Antithrombotic and fibrinolytic drugs for retinal vein occlusion:
A systematic review and a call for action

Alessandro Squizzato; Elisa Manfredi; Silvia Bozzato; Francesco Dentali; Walter Ageno
Department of Clinical Medicine, University of Insubria, Varese, Italy

Summary
Optimal management of retinal vein occlusion (RVO) is still a matter of debate. Antithrombotic and fibrinolytic drugs have been investigated after demonstration of a role of thrombosis in the complex pathogenesis of the disease. Aim of our study was to systematically summarise best available evidence on the acute treatment and on the secondary prevention of RVO with antithrombotic and fibrinolytic drugs. A computer-assisted search of the MEDLINE and EMBASE electronic databases up to January 2009 was performed. Two review authors selected all published randomised controlled trials (RCTs) from the search, assessed study quality and extracted data. Based on Jadad’s score, RCTs were stratified into three quality categories. A total of six RCTs were included. Only one RCT of high quality was identified. A total of 384 patients were investigated, 234 with central retinal vein occlusion and 150 with branch retinal vein occlusion. No study enrolled more than 100 patients. Three studies compared therapeutic doses of low-molecular-weight heparin (LMWH) with low-dose aspirin, one study compared ticlopidine with placebo and two studies compared intravenous fibrinolytic therapy followed by warfarin or aspirin with either hae-modilution or no treatment. A partial improvement of visual acuity was reported in every study, independently of the study drug. No long-term secondary prevention study was published. The present systematic review suggests that antithrombotic therapy, in particular LMWH, may be part of the therapeutic armamentarium for patients with recent onset RVO. No firm recommendation can be provided given the limited available evidence.

Keywords
Retinal vein occlusion, antithrombotic drugs, low-molecular-weight heparin, thrombolysis

Introduction
Retinal vein occlusion (RVO) is a common cause of unilateral visual loss, and is the second commonest retinal disease after diabetic retinopathy, with an estimated incidence of 0.53 to 1.6/1,000 persons/year (1). Mechanisms underlying RVO are not completely understood. Most common risk factors include systemic cardiovascular risk factors, such as hypertension and diabetes mellitus, and local risk factors such as chronic open-angle glaucoma (2–3). An association between RVO and thrombophilia has also been reported (4). Because of the complex pathogenesis of RVO, the rationale to support one or another treatment strategy for this disease can not be straightforward (5). Several medical and surgical strategies have been proposed, but well-designed clinical trials are spare and thus no unique management is widely accepted (6–7). In particular, medical treatment has been primarily based on the management of systemic risk factors, when identified, and on the administration of antithrombotic and fibrinolytic drugs (5–7). Systemic or loco-regional thrombolitics, oral vitamin K antagonists, antiplatelet agents, and either unfractionated or low-molecular-weight heparin (LMWH) have all been evaluated (6–7).

The aim of our study was to systematically summarise the best available evidence on the acute treatment and secondary prevention of RVO with antithrombotic and fibrinolytic drugs.

Methods
Study identification
A computer-assisted search of the MEDLINE and EMBASE electronic databases up to January 2009 was performed to identify high-quality published studies on acute treatment and secondary prevention of RVO with antithrombotic and fibrinolytic drugs. The following search terms (text words and MeSH or EMTREE terms, respectively) were used for the MEDLINE search: thrombolytic therapy, heparin, low molecular weight heparin, platelet aggregation inhibitors, aspirin, anticoagulants, anticoagulation, dicumarol, hydroxycoumarins, warfarin, acenocumarol, retinal vein occlusion, retinal vein thrombosis; and for the EMBASE database search: retina vein occlusion, plasminogen activator, anticoagulant...
The following data were extracted for each study: type of retinal occlusion (central or branch, ischaemic or non-ischaemic, with or without haemorrhagic lesions), exclusion criteria, diagnostic methods (clinical diagnosis, fundus examination, fluoroangiography, or other tests), treatment (type of drug, dose, route of administration, start time and duration), concomitant acute treatment (pharmacological and/or surgical), outcomes (visual acuity, neovascular complications, recurrent events, bleeding complications), duration of follow-up. No attempts to mask for authorship, journal name or institution were made.

Data synthesis and analysis

Data for qualitative variables were presented as incidence rates (i.e., number and percent). Data from continuous variables were summarised using measures of central tendency (i.e., mean, median) and dispersion (i.e., standard deviation, range).

Results

The initial search strategy identified 688 papers, 93 of which were duplicates. A total of 101 publications were considered potentially eligible based on the title and/or abstract. After excluding 95 articles not meeting the pre-specified inclusion criteria, a total of six studies were included in the final analysis (plus two additional studies with partial data of two of six) (6–16). A reference list of excluded studies is available upon request from the authors.

Table 1: Quality assessment. RCTs (Jadad's score).

<table>
<thead>
<tr>
<th>First author and publication year</th>
<th>Enrolled patients (N)</th>
<th>Randomisation</th>
<th>Double blinding</th>
<th>Follow-up (withdrawals/dropouts)</th>
<th>Quality of randomisation</th>
<th>Quality of blinding</th>
<th>Overall quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kohner 1976 (9–10)</td>
<td>40</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>Low</td>
</tr>
<tr>
<td>Houtsmuller 1984 (11)</td>
<td>89</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>Low</td>
</tr>
<tr>
<td>Farahvash 2008 (12–13) (CRVO)</td>
<td>93</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>Low</td>
</tr>
<tr>
<td>Farahvash 2008 (14) (BRVO)</td>
<td>57</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>Intermediate</td>
</tr>
<tr>
<td>Ageno 2009 (15)</td>
<td>53</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>High</td>
</tr>
<tr>
<td>Hattenbach 2009 (16)</td>
<td>52</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>Low</td>
</tr>
</tbody>
</table>

CRVO, central retinal vein occlusion; BRVO, branch retinal vein occlusion.

The following data were extracted for each study: type of retinal occlusion (central or branch, ischaemic or non-ischaemic, with or without haemorrhagic lesions), exclusion criteria, diagnostic methods (clinical diagnosis, fundus examination, fluoroangiography, or other tests), treatment (type of drug, dose, route of administration, start time and duration), concomitant acute treatment (pharmacological and/or surgical), outcomes (visual acuity, neovascular complications, recurrent events, bleeding complications), duration of follow-up. No attempts to mask for authorship, journal name or institution were made.

Study selection

Two review authors (EM, SB) concomitantly selected potentially eligible studies from the search. The studies were rejected if one could determine from the title and/or abstract that the study was not suitable for inclusion in this review. We obtained the full text of the study when the suitability of an article could not be excluded with certainty. Disagreement between reviewers was solved through discussion. In case of persisting disagreement, the opinion of a third reviewer (AS) was requested. Studies were eligible if their aim was to investigate the clinical effects of antithrombotic drugs (vitamin K antagonists, heparin, antiplatelet drugs) and fibrinolytic agents for the acute treatment or for the secondary prevention of RVO. For the purpose of this review, we decided to include only randomised controlled trials, given the low quality of non-randomised, non-controlled studies. Reviews and non-human studies were excluded. Manuscripts without outcomes were excluded. Non-English papers were excluded as well.

Quality assessment and data extraction

The same two reviewers (EM and SB) independently completed the data extraction form, which included also quality items.

For quality assessment of randomised controlled trials (RCTs), we used by Jadad’s score, which evaluates the following three characteristics: method of randomisation, methods of blinding, follow-up (8). To stratify RCTs we applied the following cut-offs: a total of five points defined high-quality studies; three and four points defined medium-quality studies; two or less points defined low-quality studies. The quality assessment form is available upon request from the authors.

agent. No language restrictions were initially applied to the search strategy.

Reference lists of all studies included in the present systematic review were searched for potential additional eligible studies.

Data synthesis and analysis

Data for qualitative variables were presented as incidence rates (i.e., number and percent). Data from continuous variables were summarised using measures of central tendency (i.e., mean, median) and dispersion (i.e., standard deviation, range).

Results

The initial search strategy identified 688 papers, 93 of which were duplicates. A total of 101 publications were considered potentially eligible based on the title and/or abstract. After excluding 95 articles not meeting the pre-specified inclusion criteria, a total of six studies were included in the final analysis (plus two additional studies with partial data of two of six) (6–16). A reference list of excluded studies is available upon request from the authors.
able in almost all studies (Table 2). Three studies compared therapeutic doses of LMWH with low-dose aspirin (12–15), one study compared ticlopidine with placebo (11), and two studies compared intravenous fibrinolytic therapy given in the first days followed by warfarin or aspirin with either haemodilution or no therapy (9, 10, 16) (Table 3). Delay between the onset of symptoms and initiation of the study treatment largely varied among studies: only one study included patients within seven days of symptom onset (9, 10). Main outcomes of the studies are summarised in Table 4. Unfortunately, study outcomes were highly heterogeneous and, in particular, no homogenous definition for the measurement of visual acuity was applied. No measures of central tendency, therefore, can be provided. A partial improvement of visual acuity was reported in every study, independently of the study drug, during a follow-up of six to 12 months. Neovascular complication rate was wide: 0 to 39%. Ocular bleeding complications occurred in 0 to 20% of patients. Briefly, LMWHs appear to have the best risk-benefit profile, in particular in comparison with aspirin. Moreover, patients with CRVO may be those who benefit the most. Unfortunately, a separate analysis for CRVO and BRVO could not be performed, mainly because in the evaluated studies the rates of neovascular and bleeding complications were not provided separately for the two sites of disease. No study was planned to investigate on the efficacy of antithrombotic drugs for the long-term secondary prevention. Only two studies reported on the incidence of recurrent RVO (0 to 10%) (9, 10, 15) (Table 4).

Discussion

The results of this systematic review of the literature stress the fact that the optimal treatment of RVO remains an unmet clinical need and represent a call for action for good quality clinical studies in this important field. Based on our findings, antithrombotic therapy, and in particular therapy with LMWH, appears to play a potentially important role in the acute treatment of RVO. However, no firm recommendation can be provided given the limited available evidence.

Theoretically, there are four main goals when managing a patient with RVO: first, to limit retinal damage during the acute phase in order to prevent subsequent complications; second, to identify and remove underlying risk factors; third, to treat subsequent ocular complications; and finally to prevent recurrent events which may occur locally as well as in other vascular beds. Unfortunately,
there are currently no widely accepted approaches to reach any of these goals (6, 7, 17). The pathogenic mechanisms of this disease remain incompletely understood. Arterial compression of the retinal veins, endothelial damage, and thrombosis may play different roles in different patients. There is in fact a wide range of risk factors (18), and because the thrombotic mechanism is not necessarily the only underlying mechanism, “retinal vein occlusion” remains a more accurate, albeit unsatisfactory, definition of the disease than “retinal vein thrombosis.” Furthermore, the pathogenesis and natural history of CRVO and BRVO are also likely to be different (18). Thus, it is first of all possible that different treatment strategies may actually be necessary for different clinical scenarios. So far, clinical studies have only enrolled rather small and heterogeneous populations, thus making the clinical significance of their results rather inconsistent. Other major limitations in the available studies include the long delay between symptoms onset and initiation of treatment (12–14), the fact that most studies were non-randomised, non-controlled or, at least, not adequately-controlled (6, 7, 17), and, last but not least, the lack of standardisation of clinical outcomes, which remain highly heterogeneous in both definitions and methods of assessment.

Antithrombotic and fibrinolytic drugs have been studied for the acute treatment of RVO since the mid of the last century, based on the hypothesis that the pathogenesis of the disease is substantially thrombotic (19–21). Despite the limited evidence, the results of the few randomised controlled studies suggest that patients may benefit from antithrombotic treatment in the acute phase of the disease, and that LMWHs appear as the most effective agents. The superiority of LMWHs over antiplatelet agent, which was shown in some of the studies (12–15), may support the hypothesis that RVO really is a venous thrombotic disorder. In addition, non-thrombotic properties have been advocated for LMWH: for example, LMWH fragments produced by the heparinase digestion of unfractioned heparin exert anti-angiogenic effects in any type of tissue in vivo; these effects are fragment-mass-specific and angiogenesis-type-specific (22). In a condition such as RVO in which neovascularisation plays a relevant role, such properties may explain the additional benefit of LMWH in comparison with other agents. However, it should be emphasized that no studies comparing LMWH with placebo or no treatment have been carried out. Thus, it is at this stage only possible to suggest a superiority of LMWH over comparator treatments, whereas no clear cut conclusions can be drawn on the potential benefits of the LMWH over no antithrombotic treatment. The role for antithrombotic agents in the long-term secondary prevention of RVO remains unexplored. In clinical practice, antiplatelet drugs are often used in elderly pa-

### Table 3: Type of treatment.

<table>
<thead>
<tr>
<th>First author and publication year</th>
<th>Study drug</th>
<th>Dose, route of administration, duration</th>
<th>Time from symptoms onset</th>
<th>Concomitant acute treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kohner 1976 (9–10)</td>
<td>Streptokinase vs no treatment</td>
<td>600,000 IU over 30 minutes plus 100,000/h for 72 h followed by unfractioned heparin for 2 days and then warfarin for 6 months</td>
<td>Within 7 days</td>
<td>NR</td>
</tr>
<tr>
<td>Hattenbach 2009 (16)</td>
<td>rt-PA vs hemodilution</td>
<td>50 mg intravenously over 60 minutes plus intravenous heparin 1,200 unit per hours for 8 days plus aspirin for 12 weeks Venesections plus starch infusions (for 8 days) plus pentoxifylline for 12 weeks</td>
<td>Within 11 days</td>
<td>NR</td>
</tr>
<tr>
<td>Farahvash 2008 (CRVO) (12–13)</td>
<td>Dalteparin vs Aspirin</td>
<td>100 IU/kg bid for 10 days subcutaneously, then od for 10 days 100 mg od, orally, for 20 days</td>
<td>Within 30 days</td>
<td>NR</td>
</tr>
<tr>
<td>Farahvash 2008 (BRVO) (14)</td>
<td>Dalteparin vs Aspirin</td>
<td>100 IU/kg bid for 10 days subcutaneously, then o.d. for 10 days 100 mg od, orally, for 20 days</td>
<td>Within 30 days</td>
<td>NR</td>
</tr>
<tr>
<td>Ageno 2009 (15)</td>
<td>Parnaparin vs Aspirin</td>
<td>6,400 IU bid for 7 days subcutaneously followed by 6,400 IU od for 81 days 100 mg od, orally, for 90 days</td>
<td>Within 15 days</td>
<td>NR</td>
</tr>
<tr>
<td>Houtsmuller 1984 (11)</td>
<td>Ticlopidine vs placebo</td>
<td>250 mg x 2 daily orally</td>
<td>Within 21 days</td>
<td>NR</td>
</tr>
</tbody>
</table>

r-tPA, recombinant tissue plasminogen activator; NR, not reported; CRVO, central retinal vein occlusion; BRVO, branch retinal vein occlusion.
<table>
<thead>
<tr>
<th>First author and publication year</th>
<th>Study drug Comparator</th>
<th>Follow-up</th>
<th>Visual acuity (VA)</th>
<th>Neovascular complications</th>
<th>Recurrent events</th>
<th>Relevant bleeding complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kohner 1976 (9–10)</td>
<td>Streptokinase plus warfarin</td>
<td>1 year</td>
<td>Improved (mean VA: from 6.9 to 5.6) Worsened (mean VA: from 5.6 to 7.1)</td>
<td>Thrombotic glaucoma: 1 pts (5%)</td>
<td>0</td>
<td>Vitreous haemorrhage: 3 pts (15%) (all in the first three days)</td>
</tr>
<tr>
<td></td>
<td>No treatment</td>
<td></td>
<td>Worsened (mean VA: from 5.6 to 7.1)</td>
<td>Thrombotic glaucoma: 4 pts (20%)</td>
<td>1 (5%) in the unaffected eye</td>
<td>Vitreous haemorrhage: 4 pts (20%) (none in the first three days)</td>
</tr>
<tr>
<td>Hattenbach 2009 (16)</td>
<td>rt-PA plus heparin plus aspirin</td>
<td>1 year</td>
<td>CRVO: Median final VA 20/60 BRVO: Median final VA 20/25</td>
<td>Neovascularisation of the iris: 4 pts (16%)</td>
<td>NR</td>
<td>One subretinal haemorrhage (4%)</td>
</tr>
<tr>
<td></td>
<td>Hemodilution plus pentoxifylline</td>
<td></td>
<td>CRVO: Median final VA 20/400 BRVO: Median final VA 20/25</td>
<td>Neovascularisation of the iris: 3 pts (11.1%)</td>
<td>NR</td>
<td>One vitreous haemorrhage secondary to neovascularisation (3.7%)</td>
</tr>
<tr>
<td>Farahvash 2008 (CRVO) (12–13) (only 47 patients for 1 year follow-up)</td>
<td>Dalteparin 6 months 1 year</td>
<td>Improved (logMAR change: –0.11±0.71) Improved (logMAR change: –0.12)</td>
<td>Neovascularisation of the iris: 2.1% 4.1%</td>
<td>NR</td>
<td>No ocular haemorrhage</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Acetilsalicilic acid 6 months 1 year</td>
<td>Worsened (logMAR change: +0.28±0.79) Worsened (logMAR change: +0.72)</td>
<td>Neovascularisation of the iris: 30.4% 39.1%</td>
<td>NR</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Farahvash 2008 (14) (BRVO)</td>
<td>Dalteparin 6 months</td>
<td>Improved (logMAR change: –0.22±0.42)</td>
<td>Neovascularisation of the iris and the disc: 0%</td>
<td>NR</td>
<td>Vitreous haemorrhage: 2.7%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Acetilsalicilic acid</td>
<td>Improved (logMAR change: –0.05±0.55)</td>
<td>Neovascularisation of the iris and the disc: 4.9%</td>
<td>NR</td>
<td>Vitreous haemorrhage: 4.9%</td>
<td></td>
</tr>
<tr>
<td>Ageno 2009 (15)</td>
<td>Parnaparin 6 months</td>
<td>Functional status Improved 18 (62.1%), Stable 5 (17.2%), Worsened 6 (20.7%) FAG CRVO: Improved 7 (87.5%), Stable 0, Worsened 1, 12.5%; BRVO: Improved 8 (42.1%), Stable 7 (36.8%), Worsened 4 (21.1%)</td>
<td>NR</td>
<td>0 pts</td>
<td>Self arresting haematuria: 1 pts (3.6%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Acetilsalicilic acid</td>
<td>Functional status Improved 11 (34.4%), Stable 2 (6.2%), Worsened 19 (59.4%) CRVO: Improved 7 (41.2%), Stable 1 (5.9%), Worsened 9 (52.9%) BRVO: Improved 1 (11.1%), Stable 1 (11.1%), Worsened 7 (77.8%)</td>
<td>NR</td>
<td>3 pts (10%)</td>
<td>Vitreous haemorrhage: 2 pts (6.7%)</td>
<td></td>
</tr>
<tr>
<td>Houtsmuller 1984 (11)</td>
<td>Ticlopidine 6 months</td>
<td>CRVO: Improved 8 (42%), Stable 6 (32%), Worsened 5 (26%) BRVO: Improved 20 (69%), Stable 7 (24%), Worsened 2 (7%)</td>
<td>NR</td>
<td>NR</td>
<td>Haemorrhagic disturbances: 1 pts (2.1%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>CRVO: Improved 6 (38%), Stable 2 (12%), Worsened 8 (50%) BRVO: Improved 13 (52%), Stable 6 (24%), Worsened 6 (24%)</td>
<td>NR</td>
<td>NR</td>
<td>Haemorrhagic disturbances: 0 pts</td>
<td></td>
</tr>
</tbody>
</table>

r-TPA, recombinant tissue plasminogen activator; NA, not applicable; NR, not reported; VA, visual acuity; CRVO, central retinal vein occlusion; BRVO, branch retinal vein occlusion; logMAR, logarithm of the minimum angle of resolution; pts, patients.
tients with RVO and concomitant cardiovascular risk factors, such as diabetes, hypertension, and dyslipidaemia. Although the efficacy of such approach is unproven, the biological rationale is plausible, at least for the prevention of subsequent cardiovascular events in this higher risk population. Whether long-term secondary prevention with aspirin could also be effective to prevent recurrent RVO is less clear. The incidence of ipsilateral RVO recurrence is estimated around 1%/year and of contralateral RVO recurrence around 10–15% overall (23, 24). However, the available estimate of the incidence rate of recurrences is likely biased by the frequent use of concomitant treatments, such as laser photocoagulation, anti-angiogenic drugs and surgery.

Overall, these data represent a ‘call for action’. Researchers and clinicians need to be aware of the limitations of the first, “pioneer” studies and all such limitations will need to be taken into account when planning future studies. First, delay between the onset of symptoms and the starting of the treatment widely varied among previous studies, and only in a minority of these studies excessive delay was an exclusion criterion. Indeed, time-to-treatment remains a critical factor to evaluate the efficacy of a therapeutic strategy. Second, it may be critical to stratify patients according to the type of RVO (ischaemic vs. non-ischaemic), because different presentations play an important role with regard to the visual prognosis. Because visual function primarily is a result of ischemia and of retinal changes such as oedema, haemorrhage or capillary non-perfusion, initial stratification would improve the assessment of the clinical outcomes. Finally, various novel experimental therapeutic approaches such as the intravitreal administration of anti-vascular endothelial growth factor drugs have been recently proposed. Whether these approaches will overcome the need for anti-coagulant therapies during the acute phase of the disease clearly remains to be understood. Future studies should also evaluate the possibility of combined approaches.

In conclusion, antithrombotic drugs may play a role in the treatment of the acute phase of RVO, at least in some patients categories. However, given the complexity of this condition, a multidisciplinary approach, concomitantly including ophthalmologic and anti-thrombotic treatment strategies (25), should be assessed to improve the management of what we can call a still ‘orphan’ disease.

References