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Perioperative Safety and Efficacy of Different Anticoagulation Strategies With Direct Oral Anticoagulants in Pulmonary Vein Isolation

A Meta-Analysis

Riccardo Gorla, MD, PhD,[a,b] Francesco Dentali, MD,[a] Matteo Crippa, MD,[a] Jacopo Marazzato, MD,[a] Matteo Nicola Dario Di Minno, MD,[c] Anna Maria Grandi, MD,[a] Roberto De Ponti, MD[a]

ABSTRACT

OBJECTIVES The purpose of this study was to evaluate the safety and efficacy of uninterrupted and interrupted direct oral anticoagulant (DOAC) administration in patients undergoing pulmonary vein isolation (PVI).

BACKGROUND The optimal periprocedural management of DOACs in patients undergoing PVI is not well defined, and different strategies are used.

METHODS A systematic search of PubMed/MEDLINE, Ovid/MEDLINE, and EMBASE was performed. Three strategies for periprocedural DOAC administration were considered: uninterrupted, mildly interrupted (<12 h), and interrupted (≥12 h). Primary endpoints were major bleeding (MB) and thromboembolic (TE) complications; pooled weighted mean incidence (WMI) was calculated using a random-effects model. A secondary endpoint was the WMI of overall bleeding (OB).

RESULTS The analysis included 43 studies for a total of 8,362 patients. DOACs showed similar safety and efficacy in the 3 subgroups. The WMI of MB was 1.02%, 1.49%, and 1.17% for the uninterrupted, mildly interrupted, and interrupted strategy, respectively; the WMI of TE complications was 0.16%, 0.46%, and 0.49% for the uninterrupted, mildly interrupted, and interrupted strategy, respectively, with no heterogeneity. OB appeared to be higher in uninterrupted (6.33%) and mildly interrupted (8.62%) groups compared with the interrupted (3.53%), with substantial heterogeneity among studies. No interaction was found between the incidence of MB and TE complications and different DOACs.

CONCLUSIONS In patients undergoing PVI, these 3 anticoagulation strategies may have similar safety and efficacy in terms of MB and TE complications. OB appears to be higher in uninterrupted and mildly interrupted strategies compared with the interrupted strategy. No substantial differences were observed among DOACs regarding the incidence of MB and TE complications. (J Am Coll Cardiol EP 2018;4:794–806) © 2018 by the American College of Cardiology Foundation.

From the [a]Department of Medicine and Surgery, University of Insubria, Varese, Italy; [b]Department of Clinical and Interventional Cardiology, IRCCS Policlinico San Donato, Milan, Italy; and the [c]Department of Translational Medical Sciences, Federico II University, Napoli, Italy. Dr. Dentali has received a grant and honoraria from Boehringer Ingelheim, Bayer, Pfizer, and Daiichi-Sankyo. Dr. Di Minno has received grants and honoraria from Bayer, Pfizer, Novo Nordisk, and Boehringer Ingelheim. Dr. De Ponti has received significant honoraria from Biosense Webster; has received honoraria for lectures from Biosense Webster and Biotronik; and has received educational grants from Medtronic, Biosense Webster, Abbott, Boston Scientific, and Biotronik. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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Pulmonary vein isolation (PVI) is a well-established treatment in patients with paroxysmal symptomatic drug-refractory atrial fibrillation (AF) (1). Uninterrupted warfarin during the periprocedural period is the standard anticoagulation protocol and is associated with fewer bleeding and thromboembolic events compared with bridging with unfractionated or low-molecular-weight heparin (2,3). Direct oral anticoagulants (DOACs) are increasingly used in patients undergoing AF ablation, and recent meta-analyses suggested that the safety and efficacy of DOACs was comparable to uninterrupted warfarin with respect to thromboembolic (TE) and bleeding events (4–7). Compared with warfarin, the pharmacokinetic properties of DOACs allow a quicker offset and onset of anticoagulation. This renders possible different strategies in their use, including the possibility of a minimal period of drug withdrawal at the time of the ablation procedure when unfractionated heparin is also administered. An expert consensus document recently endorsed both the uninterrupted anticoagulation strategy and the interrupted anticoagulation strategy, with 1 or 2 drug doses held prior to ablation when DOACs are used (8). Indeed, in clinical practice, the periprocedural management of DOACs is heterogeneous, and studies providing direct comparisons between different anticoagulation strategies are lacking. Thus, we performed a systematic review and meta-analysis of the published data to assess the safety and efficacy of different anticoagulation strategies with DOACs in the AF ablation periprocedural period.

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METHODS

REVIEW PROTOCOL. A protocol for this review was prospectively developed, detailing specific objectives, criteria for study selection, and finally, the way to assess study quality, outcomes, and statistical methods.

The safety and efficacy of DOACs was assessed considering the rate of major bleeding (MB) and TE complications during the perioperative period (intraprocedural and up to 1 month after the procedure) of PVI, in the overall population and according to the different DOAC strategies. Whenever possible, MB was defined according to the International Society of Thrombosis and Hemostasis (9). For each study, the definition of MB is reported in **Table 1**. TE complications included transient ischemic attack, stroke, and systemic embolism. Furthermore, as a secondary endpoint, overall bleeding (OB), defined as a composite of MB and clinically relevant nonmajor bleeding (CRNMB), was evaluated. For the purpose of this study, CRNMB was defined as the occurrence of groin hematoma or pericardial effusion not requiring drainage during the post-procedural period.

Anticoagulation strategies were defined based on the time of DOAC discontinuation prior to catheter ablation: uninterrupted (no discontinuation of DOACs), mildly interrupted (<12 h before PVI) and interrupted (≥12 h before PVI).

STUDY IDENTIFICATION. The search strategy was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (10). We performed an electronic search on MEDLINE and EMBASE from inception to June 2017, combining the search terms "pulmonary veins," "cryosurgery," "cardiac arrhythmias," "atrial fibrillation," "catheter ablation," "dabigatran," "rivaroxaban," "apixaban," "edoxaban," and "factor Xa inhibitors" both as medical subject headings and key words.

We supplemented our search by reviewing abstracts from the congresses of the European Society of Cardiology (2011 to 2017) and by manually reviewing the reference lists of all retrieved papers.

STUDY SELECTION. Three authors (R.G., M.C., and J.M.) independently reviewed all selected titles and abstracts. Studies were excluded if the title and/or abstract was judged not to be appropriate for the aim of meta-analysis. Full texts of all potentially relevant studies were obtained to assess eligibility. Disagreement was resolved by consensus or by the opinion of another author (F.D.), if necessary. To assess the agreement between reviewers for study selection, we used the k statistic, which measures agreement beyond chance (11). Non-English publications were considered if the abstract was in English and provided enough data. Studies were included if the following items were specified: patients were numbered according to DOAC type; periprocedural anticoagulation strategy included the time of DOAC interruption/last dose before PVI, to allow patient assignment to the "uninterrupted," "mildly interrupted," or "interrupted" strategy; and the rate of bleeding and TE complications were listed according to anticoagulation strategy.

DATA EXTRACTION. Two investigators (R.G. and M.C.) independently extracted data from each study. In each study, data regarding the DOAC population, specifically patient characteristics and outcomes,

ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation
CI = confidence interval
CRNMB = clinically relevant nonmajor bleeding
DOACs = direct oral anticoagulants
MB = major bleeding
NOS = Newcastle-Ottawa Scale
OB = overall bleeding
PVI = pulmonary vein isolation
TE = thromboembolic
WMI = weighted mean incidence