Anti-thrombotic Therapy With Cangrelor and Bivalirudin in Venoarterial Extracorporeal Membrane Oxygenation Patients Undergoing Percutaneous Coronary Intervention: A Single-Center Experience

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VA-ECMO is commonly used for patients in cardiogenic shock (CS) or refractory cardiac arrest (CA) undergoing PCI for ACS. In this setting at high risk of both thrombotic and hemorrhagic complications, optimal anti-thrombotic therapy remains ill-defined. We hypothesized that an anti-thrombotic therapy comprising a parenteral anticoagulant (bivalirudin) and a parenteral anti-platelet agent (cangrelor) may prove safe and effective in this scenario. From November 2019 to December 2021, 14 patients received at least one dose of cangrelor (starting dose: 0.125 μg/kg/min) plus bivalirudin, without background aspirin, in the context of PCI and VA-ECMO for ACS-related CS/CA, and were included in this study. Efficacy endpoint was occurrence of thrombotic events and safety endpoint was major bleeding occurrence. Median age was 58 years. The majority (64%) presented with refractory CA. A thrombotic event occurred in 14%, while major bleeding occurred in 21% patients. One patient experienced arterial thrombosis after VA-ECMO arterial cannula removal, another experienced ischemic cerebellar stroke without functional sequelae. Bleeding events were: 29% BARC 3a, 14% BARC 3b, and 7% BARC 5b. Overall in-hospital mortality was 50%. Cangrelor was continued for 5 (4–10) days; temporary discontinuation was necessary in 36%, either for VA-ECMO cannula removal or for bleeding events. A low dose of cangrelor, associated with standard-intensity anticoagulation with bivalirudin was a feasible anti-thrombotic strategy in patients undergoing PCI during VA-ECMO support for ACS-related CS/CA. Bleeding events rates outweighed thrombotic events rates in this critically-ill population, although the observed rates were lowest among available studies.

Key Words: cangrelor, bivalirudin, direct thrombin inhibitor, VA-ECMO, cardiogenic shock, cardiac arrest, percutaneous coronary intervention, PCI, stent

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Background

Venoarterial extracorporeal membrane oxygenation (VA-ECMO) support is commonly used for patients in cardiogenic shock (CS) or refractory cardiac arrest (CA),[1] including those with an acute coronary syndrome (ACS) etiology. The interface of blood and the VA-ECMO mechanical components configures an unique prothrombotic and pro-hemorrhagic milieu. In this setting, optimal anti-thrombotic therapy remains ill-defined for patients undergoing percutaneous coronary intervention (PCI) for ACS. Dual anti-platelet (DAPT), consisting of aspirin plus an oral $P2Y_{12}$-inhibitor, associated with a systemic anticoagulation therapy (i.e., triple anti-thrombotic therapy) may confer an excess hemorrhagic risk in this population prone to bleeding.[2] In our clinical experience indeed, DAPT is often withheld due to bleeding episodes: in our Institution from March 2018 to September 2020, 10 patients with PCI and concomitant VA-ECMO support for ACS were eligible for triple anti-thrombotic therapy, but only 40% received at least 1 dose of each antithrombotic drug during VA-ECMO. Indeed, concern of prolonged pharmacodynamic effects in patients with overt bleeding complications or at high hemorrhagic risk may restrain the use of oral $P2Y_{12}$-inhibtiors.

Cangrelor is an intravenous reversible adenosine-diphosphate $P2Y_{12}$ receptor antagonist. The rapid onset and offset of action make it particularly attractive in patients at a high risk of both thrombotic and hemorrhagic events potentially requiring modulation of anti-thrombotic therapy or rapid reversal of the $P2Y_{12}$-pathway inhibition, especially if compared with the long-acting oral $P2Y_{12}$-inhibitors. We hereby describe our preliminary single-center experience with an anti-thrombotic therapy comprising a single parenteral anticoagulant (bivalirudin) and a single parenteral anti-platelet agent (cangrelor) for patients undergoing PCI for ACS during VA-ECMO support for CS/CA.

Methods

All patients receiving PCI and VA-ECMO for ACS-related CA/CS at our Institution from November 2019 to December 2021 who were treated with the pre-specified anti-thrombotic regimen of cangrelor and bivalirudin were included in this study. Aspirin was withheld in all patients. Bivalirudin was started at a low dose of 0.01–0.07 mg/kg/h and subsequently adjusted by increments of ±0.02–0.04 mg/kg/h titrated to achieve an activated thromboplastin time (aPTT) of 50–70''; however, a lower intensity therapy was allowed in case of bleeding

complications or based on clinical judgment, with an aPTT target of 45–55″. Coagulation tests were obtained every 6 hours. Cangrelor dose was titrated by ±0.125 μg/kg/min dose adjustments, and up to a maximum of 0.75 μg/kg/min maintenance dose. Adjustments were made to progressively reach the 0.75 μg/kg/min target dose, based on clinical stability and absence of bleeding events. Study efficacy endpoint was occurrence of thrombotic events and safety endpoint was major bleeding occurrence (definitions in the Supplementary Information, http://links.lww.com/ASAIO/A925). Endpoints were assessed by an author (P.N.) unaware of the study design. All endpoints were considered only for the duration of cangrelor infusion. Categorical variables are reported as proportions, while continuous variables as median and interquartile range (IQR).

Results

Fourteen patients received at least one dose of cangrelor and bivalirudin in the context of PCI and VA-ECMO for ACS-related CS/CA, and were included in this study. Median age was 58 (54-67) years. The majority of patients (64%) presented with refractory cardiac arrest (cardiopulmonary resuscitation ≥30 min). Baseline characteristics are summarized in Table 1. All patients received trans-femoral VA-ECMO as ECLS; VA-ECMO systems included either the Getinge PLS (Göteborg, Sweden) set-up or the Abbott CentriMag (Chicago, USA) pump with Medos Oxy (Heilbronn, Germany) oxygenator and LivaNova (London, UK) circuit. All patients were mechanically ventilated and received inotropic support. Admission laboratory tests demonstrated severe acidosis, hyperlactatemia, severe myocardial injury, mild anemia, thrombocytopenia, and spontaneous INR prolongation. A total of 9 (64%) patients were not on any chronic anti-platelet drugs, 1 (7%) was on chronic aspirin, and 4 (29%) were on chronic DAPT; finally none was on anti-coagulant therapy. Invasive coronary angiography was performed in all patients, and the majority (71%) presented with multi-vessel disease. PCI with stent implantation was performed in 86% (Table 2). Deployed stents included: everolimus-eluting stents in 3 (21%), sirolimus-eluting stents in 3 (21%), zotarolimus-eluting stents in 8 (57%), and bare-metal stent in 1 (7%). Periprocedural anticoagulation and PCI procedure were managed according to current standard of care. Bolus of cangrelor was administered in 21%, at the discretion of the interventional cardiologist. All patients were started on a low cangrelor dose of 0.125 μg/kg/min, with a maximum maintenance dose of 0.570 μg/kg/min. Cangrelor was continued for 5 (4–10) days; temporary discontinuation was necessary in 36%, either for VA-ECMO cannula removal or for bleeding events, for a maximum discontinuation window of 11 (7–12) h. None of the patients received aspirin as initial anti-thrombotic strategy. All patients received background bivalirudin anticoagulation: overall, out of 246 blood samples during bivalirudin infusion we observed an aPTT <45″ in 18%, an aPTT 45–50″ in 22%, an aPTT 50–70″ in 46% and an aPTT >70″ in 14% (Table 3). GpIIb-IIIa inhibitor was administered intra-procedurally in 29% patients. Cangrelor was eventually switched to ticagrelor

Table 1. Study Cohort Characteristics and In-hospital Management

	Overall (*N* = 14)
Baseline clinical characteristics	
Age (y)	58 (54, 67)
Female sex	1 (7)
Weight	80 (74, 85)
History of CKD (eGFR <60 mL/min/1.73 m^2)	0 (0)
Peripheral artery disease	3 (21)
CAD	4 (29)
Refractory cardiac arrest	9 (64)
STEMI	12 (93)
SAVE score	−6 (−3, −6)
Hemodynamics	
Mean arterial pressure (mmHg)	65 (59, 80)
Systolic arterial pressure (mmHg)	90 (84, 102)
Diastolic arterial pressure (mmHg)	49 (42, 56)
Right atrial pressure (mmHg)	8 (7, 12)
Heart rate (bpm)	105 (95, 108)
Laboratory tests	
pH	7.29 (7.16, 7.37)
pO_2 (mmHg)	174 (90, 383)
pCO_2 (mmHg)	44 (37, 52)
HCO^{3-} (mEq/L)	18 (14, 20)
Serum lactate (mmol/L)	13.6 (11.9, 17.7)
Creatinine (mg/dL)	1.47 (1.20, 1.69)
hs-troponin T (ng/L)	20,520 (10,548, 39,663)
Hemoglobin (g/dL)	11.1 (10.3, 12.0)
Platelets (×10^3/mL)	121 (82, 168)
INR	1.96 (1.48, 2.26)
D-dimer (μg/mL)	12.1 (3.3, 20.0)
Total bilirubin (mg/dL)	0.86 (0.62, 1.29)

Categorial variables are expressed as count and proportions, continuous variable as medians (interquartile range).

CKD, chronic kidney disease; DAPT, dual antiplatelet therapy; DES, drug-eluting stent; LAD, left anterior descending; LCx, left circumflex; LM, left main; IABP, intra-aortic balloon pump; PCI, percutaneous coronary intervention; RCA, right coronary artery; SAVE, Survival after Veno-Arterial ECMO; STEMI, ST-segment elevation myocardial infarction; VA-ECMO, veno-arterial extracorporeal membrane oxygenation.

Table 2. In-hospital Management

	Overall (*N* = 14)
Coronary angiography	
Single-vessel disease	4 (29)
Three-vessel disease	4 (29)
Left main disease	4 (29)
Stent thrombosis	5 (36)
PCI with stent implantation	12 (86)
Treated vessel	
LM	3 (21)
LAD	11 (79)
LCx	2 (14)
RCA	1 (7)
No. of stents implanted	2 (1, 3)
DES	11/12 (92)
BMS	1 (7)
Everlimus-eluting stent	3 (21)
Sirolimus-eluting stent	3 (21)
Zotarolimus-eluting stent	8 (57)
Mechanical circulatory support	
IABP	13 (93)
Impella	11 (79)
VA-ECMO	14 (100)
IABP duration (days)	1 (1, 4)
Impella duration (days)	10 (4, 14)
VA-ECMO (days)	5 (3, 7)

Categorial variables are expressed as count and proportions, continuous variable as medians (interquartile range).

DES, drug-eluting stent; LAD, left anterior descending; LCx, left circumflex; LM, left main; IABP, intra-aortic balloon pump; PCI, percutaneous coronary intervention; RCA, right coronary artery; VA-ECMO, veno-arterial extracorporeal membrane oxygenation.

Table 3. Anti-thrombotic Therapy Management

	Overall (*N* = 14)
Anti-thrombotic drugs	
Cangrelor initial dose (μg/kg/min)	0.125 (0.119, 0.142)
Cangrelor max dose (μg/kg/min)	0.143 (0.125, 0.256)
Cangrelor min dose (μg/kg/min)	0.125 (0.119, 0.135)
Cangrelor discontinuation	5 (36)
Cangrelor duration (days)	5 (4, 10)
Cangrelor bolus	3 (21)
Bivalirudin	14 (100)
Any sample with aPTT <45”	43/246 (18)
Any sample with aPTT 45–49”	54/246 (22)
Any sample with aPTT 50–70”	114/246 (46)
Any sample with aPTT >70”	35/246 (14)
Any sample with aPTT ≥50”	149/246 (61)
Patient-level samples with aPTT <45” (%)	16 (9, 22)
Patient-level samples with aPTT 45–49” (%)	22 (10, 30)
Patient-level samples with aPTT 50–70” (%)	39 (25, 58)
Patient-level samples with aPTT >70” (%)	16 (10, 24)
GpIIb-IIIa inhibitors bolus	4 (29)
Switch to ticagrelor	6 (43)
Switch to prasugrel	0 (0)
Switch to clopidogrel	2 (14)

Categorial variables are expressed as count and proportions, continuous variable as medians (interquartile range).
aPTT, activate partial thromboplastin time.

in 43% and to clopidogrel in 14% patients, after MCS weaning (Table 3).

The primary efficacy endpoint occurred in 14% patients, while primary safety endpoint occurred in 21% patients (Figure 1A). One patient experienced arterial thrombosis after VA-ECMO arterial cannula removal, another experienced ischemic cerebellar stroke without functional sequelae. Bleeding events were BARC 3a in 29%, BARC 3b in 14% and BARC 5b in 7% patients (Table 4). Laboratory tests at time of bleeding event were: aPTT 46 (43, 55)'', a INR 1.57 (1.46, 1.97), a platelet count 40 (30, 59) × 10^3/mL; median cangrelor dose at bleeding event was 0.236 (0.155, 0.270) μg/kg/min. VA-ECMO support was continued for 5 (3, 7) days. Overall mortality was 50%, mostly cardiovascular (85%). A total of 21% required vascular surgery, 50% developed sepsis during intensive care unit stay, 71% had acute liver failure, and 29% required continuous venovenous hemodiafiltration. Overall hospital stay was 19 (12, 30) days; hospital stay in those surviving the index event was 31 (24, 43) days.

Discussion

Findings of this study may be summarized as follows (Figure 1A): (1) low maintenance cangrelor dose (0.125–0.570 μg/kg/min) was not associated with excess thrombotic risk or stent-related adverse events in the setting of VA-ECMO support for CS/CA complicating STEMI; (2) cangrelor was always associated with parenteral systemic anticoagulation with bivalirudin while aspirin, as part of DAPT, was withheld; (3) bleeding events rates outweigh thrombotic events rates in this critically-ill population, even in the setting of lower-intensity antithrombotic therapy; (4) an innovative parenteral therapy combining cangrelor and bivalirudin is a clinically viable option for patients receiving MCS for AMI-CS/CA, who experience a high burden of bleeding events and often require modulation/discontinuation of anti-thrombotic drugs.

The rapid onset and offset of cangrelor make it particularly attractive in patients at a high risk of both thrombotic and hemorrhagic complications. Indeed, in our cohort, 36% needed cangrelor transient discontinuation for up to 12 h. In the context of CS/CA patients undergoing PCI and receiving VA-ECMO, oral $P2Y_{12}$ inhibitors bioavailability is often unpredictable or inadequate as a result of longer metabolism, hypothermia, mechanical ventilation and use of concomitant drugs,[3] and cangrelor offers a more predictable pharmacokinetics[4] and does not require dose adjustment in case of renal or hepatic dysfunction.[5]

A recent study on patients on VA-ECMO for CS after PCI and treated with aspirin, cangrelor and heparin found, however, a very high rate (>75%) of bleeding complications.[2] Anti-thrombotic therapy intensity for ischemic events prevention may thus be lower in VA-ECMO patients undergoing PCI due to the MCS-related hemostasis derangements observed in this scenario,[2,6] including consumption of the circulating von Willebrand factor,[7] reduced platelet surface expression of GpIb-GpIV[8] and blunted ADP-mediated aggregation,[9] overall increasing the bleeding risk. In addition, several patients may require combined use of mechanical devices during VA-ECMO support for LV unloading and blood purification, worsening the blood-machine interaction.[10]

We therefore implemented a lower-intensity anti-thrombotic regimen combining the parenteral anticoagulant bivalirudin with the parenteral antiplatelet cangrelor. Notably, only a minority of patients received cangrelor bolus and doses

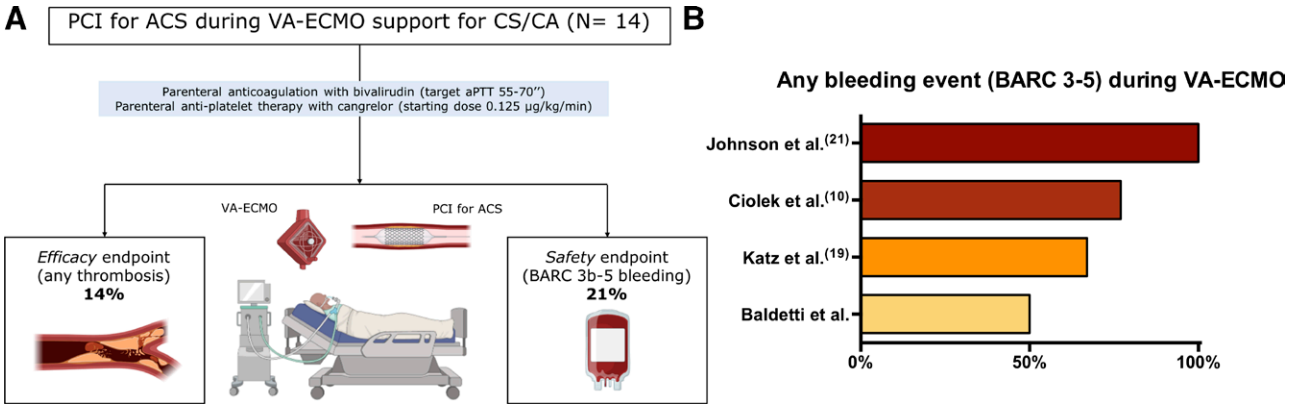

Figure 1. (A) summary of primary efficacy and safety endpoint; (B) comparison of any BARC 3–5 bleeding rates in available studies on cangrelor use during VA-ECMO support.

Table 4. In-hospital Outcomes

	Overall (*N* = 14)
Efficacy endpoint (any thrombotic event)	2 (14)
MI	0 (0)
ARC probable or definite ST	0 (0)
Arterial thrombosis	1 (7)
DVT/PE	0 (0)
Ischemic stroke	1 (7)
Safety endpoint (BARC 3b-5 bleeding)	3 (21)
Any BARC 3–5 bleeding	7 (50)
BARC 3a	4 (29)
Bleedings from nasogastric tube treated conservatively	2
Orotracheal bleeding requiring mechanical hemostasis	1
Oozing from vascular access	1
BARC 3b	2 (14)
Orotracheal severe bleeding and right hemopneumothorax	1
Iatrogenic vascular lesion requiring transfemoral support exchange and diagnostic angiography	1
BARC 5b	1 (7)
Fatal intracranial hemorrhage	1
In-hospital outcomes	
All-cause death	7 (50)
Cardiac death (overall patients; dead patients)	6/14 (43); 6/7 (85)
Any stroke	2 (14)
Major surgery	1 (7)
Vascular surgery	3 (21)
Sepsis	7 (50)
Acute liver failure	10 (71)

Categorial variables are expressed as count and proportions, continuous variable as medians (interquartile range).
ARC, Academic Research Consortium; BARC, Bleeding Academic Research Consortium; DVT/PE, deep vein thrombosis/pulmonary embolism; MI, myocardial infarction; ST, stent thrombosis.

were lower than those recommended by the manufacturer or studied in the BRIDGE trial.[11] Existing literature in CS/CA scenarios suggests a greater (20–100%) use of reduced dosages of cangrelor, and a study on cangrelor as bridging therapy for cardiac surgery demonstrated adequate antiplatelet effect with doses of 0.25–1 μg/kg/min.[2,12–16] In addition, bivalirudin exerts a combined anti-coagulant and anti-platelet effect adding up to that of cangrelor.[17] Our study confirms that major bleeding complications remain more frequent than thrombotic complications in the setting of VA-ECMO support in the critically ill patient (21 vs. 14%). In addition, all the observed ischemic events were noncoronary or multi-factorial (e.g., arterial thrombosis after VA-ECMO cannula removal). The observed excess bleeding risk was in spite of a low-intensity anti-thrombotic therapy comprising bivalirudin and cangrelor at a very low dose. In any case, major bleeding rates were lower (21 vs. 70%) than those reported in a recent study on cangrelor use in patients with MCS.[15] Notably, despite using low dose of cangrelor, in the latter study all patient received background aspirin: withholding this agent may further reduce bleeding rates without excess thrombotic risk. Finally, our BARC 3-5 bleeding event rates (50%) were the lowest among reports on cangrelor use in VA-ECMO patients, that range between 67–100% (Figure 1B).[2,15,18] Specifically, a cohort comprising CS shocks patient on VA-ECMO who received PCI found a 77% rate of BARC 3-5 bleeding; in this cohort cangrelor was chiefly combined with aspirin (in 85%) and heparin (in 92%).[2] Katz et al.[15] found a 67% rate of BARC 3–5 bleeding in a cohort of PCI patients with CS on VA-ECMO who received aspirin, heparin, and cangrelor titrated by platelet function test. Finally, in a cohort of patients receving cangrelor as bridging to surgery or if oral medications were contraindicated, BARC 3-5 bleeding rates occurred in 100% in the VA-ECMO subgroup: no other details on antithrombotic therapy in this subgroup are available.[18] The existing heterogeneity and small size of the published studies hamper a head-to-head comparison with our proposed strategy: while the anti-thrombotic therapy combining bivalirudin and cangrelor in VA-ECMO patient receiving PCI seemed feasible in our cohort, larger prospective studies will provide robust efficacy and safety data.

Conclusions

A low-maintenance dose of cangrelor, associated with standard-intensity anticoagulation with bivalirudin was a feasible anti-thrombotic strategy in patients undergoing PCI during VA-ECMO support for ACS-related CS/CA. Bleeding events rates outweighed thrombotic events rates in this critically-ill population, although the observed rates were the lowest among currently available studies.

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