Considerations for Pretreatment in PCI for NSTE-ACS

An interventional cardiologist's treatment strategies

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What is your approach to assessing a patient with acute coronary syndrome?

Acute coronary syndrome (ACS) encompasses a broad patient population that may involve a variety of clinical scenarios. As we know, the potential of high-risk sequelae in ACS makes it imperative to utilize a thoughtful approach when treating these patients. Prior to invasive treatment, an assessment of the patient's clinical acuity of presentation, risk factors, and current cardiac function is useful to assist in decision making. In terms of initial presentation, it may be useful to use risk stratification tools that include factors to understand cardiac risk, such as the GRACE 2.0 score. This allows us to provide an algorithm for the timing of invasive strategy.

How does the coronary anatomy influence your interventional approach?

Once we complete a coronary angiogram and invasive hemodynamic assessment, we are able to evaluate the anatomical and intravascular characteristics, which may or may not require hemodynamic support. Furthermore, we then can classify the myocardium at risk, depending on where the culprit lesion is located and if there is high-risk lesion morphology such as calcification, tortuosity, bifurcation, eccentricity, long lesions, and multiple tandem lesions. Lastly, we evaluate the required interventional strategy, whether it's mechanical or aspiration thrombectomy, rotational, orbital, and laser atherectomy, lithotripsy, balloon angioplasty, and/or stenting. The various combinations all confer a different risk-time potential when intervening in the intravascular space, which is inherently thrombogenic. All these factors need to be considered to predict what's necessary for treating the patient in a comprehensive and thoughtful way.

The decision for pretreatment usually depends on the clinical timeline. If a decision is made to take the patient directly to the catheterization laboratory due to a suspected case of ACS, then it is reasonable to withhold pretreatment with oral $P2Y_{12}$ inhibition and consider therapies after coronary anatomy is identified. This strategy is rational given the time required for oral $P2Y_{12}$ inhibitor uptake and therapeutic benefit.

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What do the guidelines say about pretreatment with a $P2Y_{12}$ inhibitor for (NSTE)-ACS?

The discussion of pretreatment with a $P2Y_{12}$ inhibitor is centered around the invasive strategy, timing, and clinical scenario. Early studies found that pretreatment can reduce the outcome of CV death, MI, or urgent-target vessel revascularization.[1,2] More recent studies have shown that pretreatment increases bleeding risk without any survival benefit or a reduction in ischemic events.[3] The idea of pretreatment has changed and really should be applied on a case-by-case basis. The current 2021 American College of Cardiology/American Heart Association/Society for Cardiovascular Angiography and Interventions Guideline for coronary artery revascularization does not confirm whether an oral $P2Y_{12}$ inhibitor should be given as pretreatment prior to PCI; the supportive text refers to the conflicting data and suggests that in current practice, loading after the anatomy is known may offer a similar benefit to preloading.[4]

The 2020 European Society of Cardiology (ESC) Guidelines for NSTE-ACS say that pretreating with a $P2Y_{12}$ receptor inhibitor may be considered for patients who are not expected to undergo an early invasive strategy and do not have a high bleeding risk.[5] I think the understanding is that in some cases, a patient can be admitted with NSTEMI or unstable angina who presents with stable blood work and symptoms that are under control, and may not undergo an early invasive strategy until many hours or even days later. When a delayed invasive strategy is chosen, it may be reasonable to initiate oral $P2Y_{12}$ receptor inhibition.

What do you think about the use of a parenteral antiplatelet agent, such as KENGREAL® (cangrelor)?

The most current U.S. Guideline referenced earlier also states that for patients undergoing PCI who are $P2Y_{12}$ inhibitor naive, intravenous KENGREAL may be reasonable to reduce periprocedural ischemic events.[4] I think this is extremely valuable, because years ago we did not have an intravenous (IV) $P2Y_{12}$ option for antiplatelet therapy. Now we're armed with KENGREAL for patients who were not previously started on $P2Y_{12}$ inhibition. The efficacy and safety of KENGREAL were demonstrated in the 10,942-patient CHAMPION PHOENIX trial.[6] Two important matters to consider are timing and onset of effect — more specifically, when the patient is being preloaded and when the patient will experience the therapeutic window of the medication. The various oral $P2Y_{12}$ inhibitor medications have their own pharmacokinetics that relate to different therapeutic onset of their antiplatelet effects. There are some other medications that may be administered during an ACS event that can affect the uptake and timing of oral $P2Y_{12}$ inhibitors. For example, opioids such as morphine

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and fentanyl have been shown to delay and reduce the absorption of oral $P2Y_{12}$ inhibitors, and most U.S. PCI patients routinely receive fentanyl as part of conscious sedation.[7-10]

Without critically important information about the coronary anatomy until angiography, preloading with an oral $P2Y_{12}$ inhibitor in some cases may be premature and hinder our decision-making ability, especially in the urgent NSTEMI setting requiring multivessel coronary artery bypass grafting. The PK/PD profile of KENGREAL makes it an important drug to have on hand. It has a rapid onset of action within 2 minutes, an average elimination half-life of 3-6 minutes, and a quick offset within an hour of discontinuation.[11]

For what situations have you found KENGREAL® to be a good option?

I have used KENGREAL in many clinical scenarios. In one of my recent cases, a patient presented with cardiogenic shock and Grade 5 thrombus in the left anterior descending artery that required a longer procedure with complex bifurcation PCI. The patient was intubated and could not be given an oral medication acutely without orogastric placement. KENGREAL was started, and eventually the patient had an oral gastric tube placed at the end of the procedure. It should be noted that randomized controlled trials have not been conducted to evaluate the safety and efficacy of KENGREAL in patients with cardiogenic shock.

I also look at the acuity of the case and the interventional strategy required to complete the coronary intervention. Moreover, I look at complexities within the high-risk anatomy, such as thrombus characteristics and bifurcations. When there are chronic occlusions, KENGREAL allows the flexibility to turn on antiplatelet therapy when the decision is made to proceed with intervention. In other cases, when there is a highly thrombotic lesion, I’ve noticed fewer sequelae of the thrombus.

So overall, in terms of coronary anatomy, I look to use KENGREAL when there is high thrombus burden, bifurcations, long lesions above 20 mm in length and less than 2.5 mm in diameter, chronic total occlusions, multiple tandem lesions, severe tortuosity or eccentricity, and heavily calcified arteries. KENGREAL also works well in PCI when patients cannot take or reliably absorb oral medication. If the patient has received coadministration of opioids, these are known to interfere with oral $P2Y_{12}$ absorption.[7-10] KENGREAL’s flexibility afforded by the 2-minute onset and 1 hour offset allows me to make the right clinical decisions for the patient.[11] I think that separates KENGREAL from other options. ■

Brief Summary

KENGREAL® (cangrelor) for injection, for intravenous use

Brief Summary of Prescribing Information

SEE PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

INDICATIONS AND USAGE

KENGREAL is a $P2Y_{12}$ platelet inhibitor indicated as an adjunct to percutaneous coronary intervention (PCI) for reducing the risk of periprocedural myocardial infarction (MI), repeat coronary revascularization, and stent thrombosis (ST) in patients who have not been treated with a P2Y12 platelet inhibitor and are not being given a glycoprotein IIb/IIIa inhibitor.

CONTRAINDICATIONS

Significant Active Bleeding: KENGREAL is contraindicated in patients with significant active bleeding [see Warnings and Precautions (5.1) and Adverse Reactions (6.1)].

Hypersensitivity: KENGREAL is contraindicated in patients with known hypersensitivity (e.g., anaphylaxis) to KENGREAL or any component of the product [see Adverse Reactions (6.1)].

WARNINGS AND PRECAUTIONS

Bleeding: Drugs that inhibit platelet P2Y12 function, including KENGREAL, increase the risk of bleeding.

In CHAMPION PHOENIX, bleeding events of all severities were more common with KENGREAL than with clopidogrel [see Adverse Reactions (6.1)]. Bleeding complications with KENGREAL were consistent across a variety of clinically important subgroups [see Figure 1 in Clinical Trials Experience (6.1)].

Once KENGREAL is discontinued, there is no antiplatelet effect after an hour [see Clinical Pharmacology (12.3)].

ADVERSE REACTIONS

The following adverse reactions are also discussed elsewhere in the labeling: Bleeding [see Warnings and Precautions (5.1)]

Clinical Trials Experience:

Because clinical trials are conducted under widely varying conditions, adverse reactions rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of KENGREAL has been evaluated in 13,301 subjects in controlled trials, in whom, 5,529 were in the CHAMPION PHOENIX trial.

Bleeding

There was a greater incidence of bleeding with KENGREAL than with clopidogrel. No baseline demographic factor altered the relative risk of bleeding with KENGREAL [see Table 1 and Figure 1 in Clinical Trials Experience (6.1)].

Table 1: Major Bleeding Results in the CHAMPION PHOENIX Study (Non-CABG related Bleeding)[a]

CHAMPION PHOENIX	KENGREAL (N=5529)	Clopidogrel (N=5527)
Any GUSTO bleeding, n (%)	857 (15.5)	602 (10.9)
Severe/life-threatening[b]	11 (0.2)	6 (0.1)
Moderate[c]	21 (0.4)	14 (0.3)
Mild[d]	825 (14.9)	582 (10.5)
Any TIMI bleeding, n (%)	45 (0.8)	17 (0.3)
Major[e]	12 (0.2)	6 (0.1)
Minor[f]	33 (0.6)	11 (0.2)

Abbreviations: GUSTO: Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries; TIMI: Thrombolysis in Myocardial Infarction

[a]Safety population is all randomized subjects who received at least one dose of study drug

[b]intracranial hemorrhage or bleeding resulting in substantial hemodynamic compromise requiring treatment

[c]requiring blood transfusion but not resulting in hemodynamic compromise

[d]all other bleeding not included in severe or moderate

[e]any intracranial hemorrhage, or any overt bleeding associated with a reduction in hemoglobin of ≥5 g/dL (or, when hemoglobin is not available, an absolute reduction in hematocrit ≥15%)

[f]any overt sign of bleeding (including observation by imaging techniques) that is associated with a reduction in hemoglobin of ≥3 g/dL and <5 g/dL (or, when hemoglobin is not available, an absolute reduction in hematocrit of ≥9% and <15%)

Drug Discontinuation

In CHAMPION PHOENIX, the rate of discontinuation for bleeding events was 0.3% for KENGREAL and 0.1% for clopidogrel. Discontinuation for non-bleeding adverse events was low and similar for KENGREAL (0.6%) and for clopidogrel (0.4%). Coronary artery dissection, coronary artery perforation, and dyspnea were the most frequent events leading to discontinuation in patients treated with KENGREAL.

Non Bleeding Adverse Reactions

Hypersensitivity - Serious cases of hypersensitivity were more frequent with KENGREAL (7/13301) than with control (2/12861). These included anaphylactic reactions, anaphylactic shock, bronchospasm, angioedema, and stridor.

Decreased renal function - Worsening renal function was reported in 3.2% of KENGREAL patients with severe renal impairment (creatinine clearance <30 mL/min) compared to 1.4% of clopidogrel patients with severe renal impairment.

Dyspnea - Dyspnea was reported more frequently in patients treated with KENGREAL (1.3%) than with control (0.4%).

DRUG INTERACTIONS

Thienopyridines: Clopidogrel or prasugrel administered during KENGREAL infusion will have no antiplatelet effect until the next dose is administered. Therefore, administer clopidogrel or prasugrel after KENGREAL infusion is discontinued [see Dosage and Administration (2.2) and Clinical Pharmacology (12.3)].

USE IN SPECIFIC POPULATIONS

Pregnancy:

Risk Summary

There are no available data on cangrelor use in pregnant women to evaluate for a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. Untreated myocardial infarction can be fatal to the pregnant women and fetus [see Clinical Considerations].

In animal reproduction studies, continuous infusion of cangrelor in pregnant rats and rabbits throughout organogenesis at dose approximately 2-times the maximum recommended human dose (MRHD) did not result in fetal malformations [see Data].

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Continued on next page.

Brief Summary for Kengreal (cangrelor) for injection, for intravenous use (continued)

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk

Myocardial infarction is a medical emergency in pregnancy which can be fatal to the pregnant woman and fetus if left untreated. Life-sustaining therapy for the pregnant woman should not be withheld due to potential concerns regarding the effects of cangrelor on the fetus.

Labor or delivery

Cangrelor use during labor and delivery may increase the risk for maternal bleeding and hemorrhage. Performance of neuraxial blockade procedures is not advised during cangrelor use due to potential risk of spinal hematoma. When possible, discontinue cangrelor 1 hour prior to labor, delivery, or neuraxial blockade [see Clinical Pharmacology (12.2)].

Data

Animal Data

A prenatal and postnatal development study in female rats demonstrated a slight increase in the incidence of maternal mortality in dams treated at doses up to 30 mcg/kg/min (approximately 7.5 times the MRHD) cangrelor continuous infusion from Day 6 of gestation up to Day 23 post-partum. Pregnancy rates, gestation index, length of gestation, numbers of live, dead and malformed pups, sex ratio, live birth index, and lactation of the maternal animals were unaffected.

Cangrelor administered at dose levels of ≥ 3 mcg/kg/min in pregnant rats from Day 6 to 17 post-coitum resulted in dose-related fetal growth retardation characterized by increased incidences of incomplete ossification and unossified hind limb metatarsals.

An embryo-fetal development study in rabbits administered 4, 12, or 36 mcg/kg/min cangrelor continuous IV infusion from Day 6 to Day 19 post-coitum resulted in increased incidences of abortion and intrauterine losses at ≥12 mcg/kg/min (3 times the MRHD). Fetal growth retardation occurred at 36 mcg/kg/min (9 times the MRHD) and was characterized by decreased fetal weights, slight reduction in ossification, and a slight increase in skeletal variants.

Cangrelor did not produce malformations in either the rat or rabbit embryo-fetal development studies and is not considered to be a teratogen.

Lactation:

Risk Summary

There are no data on the presence of cangrelor in human milk or animal milk, the effects on the breastfed infant, or the effects on milk production. However, due to its short-half life, cangrelor exposure is expected to be very low in the breastfed infant.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

Geriatric Use: In CHAMPION PHOENIX, 18% of patients were ≥75 years. No overall differences in safety or effectiveness were observed between these patients and those patients <75 years [see Clinical Studies (14.1)].

Renal Impairment: No dosage adjustment is required for patients with mild, moderate, or severe renal impairment [see Clinical Pharmacology (12.3)].

Hepatic Impairment: KENGREAL has not been studied in patients with hepatic impairment. However, the metabolism of KENGREAL is not dependent on hepatic function, so that dosage adjustment is not required for patients with hepatic impairment [see Clinical Pharmacology (12.3)].

OVERDOSAGE

There is no specific treatment to reverse the antiplatelet effect of KENGREAL but the effect is gone within one hour after the drug is discontinued.

In clinical trials, 36 patients received an overdose of KENGREAL, ranging from 36 to 300 mcg/kg (bolus dose) or 4.8 to 13.7 mcg/kg/min (infusion dose). The maximum overdose received was 10 times the PCI bolus dose or 3.5 times the PCI infusion dose in 4 patients. No clinical sequela were noted as a result of overdose following completion of KENGREAL therapy.

Please see Full Prescribing Information at www.KENGREAL.com.

References: 1. Mehta SR, Yusuf S, Peters RJ, et al. Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. *Lancet.* 2001;358(9281):527-533. **2.** Steinhubl SR, Berger PB, Mann JT, III, et al. Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial [published correction appears in JAMA. 2003;289(8):987]. *JAMA.* 2002;288(19):2411-2420. **3.** Montalescot G, Bolognese L, Dudek D, et al. Pretreatment with prasugrel in non-ST-segment elevation acute coronary syndromes. *N Engl J Med.* 2013;369(11):999-1010. **4.** Lawton JS, Tamis-Holland JE, Bangalore S, et al. 2021 ACC/AHA/SCAI Guideline for Coronary Artery Revascularization: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *J Am Coll Cardiol.* 2021;00:000-000. **5.** Collet JP, Thiele H, Barbato E, et al. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J.* 2021;42(14):1289-1367. **6.** Bhatt DL, Stone GW, Mahaffrey KW, et al. Effect of platelet inhibition with cangrelor during PCI on ischemic events. *N Engl J Med.* 2013;368(14):1303-1313. **7.** Ibrahim K, Shah R, Goli RR, et al. Fentanyl delays the platelet inhibition effects of oral ticagrelor: full report of the PACIFY randomized clinical trial. *Thromb Haemost.* 2018;118(8):1409-1418. **8.** BRILINTA® (ticagrelor) Prescribing Information, Astra-Zeneca, 2021. **9.** PLAVIX® Prescribing Information, Bristol Myers-Squibb, 2021. **10.** EFFIENT® (prasugrel) Prescribing Information, Eli Lilly and Co, 2020. **11.** KENGREAL® (cangrelor) Prescribing Information. 2022.

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