International Journal of Cardiology xxx (2018) xxx–xxx

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Antithrombotic therapy for patients with an indication for oral anticoagulation undergoing percutaneous coronary intervention with stent: The case of venous thromboembolism

Letizia Riva [a], Walter Ageno [b], Giuseppe Di Pasquale [a], Giancarlo Agnelli [c], Andrea Rubboli [a,*]

[a] Division of Cardiology, Ospedale Maggiore, Bologna, Italy
[b] Department of Clinical and Experimental Medicine, University of Insubria, Degenza Breve Intensiva e Centro Trombosi, Ospedale di Circolo, Varese, Italy
[c] Department of Internal and Cardiovascular Medicine – Stroke Unit, University of Perugia, Perugia, Italy

ARTICLE INFO

Article history:
Received 10 April 2018
Received in revised form 6 June 2018
Accepted 25 July 2018
Available online xxxx

Keywords:
Venous thromboembolism
Oral anticoagulation
Percutaneous coronary intervention
Stent

ABSTRACT

The management of antithrombotic therapy in patients on oral anticoagulation (OAC) for atrial fibrillation (AF) undergoing percutaneous coronary intervention with stent (PCI) is currently addressed by expert consensus documents and official Guidelines. No specific data, nor management suggestions, are available for OAC patients undergoing PCI in whom the indication for OAC is venous thromboembolism (VTE). In this article, the available evidence on VTE patients undergoing PCI, as obtained from studies where patients with various indications for PCI were included, is evaluated, and an algorithm for the management of antithrombotic therapy in this unique population is proposed.

1. Introduction

In patients with indication for oral anticoagulation (OAC) undergoing percutaneous coronary intervention with stent (PCI), an initial course of 3–6 months of triple therapy (TT) of OAC, aspirin and clopidogrel, followed by dual therapy (DT) of OAC and single antiplatelet agent (either aspirin or clopidogrel) up to 12 months, and then OAC monotherapy lifelong, is currently recommended [1]. In patients at high risk of bleeding, DT of OAC and the single antiplatelet agent clopidogrel may be started immediately after PCI, and continued up to 12 months, to be then followed by OAC monotherapy lifelong [1]. Combined OAC and dual/single antiplatelet therapy (DAPT/SAPT) is deemed the optimal combination to prevent both thromboembolism and recurrent cardiac events in these patients, although this is obtained at the price of an increased risk of bleeding [1]. To mitigate such increase in the risk of bleeding, several strategies, including the shortest possible duration of TT and a lower range of the International Normalized ratio (INR) (i.e., 2.0–2.5) when warfarin is used in TT, are recommended [1,2]. More recently, preference of a non-vitamin K-antagonist oral anticoagulant (NOAC), including dabigatran, apixaban, edoxaban or rivaroxaban, over warfarin, has been proposed as a further bleeding avoiding strategy [2]. Current recommendations are essentially derived from, and therefore directly applicable to, patient populations in whom the indication for OAC is atrial fibrillation (AF). But, would these recommendations remain valid for patients in whom the indication for OAC is venous thromboembolism (VTE)?

2. Available evidence

To date, no dedicated studies have been carried out in VTE patients on OAC undergoing PCI. When included in experiences evaluating the use and outcome of antithrombotic therapies in patients with a general indication for OAC who were submitted to PCI, the proportion of VTE patients was small, ranging from approximately 2 to 17% (10% on average), as opposed to 22 to 85% (61% on average) for AF, and, most importantly, outcome data were not given separately (Table 1) [3–33]. Also, the absolute incidence of (recurrent) VTE during follow-up was as little as less than 1%, whereas that of stroke was in the range of 0 to 9% (1.5% on average) (Table 1) [3–33].

By examining, and comparing, the recent randomized clinical trials with NOACs in AF and VTE, it appears that the two populations are rather different: VTE patients (mostly however, with unprovoked VTE) are substantially younger (56 ± 2 vs. 72 ± 1 years) and generally have less co-morbidities, including moderate renal dysfunction (approximately 7 vs. 8%) [34–42]. Accordingly, the risk of bleeding may be lower in VTE as compared to AF patients, as it has indeed been observed in the randomized clinical trials comparing NOACs with warfarin in the two clinical settings (approximately 1 vs. 3%, respectively)

* Corresponding author at: Division of Cardiology - Laboratory of Interventional Cardiology, Ospedale Maggiore, Largo Nigrisoli 2, 40133 Bologna, Italy.
E-mail address: andrea.rubboli@ausl.bologna.it (A. Rubboli).

https://doi.org/10.1016/j.ijcard.2018.07.133
0167-5273/

Table 1
Rate of major adverse events in studies including patients on OAC undergoing PCI.

	No. of patients on triple therapy (warfarin + aspirin + clopidogrel)	Age (years) (mean ± SD)	No. of AF patients (%)	No. of VTE patients (%)	Stroke rate (%)	Major bleeding rate (%)	VTE rate (%)	Death rate (%)
Mattinchak SJ et al. [3]	40	67 ± 13	17 (42)	1 (2.5)	0 (0)	6 (15) (*gastro-intestinal*)	na	1 (3)
Khurram Z et al. [4]	107	69 ± 11	85 (80)	2 (2)	na	7 (6.6)	na	1 (0.9)
Karjalainen PP et al. [5]	239	70 ± 9	168 (70)	23 (10)	7 (3.2)	18 (8.2)	na	19 (8.7)
De Eugenio D et al. [6]	97	69.9 ± 11	57 (59)	8 (8)	na	14 (14.5)	na	1 (1)
Nguyen MC et al. [7]	580	64 ± 0	130 (22)	32 (5.5)	6 (1)	34 (5.9)	na	23 (5.1)
Rogacka R et al. [8]	127	69.9 ± 8.8	75 (59.1)	10 (7.9)	na	6 (4.7)	na	5 (3.9)
Helft G et al. [9]	50	68 ± 5	31 (62)	7 (14)	0 (0)	0 (0)	na	0 (0)
Rossini R et al. [10]	102	67.9 ± 9.3	68 (66.6)	5 (4.9)	1 (1)	3 (2.9)	na	3 (2.9)
Sarafoff N et al. [11]	306	71.4 ± 9.9	207 (67)	30 (10)	3 (1)	4 (1.3)	na	6 (2)
Gilard M et al. [12]	125	71 ± 9	79 (63)	21 (17)	1 (0.8)	8 (5.6)	1 (0.8)	10 (8)
Uchida Y et al. [13]	50	68.6 ± 8.5	29 (58)	5 (10)	2 (4)	10 (20)	na	4 (8)
Baber U et al. [14]	170	69 ± 12	76 (45)	17 (10)	na	2 (1.1)	na	10 (5.9)
Ait Mokhtar O et al. [15]	208	73 ± 7.5	169 (81)	6 (2.8)	0 (0)	6 (2.9)	na	0 (0)
Pasceri V et al. [16]	165	68.5 ± 9.5	130 (79)	5 (3.5)	2 (1.3)	2 (1.3)	na	2 (1.3)
Annala A et al. [17]	248	69.2 ± 8.5	178 (72)	33 (13.3)	36/415 (8.7)	57/415 (13.8)	na	88/415 (21)
Martin-Yuste V et al. [18]	78	72.4 ± 8.6	51 (65.4)	2 (2.6)	2 (2.6)	4 (5.2)	na	10 (12)
Nikolsky E et al. [19]	105	62.3 ± 0	30 (23.8)	3 (2.4)	3 (3.3)	17 (16.7)	na	4 (4)
Smith JG et al. [20]	159	67.2 ± 0.9	63 (39.6)	11 (6.9)	3 (1.9)	21 (13.4)	na	7 (4.5)
Alonso A et al. [21]	574	73 ± 12	306 (53.7)	40 (12.2)	na	na	na	na
Sarafoff N et al. [22]	377	71.8 ± 10	292 (77.5)	30 (8)	7 (1.9)	13 (3.5)	na	16 (4.2)
Rubboli A et al. [23]	339	74 ± 9	268 (79)	16 (5)	3 (1)	14 (4)	2 (0.5)	17 (5)
Baker NC et al. [24]	97	69.5 ± 0	75 (77)	16 (16.5)	na	0 (0)	na	na
Braun OÖ et al. [25]	159	67 ± 11	63 (39.6)	11 (6.9)	2 (1.3)	11 (7)	0 (0)	5 (3.2)
Fiedler KA et al. [26]	614	73.6 ± 8.2	515 (83.9)	34 (5.5)	10 (1.6)	28 (4.6)	na	28 (4.6)
Staudacher DL et al. [27]	138	73.1 ± 9.8	98 (71)	6 (4.3)	na	13 (9.4)	na	na
Jackson LR et al. [28]	617 (*45 NOAC, 91 prasugrel*)	61.5 ± 12.5	200/347 (32.4)	69/347 (11.2)	6 (0.97)	186 (30)	na	28 (4.5)
Faza NN et al. [29]	999	69.3 ± 10.9	609 (61)	116 (11.6)	15 (1.5)	267 (26.7)	na	73 (7.3)
Fu A et al. [30]	152 (*27 ticagrelor*)	67 ± 14.3	64 (42)	11 (7.2)	6 (4)	13 (8.5)	na	11 (7.2)
Koskinas KC et al. [31]	568	72.9 ± 9.5	315 (55.4)	91 (16)	8 (1.4)	12 (2.1)	na	47 (8.3)
Secemsky EA et al. [32]	837 (*66 NOAC*)	71.7 ± 11.2	653 (78)	137 (16.4)	4 (0.5)	88 (10.5)	na	105 (12.5)
Verlinden NJ et al. [33]	168 (*32 prasugrel, 10 ticagrelor*)	63.5 ± 11.5	91 (54.2)	24 (14.3)	5 (3)	28 (16.7) (*any*)	na	7 (4.2) (*cardiac*)
	8.595	69.4 ± 8.7	5.192 (60.4)	822 (9.6)	132 (1.5)	892 (10.4)	3 (−)	531 (6.2)

AF: atrial fibrillation; VTE: venous thromboembolism; NOAC: non-vitamin K-antagonist oral anticoagulant; na: not available.

(Table 2) [34–42]. In accordance, combined OAC and DAPT/SAPT in VTE patients undergoing PCI is likely to be associated with a risk of bleeding lower than in those with AF. Also, the overall benefit observed with the NOACs rivaroxaban [43] and dabigatran [44] in DT with clopidogrel in comparison to conventional TT of warfarin, aspirin and clopidogrel in AF patients undergoing PCI is likely to be preserved in patients with VTE. What should then be different when VTE patients undergoing PCI need to be treated?

3. Management considerations

As compared to patients with AF, in those with VTE not the antithrombotic strategy but rather its time course should likely be different.

Table 2
Rate of bleeding events in clinical trials comparing NOACs and warfarin.

	Major bleeding rate (%)	
	NOAC	Warfarin
AF		
RE-LY [36]	2.9	3.4
ROCKET AF [37]	3.6	3.4
ARISTOTLE [38]	2.1	3.1
ENGAGE AF-TIMI 48 [39]	2.2	3.4
Total (mean ± SD)	2.7 ± 0.7	3.3 ± 0.1
VTE		
RE-COVER [40]	1.6	1.9
RE-COVER II [41]	1.2	1.7
EINSTEIN [42]	0.8	1.2
AMPLIFY [43]	0.6	1.8
HOKUSAI-VTE [44]	1.4	1.6
Total (mean ± SD)	1.1 ± 0.4	1.6 ± 0.3

NOAC: non-vitamin K-antagonist oral anticoagulant.

At variance of AF where the risk of stroke is essentially stable over time, the risk of (recurrent) VTE is highest early after the index event to decrease, albeit never annulling, afterwards [45] (Fig. 1). In accordance, OAC is warranted lifelong in AF as opposed to VTE patients for whom OAC is generally mandatory for the first 3 months only [46]. As regards the risk of bleeding, it is assumed to remain constant over time (and throughout OAC) both in AF and VTE (Fig. 1). In VTE patients undergoing PCI therefore, TT of OAC, aspirin and clopidogrel could be prescribed for a very limited time, namely 3 to 6 months, depending on whether PCI has been performed in stable or unstable coronary artery disease, respectively. In the absence of a clear indication to prolong OAC further, such as in the case of previous recurrent VTE episodes [46], OAC may then be stopped and standard DAPT of aspirin and clopidogrel continued up to 12 months. Aspirin monotherapy should then be continued lifelong for secondary prevention of recurrent cardiac events. Of note, aspirin may also provide some protection against recurrent VTE [47]. Should OAC be indicated indefinitely, as for patients with recurrent episodes of VTE and/or major thrombophilia and/or increased risk of fatality in case of recurrent VTE [46], one antiplatelet agent may be stopped at 3–6 months and the other at 12 months, similar to what is currently recommended for AF patients undergoing PCI [1,2]. In patients with unprovoked VTE, for whom indefinite OAC should currently be considered when the associated risk of bleeding is low [46], individual assessment appears warranted with OAC possibly being stopped in the majority of cases after a due course (i.e., 3–12 months) has been completed. The option of immediate DT of OAC and clopidogrel currently suggested for AF patients at high risk of bleeding [1,2], appears feasible in VTE patients only when aspirin is planned to be added to clopidogrel after OAC has been stopped. This is because the efficacy of clopidogrel monotherapy in preventing stent thrombosis and/or associated adverse cardiac events after early (i.e., 3–6 months) OAC discontinuation is currently unknown.

Please cite this article as: L. Riva, et al., Antithrombotic therapy for patients with an indication for oral anticoagulation undergoing percutaneous coronary intervention with stent: The case of venous thromboembolism, Int J Cardiol (2018), https://doi.org/10.1016/j.ijcard.2018.07.133