Rev Port Cardiol. 2017;xxx(xx):xxx–xxx

Revista Portuguesa de Cardiologia
Portuguese Journal of Cardiology
www.revportcardiol.org

ORIGINAL ARTICLE

Early, real-world experience with direct oral anticoagulants in the treatment of intermediate-high risk acute pulmonary embolism

Sónia Martins Santos[a,1], **Susana Cunha**[a,1], **Rui Baptista**[b,c,*], **Sílvia Monteiro**[b], **Pedro Monteiro**[b,c], **Francisco Gonçalves**[b], **Mariano Pêgo**[b]

[a] *Serviço de Medicina 2, Centro Hospitalar de Leiria, Hospital de Leiria, Leiria, Portugal*
[b] *Serviço de Cardiologia A, Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal*
[c] *Faculty of Medicine, University of Coimbra, Coimbra, Portugal*

Received 3 November 2016; accepted 12 January 2017

KEYWORDS
Anticoagulants;
Venous thromboembolism;
Real world;
Pulmonary embolism;
Intermediate-high risk;
Warfarin

Abstract
Introduction: Intermediate-high risk pulmonary embolism (IHR-PE) has a poor prognosis, but is under-represented in trials of direct oral anticoagulants (DOACs) in venous thromboembolic disease (VTE). We aimed to assess whether the administration of DOACs was equivalent to the conventional (CONV) treatment of low-molecular weight heparin bridged with warfarin for treating IHR-PE.
Methods: We conducted a retrospective cohort study including 59 consecutive patients admitted with IHR-PE and followed for up to three months after discharge. Two groups were created based on the anticoagulant strategy: CONV (n=35) and DOAC (n=24). The efficacy endpoints were death, recurrent PE, estimated pulmonary artery systolic pressure (PASP), right ventricular systolic function (RVSF) at discharge, and length of stay; the safety endpoint was major bleeding.
Results: The two groups were similar regarding demographics, PE etiology and markers of clinical severity. There were four in-hospital deaths in the CONV group and none in the DOAC group. No recurrent PE or major bleeding event was recorded in either group. At discharge, neither PASP nor RVSF was different between the groups. Patients in the DOAC group were discharged 1.7 days earlier on average than patients in the CONV group (4.7±2.4 vs. 3.0±1.5 days, p=0.002).
Conclusions: The adoption of a DOAC treatment strategy in this real-world cohort of IHR-PE patients was associated with similar efficacy and safety to the CONV approach. The fact that

* Corresponding author.
E-mail address: rui.baptista@fmed.uc.pt (R. Baptista).
[1] Both authors contributed equally to this work

https://doi.org/10.1016/j.repc.2017.01.010

Please cite this article in press as: Santos SM, et al. Early, real-world experience with direct oral anticoagulants in the treatment of intermediate-high risk acute pulmonary embolism. Rev Port Cardiol. 2017. https://doi.org/10.1016/j.repc.2017.01.010

monitoring of anticoagulation effect was unnecessary probably led to the significant reduction in length of stay.

PALAVRAS-CHAVE
Anticoagulantes;
Tromboembolismo venoso;
Mundo real;
Embolia pulmonar;
Risco intermédio a elevado;
Varfarina

Experiência inicial com os anticoagulantes orais diretos no tratamento do tromboembolismo pulmonar agudo de risco intermédio-alto: dados do mundo real

Resumo
Introdução: O tromboembolismo pulmonar de risco intermédio-elevado (TEP-IE) condiciona um prognóstico mais agravado, mas se encontra sub-representado nos ensaios dos anticoagulantes orais diretos (ACOd) na doença tromboembólica venosa (DTV). Avaliamos se a administração de ACOd foi equivalente à estratégia terapêutica convencional (CONV) (heparina de baixo peso molecular (HBPM) + varfarina) no tratamento do TEP-IE.
Métodos: Fez-se um estudo de coorte retrospetivo com 59 doentes consecutivos internados por TEP-IE, seguidos até três meses após a alta. Criaram-se dois grupos, baseados na estratégia terapêutica anticoagulante: CONV (n = 35) e DOAC (n = 24) (ACOd). Os desfechos de eficácia foram a morte, o TEP recorrente, a pressão sistólica na artéria pulmonar (PSAP), a função ventricular direita (FVD) e a duração do internamento; o desfecho de segurança foi a hemorragia *major*.
Resultados: Os grupos eram comparáveis relativamente aos aspetos demográficos, à etiologia do TEP e aos marcadores de gravidade clínica. Ocorreram quatro mortes intra-hospitalares no grupo CONV e nenhuma no grupo DOAC. Nenhum evento de TEP recorrente ou hemorragia *major* ocorreu em qualquer dos grupos. À data de alta, quer a PSAP quer a FVD não diferiram entre os dois grupos. A alta ocorreu 1,7 dia mais cedo no grupo DOAC do que no grupo CONV (4,7±2,4 *versus* 3,0±1,5 dias, p = 0,002).
Conclusões: A adoção de uma estratégia de tratamento com ACOd associou-se a um perfil de eficácia e segurança semelhante à abordagem convencional. A ausência da necessidade de monitoração do efeito anticoagulante provavelmente motivou a redução na duração de internamento.

Introduction

Pulmonary embolism (PE) is a common disease, with an estimated annual incidence of 70 cases per 100 000.[1,2] This condition can be life-threatening if not treated rapidly and appropriately and often leads to chronic disease and disability.[3] Mortality from PE, 15% at three months, exceeds that for acute myocardial infarction.[4] Risk stratification helps to optimize the selection of patients who will benefit from more aggressive therapy, such as thrombolysis or embolectomy, in addition to anticoagulation.[4] High-risk patients are also most susceptible to the dreaded complication of chronic thromboembolic pulmonary hypertension.[4] In order to predict early (in-hospital or 30-day) outcomes, both PE-related risk and the patient's clinical status and comorbidities should be taken into consideration, and can be measured using risk scores such as the pulmonary embolism severity index (PESI).[5] Intermediate-high risk patients have positive cardiac laboratory biomarkers, signs of right ventricular (RV) dysfunction on an imaging test and PESI class III-V or simplified PESI (sPESI) $\geq$1.

The conventional PE treatment approach consists of a parenteral anticoagulant such as enoxaparin for at least five days, followed by a vitamin K antagonist (VKA) such as warfarin, and continued for at least three months.[6] Although effective, this regimen is challenging, as enoxaparin requires daily subcutaneous injections and VKAs require close monitoring and dose adjustment.[7] The recently developed direct oral anticoagulants (DOACs), which inhibit factor Xa or thrombin, can overcome these limitations.[8] DOACs have been tested against conventional therapy in large phase III studies for the treatment of PE: EINSTEIN-PE for rivaroxaban, RE-COVER and RE-COVER II for dabigatran, AMPLIFY for apixaban and Hokusai-VTE for edoxaban.[1,9–11] Rivaroxaban and apixaban allow for a single drug regimen, eliminating the need for initial parenteral anticoagulation, while dabigatran and edoxaban are initiated after a course of parenteral therapy.[1] In all these studies, DOACs were shown to be at least as effective as VKAs for preventing recurrent VTE and VTE-related death, and demonstrated a similar or reduced incidence of major and/or major plus non-major clinically relevant bleeding (the principal safety

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