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

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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 haemodilution 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

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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 thrombolytics, 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

First author and publication year	Enrolled patients (N)	Random-isation	Double blinding	Follow-up (withdrawals/ dropouts)	Quality of randomi-sation	Quality of blinding	Overall quality
Kohner 1976 (9–10)	40	1	0	1	0	0	Low
Houtsmuller 1984 (11)	89	1	1	0	0	0	Low
Farahvash 2008 (12–13) (CRVO)	93	1	0	0	1	0	Low
Farahvash 2008 (14) (BRVO)	57	1	0	1	1	0	Intermediate
Ageno 2009 (15)	53	1	1	1	1	1	High
Hattenbach 2009 (16)	52	1	0	1	0	0	Low

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

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

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.

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.

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, fluoroangiografy, 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 summarises study quality. Only one RCT of high quality was identified: it was the only double-blind, double-dummy, with the assessor of the outcome masked to the treatment group, and with detailed description of withdrawal and drop-out patients (15). A total of 384 patients were investigated, 234 with central retinal vein occlusion (CRVO) and 150 with branch retinal vein occlusion (BRVO). No study enrolled more than 100 patients. Four of the six studies were published in the last two years (12–16). An accurate description of RVO severity at the time of diagnosis was unavail-

Table 2: Baseline characteristics of RVO.

First author and publication year	Main exclusion criteria	Severity			Diagnosis		
		Central/branch	Ischaemic	Haemorrhages at fundus	FAG	Fundus oculi	Other tests
Kohner 1976 (9–10)	Controindications to streptokinase	Central	NR	NR		X	X
Houtsmuller 1984 (11)	Diabetic retinopathy, severe hypertension, liver and kidney disorders, coagulopathies.	Central (35 pts) Branch (54 pts)	NR	NR	X	X	X
Farahvash 2008 (12–13) (CRVO)	Intraocular pressure more than 30 mmHg, neovascularization of the iris or retina, severe diabetic retinopathy, coagulopathies.	Central	61.7% in dalteparin group and 58.7% in aspirin group	Yes	X	X	X
Farahvash 2008 (14) (BRVO)	Intraocular pressure more than 30 mmHg, neovascularization of the iris or retina, severe diabetic retinopathy, coagulopathies.	Branch	NR	NR	X	X	X
Ageno 2009 (15)	History of major ocular surgery (with the exclusion of cataract extraction), previous RVO, major bleeding or neurosurgical procedures in the previous 3 months, serum creatinine levels of greater than 2.0 mg/dL, severe liver insufficiency, platelet count <100,000 mm3, known active peptic gastric ulcer), active malignancy.	Central (25 pts) Branch (28 pts)	NR	NR	X	X	X
Hattenbach 2009 (16)	Controindications to thrombolysis; progressive diabetic or hypertensive retinopathy; inflammatory eye disease; pts who received photocoagulation; less severe form (see original manuscript for definition)	Central (41 pts) Branch (11 pts)	NR	Yes	X	X	X

NR, no reported; CRVO, central retinal vein occlusion; BRVO, branch retinal vein occlusion; pts, patients.

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 heterogenous and, in particular, no homogenous definition for the measurement of for 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 range 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,

Table 3: Type of treatment.

First author and publication year	Study drug	Dose, route of administration, duration	Time from symptoms onset	Concomitant acute treatment
Fibrinolytic therapy				
Kohner 1976 (9–10)	Streptokinase vs no treatment	600,000 IU over 30 minutes plus 100,000/h for 72 h followed by unfractionated heparin for 2 days and then warfarin for 6 months	Within 7 days	NR
Hattenbach 2009 (16)	rt-PA vs hemodilution	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	Within 11 days	NR
Heparin				
Farahvash 2008 (CRVO) (12–13)	Dalteparin vs Aspirin	100 IU/kg bid for 10 days subcutaneously, then od for 10 days 100 mg od, orally, for 20 days	Within 30 days	NR
Farahvash 2008 (BRVO) (14)	Dalteparin vs Aspirin	100 IU/kg bid for 10 days subcutaneously, then o.d. for 10 days 100 mg od, orally, for 20 days	Within 30 days	NR
Ageno 2009 (15)	Parnaparin Vs Aspirin	6,400 IU bid for 7 days subcutaneously followed by 6,400 IU od for 81 days 100 mg od, orally, for 90 days	Within 15 days	NR
Antiplatelet drugs				
Houtsmuller 1984 (11)	Ticlopidine vs placebo	250 mg x 2 daily orally	Within 21 days	NR

r-tPA, recombinant tissue plasminogen activator; NR, not reported; CRVO, central retinal vein occlusion; BRVO, branch retinal vein occlusion.

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 4: Outcome.

First author and publication year	Study drug / Comparator	Follow-up	Visual acuity (VA)	Neovascular complications	Recurrent events	Relevant bleeding complications
Kohner 1976 (9–10)	Streptokinase plus warfarin	1 year	Improved (mean VA: from 6.9 to 5.6) Worsened (mean VA: from 5.6 to 7.1)	Thrombotic glaucoma: 1 pts (5%)	0	Vitreous haemorrhage: 3 pts (15%) (all in the first three days)
	No treatment		Worsened (mean VA: from 5.6 to 7.1)	Thrombotic glaucoma: 4 pts (20%)	1 (5%) in the unaffected eye	Vitreous haemorrhage: 4 pts (20%) (none in the first three days)
Hattenbach 2009 (16)	rt-PA plus heparin plus aspirin	1 year	CRVO: Median final VA 20/60 BRVO : Median final VA 20/25	Neovascularisation of the iris: 4 pts (16%)	NR	One subretinal haemorrhage (4%)
	Hemodilution plus pentoxifylline		CRVO: Median final VA 20/400 BRVO: Median final VA 20/25	Neovascularisation of the iris: 3 pts (11.1%)	NR	One vitreous haemorrhage secondary to neovascularisation (3.7%)
Farahvash 2008 (CRVO) (12–13) (only 47 patients for 1 year follow-up)	Dalteparin	6 months 1 year	Improved (logMAR change: –0.11±0.71) Improved (logMAR change: –0.12)	Neovascularisation of the iris: 2.1% 4.1%	NR	No ocular haemorrhage
	Acetilsalicilic acid	6 months 1 year	Worsened (logMAR change: +0.28±0.79) Worsened (logMAR change: +0.72)	Neovascularisation of the iris: 30.4% 39.1%	NR	NR
Farahvash 2008 (14) (BRVO)	Dalteparin	6 months	Improved (logMAR change: –0.22±0.42)	Neovascularisation of the iris and the disc: 0%	NR	Vitreous haemorrhage: 2.7%
	Acetilsalicilic acid		Improved (logMAR change: –0.05±0.55)	Neovascularisation of the iris and the disc: 4.9%	NR	Vitreous haemorrhage: 4.9%
Ageno 2009 (15)	Parnaparin	6 months	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%)	NR	0 pts	Self arresting haematuria: 1 pts (3.6%)
	Acetilsalicilic acid		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%)	NR	3 pts (10%)	Vitreous haemorrhage: 2 pts (6.7%)
Houtsmuller 1984 (11)	Ticlopidine	6 months	CRVO: Improved 8 (42%), Stable 6 (32%), Worsened 5 (26%) BRVO: Improved 20 (69%), Stable 7 (24%), Worsened 2 (7%)	NR	NR	Haemorrhagic disturbances: 1 pts (2.1%)
	Placebo		CRVO: Improved 6 (38%), Stable 2 (12%), Worsened 8 (50%) BRVO: Improved 13 (52%), Stable 6 (24%), Worsened 6 (24%)	NR	NR	Haemorrhagic disturbances: 0 pts

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 controlateral 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 anticoagulant 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 antithrombotic treatment strategies (25), should be assessed to improve the management of what we can call a still 'orphan' disease.

References

1. Klein R, Klein BE, Moss SE, et al. The epidemiology of retinal vein occlusion: the Beaver Dam Eye Study. Trans Am Ophthalmol Soc 2000; 98: 133–143.
2. Hayreh SS, Zimmerman B, McCarthy MJ, et al. Systemic diseases associated with various types of retinal vein occlusion. Am J Ophthalmol 2001; 131: 61–77.
3. Koizumi H, Ferrara DC, Bruè C, et al. Central retinal vein occlusion case-control study. Am J Ophthalmol 2007; 144: 858–863.
4. Janssen MC, den Heijer M, Cruysberg JR, et al. Retinal vein occlusion: a form of venous thrombosis or a complication of atherosclerosis? A meta-analysis of thrombophilic factors. Thromb Haemost 2005; 93: 1021–1026.
5. Prisco D, Marcucci R. Retinal vein thrombosis: risk factors, pathogenesis and therapeutic approach. Pathophysiol Haemost Thromb 2002; 32: 308–311.
6. Mohamed Q, McIntosh RL, Saw SM, et al. Interventions for central retinal vein occlusion: an evidence-based systematic review. Ophthalmology 2007; 114: 507–519.
7. McIntosh RL, Mohamed Q, Saw SM, et al. Interventions for branch retinal vein occlusion: an evidence-based systematic review. Ophthalmology 2007; 114: 835–854.
8. Jadad AR, Moore AR, Carrol D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Controlled Clin Trials 1996; 17: 1–12.
9. Kohner EM, Hamilton AM, Bulpitt CJ, et al. Streptokinase in the treatment of central retinal vein occlusion. Trans Ophthal Soc UK 1974; 94: 599–603.
10. Kohner EM, Pettit JE, Hamilton AM, et al. Streptokinase in central retinal vein occlusion: a controlled clinical trial. Br Med J 1976; 1: 550–553.
11. Houtsmuller AJ, Vermeulen JA, Klompe M, et al. The influence of ticlopidine on the natural course of retinal vein occlusion. Agents Actions Suppl 1984; 15: 219–229.
12. Farahvash MS, Moghaddam MM, Moghimi S, et al. Dalteparin in the management of recent onset central retinal vein occlusion: a comparison with acetylsalicylic acid. Can J Ophthalmol 2008; 43: 79–83.
13. Farahvash MS, Farahvash MM, Moradimogadam M, et al. Long-term effect of dalteparin in the prevention of neovascularization of iris in recent-onset central retinal vein occlusion. Arch Iran Med 2008; 11: 539–543.
14. Farahvash MS, Moradimogadam M, Farahvash MM, et al. Dalteparin versus aspirin in recent-onset branch retinal vein occlusion: a randomized clinical trial. Arch Iran Med 2008; 11: 418–422.
15. Ageno W, Cattaneo R, Manfredi E, et al. Parnaparin versus aspirin in the treatment of retinal vein occlusion. A randomized, double blind, controlled study. Thromb Res 2009; Epub ahead of print.
16. Hattenbach LO, Friedrich AC, Lerche R, et al. Retinal vein occlusion and low-dose fibrinolytic therapy (R.O.L.F.): a prospective, randomized, controlled multicenter study of low-dose recombinant tissue plasminogen activator versus hemodilution in retinal vein occlusion. Retina 2009; 29: 932–940.
17. Berker N, Batman C. Surgical treatment of central retinal vein occlusion. Acta Ophthalmol 2008; 86: 245–252
18. Hayreh SS. Prevalent misconceptions about acute retinal vascular occlusive disorders. Prog Retin Eye Res 2005; 24: 493–519.
19. Vannas S, Raitta C. Anticoagulant treatment of retinal venous occlusion. Am J Ophthalmol 1966; 62: 874–884.
20. Vannas S, Orma H. Experience of treating retinal venous occlusion with anticoagulant and antisclerosis therapy. AMA Arch Ophthalmol 1957; 58: 812–828.
21. Hecker SP, Zweng HC. Central retinal artery occlusion successfully treated with plasmin. J Am Med Assoc 1961; 176: 1067–1069.
22. Norrby K. Low-molecular-weight heparins and angiogenesis. APMIS 2006; 114: 79–102.
23. Williamson TH. Central retinal vein occlusion: what's the story? Br J Ophthalmol 1997; 81: 698–704.
24. Sodi A, Giambene B, Marcucci R, et al. Atherosclerotic and thrombophilic risk factors in patients with recurrent central retinal vein occlusion.Eur J Ophthalmol 2008; 18: 233–238.
25. Sofi F, Marcucci R, Bolli P, et al. Low vitamin B6 and folic acid levels are associated with retinal vein occlusion independently of homocysteine levels. Atherosclerosis 2008; 198: 223–227.

