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Guideline recommendations for cangrelor should be upgraded: pros and cons

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Introduction

Cangrelor is an intravenous (IV) $P2Y_{12}$ receptor inhibitor that is characterised by high potency and a more rapid onset and offset of the pharmacological effect as compared to oral $P2Y_{12}$ inhibitors. The latest European guidelines on acute coronary syndromes (ACS) recommend its use in $P2Y_{12}$ receptor inhibitor-naïve patients undergoing percutaneous coronary intervention (PCI). This statement has been provided with a Class IIb recommendation and a Level of Evidence A, therefore meaning that the current evidence on the use of cangrelor is still not definitive. Randomised trials of cangrelor have yielded mixed results, and a meta-analysis of these trials has shown that cangrelor was associated with reduced ischaemic events and increased minor bleeding. However, the benefit of cangrelor was reduced when compared to upfront clopidogrel, and no conclusive data are available in case of administration of potent oral $P2Y_{12}$ inhibitors (i.e., prasugrel or ticagrelor). Based on current evidence, cangrelor is not the standard antithrombotic strategy for unselected ACS patients undergoing PCI, and whether the current recommendation should be upgraded is a matter of debate.

Pros

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Cangrelor is an IV $P2Y_{12}$ receptor inhibitor used as an adjunct to PCI to mitigate the risk of periprocedural myocardial infarction (MI), stent thrombosis (ST), and repeat coronary revascularisation in patients who have not been treated with a $P2Y_{12}$ receptor inhibitor. Cangrelor offers a unique pharmacokinetic-pharmacodynamic profile that has rationally increased its utilisation over the past years. This includes its rapid onset of action, high level of antiplatelet potency (with a linear dose-dependent pharmacokinetic profile), and a relatively good safety profile given its fast offset.

Recent guidelines from the 2023 European Society of Cardiology for the management of ACS attribute a Class IIb recommendation for the use of cangrelor in patients undergoing PCI who are $P2Y_{12}$ receptor inhibitor-naïve[1]. This recommendation is based on high-quality data from three large randomised clinical trials (CHAMPION PCI, CHAMPION PLATFORM, and CHAMPION PHOENIX) and a pooled patient-level meta-analysis[2]. The latter demonstrated a significant reduction in periprocedural events (i.e., ST and periprocedural MI) and procedural angiographic complications (i.e., acute ST, new/suspected thrombus, and need for bailout glycoprotein IIb/IIIa inhibitor) with cangrelor versus oral clopidogrel/placebo within 48 hours of PCI[2]. Furthermore, these benefits were observed consistently across different subgroups, including patients undergoing PCI for acute MI and stable coronary artery disease. The corollary to the ischaemic benefits was an increased risk of minor bleeding, whereas life-threatening and major bleeding events occurred at similar rates in both treatment arms. Of note, the control arms in all three trials included some patients on placebo, which could have attenuated the bleeding event rates.

On the other hand, oral $P2Y_{12}$ receptor inhibitors, including the more potent ones such as prasugrel and ticagrelor, have a slower onset of action and require several hours to reach

effective platelet inhibition. In addition, they may have variable pharmacokinetics and pharmacodynamics that result in an unpredictable response to the loading dosage, an issue that becomes particularly relevant during the procedure itself and in acute settings with relative gastroparesis or impaired gut absorption due to the use of opiates, decreased gut perfusion, and nausea[3]. In a real-world high-risk population, the theoretical advantages of cangrelor in patients with cardiogenic shock were indeed realised at 48 hours after PCI[4]. Second, cangrelor allows fast platelet function recovery – within an hour of discontinuation – whereas oral agents require at least 48 hours and can take up to seven days. This can be very practical in situations where there is an urgent need for surgery. In the BRIDGE trial, cangrelor versus placebo use was associated with significantly higher rates of platelet inhibition without an excess of bleeding complications among patients undergoing cardiac surgery[5]. This can be relevant if bleeding complications occur periprocedurally or if an urgent surgical intervention becomes necessary. Finally, patients undergoing PCI for ST-segment elevation MI (STEMI) pretreated with oral agents immediately before the procedure may not have optimal/maximum platelet inhibition periprocedurally, and cangrelor can alleviate this issue[6].

Hence, cangrelor may reasonably deserve a higher level of guideline recommendation for patients with inadequate platelet inhibitor absorption/activity during urgent or emergent PCI, perhaps even more so for acute MI and shock than for the lower-risk categories of ACS. Furthermore, cangrelor may be considered for a "bridging" recommendation in patients with recent coronary stenting ahead of surgery or other major invasive procedures. Its unique, fast on/off capability supports its use in challenging clinical scenarios that may not be suitable even for large randomised trials.

Conflict of interest statement

G. Dangas has received research grants to his institution from Bayer and Daiichi Sankyo as principal investigator for a clinical trial and relevant consultation/lectures. J. Nicolas has no conflicts of interest to declare.

Cons

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Cangrelor is a direct, reversible, short-acting, intravenously administrable $P2Y_{12}$ receptor inhibitor that has been evaluated in chronic coronary syndrome (CCS) and ACS patients undergoing PCI in prospective randomised clinical trials and compared to clopidogrel[7,8,9]. Although only tested against the weaker $P2Y_{12}$ inhibitor, clopidogrel, the results from two of these three trials did not demonstrate the superiority of cangrelor versus clopidogrel: CHAMPION PCI and CHAMPION PLATFORM[7,9]. In contrast, the clinical outcome of CHAMPION PHOENIX[8] and a meta-analysis of all three trials[2] exhibited superiority with respect to a significant reduction of a composite primary endpoint (death, MI, ischaemia-driven revascularisation 48 hours after PCI)[2] and with respect to ST[2,8]. These positive data have led to a guideline-recommended use of IV cangrelor in ACS patients who are naïve to $P2Y_{12}$ inhibitors in order to optimise platelet inhibition during coronary angiography and PCI[1].

The main question that remains is why cangrelor, which has an optimal antiplatelet effect measured minutes after IV injection[10,11], is not consistently superior to clopidogrel – a $P2Y_{12}$ inhibitor which only reaches optimal platelet inhibition between 4 and 6 hours after oral use[12]. This can, on one hand, depend on the different study designs and on the duration of cangrelor infusion. On the other hand, a possible answer is that optimal platelet inhibition during PCI in ACS patients is more of a theoretical advantage than one of true clinical importance, although this is not in line with the current belief.

Optimal flow after PCI in the culprit vessel could be more important than optimal platelet inhibition in the early phase of intervention, and some extent of platelet inhibition usually already exists because of early ingestion of acetylsalicylic acid (ASA) and its fast action on platelet activity[13]. An optimal antiplatelet effect after 4-6 hours, which is the case for clopidogrel as well as prasugrel and ticagrelor in the majority of patients – it has been shown that almost every second or third patient treated with oral $P2Y_{12}$ inhibitors has no optimal platelet inhibition within 2-4 hours after ingestion[14] – might be necessary mainly to avoid early ST and related ischaemic events in the postinterventional phase. Early cessation of cangrelor infusion after 2 hours, which leads to a fast return of platelet activity, would be avoided by a prolonged 4-hour infusion[15]. This would also help to avoid early ST by reaching optimal antiplatelet action 4 to 6 hours after PCI. However, the early optimal action of cangrelor, in addition to oral $P2Y_{12}$ inhibition, may be important in patients with a high thrombus load during PCI[16].

The recent ACS guidelines show that pretreatment with $P2Y_{12}$ inhibitors in ACS patients is no longer necessary in non-ST-segment elevation [NSTE]-ACS patients and has a low-grade recommendation in STEMI patients[1]. Moreover, these guidelines recommend the use of prasugrel over ticagrelor in NSTE-ACS patients only after the coronary anatomy is known[1]. Why should a $P2Y_{12}$ inhibitor-naïve NSTE-ACS patient then be treated with IV cangrelor? The use of cangrelor in high ischaemic risk CCS patients, as shown by an Italian registry, is also not based on prospective clinical outcome trials[17].

As a remaining indication, IV cangrelor may yet have a role in $P2Y_{12}$ inhibitor-naïve STEMI patients[1], especially in patients who are unable to swallow oral $P2Y_{12}$ inhibitors[18,19], in $P2Y_{12}$ inhibitor-naïve ACS patients with a high intracoronary thrombus load[16], or as a bridging strategy in high-risk patients under dual antiplatelet therapy who are undergoing urgently needed surgery[1]. Widespread use without guideline-confirmed indications should be avoided.

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K. Huber reports lecture fees from AstraZeneca, Daiichi Sankyo, Chiesi, and Ferrer. P. Harbich has no conflicts of interest to declare.

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