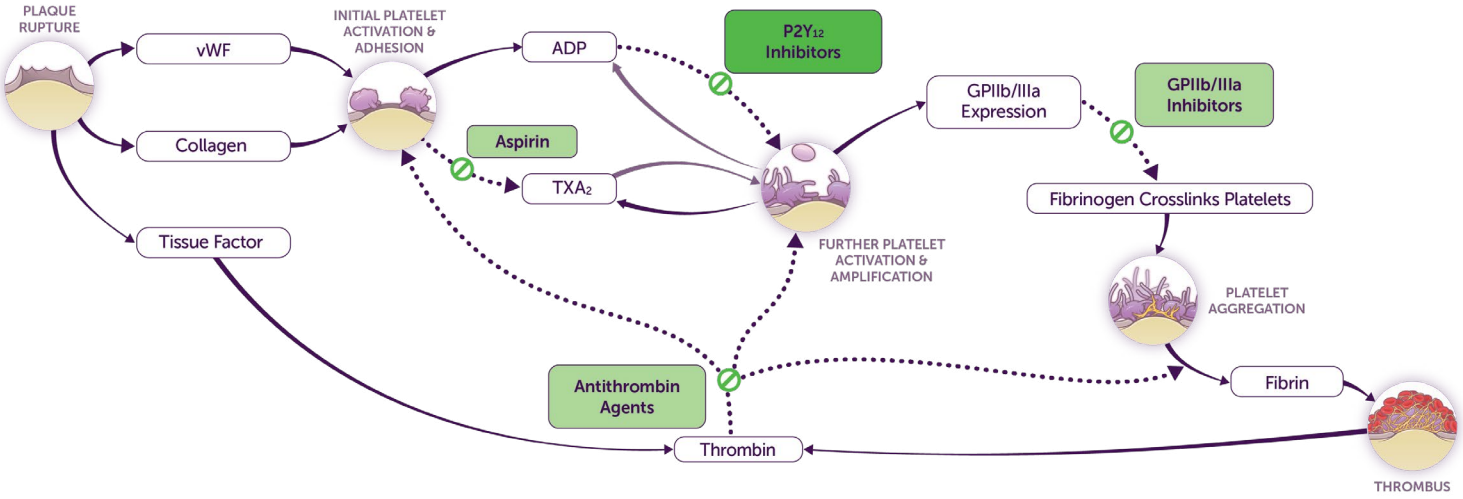
SECTION 1: THE IMPORTANCE OF PERIPROCEDURAL PLATELET MANAGEMENT IN PCI

Thrombosis, a product of spontaneous or PCI-induced vessel injury, is largely a platelet-mediated process. Activation, adhesion, amplification, and aggregation occurring during the platelet cascade result in the activation and expression of a variety of surface receptors that promote the release of prothrombotic factors. Available therapeutic options target different stages of the thrombotic pathway and as a result, produce different physiological effects (see Figure 1).[1]



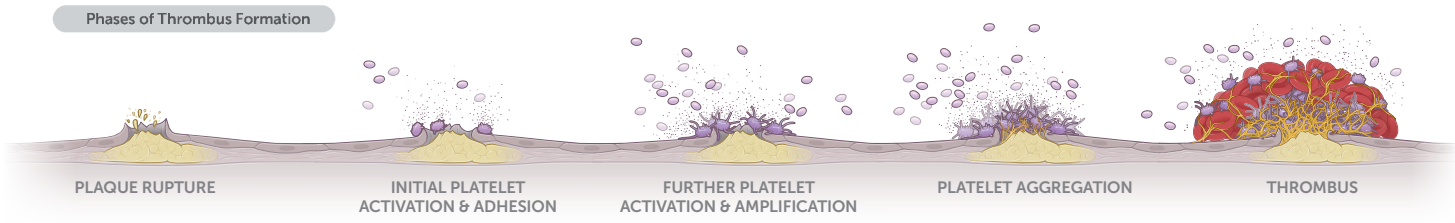


Figure 1. For illustrative purposes only. Platelet activation pathways and antithrombotic drug targets.

Clinical studies have not established superior efficacy or safety that is the result of where a product impacts the platelet cascade. The diagram is not intended to imply effects on clinical outcomes.

Effective platelet inhibition can affect outcomes

Effective platelet inhibition is critical due to an increased risk of periprocedural thrombotic complications that can occur during and after PCI. These complications can occur early in the acute period during PCI and have shown an early window of vulnerability, thereby making efficient and effective platelet management imperative.[2]

Furthermore, identification of patients who may be at increased risk of such events due to age, previous MI, or comorbid conditions such as diabetes, hypertension, or hyperlipidemia may also help improve outcomes and reduce the risk of thrombotic events.[3,4]

Potential periprocedural complications:

- Stent thrombosis
- Ischemia-driven revascularization
- Myocardial infarction
- Bleeding
- Death

Cost implications of periprocedural events

Intraprocedural PCI complications are less common due to newer and more effective treatments. However, when they do occur, the incidence of stent thrombosis, stroke, recurrent myocardial infarction, and bleeding, among others, can contribute to an increase in healthcare costs.

Such events can incur costs ranging from $2,000 to upwards of $40,000, placing a large financial burden on both patients and hospitals. Longer length of stay, ICU care, and readmissions related to these complications can also contribute to an increase in costs associated with PCI complications. When considering the frequency of these events in totality, rather than incrementally, the net cost to the US healthcare system can amount to billions of dollars.[5]

2

SECTION 2: MANAGING RISK DURING PCI

Antiplatelet and anticoagulant agents have tradeoffs and physicians must balance the risks of thrombosis formation and chances of bleeding (see Figure 2). This balance determines the net clinical benefit, or harm, observed.[6]

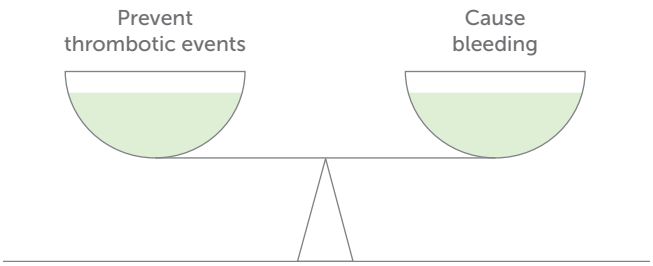


Figure 2. Tradeoffs of antiplatelet and anticoagulant agents.[6]

In addition, patient-specific clinical and lesion-specific risk factors can complicate risk management during PCI and should be taken into account when determining the proper treatment strategy.[6,7]

Consider whether your hospital has implemented quality initiatives for:

- Ischemic event rate[8]
- Bleeding[9,10]
- Length of stay[9,11]
- Readmission[11-13]

3

SECTION 3: FACTORS TO CONSIDER IN CHOICE OF PLATELET INHIBITION

Determining the right antiplatelet agent requires consideration of the entire care pathway, which encompasses patient as well as clinical and angiographic risk factors. Consideration should also be given to situational factors that may influence or even necessitate the selection of a particular agent based on its indication and distinctive properties, such as route of administration, onset, offset, and contraindications, among others.

Examples of situations that may influence time to effect and factor into choice of antiplatelet agent:

- **Need for surgical revascularization:** consider the time needed for $P2Y_{12}$ inhibitor washout[14]
- **Inability to administer treatment orally:** could be due to unconscious state, inability to swallow, or intubation; furthermore, vomiting, and conditions including cardiogenic shock or therapeutic hypothermia can compromise absorption with some orally administered agents[14,15]
- **Drug-drug interaction concerns:** particularly with opioids, coadministration can result in delay and reduced absorption, presumably due to slowed gastric emptying[16-18]
  - In 2018, labels for clopidogrel, prasugrel, and ticagrelor were updated to include language to consider use of a parenteral antiplatelet agent in patients requiring coadministration of morphine or other opioid agonists

$P2Y_{12}$ receptor inhibiting agents

The $P2Y_{12}$ receptor is the predominant receptor involved in the ADP-stimulated activation of the glycoprotein IIb/IIIa receptor. Drugs that inhibit the binding of ADP to the $P2Y_{12}$ receptor may impact platelet recruitment, attenuate aggregation, and mitigate the propagation of thrombus.[1,19] Multiple oral $P2Y_{12}$ platelet inhibitors are available with different pharmacologic profiles (see Table 1). Another parenteral platelet inhibitor currently available will be discussed in Section 5.

Administration	Oral		
	Ticagrelor[16]	**Prasugrel[17]**	**Clopidogrel[18]**
Compound class	CPTP	Thienopyridine	Thienopyridine
Action	Direct acting*	Prodrug	Prodrug
Onset of PD effect	30 min†	30 min†	2 hours
Time to maximal effect	~2 hours	~2 hours	3–7 days‡
Maximum platelet inhibition	88%	~80%	40%–60%§
Reversible $P2Y_{12}$ receptor binding	Yes	No	No
Half-life	~7 hours*	~7 hours	~6 hours¶
Platelet function returns to baseline after discontinuation	5 days	5–9 days	5 days

Table 1. Pharmacological profiles of oral $P2Y_{12}$ inhibiting agents.

*Ticagrelor has an active metabolite with a half-life of 9 hours.
†First timepoint at which inhibition of platelet aggregation was measured.
‡Based on 75-mg daily dose, when platelet inhibition reaches steady state. Time to maximal effect for a 600-mg loading dose is not provided in the Prescribing Information.
§Refers to average inhibition at steady state.
¶Active metabolite of clopidogrel has a half-life of 30 minutes.

Glycoprotein IIb/IIIa inhibiting agents

Glycoprotein IIb/IIIa inhibitors are another class of platelet-inhibiting agents, which unlike $P2Y_{12}$ inhibitors that work upstream, inhibit fibrinogen crosslinking during the later phase of the platelet cascade.[20]

Glycoprotein IIb/IIIa inhibitors have been shown to provide rapid and potent antiplatelet effects and to reduce periprocedural ischemic events. In addition, STEMI and NSTE-ACS have a high incidence of chronic kidney disease (CKD)—30.5% and 42.9%, respectively; and CKD in this population has been associated with worse outcomes, including higher rates of mortality and bleeding.[21] As a result, consideration should be given prior to using a glycoprotein IIb/IIIa inhibitor as it may not be a viable option for some patients, such as those on renal dialysis.[22,23] The two available options, eptifibatide and tirofiban, are described in Table 2.

	Eptifibatide[22]	Tirofiban[23]
Indication	• Treatment of ACS managed medically or with PCI • Treatment of patients undergoing PCI (including intracoronary stenting)	• Reduction in rate of thrombotic cardiovascular events (combined endpoint of death, myocardial infarction, or refractory ischemia/repeat cardiac procedure) in patients with NSTE-ACS
Dosing	PCI: double bolus followed by 18–24-hour infusion (minimum of 12 hours recommended)	Bolus followed by infusion up to 18 hours
Max platelet inhibition and timing	>80% at 5 minutes[24]	>90% at 10 minutes
Half-life	2.5 hours	2 hours
Offset	4–8 hours[24]	4–8 hours
Clearance route	50% renal	39%–69% renal
Renal dose adjustment	Yes	Yes
Notable contraindications (not exclusive)	• History of bleeding diathesis, or evidence of active abnormal bleeding • Severe uncontrolled hypertension • Recent (<6 weeks) major surgery • Stroke within 30 days or any history of hemorrhagic stroke • Dependency on renal dialysis	• History of thrombocytopenia following prior exposure to Tirofiban • Active internal bleeding or history of bleeding diathesis • Major surgical procedure or severe physical trauma within the previous month
Warnings and precautions (not exclusive)	• Associated with increase in major and minor bleeding • Acute, profound thrombocytopenia has been reported	• Can cause serious bleeding; most common complication is bleeding • Profound thrombocytopenia has been reported

Table 2. Select characteristics of glycoprotein IIb/IIIa inhibitors.*

*Abciximab is another glycoprotein IIb/IIIa inhibitor that is indicated as an adjunct to PCI for the prevention of cardiac ischemic complications. It has been discontinued by the manufacturer and is no longer available for order.[25,26]

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SECTION 4: CLINICAL CONSIDERATIONS AND NOTABLE GUIDELINE RECOMMENDATIONS FOR PLATELET INHIBITORS

2021 ACC/AHA/SCAI Guideline for Coronary Artery Revascularization Recommendations in patients undergoing PCI*†[27]

Selected recommendations for aspirin and oral $P2Y_{12}$ inhibitors

- **Class 1:** In patients undergoing PCI, a loading dose of aspirin, followed by daily dosing, is recommended to reduce ischemic events (LOE B-R)
- **Class 1:** In patients with ACS undergoing PCI, a loading dose of $P2Y_{12}$ inhibitor, followed by daily dosing, is recommended to reduce ischemic events (LOE B-R)
- **Class 1:** In patients with SIHD undergoing PCI, a loading dose of clopidogrel, followed by daily dosing, is recommended to reduce ischemic events (LOE C-LD)

Recommendations for intravenous $P2Y_{12}$ inhibitors

- **Class 2b:** In patients undergoing PCI who are $P2Y_{12}$ inhibitor naïve, intravenous cangrelor may be reasonable to reduce periprocedural ischemic events (LOE B-R)

Recommendations for intravenous glycoprotein IIb/IIIa inhibitors‡

- **Class 2a:** In patients with ACS undergoing PCI with large thrombus burden, no-reflow, or slow flow, intravenous glycoprotein IIb/IIIa inhibitor agents are reasonable to improve procedural success (LOE C-LD)
- **Class 3:** In patients with SIHD undergoing PCI, the routine use of an intravenous glycoprotein IIb/IIIa inhibitor agent is not recommended (No benefit, LOE B-R)

The 2021 ACC/AHA/SCAI Guidelines replaced the antiplatelet recommendations for PCI within the 2013 ACCF/AHA Guidelines for STEMI and the 2014 AHA/ACC Guidelines for NSTE-ACS.

> "There are conflicting data on the benefits of pretreatment with a $P2Y_{12}$ inhibitor before the anatomy is known, particularly in patients with NSTE-ACS.[27] In contemporary times, with most patients with ACS undergoing early angiography, a strategy of loading with a $P2Y_{12}$ inhibitor after the anatomy is known appears to offer similar benefit to preloading.[27]"
>
> –2021 ACC/AHA/SCAI Guidelines

PCI, Percutaneous coronary intervention; ACS, Acute coronary syndrome; SIHD, stable ischemic heart disease

*Recommendations regarding antiplatelet treatment use described in clinical guidelines are largely evidence based and attempt to define practices that meet the needs of most patients in most circumstances; however, recommendations may not match FDA-approved product labeling. The ultimate judgement regarding care of a particular patient must be made by the healthcare provider and patient in light of all the circumstances presented by that patient.

†Contraindications to ticagrelor: previous intracranial hemorrhage or ongoing bleeding.[27] Contraindications to prasugrel: previous intracranial hemorrhage, previous ischemic stroke or transient ischemic attack, or ongoing bleeding.[27] Prasugrel should be used with caution at a lower dose in patients ≥75 years of age or with a body weight <60 kg.[27]

‡Eptifibatide is indicated for treatment or ACS managed medically or with PCI; treatment of patients undergoing PCI (including intracoronary stenting).[22] Tirofiban is indicated for reduction in rate of thrombotic cardiovascular events (combined endpoint of death, myocardial infarction, or refractory ischemia/repeat cardiac procedures) in patients with NSTE ACS.[23]

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European Society of Cardiology (ESC) Guidelines

NSTE-ACS Recommendations*

2020 ESC Guidelines†‡[6]

- **Class I:** A $P2Y_{12}$ receptor inhibitor is recommended in addition to aspirin, and maintained over 12 months unless there are contraindications or an excessive risk of bleeding (LOE: A)
- **Class IIa:** Glycoprotein IIb/IIIa antagonists should be considered for bailout if there is evidence of no reflow or a thrombotic complication (LOE: C)
- **Class IIb:** Cangrelor may be considered in $P2Y_{12}$ receptor inhibitor-naïve patients undergoing PCI (LOE: A)
- **Class IIb:** Pre-treatment with a $P2Y_{12}$ receptor inhibitor may be considered in patients with NSTE-ACS who are not planned to undergo an early invasive strategy and do not have a high bleeding risk (LOE: C)
- **Class III:** Treatment with glycoprotein IIb/IIIa antagonists in patients in whom coronary anatomy is not known is not recommended (LOE: A) and it is not recommended to administer routine pre-treatment with a $P2Y_{12}$ receptor inhibitor in patients in whom coronary anatomy is not known and an early invasive management is planned (LOE: A)

STEMI Recommendations*

2017 ESC Guidelines†‡[28]

- **Class I:** A potent $P2Y_{12}$ inhibitor (prasugrel or ticagrelor), or clopidogrel if these are not available or are contraindicated, is recommended before (or at latest at the time of) PCI and maintained over 12 months, unless there are contraindications such as excessive risk of bleeding (LOE: A)
- **Class IIa:** Glycoprotein IIb/IIIa inhibitors should be considered for bailout if there is evidence of no reflow or a thrombotic complication (LOE: C)
- **Class IIb:** Cangrelor may be considered in patients who have not received $P2Y_{12}$ receptor inhibitors (LOE: A)

*Recommendations regarding antiplatelet treatment use described in clinical guidelines are largely evidence based and attempt to define practices that meet the needs of most patients in most circumstances; however, recommendations may not match FDA-approved product labeling. The ultimate judgement regarding care of a particular patient must be made by the healthcare provider and patient in light of all the circumstances presented by that patient.

†European Society of Cardiology (ESC) recommendations should be interpreted with caution as expert opinion and differences in regional clinical practice should be considered.

‡Eptifibatide is indicated for treatment or ACS managed medically or with PCI; treatment of patients undergoing PCI (including intracoronary stenting).[22] Tirofiban is indicated for reduction in rate of thrombotic cardiovascular events (combined endpoint of death, myocardial infarction, or refractory ischemia/repeat cardiac procedures) in patients with NSTE ACS.[23]

Important Safety Information

KENGREAL® (cangrelor) is contraindicated in patients with known hypersensitivity (e.g., anaphylaxis) to cangrelor or any component of the product.

Please see additional Important Safety Information throughout and Full Prescribing Information.

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SECTION 5: KENGREAL® (cangrelor) PROFILE

KENGREAL is a $P2Y_{12}$ platelet inhibitor indicated as an adjunct to PCI to reduce the risk of periprocedural MI, repeat coronary revascularization, and stent thrombosis (ST) in patients who have not been treated with a $P2Y_{12}$ platelet inhibitor and are not being given a glycoprotein IIb/IIIa inhibitor.[14]

KENGREAL is administered as a weight-based IV bolus of 30 mcg/kg followed immediately by a 4 mcg/kg/min IV infusion continued for at least 2 hours or for the duration of PCI, whichever is longer.[14]

Pharmacology

KENGREAL works directly to block ADP-induced platelet activation and aggregation. Following administration, platelet inhibition occurs within 2 minutes and is maintained for the duration of the infusion.[14] Whole blood impedance aggregometry demonstrated pharmacodynamic effect of >98% inhibition of platelet aggregation.[29] Following discontinuation of the infusion, the effect decreases rapidly and platelet function returns to baseline within 1 hour, allowing patients needing revascularization to continue to coronary artery bypass graft surgery (CABG) or surgery soon after. Due to its linear dose-dependent pharmacokinetic profile, KENGREAL produces consistent antiplatelet effects (see Figure 3).[14,30]

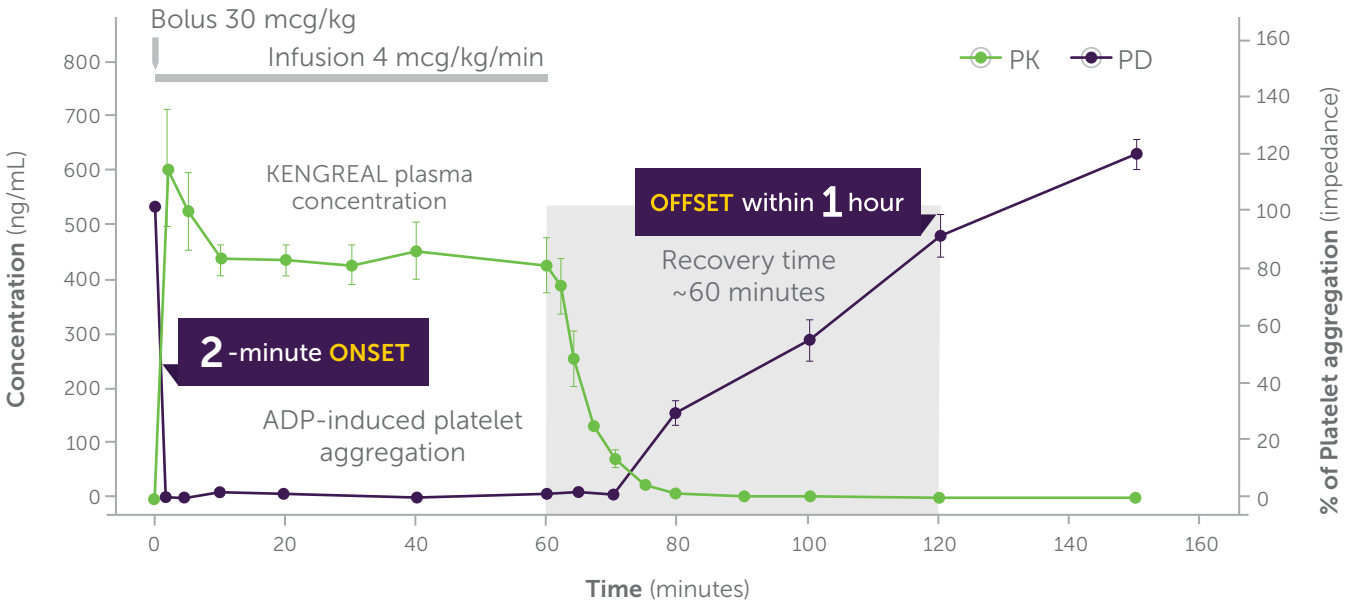

Figure 3. KENGREAL pharmacology.[14,30]

Phase I study in healthy volunteers (n=9); dose: 30 mcg/kg IV bolus + 4 mcg/kg/min IV infusion. KENGREAL blood levels and platelet activity were assessed over 150 minutes by whole blood impedance aggregometry in response to 20 µM of ADP.[30]

Infusion should be continued for at least 2 hours or the duration of the procedure, whichever is longer.[14]

Important Safety Information

The most common adverse reaction is bleeding.

Please see additional Important Safety Information throughout and Full Prescribing Information.

Metabolism[14]

KENGREAL® (cangrelor) is metabolized in the circulation via rapid dephosphorylation and does not interfere with drugs that are metabolized by hepatic enzymes. Pharmacokinetics are not affected by sex, age, renal status, or hepatic function; no dose adjustment is needed for these factors.

Elimination and transition to oral therapy

The average KENGREAL elimination half-life of 3–6 minutes allows for quick recovery of platelet function with return to baseline within 1 hour after cessation of the infusion. KENGREAL is mostly eliminated in the urine and through biliary excretion.[14]

Ultimately, patients receiving KENGREAL will be switched to an oral $P2Y_{12}$ inhibitor to maintain platelet inhibition. The binding site of these antiplatelet agents determines the temporal administration of KENGREAL relative to oral agents (see Figure 4). The thienopyridines, clopidogrel and prasugrel, must be administered after the KENGREAL infusion due to the competitive binding for the same ADP-binding site on the $P2Y_{12}$ receptor. Because ticagrelor binds to the $P2Y_{12}$ receptor at a different binding site in a non-competitive manner, ticagrelor can be administered at any time during or after KENGREAL infusion.[31-35]

To maintain platelet inhibition after discontinuation of KENGREAL, administer the selected oral $P2Y_{12}$ inhibitor at the recommended loading dose[14]:

- Ticagrelor 180 mg at any time during KENGREAL infusion or immediately after discontinuation
- Clopidogrel 600 mg immediately after KENGREAL discontinuation*
  - Do not administer prior to KENGREAL discontinuation
- Prasugrel 60 mg immediately after KENGREAL discontinuation*
  - Do not administer prior to KENGREAL discontinuation

*If prasugrel or clopidogrel is administered during KENGREAL infusion, it will have no antiplatelet effect until the next dose is administered.

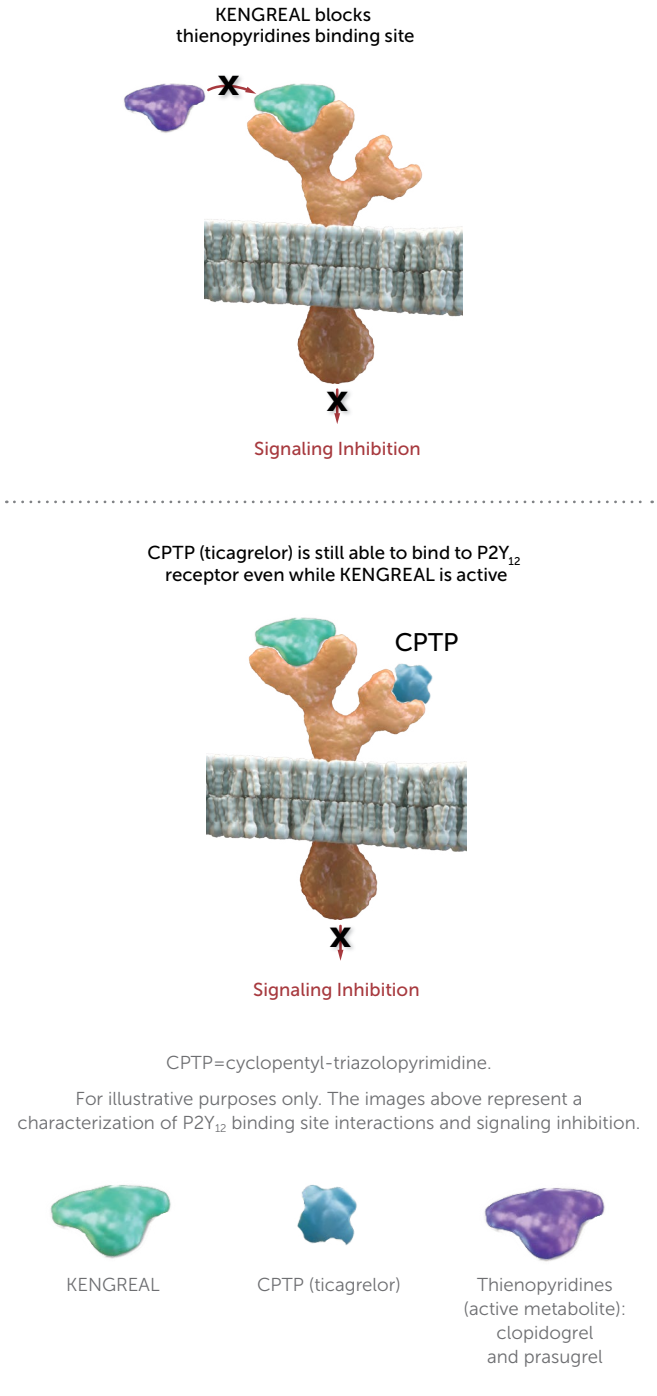

Figure 4. Transition rationale based on $P2Y_{12}$ binding site interactions.[31-35]

Important Safety Information

Drugs that inhibit platelet $P2Y_{12}$ function, including KENGREAL® (cangrelor), increase the risk of bleeding. In CHAMPION PHOENIX, bleeding events of all severities were more common with KENGREAL® than with clopidogrel. Bleeding complications with KENGREAL® were consistent across a variety of clinically important subgroups. Once KENGREAL® is discontinued, there is no antiplatelet effect after an hour.

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KENGREAL® (cangrelor) efficacy and safety in CHAMPION PHOENIX[4,36]

CHAMPION PHOENIX was a randomized, double-blind, phase III trial evaluating the efficacy and safety of KENGREAL vs clopidogrel in patients who were undergoing urgent or elective PCI and receiving guideline-recommended therapy in cases of STEMI, non-ST-segment elevation ACS, or stable angina (see Figure 5).

Primary and secondary endpoints[4]

- Primary endpoint: composite of death, MI, ischemia-driven revascularization, or stent thrombosis at 48 hours
- Key secondary endpoint: stent thrombosis at 48 hours
- Primary safety endpoint: severe bleeding not related to CABG at 48 hours, according to the Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) criteria

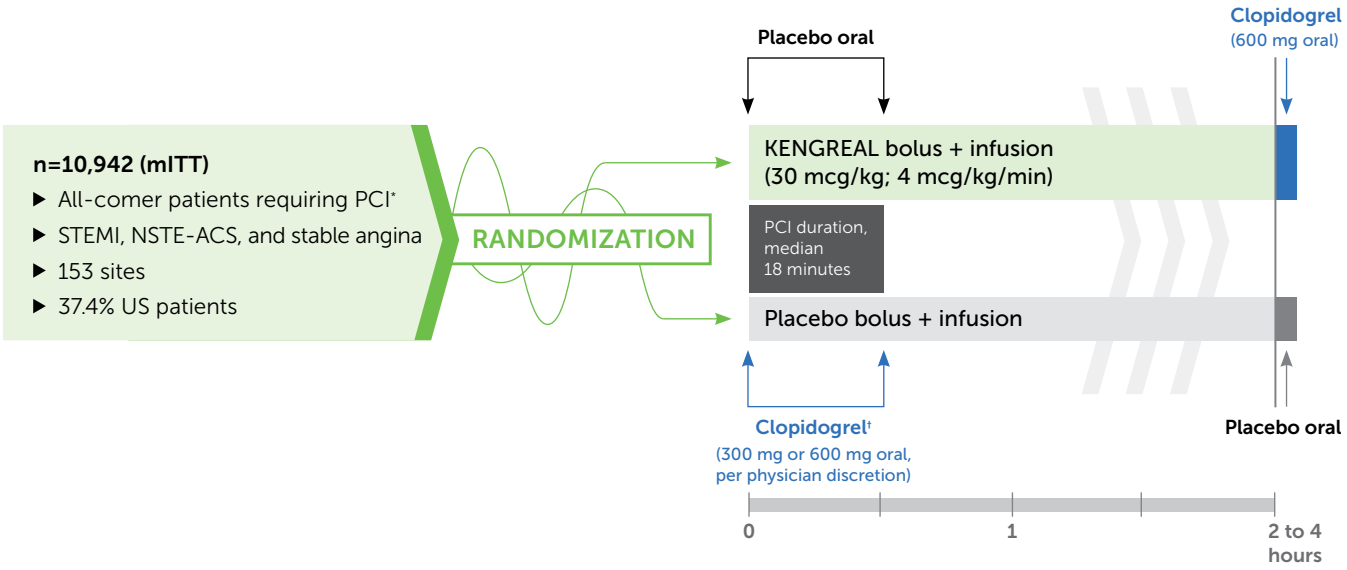

Figure 5. CHAMPION PHOENIX study design and patient population overview.[36]

KENGREAL bolus was administered prior to start of PCI. Clopidogrel 300 mg or 600 mg was administered shortly before or shortly afterwards in patients randomized to clopidogrel. The protocol also called for clopidogrel (75 mg) to be administered during the first 48 hours.

*$P2Y_{12}$ inhibitor naïve.
†Administration (dose and timing) of loading dose of clopidogrel was at the operator's discretion.

Patients were excluded if they had received any $P2Y_{12}$ inhibitor or abciximab within 7 days or fibrinolytic or glycoprotein IIb/IIIa inhibitors in the last 12 hours.

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Figure 6. CHAMPION PHOENIX primary (A) and secondary (B) endpoint results at 48 hours in an all-comer PCI cohort. The primary endpoint was a composite measure of death/MI/IDR/ST at 48 hours. The secondary endpoint was the rate of stent thrombosis (ARC-ST or intraprocedural) at 48 hours.[4,14]

*The mITT population is all randomized subjects who received at least 1 dose of study drug and underwent the index PCI procedure.

IDR=ischemia-driven revascularization; MI, myocardial infarction; mITT, modified intention-to-treat; ST, stent thrombosis.

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CHAMPION PHOENIX results[4,14]

KENGREAL® (cangrelor) significantly reduced the composite of death, MI, ischemia-driven revascularization, or stent thrombosis at 48 hours compared with the clopidogrel group (22% relative risk reduction; 4.7 vs 5.9%; *P*=0.005) (see Figure 6A). This benefit was not accompanied by a significant increase in severe bleeding or in the need for transfusions. The treatment effect was also consistent across subgroups regardless of the indication for PCI and whether the patient received a clopidogrel 300-mg or 600-mg loading dose.

With KENGREAL, there was a 38% relative risk reduction in the rate of stent thrombosis (0.8% vs 1.4%) (see Figure 6B) and 20% relative risk reduction in the rate of MI (3.8% vs 4.7%). The reduction in the primary efficacy end point with KENGREAL was consistent across multiple subgroups—STEMI, NSTEMI/unstable angina, and stable angina. The odds of an ischemic event were 22% lower with KENGREAL than with clopidogrel, and this benefit was not accompanied by a significant increase in severe bleeding or in the need for transfusions. The rate of procedural complications was lower with KENGREAL than with clopidogrel (3.4 vs 4.5%; *P*=0.002) and KENGREAL significantly reduced the rate of intraprocedural stent thrombosis compared with clopidogrel (0.6 vs 1.0%; *P*=0.04). The primary safety endpoint, GUSTO severe bleeding, was infrequent, and the rates were not significantly different between groups (0.16% vs 0.11%; *P*=0.44).

Bailout with glycoprotein IIb/IIIa inhibitors in patients treated with KENGREAL[4]

Bailout/rescue therapy with a glycoprotein IIb/IIIa inhibitor was 2.3% with KENGREAL compared to 3.5% with clopidogrel (odds ratio, 0.65; 95% CI, 0.52 to 0.82; *P*<0.001). Glycoprotein IIb/IIIa inhibitor use was allowed only as bailout/rescue therapy at physician discretion during PCI to treat new or persistent thrombus formation, slow or no reflow, side branch compromise, dissection, and distal embolization.

The data presented is not intended for clinical comparison of KENGREAL and glycoprotein IIb/IIIa inhibitors.

Post hoc analyses of CHAMPION PHOENIX

The following findings are based on post hoc analyses that supplement the predefined primary results of the CHAMPION PHOENIX trial.

Vast majority of more severe events happened in first 2 hours from start of PCI[37]

A supplemental post hoc analysis of CHAMPION PHOENIX revealed that the majority of thrombotic complications including death, SCAI MI, IDR, or ARC-ST occurred within a narrow window, within 2 hours, from the start of PCI. The frequency of events evaluated was notably greater for patients on clopidogrel within the first 2 hours compared to KENGREAL (115 vs 56 events, respectively, an observed difference of 51%) (see Figure 7).

Results should be interpreted with caution and with considerations of study limitations; further research may be warranted.

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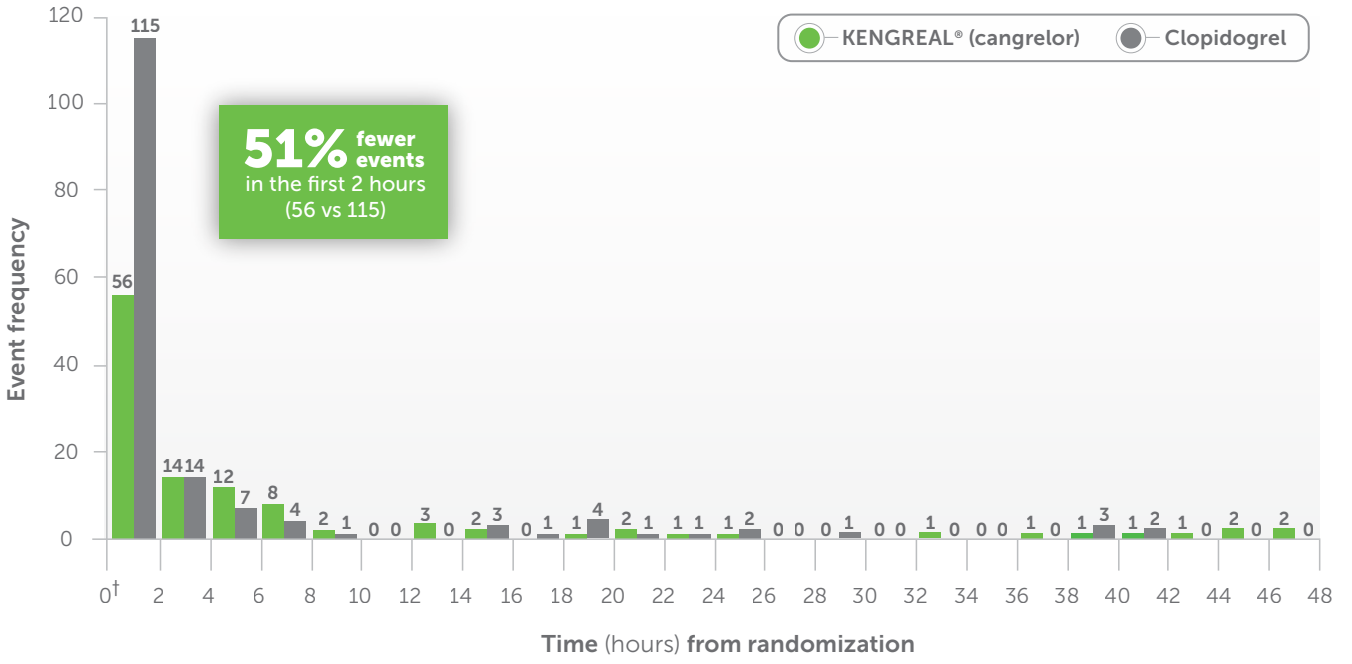

Figure 7. Post hoc analysis of CHAMPION PHOENIX evaluating time to death or a thrombotic event from PCI start.*[37]

Results should be interpreted with caution and with considerations of study limitations; further research may be warranted.

*Data derived represents a post hoc supplemental analysis in which the study was powered for superiority at the 48-hour time frame. SCAI MI: CK-MB ≥10X ULN, or CK-MB ≥5X ULN with new Q waves or new LBBB. ARC-ST defined according to the ARC definition.
†Time 0 represents the start of PCI. KENGREAL for injection was administered at the time of PCI. Clopidogrel oral 300 mg or 600 mg was administered shortly before PCI or shortly afterward in patients randomized to clopidogrel.

ARC=Academic Research Consortium. CK-MB=creatine kinase MB isoenzyme. IDR=ischemia-driven revascularization. LBBB=left bundle branch block. MI=myocardial infarction. SCAI=Society for Cardiovascular Angiography and Interventions. ST=stent thrombosis. ULN=upper limit of normal.

CANTIC study evaluating KENGREAL + crushed ticagrelor[38]

At the time the CHAMPION PHOENIX trial was designed, clopidogrel was the standard of care in ACS; however, newer oral $P2Y_{12}$ agents such as ticagrelor have since been approved and are now also used.[16,18,39] The CANTIC study was a prospective, randomized, double-blind, placebo-controlled study to assess the comparative pharmacodynamic effects of KENGREAL plus crushed ticagrelor versus placebo and crushed ticagrelor in STEMI patients undergoing primary PCI (n=50; pharmacodynamic population=44). The addition of KENGREAL to crushed ticagrelor led to more prompt and potent platelet inhibitory effects compared with crushed ticagrelor alone, with significant differences observed as early as 5 minutes post-bolus administration. Accordingly, high on-treatment platelet reactivity rates were reduced with KENGREAL. After discontinuation of KENGREAL/placebo infusion, there were no differences in levels of platelet reactivity between groups.[38]

It is important to note that while all patients in the study were treated with both crushed ticagrelor and fentanyl, which is known to interfere with absorption of oral $P2Y_{12}$ inhibitors, the significance of the interaction on these pharmacodynamic findings is unknown. Furthermore, these pharmacodynamic findings should be interpreted with caution and do not represent adequate evidence of clinical implications. High on-treatment platelet reactivity rates are suggestive of thrombotic complications, but their relevance to safety or efficacy on clinical endpoints has not been established. Assessment of clinically relevant endpoints warrant further investigation in an adequately powered clinical trial.

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Patients at higher risk for thrombotic events benefited even more from KENGREAL® (cangrelor)[3]

In a post hoc analysis of CHAMPION PHOENIX, the efficacy of KENGREAL during PCI was investigated in patients with simple versus complex target lesion coronary anatomy.

The nine prespecified angiographic high-risk lesion features (HRFs) that were included in the analysis were:

- long lesions (>20 mm)
- thrombotic lesions
- eccentric lesions
- left main lesions
- tortuous lesions
- calcified lesions
- bifurcation lesions
- angulated lesions
- multi-lesion PCI

Blinded angiographic core laboratory analysis was completed in 10,854 of the 10,942 (99.2%) randomized modified intention-to-treat patients in CHAMPION PHOENIX (13,418 target lesions).

Nearly 25% of patients had ≥3 high-risk lesions and the rates of stent thrombosis, MI, and composite MACE at 48 hours increased progressively with the number of HRFs treated. The primary 48-hour MACE endpoint increased progressively with PCI target lesion complexity from 2.5% with 0 HRFs to 7.5% with ≥3 HRFs (*P*<0.0001) and patients with ≥3 high-risk features treated had an 8-fold increase in stent thrombosis compared to patients with no high-risk features treated (from 0.2% to 1.6%, *P*<0.0001) (see Figure 8).

Regardless of number of HRFs, KENGREAL offered a consistent benefit in the reduction of MACE and stent thrombosis compared to clopidogrel (see Figure 9). The benefit was most pronounced in patients with 3 or more HRFs treated, suggesting the absolute benefit/risk profile for KENGREAL may be greatest during PCI in patients with complex coronary anatomy.

This is a post hoc analysis and presents findings that supplement the predefined, primary result of the CHAMPION PHOENIX trial. The CHAMPION PHOENIX trial was not designed nor powered to examine the impact of cangrelor and clopidogrel on specific angiographic risk characteristics, lesion types, and outcomes.

It is important to note that PCI patients with high-risk characteristics can differ in disease severity and comorbidities. Treatment protocols should account for individualization of care as KENGREAL may not be appropriate for some patients.

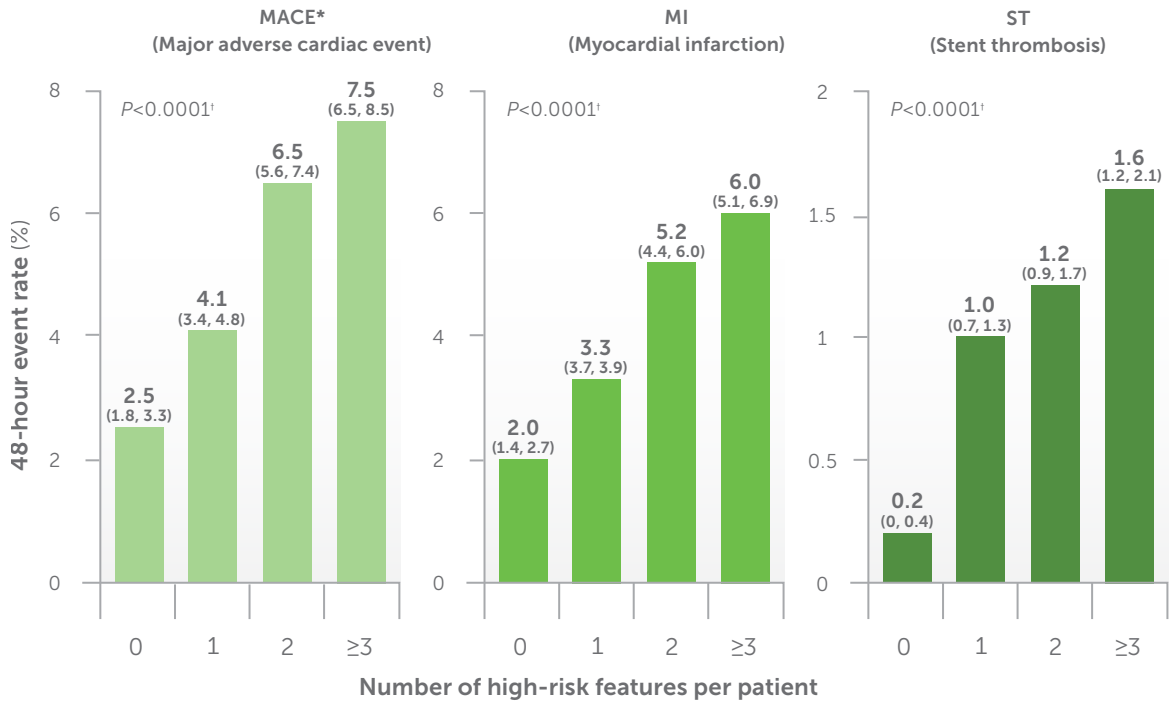

Figure 8. Post hoc analysis of CHAMPION PHOENIX evaluating 48-hour event rates by number of angiographic high-risk features treated.[3]

95% confidence intervals appear under each rate estimate in parentheses.
*MACE is the measure of death, MI, ischemia-driven revascularization, or ST.
†Comparison between 0 and ≥3 high-risk features.

Important Safety Information

KENGREAL® (cangrelor) for Injection is contraindicated in patients with significant active bleeding.

Please see additional Important Safety Information throughout and Full Prescribing Information.

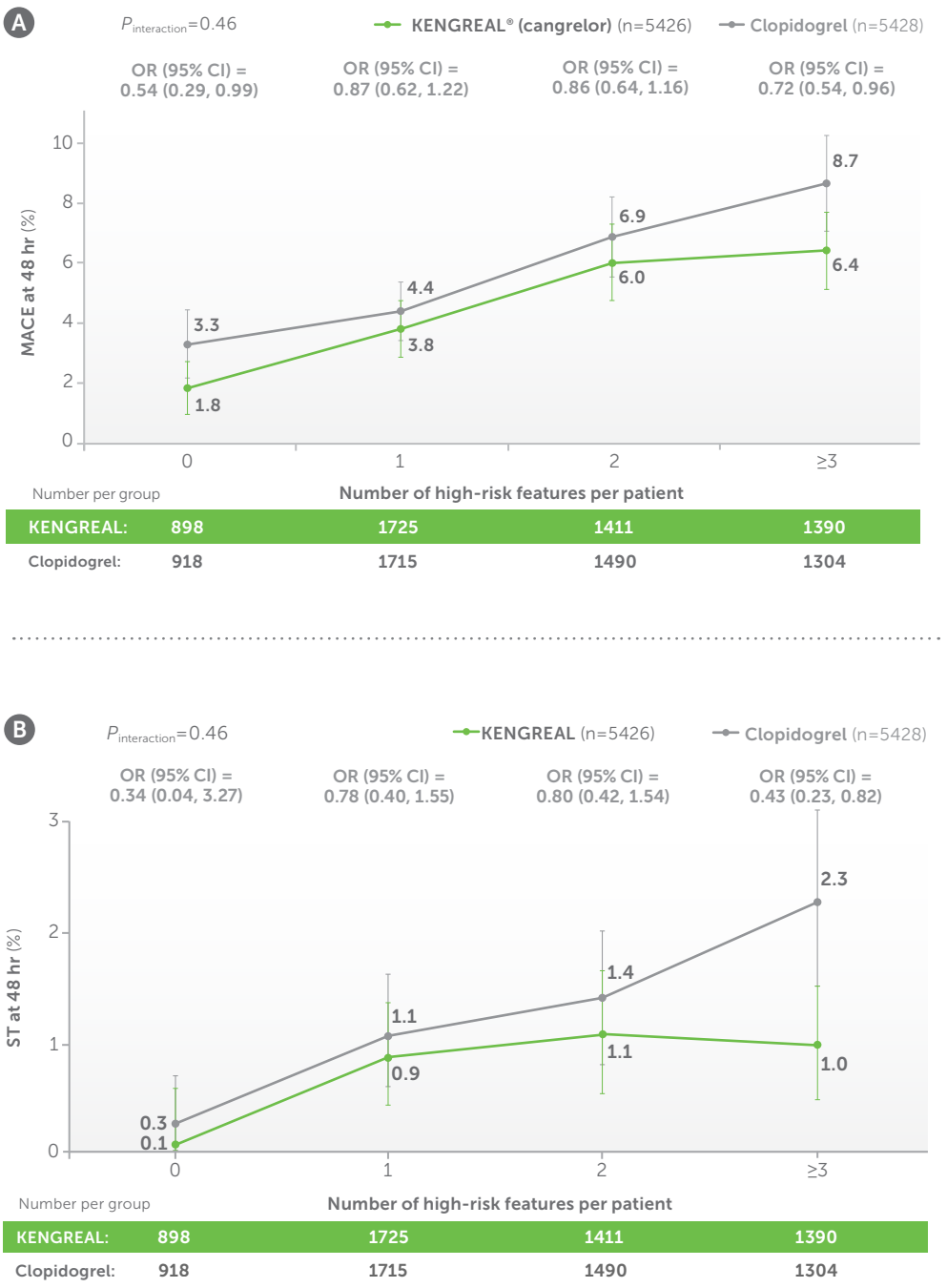

Figure 9. Post hoc analysis of CHAMPION PHOENIX evaluating rates of MACE (A) and stent thrombosis (B) at 48 hours by angiographic high-risk lesion features treated.[3]

It is important to note that not all high-risk lesion characteristics were accounted for in the present analysis.

Important Safety Information

KENGREAL® (cangrelor) is contraindicated in patients with known hypersensitivity (e.g., anaphylaxis) to cangrelor or any component of the product.

Please see additional Important Safety Information throughout and Full Prescribing Information.

6

SECTION 6: CONCLUSIONS AND APPROPRIATE USE OF KENGREAL® (cangrelor)

With the majority of periprocedural major adverse cardiac events occurring in the early window during/after PCI, rapid platelet inhibition is essential. Patients presenting with high-risk lesion features are also at a progressively increased risk of these adverse events. In patients for whom invasive management is planned, such as ACS, the presence of shock, vomiting or sedation may prevent the use of oral $P2Y_{12}$ inhibiting agents. Patients with renal impairment, a high-risk subgroup for bleeding events, or with comorbidities such as diabetes, that can be associated with high risk of recurrent ischemic events, may also require additional consideration prior to treatment selection.

KENGREAL, an intravenous $P2Y_{12}$ receptor antagonist, has rapid onset and quick offset of action and dosing that is independent of renal or hepatic function. Clinical studies showed KENGREAL significantly reduced periprocedural thrombotic events, and patients at higher angiographic risk benefitted even more from KENGREAL. The results from clinical trials establish KENGREAL as a potent therapeutic option appropriate for a variety of clinical and high-risk cases in PCI.

Consider KENGREAL in these types of cases

- Acute coronary syndrome[4]
  - STEMI
  - NSTEMI with early invasive strategy
- High angiographic risk or complex anatomy[3]
- Known or potential need for surgery soon after PCI—washout avoidance*[14]
- Inability to administer or reliably absorb oral medication*[14]
- High-risk comorbidities (e.g., diabetes)[4]
- Renal or hepatic impairment, or unknown renal status†[14]
- Fentanyl and/or morphine coadministration in ACS[16-18]
  - Opioids are known to interfere with oral $P2Y_{12}$ inhibitor absorption

*IV administration with onset of 2 minutes and offset within 1 hour.[14]
†No dosage adjustment required for renal or hepatic impairment.[14]

Important Safety Information

Drugs that inhibit platelet $P2Y_{12}$ function, including KENGREAL® (cangrelor), increase the risk of bleeding. In CHAMPION PHOENIX, bleeding events of all severities were more common with KENGREAL® than with clopidogrel. Bleeding complications with KENGREAL® were consistent across a variety of clinically important subgroups. Once KENGREAL® is discontinued, there is no antiplatelet effect after an hour.

Please see additional Important Safety Information throughout and Full Prescribing Information.

CHIESI RESOURCES

Contact **kengreal@chiesi.com** for any questions or to reach a sales representative.

For Medical Information, please contact **1-888-661-9260** or **US.Medical@chiesi.com**.

Healthcare Economics Information

Chiesi has a dedicated Health Economics and Value team that supports these areas: risk stratification analysis, economic impact analysis, value-based considerations, reimbursement, quality measures and improvement initiatives, and length of stay and associated costs.

Contact **us.healtheconomics@chiesi.com** or your local KENGREAL® (cangrelor) representative to learn more.

Please note that health economic and value information can be provided to a payor, formulary committee, or other similar entity with knowledge and expertise in the area of healthcare economic analysis, carrying out its responsibilities for the selection of drugs for coverage or reimbursement.

Indication

KENGREAL® (cangrelor) for Injection is a $P2Y_{12}$ platelet inhibitor indicated as an adjunct to percutaneous coronary intervention (PCI) to reduce the risk of periprocedural myocardial infarction (MI), repeat coronary revascularization, and stent thrombosis (ST) in patients who have not been treated with a $P2Y_{12}$ platelet inhibitor and are not being given a glycoprotein IIb/IIIa inhibitor.

Important Safety Information

KENGREAL® (cangrelor) for Injection is contraindicated in patients with significant active bleeding.

KENGREAL® is contraindicated in patients with known hypersensitivity (e.g., anaphylaxis) to cangrelor or any component of the product.

Drugs that inhibit platelet $P2Y_{12}$ function, including KENGREAL®, increase the risk of bleeding. In CHAMPION PHOENIX, bleeding events of all severities were more common with KENGREAL® than with clopidogrel. Bleeding complications with KENGREAL® were consistent across a variety of clinically important subgroups. Once KENGREAL® is discontinued, there is no antiplatelet effect after an hour.

The most common adverse reaction is bleeding.

Please see Full Prescribing Information.

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For more information, please visit **KENGREAL.com**

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