

Antithrombotic therapy in retinal vein occlusion: many questions, few evidence-based answers

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Retinal vein occlusion (RVO) is a common cause of visual impairment, yet considerable uncertainty remains regarding the role of systemic anticoagulation and, if prescribed, its optimal regimen.¹ In the position statement of the Italian Society for the Study of Thrombosis and Haemostasis (SISST), therapeutic dose of low-molecular-weight heparin (LMWH) for the first week, followed by half therapeutic dose of LMWH for 1-3 months, was recommended in patients with recent-onset RVO (within 15-30 days) who are at low risk of bleeding and have no

local predisposing ocular factors (e.g., hyperopia, glaucoma).² This recommendation was necessarily based on limited evidence and expert opinion. We therefore recognize that its three key components – when treatment should be initiated, which anticoagulant and dose should be used, and how long treatment should be continued – remain open to debate and warrant further consideration.

With respect to treatment timing, no randomized controlled trial or observational study has directly compared anticoagulation initiated during the acute phase with treatment started at a later stage of RVO. Nevertheless, all available randomized trials exclusively enrolled patients with recent-onset disease. Eligibility was restricted to patients with symptom onset within 15 days in the Ageno trial and within 30 days in the Farahvash trials.³⁻⁵ The mean interval from symptom onset to treatment initiation was approximately 7.2 days in the Ageno trial. In the two Farahvash trials, the reported mean number of days of disease onset before enrolment – serving only as a proxy for the time to treatment – was 13.9 and 17.7 days for central and branch RVO, respectively. Accordingly, although a potential benefit of anticoagulant therapy in patients presenting beyond the first 15-30 days cannot be excluded, the available evidence is insufficient to support its routine use in this setting. Treatment decisions in these patients should therefore be individualized by carefully weighing the uncertain potential benefits against the individual bleeding risk.

With respect to the choice and dosing of anticoagulant therapy, we acknowledge that LMWH is no longer the preferred first-line option for most patients with acute venous thromboembolism (VTE). However, no randomized study has evaluated oral anticoagulants for the treatment of established RVO, and all available randomized evidence concerns LMWH regimens that differ in dose and duration from contemporary VTE treatment schedules.^{2,6} The applicability of these regimens to current clinical practice therefore remains uncertain. Two recent observational studies provide indirect and conflicting evidence in patients with atrial fibrillation, a condition closely associated with RVO and sharing several risk factors with it.⁷⁻¹⁰ The Korean study reported a higher risk of incident RVO among direct oral anticoagulant (DOAC) users than among warfarin users (adjusted hazard ratio, 1.80; 95% confidence interval [CI], 1.45-2.22).⁹ Conversely, a large propensity-score-matched US database study, that did not specify treatment indications and duration, found a higher risk among warfarin users than among DOAC users (risk ratio, 1.49; 95%CI, 1.42-1.57).¹⁰ Importantly,

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both studies evaluated the occurrence of new RVO in patients receiving anticoagulation for other indications and their retrospective designs also render them susceptible to residual confounders. Together with their discordant findings, these limitations preclude any firm conclusions regarding the therapeutic role of oral anticoagulants in acute RVO or the preferred agent and dosing regimen. It is however noteworthy that RVO continued to occur among patients prescribed oral anticoagulation. In the Korean cohort, the incidence rates were 3.50 and 2.06 per 1,000 person-years among DOAC and warfarin users, respectively, which are of the same order of magnitude as published estimates in the general population – approximately 3.77 and 0.65 per 1,000 person-years for branch and central RVO, respectively.^{1,9} This indirect comparison should be interpreted cautiously because of substantial differences in patient characteristics, outcome definitions, and diagnostic criteria.

Regarding treatment duration, the diagnostic work-up of RVO may identify persistent prothrombotic conditions, such as antiphospholipid syndrome – for which RVO may represent the qualifying thrombotic event – that independently warrant extended or indefinite anticoagulation.² In such cases, both the duration of treatment and the choice of anticoagulant should be reconsidered according to the underlying condition, the patient's thrombotic and bleeding risk profile, and disease-specific recommendations. Conversely, in the absence of an independent indication for long-term anticoagulation, current evidence is insufficient to support treatment beyond the therapeutic regimens of the available trials.

Overall, the available evidence remains sparse; given that adequately powered randomized trials are unlikely to be conducted, prospective registries may provide valuable real-world data on the effectiveness and safety of empirical antithrombotic strategies. In this context, the START-OVR project, was specifically designed to collect prospective data on antithrombotic management, risk factors, and long-term outcomes in patients with RVO. Although registries cannot eliminate bias from treatment allocation, standardized prospective data collection may help support current therapeutic approaches and inform future recommendations. Until further evidence becomes available to help daily clinical practice, treatment should be individualized through multidisciplinary assessment – ideally involving ophthalmologists, internists, and hematologists – at centers with relevant expertise.

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