Will cangrelor become the favored agent for acute coronary syndrome treatment?

Clopidogrel has been widely investigated, even if resistance limits its efficacy. Prasugrel and ticagrelor obtain a greater and homogeneous inhibition of platelet aggregation, but a delay onset of action in patients with stent thrombosis elevation myocardial infarction and an increased bleeding risk in case of surgical revascularization have been reported. Cangrelor is an intravenous reversible $P2Y_{12}$ inhibitor with an immediate onset and a quick offset of action. Based on its pharmacokinetic and pharmacodynamic profile, and on clinical data, cangrelor could become the antiplatelet of choice in case of elective percutaneous coronary intervention without clopidogrel pretreatment and in acute coronary syndrome requiring urgent coronary angiography. However, in acute setting, data of comparison with prasugrel and ticagrelor are needed.

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Oral $P2Y_{12}$ inhibitors limitations

Vascular endothelium damage after percutaneous coronary intervention (PCI) and atherosclerotic plaque rupture at the moment of acute coronary syndrome (ACS) both cause subendothelial matrix exposure and prothrombotic factors release with platelet activation and aggregation; subsequent exposure of binding site for coagulation factors on platelet membrane facilitates clot formation [1]. Based on previous considerations, antiplatelet and anticoagulant agents represent the cornerstone of ACS medical management; antiplatelet agents currently recommended for this clinical setting include aspirin, thienopyrides (clopidogrel and prasugrel), the oral reversible $P2Y_{12}$ receptor antagonist ticagrelor and intravenous glycoprotein Gp IIb/IIIa inhibitors (Gp I) [2,3].

A large randomized clinical trial in patients with non-ST-elevation myocardial infarction (NSTEMI) concluded that dual antiplatelet therapy (DAPT) with clopidogrel (300 mg loading dose followed by 75 mg/day) plus aspirin (75–325 mg/day) significantly reduced cardiovascular mortality, nonfatal MI and stroke at 9 months follow-up [4]; a subset analysis in patient undergoing PCI after 10 days of treatment confirmed the beneficial effect of DAPT [5].

Optimal level of platelet inhibition at the moment of PCI was matter of numerous studies and still not yet clearly defined.

A specific randomized clinical trial for clopidogrel use in patients with ST-elevation myocardial infarction (STEMI) undergoing primary PCI is not available, but many large observational studies and registries confirmed its efficacy even in this clinical setting favoring an early loading dose administration before angiography [6]. Despite its clinical efficacy, clopidogrel nonresponsiveness has been reported in approximately 30% of the treated patients potentially causing recurrent thrombotic events. Different mechanism might explain clopidogrel resistance involving its pharmacokinetic and pharmacodynamic profile: an inadequate active metabolite production can be caused by a reduced intestinal absorption and by a decreased hepatic conversion for cytochrome polymorphism or for interaction with other

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drugs; an increased turnover of platelets with a high numbers of $P2Y_{12}$ receptors and polymorphisms of the same receptors or of the intracellular pathway has been further described as possible mechanisms of suboptimal response to clopidogrel [7]. A late onset of action after the loading dose and a wide response variability with a modest value of platelet inhibition both in acute phase and during chronic treatment have been described; furthermore the irreversible effect on platelet function may increase bleeding risk in patients requiring cardiac and noncardiac surgery [1,8,9].

Prasugrel is a third-generation thienopyridine: its pharmacodynamic and pharmacokinetic properties overcome most clopidogrel limitations with subsequent less response variability and lower rate of non-responsiveness [10]; in patients undergoing PCI, prasugrel 60 mg loading dose followed by 10 mg/day, significantly increased inhibition of platelet aggregation (IPA) compared with clopidogrel 600 mg followed by 75 mg/day, already 30 min after administration [11]. In the TRITON-TIMI 38 trial 13608 clopidogrel-naive patients with ACS (STEMI and unstable angina/NSTEMI) treated with PCI, were randomized to prasugrel versus clopidogrel after coronary anatomy determination (with the exception of primary PCI); the most powerful antiplatelet effect of study drug significantly reduced the incidence of the composite end point (cardiovascular death, nonfatal death and nonfatal stroke), despite an increase risk of bleeding [12]. Otherwise, pretreatment with prasugrel 30 mg in NSTEMI patients, recently investigated in the ACCOAST trial, had no beneficial effect on ischemic events with a harmful effect on bleeding risk [13].

Ticagrelor is a reversible $P2Y_{12}$ inhibitor: its direct action on platelet receptor (independent by cytochrome activation) is associated with a faster, stronger and less variable IPA compared with clopidogrel; furthermore, the reversible inhibition allows a more rapid offset of action potentially useful in particular clinical setting [14].

In the PLATO trial, ticagrelor (180 mg loading dose, 90 mg twice a day maintenance) was compared with clopidogrel (300/600 mg loading dose, clopidogrel 75 mg twice a day maintenance) in 18,624 patients with ACS (NSTEMI and STEMI) regardless conservative or invasive strategy and clopidogrel pretreatment: study drug significantly reduced the 12 months incidence of the composite end point (cardiovascular death, MI and stroke) with an increase of major bleeding not related to coronary artery by pass surgery [15].

Data on new oral $P2Y_{12}$ inhibitors indicate a faster and greater IPA compared with clopidogrel, and clinically a significant decrease of ischemic events despite an increase risk of bleeding particularly in patients undergoing surgical procedures.

However, most pharmodynamic data have been obtained from healthy volunteers and patients undergoing PCI for stable coronary artery disease. In STEMI patients, prasugrel 60 mg loading dose induced a suboptimal IPA (stimulated with 20 μmol/l ADP) 30 min after administration, and a stable inhibition of 75% was obtained only after 6 h [16]; in the RAPID study, more than half of the enrolled patients (STEMI undergoing primary PCI randomized to prasugrel vs ticagrelor) presented a high residual platelet reactivity 2 h after the loading dose of both drugs [17]. Therefore, in patients with ACS, particularly STEMI, where antiplatelet effect has a crucial role, IPA seems lower than expected in different clinical settings.

Effectiveness of new oral ADP-antagonists appears more related to cardiovascular events prevention during long term follow-up rather than to procedural ones; furthermore time to PCI significantly shortened over years: in the PCI CURE trial [5], myocardial revascularization was performed after a median of 6 days, while in the recent ACCOAST trial after only 4 h [13]. The opposite result of previous and other studies probably explains the great variability in clinical practice to pretreat or not patients undergoing coronary angiography [18] with a consequent lower protection on events procedure related (if not done), and an increased risk of bleeding in case of urgent surgical revascularization (if chosen). The 'ideal' antiplatelet drug in patients undergoing PCI, should have a rapid onset of action, obtain a strong effect and have a quickly offset in case of complications or surgery.

Cangrelor
Pharmacology
Cangrelor is an intravenous adenosine triphospate analog with a high selectivity for $P2Y_{12}$ receptors [19]. Cangrelor is a direct acting drug not requiring cytochrome 450 or other enzymatic activation. Pharmacology of cangrelor has been studied in healthy volunteers and in patients with CAD including ACS. The inhibitory effect of cangrelor on $P2Y_{12}$ receptor is predominantly competitive; bolus dose administration achieves highest level of receptors inhibition within few minutes; continuous infusion without bolus reaches steady state of inhibition within 15–30 min and it is sustained for the entire duration of drug infusion [20]. Cangrelor is directly inactivated through dephosphorylation, with a mean plasma half-life of 9 min in patients with ACS [21]. Based on its reversible binding to receptors and on its very short half-life, platelet function resumption can be obtained within 1 h after the end of infusion.

Different infusion doses (without initial bolus) showed a rapid onset of action and a rapid achievement of steady state level of inhibition, and a dose-dependent effect on IPA. However maximal IPA induced by ADP required at least 30 min and the inhibitory effect was stable up to 72 h during continuous infusion [21].

Bolus addition concomitantly with a continuous infusion in healthy volunteers obtained a more rapid and complete inhibition of $P2Y_{12}$ receptors: pharmacokinetic and pharmacodynamic data showed an extremely short half-life (3.3 min), a low volume of distribution and a selective inhibition of ADP-induced platelet aggregation; high dose regimen (bolus 30 µg/kg + infusion 4 µg/kg/min) provided greater inhibition of ADP-induced P-selectin expression. Almost completely recovery of platelet function was obtained within 60–90 min after the end of infusion even at these doses [22].

Cangrelor's pharmacological profile is characterized by an immediate onset of action, a strong and consistent inhibition of platelet function and a rapid offset, with a potential 'ideal' use in patients requiring PCI, particularly in acute setting such as NSTEMI and STEMI where a strong IPA is required; quickly recovery of platelets might be 'ideal' too in case of urgent surgery where $P2Y_{12}$ inhibition cessation is necessary to limit bleeding.

Clinical studies

Cangrelor was tested in Phase II studies, mostly in ACS and in patients undergoing PCI. Given as an infusion, up to 4 µg/kg/min, cangrelor showed a dose-dependent effect evident at 2.5 h at a dosage of 0.05 µg/kg/min and at 1.5 h at a dosage of 1 µg/kg/min [21]. Dosages of 2 and 4 µg/kg/min provide almost complete (>80%) inhibition of ADP-induced platelet aggregation [23,24]; the latter dosage has faster onset with no evidence of excessive bleeding compared with placebo or to other agents, including clopidogrel, abciximab and alteplase [23,25]. Of note, a trend to less bleeding with cangrelor compared with abciximab was reported, although not statistical significant [23].

CHAMPION program

Cangrelor has been tested in several trials; the most important three carried out by the same study group and called CHAMPION. The CHAMPION program consisted of three randomized 1:1, double-blind, double-dummy trials (CHAMPION-PCI, CHAMPION-PLATFORM and the latest CHAMPION-PHOENIX) designed to test whether cangrelor at the time of PCI followed by transition to oral clopidogrel is superior to control (oral clopidogrel), given at the beginning or at the end of PCI, in reducing the rate

of thrombotic events during and immediately after revascularization [26–28].

CHAMPION-PCI and CHAMPION-PLATFORM both started in 2007. Bolus and infusion were administered as soon as possible after confirmation of coronary anatomy suitable in patients with stable angina or non-ST-elevation ACS (NSTEACS); otherwise in patients with STEMI study drug could be administered before knowing coronary anatomy. At the end of infusion, patients in the cangrelor arm received 600 mg of clopidogrel loading dose. The comparator arm (clopidogrel 600 mg) in CHAMPION-PCI was administered before PCI start, while in PLATFORM after the end of procedure). Moreover only clopidogrel naive patients were eligible in PLATFORM while patients on chronic clopidogrel therapy could be included in the CHAMPION-PCI and patients with STEMI were eligible in the last but not in PLATFORM.

CHAMPION PCI randomized 8877 patients to cangrelor versus 600 mg of oral clopidogrel administered before PCI in ACS setting. The primary efficacy end point (a composite of death from any cause, myocardial infarction or ischemia-driven revascularization [IDR]) at 48 h was not reduced with cangrelor, occurring in 7.5 versus 7.1% of the patients (odds ratio [OR]: 1.05; 95% CI: 0.88–1.24; p = 0.59). A secondary exploratory end point of death from any cause, Q-wave MI or IDR showed a trend toward a reduction with cangrelor, but not statistically significant (OR: 0.67; 95% CI: 0.39–1.14; p = 0.14). In CHAMPION PLATFORM, 5362 clopidogrel naive patients were randomly assigned to cangrelor or placebo at the time of PCI (STEMI patients excluded), followed by 600 mg of clopidogrel. The primary end point (the same of CHAMPION PCI) occurred in 7% of patients receiving cangrelor versus 8% in patients receiving placebo (8.0%; OR: 0.87; 95% CI: 0.71–1.07; p = 0.17). In the cangrelor group two prespecified secondary end points were significantly reduced at 48 h: the rate of stent thrombosis (ST), from 0.6 to 0.2% (OR: 0.31; 95% CI: 0.11–0.85; p = 0.02), and the rate of death from any cause, from 0.7 to 0.2% (OR: 0.33; 95% CI: 0.13–0.83; p = 0.02).

In 2009 both studies were prematurely interrupted after interim analysis due to futility on primary end point (death, MI or IDR) at 48 h, although a significant benefit has been observed across the two trials on secondary but relevant end points, such as death, ST or Q-wave MI. Moreover, the definition of MI used in PCI and PLATFORM was previous to the universal definition of MI [29]. This definition relied on clinical judgment rather than on a strict assessment of biomarker status. The time from hospital admission to cardiac

catheterization was much shorter than expected, so many patients had only one or none cardiac marker value prior to PCI or cardiac markers were still increasing at the time of revascularization: PCI-related MI adjudication through the biomarkers trend was not possible. A subgroup analyses suggested enhanced efficacy of cangrelor in patients with stable angina, where procedural MI is more easily to define. Two independent analyses of the CHAMPION data set were developed using the universal definition of MI, showing a reduced number of PCI-related MI events and a more favorable treatment effects for cangrelor [30,31].

CHAMPION PHOENIX [32] tested whether cangrelor improves outcome compared with clopidogrel in patients undergoing PCI naive for $P2Y_{12}$ inhibitors. Comparator arm was clopidogrel 300 or 600 mg, at site investigator discretion (in the treatment arm, cangrelor infusion was followed by clopidogrel 600 mg); primary end point was the composite of death, MI, IDR or ST at 48 h; PCI-related MI could only be assessed if troponin pre-PCI was normal or elevated but stable or falling using at least two samples 6 h apart (the second universal definition of MI was applied for events adjudication, with some elements that were later included in the subsequent third universal MI definition, mainly concerning the definition of PCI-related (type 4a) MI [33].

Cangrelor significantly reduced the primary end point (4.7 vs 5.9%; OR: 0.78; 95% CI: 0.66–0.93; p = 0.005) [28]. There were no significant excess in GUSTO severe bleeding (0.16 vs 0.11%; OR: 1.5; 95% CI: 0.53–4.22; p = 0.44) or transfusions (p = 0.16); however, there was more ACUITY major bleeding (4.3 vs 2.5%; OR: 1.72; 95% CI: 1.39–2.13; p < 0.001) with cangrelor compared with clopidogrel. Efficacy results were similar at 30 days. There was no difference in mortality and in IDR, while MI was significantly reduced by cangrelor (3.8 vs 4.7%; OR: 0.80; 95% CI: 0.67–0.97; p = 0.02). ST, the key secondary end point, was significantly reduced by 38% in the cangrelor arm (OR: 0.62; 95% CI: 0.43–0.90; p = 0.01).

ST is a rare complication, in most cases associated to death or MI. The risk of ST is particularly increased in patients undergoing PCI for ACS, in those with diabetes and in complex coronary anatomy such as bifurcation, left main and in case of multiple stents implantation [34].

In addition to antiplatelet therapy, procedural anticoagulation is an essential part of PCI, particularly in ACS [2,3].

In the HORIZON-AMI trial, the direct thrombin inhibitor bivalirudin, compared with unfractionated heparin (UHF) plus Gp I, significantly reduced major bleeding and mortality in patients with STEMI undergoing primary PCI; an increased risk of acute (<24 h) ST was however reported in patients receiving bivalirudin [35]. Because study drug was stopped at the end of PCI and ST was not increased in patients pretreated with UHF bolus and in patients treated with clopidogrel 600 mg loading dose [36], an inadequate postprocedural 'antithrombotic protection' appears as the potential mechanism of the increased risk. Furthermore the HORIZON-AMI was performed before the availability of the new $P2Y_{12}$ inhibitors.

In the TIMI 38 study, in patients treated with at least one coronary stent, prasugrel significantly reduced definite or probable ST by 59% within 30 days after stent placement and by 40% after 30 days; acute ST (despite occurred in few cases) was only numerically lowered [37].

A specific analysis of the PLATO trial showed that ticagrelor reduced definite or probable ST compared with clopidogrel (hazard ratio: 0.75; 95% CI: 0.59–0.95; p = 0.017), with a greater benefit for late (>30 days) compared with subacute (24 h–30 days) and acute thrombosis (<24 h): in acute phase there was no statistical difference between the two drugs about ST regardless of definition (definite/possible/probable) [38].

The more recent EUROMAX trial (comparing prehospital bivaluridin vs UHF plus optional Gp I in STEMI treated with primary PCI) confirmed the positive results of the HORIZON-AMI on bleeding reduction; despite 90% of the enrolled patients received oral $P2Y_{12}$ inhibitor before PCI (50% prasugrel or ticagrelor) and study drug infusion was prolonged after procedure, acute ST was still significantly increased in the bivalirudin group [39].

ST, differently from previous trial, was a key secondary end point of the CHAMPION PHOENIX; it was defined as the occurrence of intraprocedural ST (IPST) or Academic Research Consortium (ARC) ST (classified as definite, probable or possible [40]); IPST was specifically assessed by an independent blinded angiographic Core Laboratory in a frame by frame analysis. IPST, defined as any angiographically new or worsening thrombus occurring during PCI and related to stent implantation, ranges from 0.5 to 0.7% [41]. In the CHAMPION PHOENIX study IPST was a strong independent predictor of short and long term mortality and of MI, and an independent predictor of ARC-definite ST at 48 h and at 30 days. PCI procedure in patients with STEMI and NSTE-ACS doubled the odds of IPST, and cangrelor use reduced its rate by 35% irrespective of clinical setting. The immediate inhibition of ADP receptors offered by cangrelor may be advantageous in preventing IPST and consequently ST in patients undergoing PCI not pretreated with

different antiplatelet drugs and in patients with STEMI where oral $P2Y_{12}$ inhibitors present a late onset of action caused by a delayed gastrointestinal absorption [42]. The protective effect of prasugrel and ticagrelor on ST is clearly evident after the first 24 h postimplantation, and cangrelor could be superior in the prevention of this potential catastrophic event particularly in the first hours after primary PCI: a randomized clinical trial comparing cangrelor with the new oral $P2Y_{12}$ inhibitors in STEMI is however needed to demonstrate this theoretical statement.

BRIDGE trial: a potential different & peculiar application

The BRIDGE trial prospectively randomized 210 patients receiving oral thienopyridines awaiting coronary artery by pass (CABG) surgery to cangrelor (0.75 μg/kg/min) or placebo, administrated for at least 48 h after thienopyridines cessation; study drug was stopped 1 to 6 h before intervention. The primary efficacy end point, platelet reactivity defined as PRU <240, was reduced in cangrelor arm (98.8 vs 19.0%, risk ratio [RR]: 5.2; 95% CI: 3.3–8.1; p < 0.001). CABG surgery-related bleeding occurred in 11.8 versus 10.4%, respectively, in cangrelor and placebo group (RR: 1.1; 95% CI: 0.5–2.5; p = 0.763). There were no significant differences in major bleeding prior to CABG surgery, although minor bleeding was numerically higher with cangrelor [43].

This study applies a pharmacologic feature of cangrelor to a relevant and not uncommon clinical setting in which balance between ischemic and bleeding risk over time is crucial. In this case cangrelor efficiently inhibits platelets (as showed by reduction of PRU) without a concomitant significant increase of bleeding, prior or surgery related.

CHAMPIONs & beyond

A recent pooled analysis of patient-level data from the three CHAMPION trials, including about 25,000 patients, showed a reduction in the primary end point (composite of death, MI, IDR or ST at 48 h) with cangrelor use by 19% (3.8% for cangrelor vs 4.7% for control; OR: 0.81; 95% CI: 0.71–0.91; p = 0.0007), and ST by 41% (0.5 vs 0.8%; OR: 0.59; 95% CI: 0.43–0.80; p = 0.0008) [44]. These benefits were maintained at 30 days with no significant difference in the primary safety outcome (GUSTO sever bleeding not related to CABG, 0.2% in both groups), in GUSTO moderate bleeding (0.6 vs 0.4%), or in transfusion (0.7 vs 0.6%); cangrelor only significantly increased GUSTO mild bleeding (16.8 vs 13.0%; p < 0.0001). The benefit of cangrelor on the primary end point was consistent across all of the prespecified subgroups, includ-

ing patients with all clinical presentations (STEMI, NSTEACS or stable angina).

In a recent trial-level data meta-analysis [45] of the CHAMPION trials cangrelor was not different from control in terms of all cause death (0.26% vs 0.36%; RR: 0.72; 95% CI: 0.36–1.43) and MI (5.3 vs 5.7%; RR: 0.94; 95% CI: 0.78–1.13); conversely it was superior in terms of Q-wave MI (0.15 vs 0.28%; RR: 0.53; 95% CI: 0.30–0.92; p = 0.03; number need to treat [NNT]: 728), IDR (0.52 vs 0.74%; RR: 0.72; 95% CI: 0.52–0.98; p = 0.04; NNT: 474) and ST (0.49 vs 0.84%; RR: 0.60; 95% CI: 0.44–0.82; p = 0.001; NNT: 287). GUSTO severe bleeding and TIMI major bleeding were not different between cangrelor and control.

Another study group did not find a difference in the composite end point of death from all causes, MI or IDR at 48 h between cangrelor and clopidogrel, but cangrelor was associated with a lower risk of ST, Q-wave MI and IDR, without a significant increased risk of GUSTO-severe or life-threatening bleeding [46].

Different authors have instead raised concerns about cangrelor safety: pooling data from CHAMPION trials and BRIDGE, they reported that cangrelor caused a significantly increased risk for major bleeding at 48 h according to the ACUITY scale, and a trend toward an increased risk for any transfusions [47].

The main limitation of the latter analysis is to be not patient-leveled: results show mild to moderate heterogeneity, probably related to inter-trial different patients characteristics, trial methodology and different comparator drugs and doses. Furthermore, events were not readjudicated, and so the universal definition of MI was not uniformly applied.

The main limitation of the CHAMPION PHOENIX is the use of clopidogrel as comparator. Current guidelines recommend prasugrel or ticagrelor (if not contraindicated) over clopidorel in patients with ACS, for the positive clinical results of the previous reported trials [12,15]. The second main limitations were the different clopidogrel loading dose use in the two arms (600 mg after cangrelor infusion vs 300 or 600 mg in the comparator at site investigators discretion) and the delay in receiving it. A logistic regression analysis of the primary end point in the clopidogrel arm, reported a relative risk increase comparing 300 versus 600 mg and per each 15 min of delay in the loading dose administration [48].

The US FDA advisory panel rejected the approval of cangrelor based on the negative results of the first two randomized trial and on concerns about PHOENIX results. These last included the use of clopidogrel in the control arm and concerns about the type of MIs (mainly periprocedural) prevented by cangrelor, considered not

so clinically meaningful; in addition, the increase of bleeding events with different definition used, concluded for a not clear risk/benefit profile of the drug.

Switch from cangrelor to oral P2Y$_{12}$ inhibitors

Patients treated with coronary stent, after cangrelor infusion will require a long-term treatment with an oral ADP blocker and possible interactions during the switch have been investigated.

In healthy volunteers, the anticipated degree of platelet inhibition obtained with clopidogrel 600 mg loading was lost during simultaneous cangrelor infusion, but not if the administration was postponed immediately upon termination of drug infusion [49].

Despite the exact mechanism of how cangrelor reduces the action of clopidogrel is unknown, a high level of P2Y$_{12}$ receptors occupancy may reduce the access of clopidogrel active metabolite to its binding site [50], and the active metabolite of clopidogrel is highly reactive and unstable with a very short half-life of only 20 min [51].

In an *ex vivo* canine model no pharmacodynamic interaction between cangrelor and ticagrelor has been observed; because both agents have a reversible action, IPA is directly related to their plasma concentration and so, when cangrelor is quickly cleared after the end of infusion, available receptors can rapidly be occupied by ticagrelor and maintain antagonism [52].

The switch from intravenous to oral P2Y$_{12}$ blockers, or vice versa could affect efficacy and safety of antithrombotic therapy, potentially increasing the risk of ischemic events or bleedings. The TRANSITION I trial recently showed that ticagrelor does not attenuate cangrelor pharmacodynamic effect, given before or during drug infusion; the effect of ticagrelor was preserved when given during infusion of cangrelor [53]. TRANSITION II (NCT01852019) investigating transition to and from prasugrel has been recently completed and results will be soon reported.

Conclusion

Cangrelor is a novel, reversible and direct acting inhibitor of P2Y$_{12}$ platelet receptors. DAPT including aspirin and an oral thienopiridine or ticagrelor is recommended in patients with ACS and the association aspirin plus clopidogrel has to be administered in all patients with stable CAD undergoing PCI with stent implantation [2,3,54]. Time from hospital admission to PCI has shortened in all clinical settings. Despite administration of a loading dose, oral P2Y$_{12}$ inhibitors need gastrointestinal absorption and specific metabolism, that in case of clopidogrel requires a two-step activation [7]; furthermore, in ACS, particularly STEMI, even prasugrel and ticagrelor present a late onset of action and a level of IPA

lower than expected in patients with stable CAD and in healthy volunteers [16,17]. In acute setting, sedation, nausea, vomiting, shock condition and endotracheal intubation contribute to limit antiplatelet efficacy of oral antiplatelet agents [42,55]. Randomized clinical trials investigating pretreatment with DAPT in patients with NSTEACS showed contradictory results with potential increase of bleeding risk; data about upstream administration of oral antiplatelet drugs in STEMI undergoing primary PCI are lacking [6,13]. In clinical practice incidence and time to ADP antagonists loading dose vary between different sites [18].

All together, previous considerations indicate a potential inadequate protection during and in the first hours post-PCI, where a stent has been placed shortly before. Cangrelor intravenous administration overcome limitations of GI absorption and the immediate and strong IPA [22,23] may be particularly useful in case of urgent/emergent coronary angiography as high risk NSTEACS and STEMI undergoing primary PCI.

Prasugrel and ticagrelor induced a greater IPA compared with clopidogrel with a subsequent superior protection on ischemic events, but with an increase of major bleeding related to CABG [12,15]; a withdrawal of 7 days for prasugrel and of 5–7 days for clopidogrel and ticgarelor before major surgery is recommended [2].

Cangrelor compared with clopidogrel in different clinical setting reduced ischemic events, particularly periprocedural MI and ST; its quickly offset of action after the end of infusion can overcome previous limitations of oral drugs with a more acceptable risk profile in case of complications during PCI or in case on complex anatomy requiring urgent surgical revascularization.

Based on its pharmcodynamic characteristics, cangrelor could be the drug of choice in case of ACS undergoing urgent coronary angiography, but a dedicated comparison with prasugrel and ticagrelor in acute setting is needed to confirm an although concrete theoretical speculation.

Future perspective

Future research to support cangrelor use as the drug of choice in patients with STEMI undergoing primary PCI or high-risk NSTEACS should include specific large randomized trials using prasugrel and/or ticagrelor as comparator.

Another limitation of cangrelor that will need an adequate investigation is the optimal transition to oral P2Y$_{12}$ inhibitor to avoid a vulnerable window increasing the risk of thrombotic events.

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ticle was given the opportunity to review the manuscript for factual accuracy. Changes were made at the discretion of the authors and based on scientific or editorial merit only.

Executive summary

- P2Y$_{12}$ inhibitors have a crucial role in medical treatment of acute coronary syndromes, particularly in percutaneous coronary intervention setting.
- Clopidogrel has been worldwide used, but several limitations of this drug can affect its efficacy (e.g., slow onset of action, nonresponsiveness affecting up to a third of patients, reduced absorption or metabolism, hemodynamic impairment, irreversibility of action and lack of antidote).
- New oral P2Y$_{12}$ inhibitors (prasugrel and ticagrelor) overcome many but not all clopidogrel, particularly slow onset of action in acute coronary syndrome.
- Cangrelor is a new antiplatelet drug, with a rapid, potent and reversible effect, and for its intravenously administration it can overcome most limitations of the oral agents.
- CHAMPION program showed efficacy and safety of this molecule in percutaneous coronary intervention setting and markedly reduction of stent thrombosis suggests its usefulness in acute coronary syndrome.
- BRIDGE trial showed that cangrelor may be a safe and effective in maintaining P2Y$_{12}$ inhibition when oral thienopyridines are interrupted for surgery.
- Further studies are needed to confirm efficacy and safety of cangrelor in populations with different ischemic and bleeding risk.

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