Emerging strategies for rapid reversal of anticoagulation in patients undergoing catheter-based interventions: aptamers enter the RADAR

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Anticoagulation is a crucial component of the pharmacological cocktail administered to patients with non-ST-elevation acute coronary syndromes (NSTE-ACS). The available options include unfractionated heparin (UFH), enoxaparin, bivalirudin and fondaparinux. In NSTE-ACS patients undergoing percutaneous coronary intervention (PCI), a general recommendation is to continue the initial therapy and avoid switching between antithrombins, with the exception of adding UFH to fondaparinux[1]. The scope of anticoagulation during PCI is to suppress thrombotic events during and in the early term after the procedure. However, fine-tuning the balance between ischaemic and bleeding complications is a challenge with current anticoagulant pharmacotherapy. Bleeding *per se* may significantly jeopardise the clinical outcomes[2], hence careful selection and dosing of anticoagulants is needed, particularly in the era of antiplatelet agents more potent than clopidogrel.

The ideal anticoagulant reduces thrombus formation with minimal bleeding, and is easily administered and monitored. An additional benefit of such an ideal compound would include the possibility to administer a reversal agent in case of clinical need (e.g., bleeding), or when anticoagulation is no longer necessary (e.g., for facilitating early sheath removal after catheterisation). Marketed anticoagulants' lack of one or more of these ideal features **(Table 1)** has prompted investigation into alternative agents. Otamixaban - an intravenous direct factor Xa inhibitor – recently failed to hit the "sweet spot" of reducing both ischaemic and bleeding complications in a large trial[3].

While currently used anticoagulants typically target factors IIa (bivalirudin, UFH, enoxaparin) and Xa (UFH, enoxaparin, fondaparinux) of the coagulation cascade, a novel approach aimed at suppressing the activity of factor IXa, an upstream protease activated in the early steps of coagulation, is attractive for a number of reasons. First, factor IXa plays a central role in the generation of factor Xa and in the initiation and propagation of clot on the surface of activated platelets. Second, factor IXa is responsible for the activation of factor Xa through the intrinsic pathway and is directly activated in response to contact with foreign surfaces, which may become useful in the setting of catheter-based interventions. Third, factor IXa is present at lower and more stable concentrations than other downstream proteases, which makes its inhibition more consistent and predictable. Fourth, inhibition of factor IXa results in prolonged activated partial thromboplastin time, similar to its pathophysiological correlate haemophilia B, thus allowing easy monitoring of anticoagulation with a simple blood test.

In this issue of EuroIntervention, Povsic and colleagues report on the results of PCI patients included in the RADAR trial, a phase II

investigation of a factor IXa inhibitor named pegnivacogin (formerly known as RB006), used for anticoagulation in patients with NSTE-ACS[4,5]. Pegnivacogin is a single-strand RNA which belongs to the class of aptamers, modified oligonucleotides that bind to proteins based on their three-dimensional configuration. Unique to aptamers is the possibility to engineer their own

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Table 1. Summary of approved and investigational parenteral anticoagulants for patients with non-ST-elevation acute coronary syndromes.

	Unfractionated heparin	Enoxaparin	Bivalirudin	Fondaparinux	Otamixaban	Pegnivacogin
Status	Approved	Approved	Approved	Approved	Investigational	Investigational
Action	Indirect	Indirect	Direct	Direct	Direct	Direct
Target	fXa > thrombin	fXa >>> thrombin	Thrombin	fXa	fXa	fIXa
Route	Intravenous, subcutaneous	Intravenous, subcutaneous	Intravenous	Subcutaneous	Intravenous	Intravenous
Protein binding	Yes	Yes	No	No	No	No
Bioavailability	Low	High	High	High	High	High
Variable PK-PD	Yes	No	No	No	No	No
Renal adjustment	No	Yes	Yes	Yes	No	No
Neutralisation	Protamine sulphate	Protamine sulphate	Not available	Not available	Not available	Anivamersen
Monitoring assay	aPTT	anti-fXa levels	ACT, ECT	anti-fXa levels	anti-fXa levels	aPTT
Platelet activation	Yes	Yes	No	No	No	No
Half-life	30 minutes*	4.5-7 hours**	25 minutes	17-21 hours	30 minutes	10 minutes****
Risk of HIT	Yes	Yes	No	No	No	No
Femoral sheath removal (manual compression)	When ACT <150-180 seconds	6 hours after the last dose	2 hours after discontinuation	-***	1 hour after discontinuation	10 minutes after antidote administration

*intravenous route; **subcutaneous route; ***use of fondaparinux alone is not recommended for PCI; ****in combination with anivamersen; 100 hours without anivamersen. ACT: activated coagulation time; aPTT: activated partial thromboplastin time; ECT: ecarin clotting time; HIT: heparin-induced thrombocytopaenia; PCI: percutaneous coronary intervention; PD: pharmacodynamics; PK: pharmacokinetics

complementary reversal agent based on Watson-Crick base pairing. The controlling agent of pegnivacogin, named anivamersen (formerly known as RB007), has no biological effect other than rapidly and irreversibly binding to pegnivacogin, resulting in its dissociation from the factor IXa binding site and prompt reversal of the anticoagulant effect. In the RADAR trial, at least 50% reversal with anivamersen was required to allow safe sheath removal with manual compression or vascular closure devices immediately after cardiac catheterisation via the femoral approach. Interestingly, in control patients treated with heparin, the sheath was removed from coronary angiography or PCI at a median of 184 minutes (versus 23 minutes in the pegnivacogin/anivamersen group). The RADAR-PCI substudy extends those prior observations with encouraging angiographic findings and ischaemic endpoints in support of further clinical testing of pegnivacogin for the safe conduct of PCI in NSTE-ACS[4]. Indeed, among 388 patients undergoing PCI of the 640 enrolled in RADAR, catheter-related complications (e.g., thrombus formation during PCI) did not significantly exceed those of the heparin controls. Also, reassuringly, the composite of death, myocardial infarction, urgent revascularisation and recurrent ischaemia was statistically similar (and numerically lower) with pegnivacogin compared with heparin (4.4% vs. 7.3%, p=0.30), despite prasugrel being used more frequently in heparin patients, probably due to unfamiliarity with the investigational anticoagulant. A minority of patients received glycoprotein IIb/IIIa inhibitors (GPIs) during PCI in both the pegnivacogin and heparin groups, despite GPIs being recommended by protocol in the heparin arm. Not surprisingly, thirty-day bleeding was increased with the addition of GPIs, but there were no notable differences between patients receiving pegnivacogin and those receiving heparin.

Although representing a non-randomised subgroup analysis and being largely underpowered for clinical endpoints, the findings from RADAR-PCI are reassuringly consistent with those from RADAR, and represent a positive step in view of the further clinical development of pegnivacogin. However, they also share with RADAR some concerns that should be underscored. First, the administration of pegnivacogin and heparin was open-label, raising the potential for ascertainment bias, particularly when subjective endpoints are considered. Second, the RADAR trial was halted prudentially after three patients had allergic-like reactions shortly after pegnivacogin administration, an issue which warrants consideration. It cannot be excluded, however, that those cases represent just a random clustering of otherwise rare events in subjects with a prior history of allergic reactions. Third, whether prompt reversal of anticoagulation after PCI results in withdrawal of protection with potential for increased ischaemic events needs further investigation in larger populations. Finally, the relative role of pegnivacogin in patients undergoing PCI with other approaches (e.g., radial), clinical presentations (e.g., ST-elevation myocardial infarction), different controls (e.g., UFH plus systematic protamine; bivalirudin) or higher proportions of newer antiplatelet agents (e.g., prasugrel, ticagrelor) remains unexplored.

Intriguingly, the theoretical benefit of early and safe sheath removal may apply to other catheter-based interventions (e.g., transcatheter aortic valve replacement), which makes further investigation of aptamers attractive, although this hypothesis needs rigorous verification[6]. The history of antithrombotic drug development contains many agents which failed to confirm the positive results of early phase II investigations when larger studies were conducted on a more clinical basis. The REGULATE-PCI trial (NCT01848106) is designed to investigate the efficacy and safety of the pegnivacogin/

anivamersen combination compared to bivalirudin in 13,200 patients undergoing PCI, however enrollment has been paused at the time of writing this editorial. The Data Safety and Monitoring Board (DSMB) is conducting an unplanned full risk-benefit analysis of the more than 3,200 patients enrolled to date, with a focus on serious adverse events related to allergic reactions. Subsequently the United States Food and Drug Administration (FDA) has placed a "clinical hold" on the study. Recommendations to re-initiate enrollment and dosing in the trial will be reliant on FDA agreement. Are aptamers the next big thing in the anticoagulation field? Time will tell.

Conflict of interest statement

D. Capodanno is a member of the advisory board of, and has received speaker's honoraria from Eli Lilly, Daiichi Sankyo and AstraZeneca.

References

1. Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS); European Association for Percutaneous Cardiovascular Interventions (EAPCI), Wijns W, Kolh P, Danchin N, Di Mario C, Falk V, Folliguet T, Garg S, Huber K, James S, Knuuti J, Lopez-Sendon J, Marco J, Menicanti L, Ostojic M, Piepoli MF, Pirlet C, Pomar JL, Reifart N, Ribichini FL, Schalij MJ, Sergeant P, Serruys PW, Silber S, Sousa Uva M, Taggart D. Guidelines on myocardial revascularization. *Eur Heart J.* 2010;31:2501-55.

2. Mehran R, Pocock SJ, Stone GW, Clayton TC, Dangas GD, Feit F, Manoukian SV, Nikolsky E, Lansky AJ, Kirtane A, White HD, Colombo A, Ware JH, Moses JW, Ohman EM. Associations of major bleeding and myocardial infarction with the incidence and timing of mortality in patients presenting with non-ST-elevation acute coronary syndromes: a risk model from the ACUITY trial. *Eur Heart J.* 2009;30:1457-66.

3. Steg PG, Mehta SR, Pollack CV Jr, Bode C, Cohen M, French WJ, Hoekstra J, Rao SV, Ruzyllo W, Ruiz-Nodar JM, Sabate M, Widimsky P, Kiss RG, Navarro Estrada JL, Hod H, Kerkar P, Guneri S, Sezer M, Ruda M, Nicolau JC, Cavallini C, Ebrahim I, Petrov I, Kim JH, Jeong MH, Ramos Lopez GA, Laanmets P, Kovar F, Gaudin C, Fanouillere KC, Minini P, Hoffman EB, Moryusef A, Wiviott SD, Sabatine MS. Anticoagulation with otamixaban and ischemic events in non-ST-segment elevation acute coronary syndromes: the TAO randomized clinical trial. *JAMA.* 2013;310:1145-55.

4. Povsic TJ, Vavalle JP, Alexander JH, Aberle LH, Zelenkofske SL, Becker RC, Buller CE, Cohen MG, Cornel JH, Kasprzak JD, Montalescot G, Fail PS, Sarembock IJ, Mehran R. Use of the REG1 anticoagulation system in patients with acute coronary syndromes undergoing percutaneous coronary intervention: results from the phase II RADAR-PCI study. *EuroIntervention.* 2014;10:431-8.

5. Povsic TJ, Vavalle JP, Aberle LH, Kasprzak JD, Cohen MG, Mehran R, Bode C, Buller CE, Montalescot G, Cornel JH, Rynkiewicz A, Ring ME, Zeymer U, Natarajan M, Delarche N, Zelenkofske SL, Becker RC, Alexander JH. A Phase 2, randomized, partially blinded, active-controlled study assessing the efficacy and safety of variable anticoagulation reversal using the REG1 system in patients with acute coronary syndromes: results of the RADAR trial. *Eur Heart J.* 2013;34:2481-9.

6. Rodes-Cabau J, Dauerman HL, Cohen MG, Mehran R, Small EM, Smyth SS, Costa MA, Mega JL, O'Donoghue ML, Ohman EM, Becker RC. Antithrombotic treatment in transcatheter aortic valve implantation: insights for cerebrovascular and bleeding events. *J Am Coll Cardiol.* 2013;62:2349-59.