Low molecular weight heparin for the treatment of retinal vein occlusion: a systematic review and meta-analysis of randomized trials

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ABSTRACT

Retinal vein occlusion is a frequent cause of visual loss for which few effective therapies are available. Anticoagulation with low molecular weight heparin might be of value in its treatment. We conducted a systematic review and meta analysis of randomized trials evaluating the effect of low molecular weight heparin in patients with retinal vein occlusion. Data sources included MEDLINE, EMBASE, HealthSTAR, the Cochrane Library, Lilacs, the Investigative Ophthalmology and Visual Science database and gray literature. Main outcome was the mean difference between the visual acuity measured at baseline and at six months expressed in the logMAR scale. Secondary outcome was a composite of any adverse ocular outcome including: worsening of visual acuity, visual fields or fluorescein angiography, or development of iris neovascularization, any neovascularization or neovascular glaucoma. Subgroup analyses for branch *versus* central retinal vein occlusion were conducted. We identified 1,084 references of which 3 studies comparing low molecular weight heparin with aspirin (229 evaluable patients) were included. Overall, the pooled mean visual acuity difference was -0.23 logMAR (95% CI -0.38, -0.09; P=0.002) in favor of low molecular weight heparin. Low molecular weight heparin was associated with a 78% risk reduction for developing any adverse ocular outcome (pooled RR 0.22; 95% CI 0.10, 0.46; P<0.001). In subgroup analyses benefits seemed lower in branch retinal vein occlusion. No increased vitreous hemorrhages were observed. In patients with retinal vein occlusion treatment with low molecular weight heparin seems to be associated with improvement in the visual acuity and less adverse ocular outcomes. These benefits might differ in patients with central as opposed to branch retinal vein occlusion. Further studies are required to confirm these findings and clarify its benefits in specific subgroups of patients before definitive recommendations can be made.

Key words: retinal vein occlusion, low molecular weight heparin, aspirin, systematic review, meta analysis

Citation: Lazo-Langner A, Hawel J, Ageno W, and Kovacs MJ. Low molecular weight heparin for the treatment of retinal vein occlusion: a systematic review and meta-analysis of randomized trials. Haematologica 2010;95(9):1587-1593. doi:10.3324/haematol.2010.023614

Introduction

Retinal vein occlusion (RVO) is a common and important cause of visual loss. In population-based studies its prevalence has been reported to be around 0.6% and up to 4.6% in patients 80 years old or older with a 10-15 year cumulative incidence ranging between 1.6 and 1.8%.[1-4] Studies evaluating predictors of RVO have consistently shown an association with risk factors for atherosclerosis such as hypertension, dyslipidemia, and diabetes[4,5] as well as ocular comorbidities such as glaucoma;[5,6] conversely, it has been suggested that the presence of RVO in patients under 70 years of age might be associated with increased cardiovascular mortality.[7] In contrast, the association between RVO and thrombophilic risk factors for venous thrombosis, such as factor V Leiden, prothrombin G20210A, and deficiencies of antithrombin, protein C and protein S seems to be weak at best. The exceptions are hyperhomocysteinemia and the presence of antiphospholipid antibodies which are associated with an odds ratio (OR) for developing RVO of 8.9 and 3.9, respectively.[8]

Long-term complications of RVO include decreased visual acuity, iris neovascularization and neovascular glaucoma, and although it has been shown that they depend greatly on the initial visual acuity, up to 35% of patients with good baseline acuity will experience some degree of deterioration which could be as severe as or worse than 20/200 in up to 10% of all patients.[9] Therefore, interventions able to modify the natural history and improve functional prognosis in this condition are highly desirable. Two published systematic reviews evaluating interventions for central (CRVO) and branch RVO (BRVO) found limited high quality evidence for such interventions.[10,11] Different strategies have been evaluated and reported with varying degrees of benefit, including grid macular laser photocoagulation, hemodilution, ticlopidine, troxerutin, streptokinase, intravitreal steroids, and recently the use of angiogenesis inhibitors such as bevacizumab.[10-12]

The use of antiplatelet and anticoagulant agents has been repeatedly proven to be effective for the primary and second-

Manuscript arrived on February 9, 2010. Revised version arrived on March 8, 2010. Manuscript accepted on March 10, 2010
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ary prevention and treatment of arterial vascular events and venous thromboembolic disease[13-18] and although many anticoagulants including vitamin K antagonists, unfractionated heparin and low molecular weight heparin (LMWH) are available for clinical use, the pharmacological characteristics of the latter allow a safe and effective treatment of in- and outpatients with varying indications. Additionally, heparin and heparin derivatives have been shown to have anti-inflammatory and immunomodulatory properties beyond their anticoagulant action.[19,20] Given the association of RVO with arterial risk factors it is biologically plausible that the use of these agents might be beneficial for this indication. Initial reports on the use of anticoagulants for the treatment of RVO date back to the late 1940s[21] and more recent uncontrolled studies suggest that LMWHs might be useful in this condition.[22-24] We, therefore, aimed to conduct a systematic review and if feasible, a meta analysis of randomized trials evaluating the use of low molecular weight heparin for the treatment of retinal vein occlusion. We believe that our review was justified because of the aforementioned physiological and pharmacological considerations. Furthermore, the previous systematic reviews[10,11] did not find specific evidence regarding LMWH in RVO and at the time the review was conducted new evidence was emerging in this regard. Finally, the previous reviews failed to provide a summary effect measure of the interventions, most likely as a result of their heterogeneous nature.

Design and Methods

Search strategy

We included only randomized trials evaluating the use of a low molecular weight heparin in patients with an objectively demonstrated central or branch retinal vein occlusion. The search was conducted in July and August 2009 in the MEDLINE database using the Pubmed interface and in the EMBASE and HealthSTAR databases using the OVID SP interface. The search terms used were: retinal vein occlusion OR retinal vein thrombosis AND anticoagulants OR anticoagulation OR heparin OR aspirin OR warfarin OR acenocoumarol OR phenprocoumon OR dicoumarol OR vitamin k antagonists OR dalteparin OR tinzaparin OR parnaparin OR bemiparin OR enoxaparin OR nadroparin OR certoparin OR reviparin OR low molecular weight heparin. We also searched the following databases: The Cochrane Library (including The Cochrane Database of Systematic Reviews, The Database of Abstracts of Reviews of Effects, and The Cochrane Central Register of Controlled Trials), Lilacs and the Investigative Ophthalmology and Visual Science (IOVS) database. We also conducted a search of the electronic versions of the proceedings of the meetings of the American Society of Hematology (2004-2008), the International Society on Thrombosis and Haemostasis (2003-2009), and The Association for Research in Vision and Ophthalmology (2006-2009), which were considered gray literature. All of these databases were searched using the terms 'retinal vein occlusion' OR 'retinal vein thrombosis'. Finally, we searched the reference lists of retrieved articles for cross-referencing. We restricted the search to articles published in English, Spanish, French or Portuguese and to studies published after 1980 since no low molecular weight heparin was in clinical use prior to this date.

The retrieved references were assessed for possible inclusion based on the evaluation of the title and the abstract. If no abstract was available we evaluated the reference in full. Letters to the editor, review articles, editorials and commentaries were excluded.

Assessment of study quality, data extraction and study outcomes

Data extraction and quality assessment was made by one reviewer and accuracy was independently verified by a second reviewer. Discrepancies were resolved by consensus. The main outcome measure was the mean difference between the visual acuity at baseline and at six months expressed in the logarithm of the minimum angle of resolution (logMAR) scale. If visual acuity was reported in a different scale it was transformed to the logMAR scale using the Visual Acuity Calculator tool in the Optometric Toolbox software (Thompson Software Solutions, Hatfield, UK). The secondary outcome measure was a composite of any adverse ocular outcome including worsening of visual acuity, visual fields or fluorescein angiography, or development of iris neovascularization, any neovascularization or neovascular glaucoma. We planned to assess safety based on the occurrence of major bleeding episodes defined according to the criteria of the International Society on Thrombosis and Haemostasis which includes the occurrence of intraocular bleeding.[25] Quality of the studies was assessed using the criteria proposed by Jadad and coworkers[26] and we defined allocation concealment as appropriate or inappropriate according to the criteria proposed by Schulz and Grimes.[27] The possibility of publication bias was explored using inverted funnel plots of effect size *versus* precision.

Statistical analysis

Categorical variables were compared across groups using χ^2 tests. For the main outcome we conducted a meta analysis using the generic inverse variance method under the assumption of a random-effects model. We used the means and standard deviations (SD) reported in the trials. For one study that did not report mean difference visual acuity but did report mean visual acuity at baseline and at six months we estimated the mean difference and its variance through Monte Carlo simulations using 1,000 iterations and assuming a normal distribution bounded by 0 and 4. In order to test the robustness of the findings, sensitivity analyses were conducted using the values of the 95% confidence limits for the SD calculated from exact *P* values assuming a normal distribution and by imputation of standard deviations from other studies.[28] For the secondary outcome, we conducted a meta analysis using a random-effects model according to the method of DerSimonian and Laird[29] and because of a lack of consensus regarding the best summary statistic for evaluation of pooled effect estimates in meta-analysis[30-33] we present the results as odds ratio (OR) and risk ratio (RR). Differences between effects were tested using a *z* test and *P* values less than 0.05 were considered significant. Statistical heterogeneity was calculated using the Mantel-Haenszel method[34] considering a *P* value less than 0.1 for the χ^2 as indicative of heterogeneity, and the Higgins' I^2 statistic for which heterogeneity was defined as low if less than 25%, moderate if between 25-50%, or high if more than 50%.[35] Sensitivity analyses were planned for the main and secondary outcomes, if feasible, for CRVO and BRVO in separate sub-analyses.

Calculations were made using Microsoft Excel 2003 (Microsoft Corp., Seattle, WA, USA), OpenEpi version 2.3[36] and Review Manager (RevMan) version 5.0.[37]

Results

Literature search results

The search yielded 1,083 references with one additional reference having been identified through the review of the reference lists. Fifty-nine potentially relevant references were identified; of these 53 were excluded because they

were published before 1980, were published in other languages, did not report on randomized trials, and one reference could not be retrieved. Five references were fully evaluated and 2 were excluded because one reported on long-term complications in the same group of patients of another study being concurrently assessed,[38] and one report was a meeting abstract[39] which was subsequently published in full. Three studies were included in the final review (Figure 1).[40-42]

Characteristics of included studies and methodological quality

The 3 included studies randomized 238 patients with recent-onset RVO (less than 30 days) of which 229 were evaluable (Table 1). In all studies, retinal vein occlusion was diagnosed by ophthalmologists based on clinical findings, e.g. tortuosity and engorgement of retinal veins, dot-blot and flame-shaped hemorrhages, macular and optic disc edema, cotton-wool spots. One study included patients with both CRVO or BRVO and the other studies included only either one or the other. One study was a double-blind, double-dummy randomized controlled trial. This study was terminated early by the steering committee because of slow accrual after enrolling 39% of the originally planned sample size. The other 2 studies were open-label randomized controlled trials. Only one study had high quality according to the Jadad's score. All studies compared a low molecular weight heparin *versus* aspirin alone in the control group. One study used parnaparin for 90 days and the other 2 used dalteparin for 20 days. Aspirin was given at the same dose in all 3 studies. There were differences in the definition of the main outcomes and in 2 studies the secondary outcomes were not clearly stated. Only one study included clearly defined safety end points. We did not detect publication bias although this

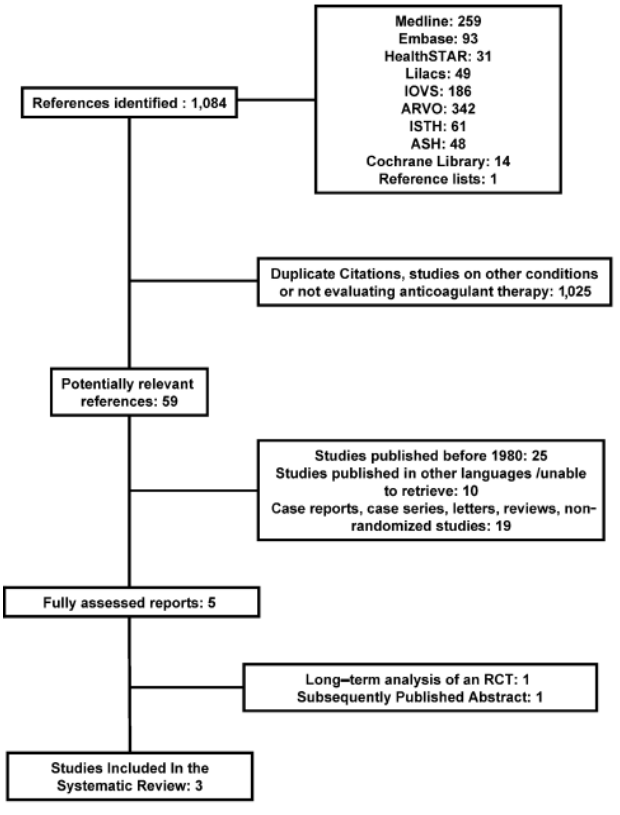

Figure 1. Flow diagram of the systematic review. IOVS Investigative Ophthalmology and Visual Science; ASH American Society of Hematology; ISTH International Society on Thrombosis and Haemostasis; ARVO Association for Research in Vision and Ophthalmology; RCT Randomized controlled trial.

Table 1. Characteristics of included studies.

	Ageno *et al.* 2009[40]	[a]Farahvash *et al.* 2008[41]	[b]Farahvash *et al.* 2008[42]
Design	Double-blind, double-dummy randomized controlled trial	Open-label randomized controlled trial	Open-label randomized controlled trial
Participants/controls evaluable (N)	28/30[a]	47/46	37/41
Jadad's score	5	2	2
Allocation concealment	Adequate	Inadequate /unclear	Inadequate / unclear
Inclusion criteria	CRVO or BRVO ≤15 days between symptoms, diagnosis and inclusion	CRVO ≤ 30 days since symptoms onset	BRVO ≤30 days since symptoms onset
Interventions	Parnaparin 6,400 IU BID SC days 1-7 days followed by 6,400 IU OD days 8-90 Aspirin 100 mg OD PO days 1-90	Dalteparin 100 IU/Kg SC BID days 1- 10 followed by 100 IU/Kg SC OD days 11-20 Aspirin 100 mg OD PO days 1-20	Dalteparin 100 IU/Kg SC BID days 1-10 followed by 100 IU/Kg SC OD days 11-20 Aspirin 100 mg OD PO days 1-20
Primary efficacy end point	Incidence of functional worsening of affected eye at 6 months based on best corrected visual acuity (decimal scale), visual field and fluorescein angiography	Best corrected visual acuity at 6 months (Early Treatment Diabetic Retinopathy Study Chart) transformed to logMAR scale	Best corrected visual acuity at 6 months (Early Treatment Diabetic Retinopathy Study Chart) transformed to logMAR scale
Secondary efficacy end point	Proportion of cases requiring laser treatment, incidence of RVO recurrence	Neo-vascularization of the iris[b]	Neo-vascularization of the iris Any neo-vascularization[b]
Primary safety end-point	Major and minor bleeding	NS	NS

CRVO central retinal vein occlusion; BRVO branch retinal vein occlusion; IU international units; BID twice daily; SC subcutaneous; OD once daily; PO by mouth; logMAR logarithm of the minimum angle of resolution; RVO retinal vein occlusion; NS not specified; [a]This study randomized 34 patients and 33 controls. The numbers shown are for evaluable patients; [b]Not clearly stated as secondary efficacy end-points.

cannot be totally excluded due to the small number of studies included.

Patients' characteristics are shown in Table 2. The median age at inclusion and the proportion of male patients were similar in the 3 studies. There were differences in the time between symptoms' onset and diagnosis which is explained by the different inclusion criteria used. There were no differences in the proportion of patients with hypertension (χ^2=6.979, *P*=0.222) or hypercholesterolemia (χ^2=5.505, *P*=0.357).

Meta-analysis

We performed a formal meta analysis for both main and secondary outcomes. One study reported visual acuity at six months in decimal scale and 2 studies reported it in logMAR scale. The mean difference in visual acuity favored the LMWH group in all studies, with a pooled mean difference of -0.23 logMAR (95% CI -0.38,-0.09; *P*=0.002) in favor of LMWH, which represents an improvement of approximately two lines in a standard Snellen chart. This result had low statistical heterogeneity (Figure 2). Sensitivity analyses conducted using imputed standard deviations suggested that this result was robust. For the secondary outcome we found that compared to aspirin the use of low molecular weight heparin was associated with an overall 78% risk reduction for developing any adverse ocular outcome (pooled RR 0.22; 95% CI 0.10, 0.46; *P*<0.001). This finding was consistent for both CRVO (pooled RR 0.13; 95%CI 0.03, 0.52; *P*=0.004) and BRVO (pooled RR 0.27; 95%CI 0.11, 0.65; *P*=0.004). The results were consistent when the effect measure analyzed was the odds ratio and we did not find statistical heterogeneity in these analyses (Figure 3). Safety end points were explicitly defined in only one study but all 3 studies commented on the occurrence of vitreous hemorrhages: one study reported 2 vitreous hemorrhages in the aspirin group and hematuria in one patient in the LMWH group, another study mentioned that 2 patients in the aspirin group and one in the LMWH group developed vitreous hemorrhage whereas the other study did not report the occurrence of bleeding complications. The pooled risk ratio for vitreous hemorrhage was 0.38 (95% CI 0.06, 2.45; *P*=0.31).

Discussion

Retinal vein occlusion remains an important cause of blindness for which few therapeutic options have been proven to be effective. Numerous interventions have been described for central and retinal RVO all of which aim mainly to prevent neovascularization and there is limited evidence that they indeed improve visual acuity.[10,11] Given the pathophysiology of RVO, it is possible that the use of anticoagulant or antiplatelet agents might be of benefit. The results of the present systematic review and meta-analysis suggest that the use of LMWH results in improved visual acuity six months after symptoms onset and also in a 78% risk reduction of developing adverse ocular outcomes defined as any of the following: worsening of visual acuity, visual fields or fluorescein angiography, or development of iris neovascularization, any neovascularization or neovascular glaucoma. Furthermore, our analysis suggests that the benefit is maintained for both CRVO and BRVO, although for the latter there seems to be less benefit. Finally, our results also suggest that the use of low molecular weight heparin in this particular setting is safe and might not be associated with an

Table 2. Characteristics of patients included in randomized trials evaluating the use of low molecular weight heparin in the treatment of retinal vein occlusion.

	Ageno *et al.* 2009[40]		[a]Farahvash *et al.* 2008a[41]		[b]Farahvash *et al.* 2008b[42]	
	LMWH group N=28	ASA group N= 30	LMWH group N=47	Control group N=46	LMWH group N=37	Control group N=41
Median age at entry (years)	57.9	58.1	56.5	56.4	53.7	57.5
Male gender (%)	50	50	63.8	60.8	37.8	43.9
CRVO [N (%)]	8 (28.6)[a]	17 (56.7)[a]	47 (100)	46 (100)	_	_
BRVO [N (%)]	20 (71.4)	13 (43.3)	_	_	37 (100)	41 (100)
Time between symptoms onset and diagnosis (days) [Mean (SD)]	7.2 (4.4)	6.7 (4.6)	13.9 (7.6)	16.1 (8.8)	17.7 (8.6)	20.4 (8.4)
Time between diagnosis and enrolment (days) [Mean (SD)]	1.1 (1.4)	1.2 (2.1)	NS	NS	NS	NS
Mean treatment duration (days)	89.2	83.6	NS	NS	NS	NS
Any potential risk factor [N (%)]	17 (60.7)	18 (60.0)	NS	NS	NS	NS
Hypertension [N (%)]	12 (42.9)	15 (50.0)	27 (57.4)	25 (54.3)	26 (70.2)	27 (65.8)
Hypercholesterolemia [N (%)]	6 (21.4)	6 (20.0)	13 (27.7)	14 (30.4)	15 (41.6)[c]	12 (36.3)[c]
Hypertriglyceridemia [N (%)]	NS	NS	8 (17.0)	14 (30.4)	11 (40.7)[d]	8 (27.6)[d]
Cardiovascular disease [N (%)]	NS	NS	11 (23.4)	13 (28.3)	4 (14.8)[d]	6 (20.7)[d]
Diabetes [N (%)]	NS	NS	5 (10.6)	6 (13.0)	5 (18.5)[d]	4 (13.8)[d]
Coexisting ophthalmological conditions [N (%)]	2 (7.1)	6 (20.0)	2 (4.3)[b]	4 (8.7)[b]	NS	NS

LMWH low molecular weight heparin; ASA aspirin; N number; NS not specified; CRVO central retinal vein occlusion; BRVO branch retinal vein occlusion; SD standard deviation.
[a]P=0.005 for difference between groups; [b]Study reported only on ocular hypertension; [c]Information available in 36 and 33 patients in the LMWH and ASA groups, respectively; [d]Information available in 27 and 29 patients in the LMWH and ASA groups, respectively.

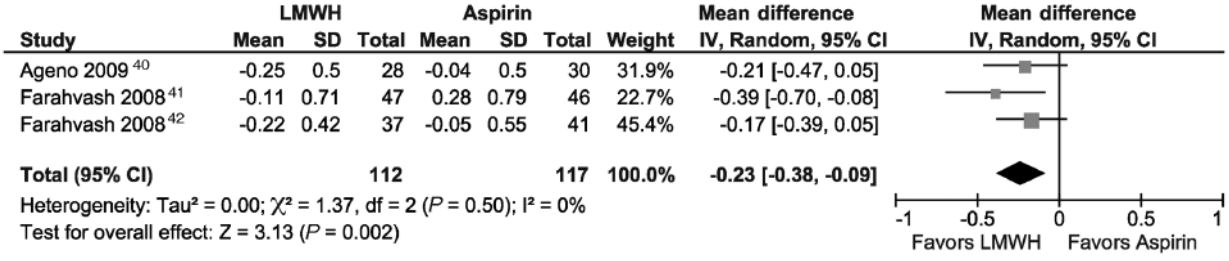

Figure 2. Forest plot of the mean difference in visual acuity expressed in the logarithm of the minimum angle of resolution (logMAR) scale in studies comparing low molecular weight heparin *versus* aspirin for the treatment of recent-onset retinal vein occlusion. LMWH low molecular weight heparin; SD standard deviation; IV inverse variance; CI confidence interval

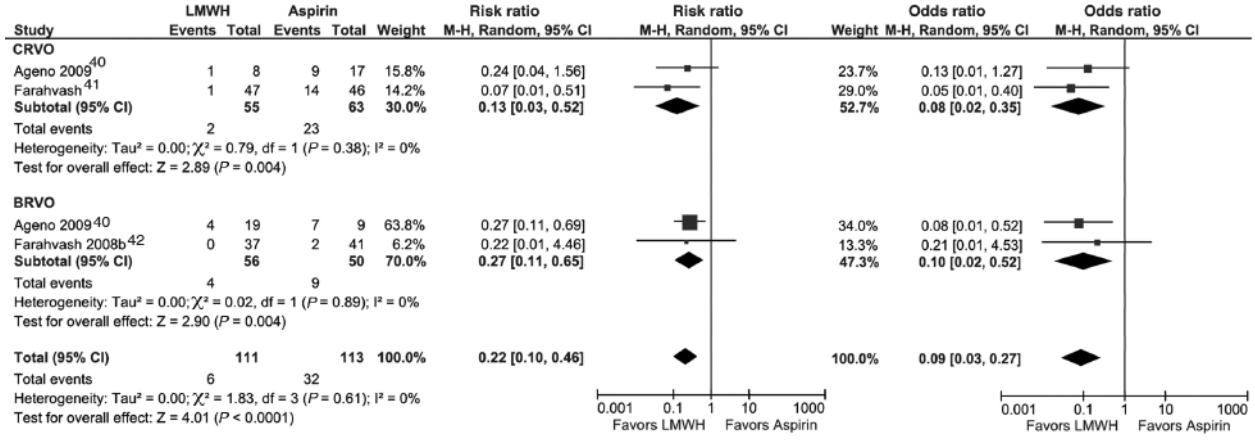

Figure 3. Forest plots showing the odds ratios and risk ratios for the occurrence of any adverse ocular outcome (see text for definition) in studies comparing low molecular weight heparin *versus* aspirin for the treatment of recent-onset retinal vein occlusion. LMWH low molecular weight heparin; CI confidence interval; CRVO central retinal vein occlusion; BRVO branch retinal vein occlusion.

increased risk of vitreous hemorrhage.

We believe that the results of our meta analysis are robust based on the results of the sensitivity analyses and on the fact that they had low statistical heterogeneity; furthermore, the number of patients included in the meta analysis would achieve enough power to detect a 50% risk reduction in the occurrence of adverse ocular outcomes, partially overcoming the limited number of patients included in individual trials. However, a number of limitations preclude definitive conclusions to be drawn from our work. First, since the studies included used different agents, the optimal low molecular weight heparin, dosing schedule and duration of treatment remain unknown. Whereas one study administered parnaparin for three months, the other two studies used dalteparin for only 20 days. Since the latter studies reported clinical benefit in patients with central[41] but not branch RVO[38] it might be possible that a more prolonged period of anticoagulation might actually result in a benefit for patients with BRVO, as suggested by the results of the study by Ageno and co-workers.[40] This is, in our opinion, one of the most important issues yet to be determined. Second, even though our results suggest that early anticoagulation initiation is necessary, the optimal time of initiation is still not known. Third, the optimal outcome measure is yet to be defined. Whereas all 3 studies reported on visual acuity, other potentially relevant outcomes such as worsening of visual fields or fluorescein angiography were only systematically evaluated in one study. We believe that the outcome definition proposed by Ageno and co-workers is a reasonable one. Finally, as in any other study evaluating the use of anticoagulant drugs, a systematic safety assessment is necessary but this was only made in one study.

In addition to the aforementioned limitations, our review identified a number of potential hurdles that might adversely affect the feasibility and design of future clinical trials in this area. First, the use of a double blind, double dummy design might adversely affect patient accrual, particularly in trials involving a parenteral placebo. The use of a carefully controlled open-label design, although relatively less methodologically stringent, might solve this issue. Second, although our findings suggest that early enrollment after symptom onset might be necessary, the optimal timeframe is unknown. Since a stringent enrollment window might affect accrual, it might be necessary to have a more flexible enrollment period. Third, since all studies compared low molecular weight heparin with aspirin, but no study compared active treatment with placebo, the clinical history of the disease without antithrombotic treatment is unknown. It cannot be deter-

mined whether aspirin is marginally beneficial, totally ineffective or might even have a negative impact on the natural history of retinal vein occlusion and, unfortunately, the literature on this issue is rather scarce. However, given the magnitude of the effect of low molecular weight heparin compared to aspirin we believe that it is unlikely that our conclusions regarding the beneficial effect of low molecular weight heparin would change. Finally, since there is a potential difference in the benefits of low molecular weight heparin between patients with central or branch retinal vein occlusion, stratification by diagnosis is necessary.

In summary, the use of anticoagulation with low molecular weight heparin for the treatment of retinal vein occlusion has biological plausibility, is convenient and easy to implement and there is extensive experience and supporting evidence of its efficacy and safety for the treatment of arterial and venous thrombosis in other areas. The findings of our study seem to suggest that low molecular weight heparin might be useful in the management of recent-onset retinal vein occlusion (particularly CRVO and less clearly in BRVO) but more studies are required before definitive recommendations can be made.

Authorship and Disclosures

AL-L is responsible for the conception of the study. AL-L and JH are responsible for the literature search, data collection and data analysis. AL-L and JH are responsible for Tables 1 and 2 and Figure 1. AL-L is responsible for Figures 2 and 3. All authors are responsible for data interpretation, drafted the manuscript, provided critical revisions and approved the final version.

The information provided by the authors about contributions from persons listed as authors and in acknowledgments is available with the full text of this paper at www.haematologica.org.

Financial and other disclosures provided by the authors using the ICMJE (www.icmje.org) Uniform Format for Disclosure of Competing Interests are also available at www.haematologica.org.

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