Mahidol University
Faculty of Medicine Siriraj Hospital

Siriraj Stroke Center

What to do when stroke hits the eye(s)?

Yongchai Nilanont, MD

Siriraj Stroke Center, Siriraj Hospital, Mahidol University, Thailand

Dept. of Clinical Neurological Sciences, Schulich School of Medicine and Dentistry, Western University, Canada

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outline

- Why retinal stroke?
- Antithrombotic and thrombolytic medications: Review of the evidence
- How do we treat?
  - What is our current practice?
- How can we make a different?
  - The LIRIC Study

Why retinal stroke?

- **2nd most common retinal vascular disease after diabetic retinopathy.**
- **Middle age to elderly, affected 1.6% in persons ≥ 49 yr with a 10-yr incidence of 1.6%**
- **RVO Natural history:**
  - **"None of VA improvement better than 20/40"**
  - **Up to 1/3 of non-ischemic CRVO converted to ischemic over 3 years.**
  - **Untreated CRVO eyes generally had poor VA which decline further over time.**
- **Result in substantially higher medical costs and resource utilization than glaucoma or systemic HT.**
- **Negative impact on QoL independent of the visual outcome**
- **Increased stroke risk (1.5 OR)**

What is already known in this area?

- Long-term complications: reduced VA, iris neovascularization and neovascular glaucoma
- Rx laser photocoagulation, hemodilution, intravitreal steroid, angiogenesis inhibitor (anti-VGF)
- Associated with atherosclerosis risk factors including hyperhomocysteinemia and APA+
- Associated with atherosclerosis risk factors including hyperhomocysteinemia and APA+
- Questionable Role of anti-thrombotic medication

Rx of RVO

- **Identification and therapy of the detectable risk factors**
- **Specific treatment aimed at the occlusive form**
- **Treatment of RVO complications**

Risk Factor	N	%
• HT	1,280	61.8
• Hyperlipidemia	795	38.4
• DM	753	36.4
• Previous MI	164	7.9
• Prior stroke / TIA	152	7.3
• Malignancy	88	4.2
• AF	56	2.7
• Smoking	127	1.3
• Autoimmune disease	122	1.1
• Thrombophilia	8	0.4

Variables	**PrEViSTA** n=334	**NEMESIS** **n=1316**	**MSIS** n=624	P value
Age (mean +/- SD)	70.9 (15.0)	73.9 (14.5)	64.5 (14.8)	<0.001
Sex: Female, n (%)	175 (52.4)	731 (55.5)	297 (47.6)	0.005
Hypertension, n (%)	263 (79.2)	703 (54.4)	373 (60.2)	<0.001
Atrial fibrillation, n (%)	54 (16.2)	286 (21.7)	52 (8.60)	<0.001
Diabetes, n (%)	59 (17.7)	228 (17.5)	187 (30.1)	<0.001
Current smoking	43 (12.9)	188 (16.7)	98 (15.6)	0.23
Hyperlipidemia, n (%)	77 (23.10)	NA	148 (24.0)	0.80
Alcohol consumption, n (%)	20 (6.0)	618 (57.6)	18 (2.9)	<0.001
Rheumatic heart disease, n (%)	NA	9 (0.7)	16 (2.6)	0.001
Other valvular heart disease, n (%)	NA	32 (2.5)	7 (1.1)	0.05
Transient ischemic attack, n (%)	18 (5.4)	399 (30.3)	49 (7.9)	<0.001
Previous myocardial infarction, n (%)	18 (5.4)	174 (13.4)	67 (10.7)	<0.001

Table 6. Treatment received

	n	%
• Intravitreal anti-VEGF injection	796	38.4
• Panretinal photocoagulation	550	26.6
• ASA	161	7.8
• Vitrectomy	134	6.5
• Clopidogrel	55	2.7
• Intravitreal steroid injection	46	2.2
• Other antiplatelet	32	1.5
• Heparin/LMWH	6	0.3

	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] **(predicted N 172 pts, Randomized 67)**	47/46	37/41
Jadad's score	5 **Early stopped trial**	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.

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;

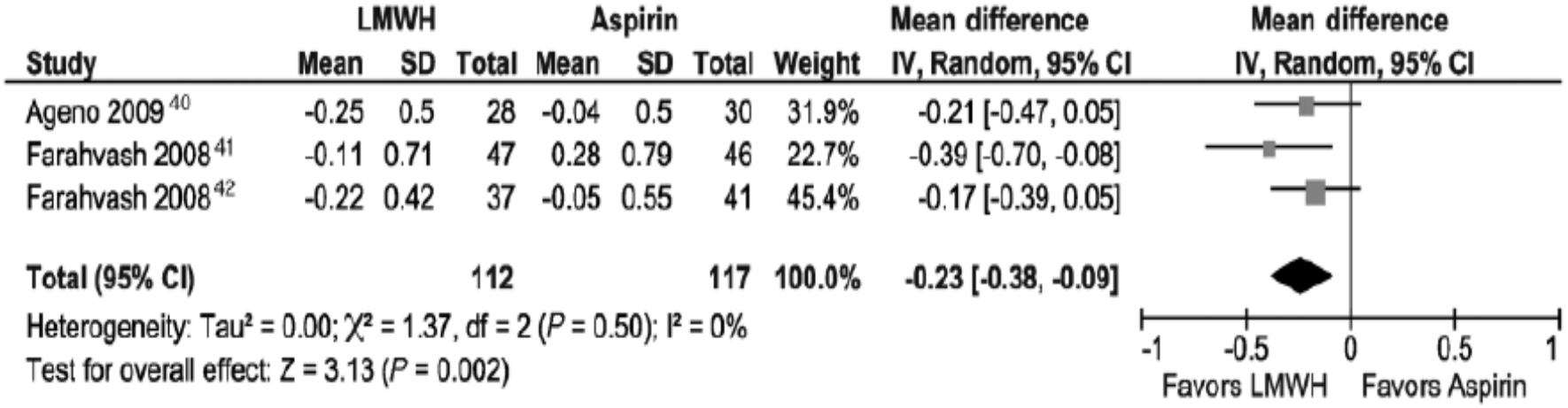


Figure 2. Forest plot of the mean difference in visual acuity expressed in the logarithm of the minimum angle of resolution (logMAR) scale in studies comparing low molecular weight heparin *versus* aspirin for the treatment of recent-onset retinal vein occlusion. LMWH low molecular weight heparin; SD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

- 664 RVO pts: 284 on ASA, 380 no ASA
  - ASA user showed significantly greater severity of fundus hemorrhage compared to non ASA user (p,0.001)
  - Pt with ischemic CRVO and hemi CRVO showed NO significant effect of ASA use on VA.
  - ASA use did not have a significant effect on time to resolution to macular edema.

  Ophthalmology 118 (8) (2011) 1603-1611
- 78 pts with BRVO: 37 dalteparin, 41 ASA (RCT)
  - No statistically significant differences were found regarding mean VA as well as resolution of macular edema at 1,2,3 and 6 months
- DOAC: no evidence available!

General recommendations for RVO workup

- **Risk factors for RVO include hypertension, dyslipidemia, diabetes and obstructive sleep apnea. Therefore, if those risk factors have not been diagnosed before, a full work up for all of these risk factors should be conducted when encountering a new diagnosis of RVO.**

- **Thrombophilia screening is not required in RVO, expect for antiphospholipid antibodies. This work up might only be reserved for patients < 50 years of age.**

- **Homocysteine quantification is controversial and there is no information on the effect of vitamin B12 and folic acid supplementation on the outcome of RVO.**

Treatment recommendations in RVO

- **No high-quality evidence exists to support routine use of antithrombotic drugs for RVP patients.**

- **Anticoagulation may be considered in patients with recent onset of symptoms (<15 days). No local risk factors such as glaucoma, and no contraindications.**

- **If anticoagulation is considered LMWH is preferred using full doses for 10-15 days, followed by half dose for a total of 90 days.**

- **ASA may be prescribed indefinitely to patients with coexisting cardiovascular conditions.**

- **Long term anticoagulation may be considered for patients with persistently positive antiphospholipid antibodies. The optimal agent is unknown but warfarin may be used.**

- **Experience with direct oral anticoagulants such as apixaban, rivaroxaban and dabigatran is lacking.**

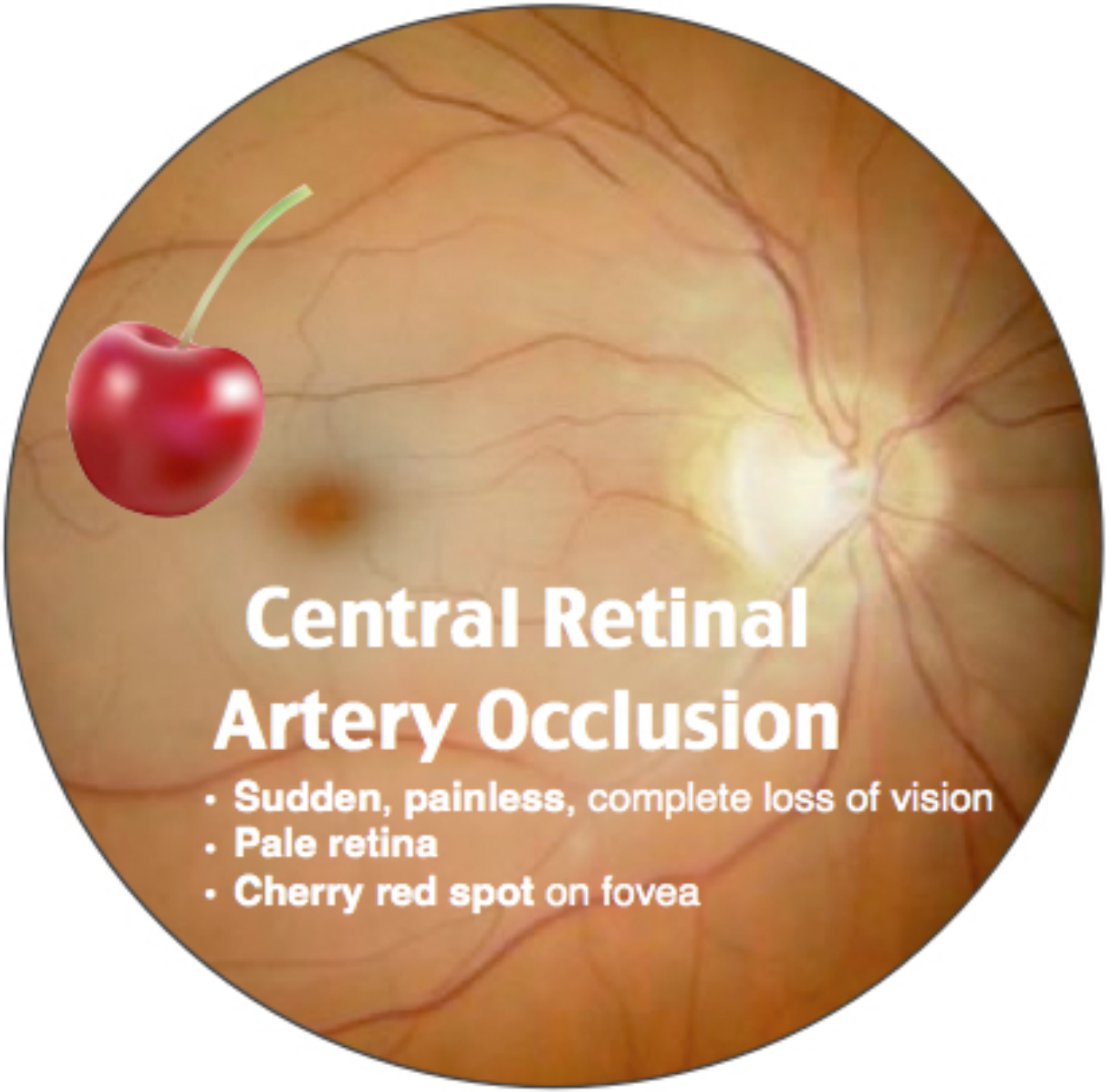
The LIRIC study:

a feasibility randomized controlled study of

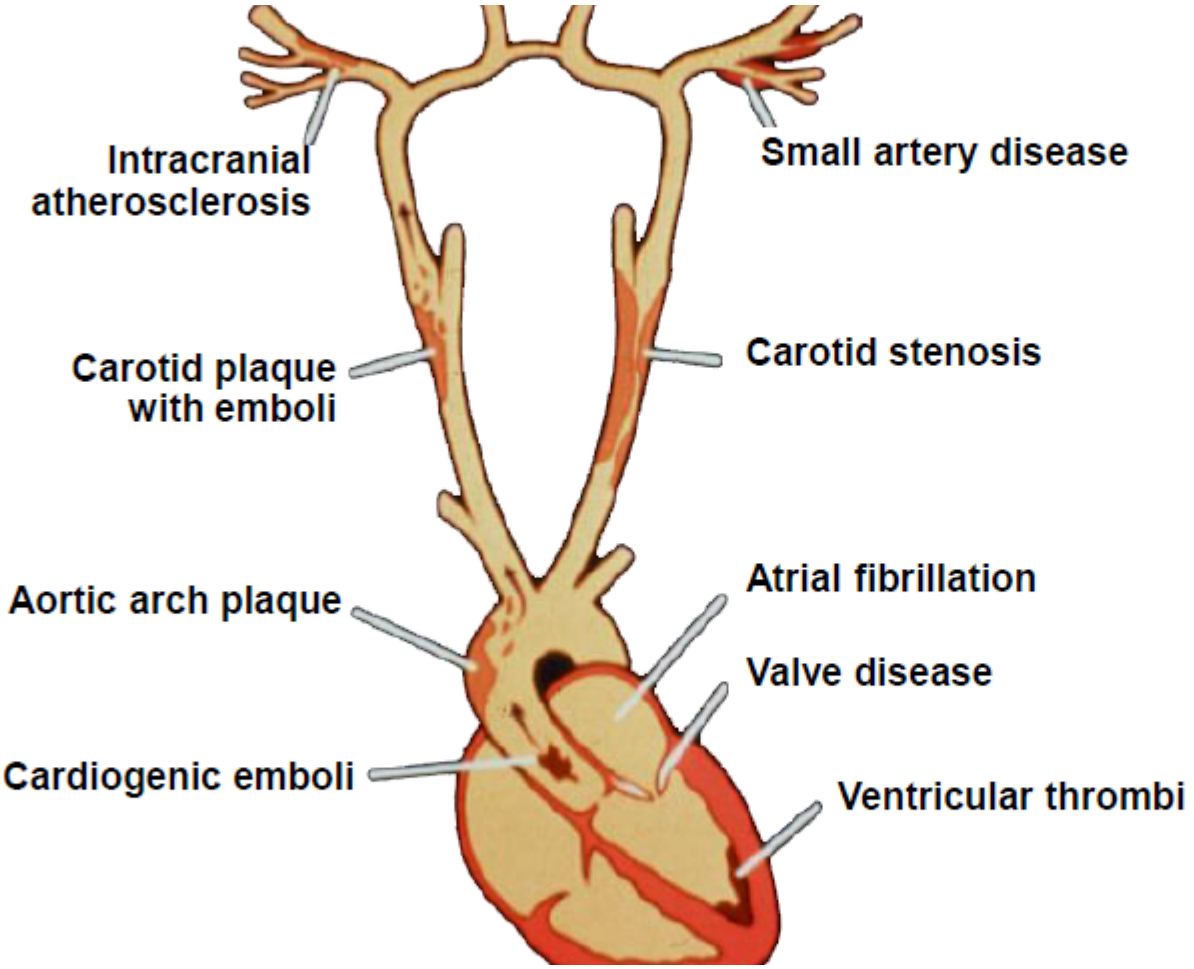
Low molecular weIght heparin versus usual

care in Retinal veIn oCclusion

- An opened labelled RCT study
- 40 patients (1:1 randomization)
- Newly dx of RVO pts within 3 weeks
  - LMWH (Enoxaparin) at 1 mg/kg subcutaneously q 12 hours for the first 7 days followed by 1 mg/kg OD until completing 12 weeks
  - Usual care
- Feasibility outcomes:
  - recruitment rate
  - proportion of patients with timely enrollment and complete follow up
  - rate of protocol adherence


Central Retinal Artery Occlusion
• Sudden, painless, complete loss of vision
• Pale retina
• Cherry red spot on fovea

Thrombosis or thromboembolism, primary or secondary, is involved in most mechanisms of ischemic stroke



Recurrent strokes 25-30% of all preventable strokes, frequently ischemic, more disabling, fatal and costly than first stroke

IV thrombolysis Rx in CRAO

Table 2. Characteristics of CRAO Cohorts

Characteristic	Cohort			Time to Treatment, h			
	Natural History (n = 396)	Conservative Treatment (n = 419)	Total Fibrinolysis (n = 147)	0 to 4.5 (n = 34)	>4.5 to 12.0 (n = 48)	>12.0 to 24.0 (n = 33)	>24.0 (n = 34)
Female sex, No. (%)	170 (42.9)	134 (32.0)	60 (40.8)	4 (11.8)	29 (60.4)	13 (39.4)	19 (55.9)
Age, mean (SD), y	57.2 (13.0)	65.2 (14.3)	62.8 (12.2)	59.6 (14.4)	64.5 (11.8)	62.3 (12.4)	64.2 (11.8)
VA of LP or less (at first evaluation), No. (%)	174 (43.9)	88 (21.0)	56 (38.1)	11 (32.4)	18 (37.5)	19 (57.6)	9 (26.5)
Agent used, No. (%)							
Urokinase	NA	NA	41 (27.9)	4 (11.8)	10 (20.8)	10 (30.3)	19 (55.9)
Streptokinase	NA	NA	69 (46.9)	17 (50.0)	15 (31.2)	22 (66.7)	15 (44.1)
tPA	NA	NA	37 (25.2)	13 (38.2)	23 (47.9)	1 (3.0)	0
VA, mean (SD)[a]							
Starting	NA	NA	12.1 (1.1)	12.0 (0.9)	12.1 (1.0)	12.4 (1.1)	11.7 (1.0)
Final	NA	NA	9.0 (4.3)	7.4 (4.4)	9.2 (3.9)	9.8 (4.3)	9.2 (4.3)
VA recovered to at least 20/100, No. (%)	70 (17.7)	31 (7.4)	47 (32.0)	17 (50.0)	13 (27.1)	8 (24.2)	9 (26.7)

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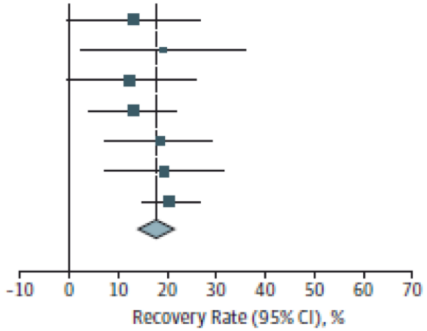
Figure 1. Forest Plot for Estimated Rate of Spontaneous Visual Recovery

A Natural history

Source	Recovery Rate (95% CI), %	Weight, %
Minton,[24] 1937	13 (-1 to 27)	7.31
Henkes,[25] 1954	19 (2 to 36)	4.90
Ellis et al,[26] 1964	13 (-1 to 26)	7.90
Imamura,[27] 1968	13 (4 to 23)	17.24
Karjalainen,[28] 1971	18 (8 to 29)	11.77
Küchle and Richard,[29] 1979	19 (7 to 32)	9.33
Hayreh and Zimmerman,[30] 2005	21 (15 to 26)	41.55
Summary statistics	17.7 (13.9 to 21.4)	

$Q = 4.3$; $P = .75$; $I^2 = 0\%$ (95% CI, 0%-67.6%)

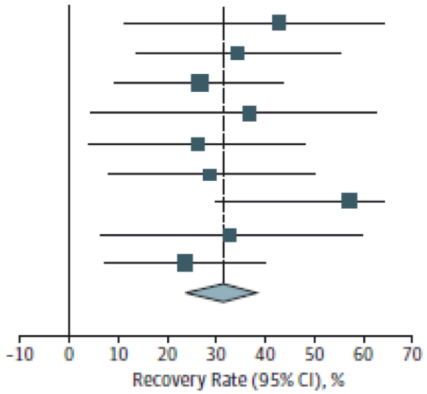


B Systemic fibrinolysis

Source	Recovery Rate (95% CI), %	Weight, %
Rossmann,[40] 1966	44 (12 to 76)	5.33
Sautter and Rossmann,[41] 1971	35 (14 to 56)	12.67
Boljka et al,[42] 1984	27 (10 to 44)	19.17
Kamel et al,[44] 1985	38 (3 to 71)	4.96
Yotsukura and Adachi-Usami,[45] 1993	27 (4 to 49)	11.16
Hagimura et al,[46] 1994	29 (8 to 51)	11.99
Rumelt et al,[43] 1999	58 (30 to 86)	7.20
Kattah et al,[38] 2002	33 (6 to 60)	7.62
Hattenbach et al,[39] 2008	24 (7 to 41)	19.89
Summary statistics	31.8 (24.3 to 39.3)	

$P < .001$ vs natural history

$Q = 5.6$; $P = .69$; $I^2 = 0\%$ (95% CI, 0%-64.8%)

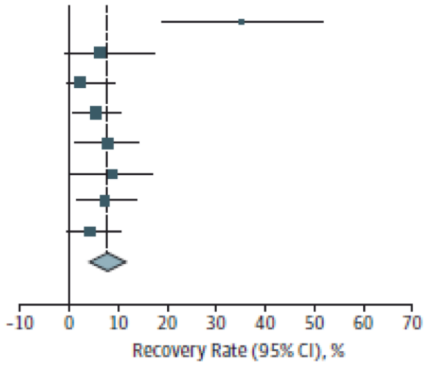


C Conservative treatment

Source	Recovery Rate (95% CI), %	Weight, %
Augsburger and Magargal,[31] 1980	35 (19 to 51)	4.48
Duker et al,[32] 1991	7 (-4 to 18)	7.78
Schmidt et al,[33] 1992	2 (-4 to 9)	14.10
Atebara et al,[34] 1995	6 (1 to 17)	17.81
Neubauer et al,[35] 2000	8 (1 to 14)	14.32
Framme et al,[36] 2001	9 (1 to 17)	11.20
Mueller et al,[7] 2003	8 (2 to 14)	15.35
Ahn et al,[37] 2013	5 (-2 to 9)	14.95
Summary statistics	7.4 (3.7 to 11.1)	

$P < .001$ vs natural history

$Q = 15.0$; $P = .04$; $I^2 = 52.3\%$ (95% CI, 0%-79.0%)



. Effect of Fibrinolysis by Time to Administration

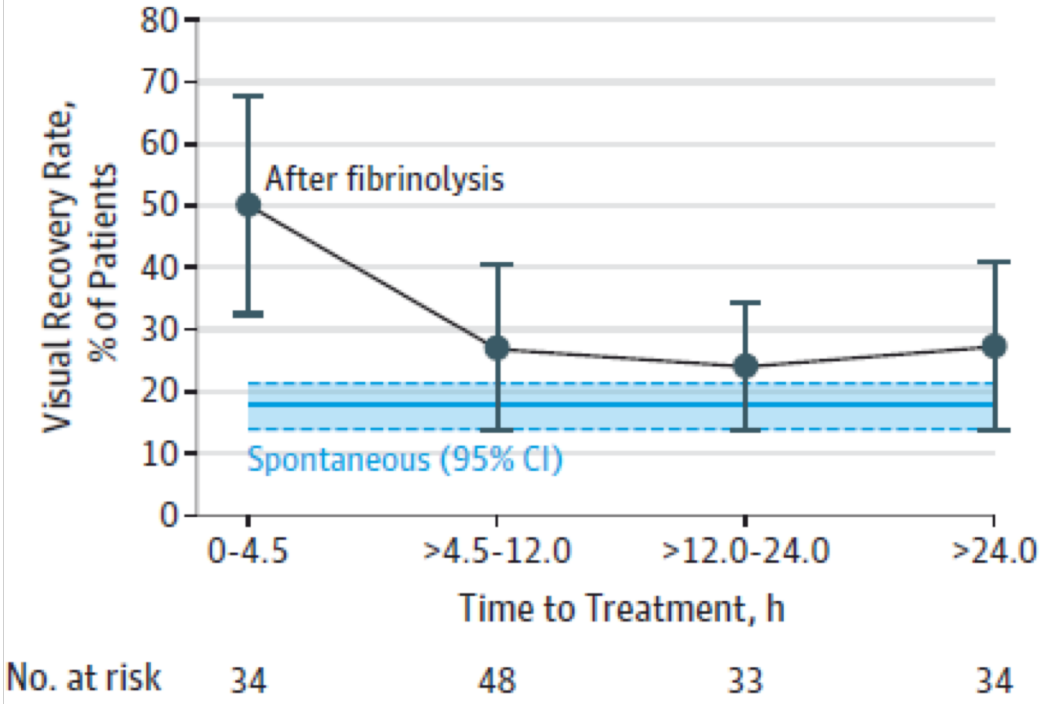


Table 1 Published studies investigating outcome of intra-arterial thrombolysis for central retinal artery occlusion (CRAO)

IA tPA

Authors, year	No. of patients	Study type	Fibrinolytic agent	Time to treatment	Pretreatment VA	Post-treatment VA	Angiographically confirmed?	Comments
Annonier *et al*, 1984,[28] 1988[29]	2, 5	Case series	Urokinase	NA	NA	NA	NA	1988 study is the continuation of the 1984 study
Mach *et al*, 1992[30]	1	Case report	Urokinase	NA	NA	NA	NA	Czech
Schumacher *et al*, 1991,[16] 1993[18]	6, 23	Cohort	Urokinase (n = 18)	4 h to 2.5 days	20/200 or worse in 100% (23/23)	Marked or total improvement in 26% (6/23) Partial improvement in 48% (11/23)		1993 paper is the continuation of the 1991 and 1992 study
Schmidt *et al*, 1992[17]	14		rtPA (n = 5)			Poor results in 26% (6/23)		
Brassel, 1993[31]	NA	Review	NA	NA	NA	NA	NA	
Turner *et al*, 1993[32]	NA	Animal study	NA	NA	NA	NA	NA	German
Van Cauwenberge, 1993[33]	NA	Review	NA	NA	NA	NA	NA	French
Vulpius *et al*, 1996[34]	9	Case series	rtPA	10–37 h	HM in 33% (3/9)	12/20 in 33% (3/9) Improvement in visual acuity in 63% (5/8)	NA	German
Ma *et al*, 1996[35]	4	NA	Urokinase	NA	NA	NA	NA	Chinese
Weber *et al*, 1998[20]	17	Cohort	Urokinase	4.2 h (range: 1–6 h)	20/250 or worse	20/30 or better in 29% (5/17) vs 0% (10/15) in control group, p = 0.01 Some improvement in 35% (6/17) No change in 35% (6/17) vs 67% (10/15), p = 0.01	No	
Weill *et al*, 1998[21]	7	Case series	Urokinase	12.5 h (range: 9–20)	LP in 57% (4/7) HM in 29% (2/7) 4/10 P2 in 14% (1/7)	20/20 in 43% (3/7) >20/40 in 28% (2/7) No change in 29% (2/7)	NA	French
Wirostko *et al*, 1998[36]	1	Case report	Urokinase	4 h	CF	20/20	No	
Hattenbach, 1998[37]	NA	Review	NA	NA	NA	NA	NA	German
Richard *et al*, 1999[22]	53 (46 CRAO, 7 BRAO)	Case series	rtPA	14 h (range: 3–50 h)	HM, FC, some LP or no LP in 70% (37/53)	Overall improvement in 66% (35/53), p<0.0001 Improvement of more than two lines in 47% (25/53) Improvement of one to two lines in 19% (10/53) 9% (4/46) achieved 20/20 or better 20% (9/43) achieved 20/40 or better 41% (19/43) achieved 20/400 or better	Yes	
Padolecchia *et al*, 1999[38]	3	Case series	rtPA	Unknown	Unknown	All patients showed a visual improvement	Unknown	
Framme *et al*, 2001[39]	17	Comparative study	Urokinase (n = 7), rtPA (n = 10)	<8 h	Uknown	Improvement of more than two lines in 24% (4/17) vs 36% (16/45) in the control group No change in 71% (12/17) vs 64% (29/45) Decline of more than two lines in 6% (1/17) vs 0% (0/45)	Unknown	German
Korner-Stiefbold, 2001[40]	NA	Review	NA	NA	NA	NA	NA	German
Kattah *et al*, 2002[15]	12	Case series	rtPA	5.75 h	HM in 67% (8/12) LP in 25% (3/12) FC in 8% (1/12)	20/25 to 20/800 in 83% (10/12) No change in 8% (1/12) Decline in 8% (1/12)	No	Did not use intra-arterial thrombolysis but intravenous tPA

Continued

IA tPA

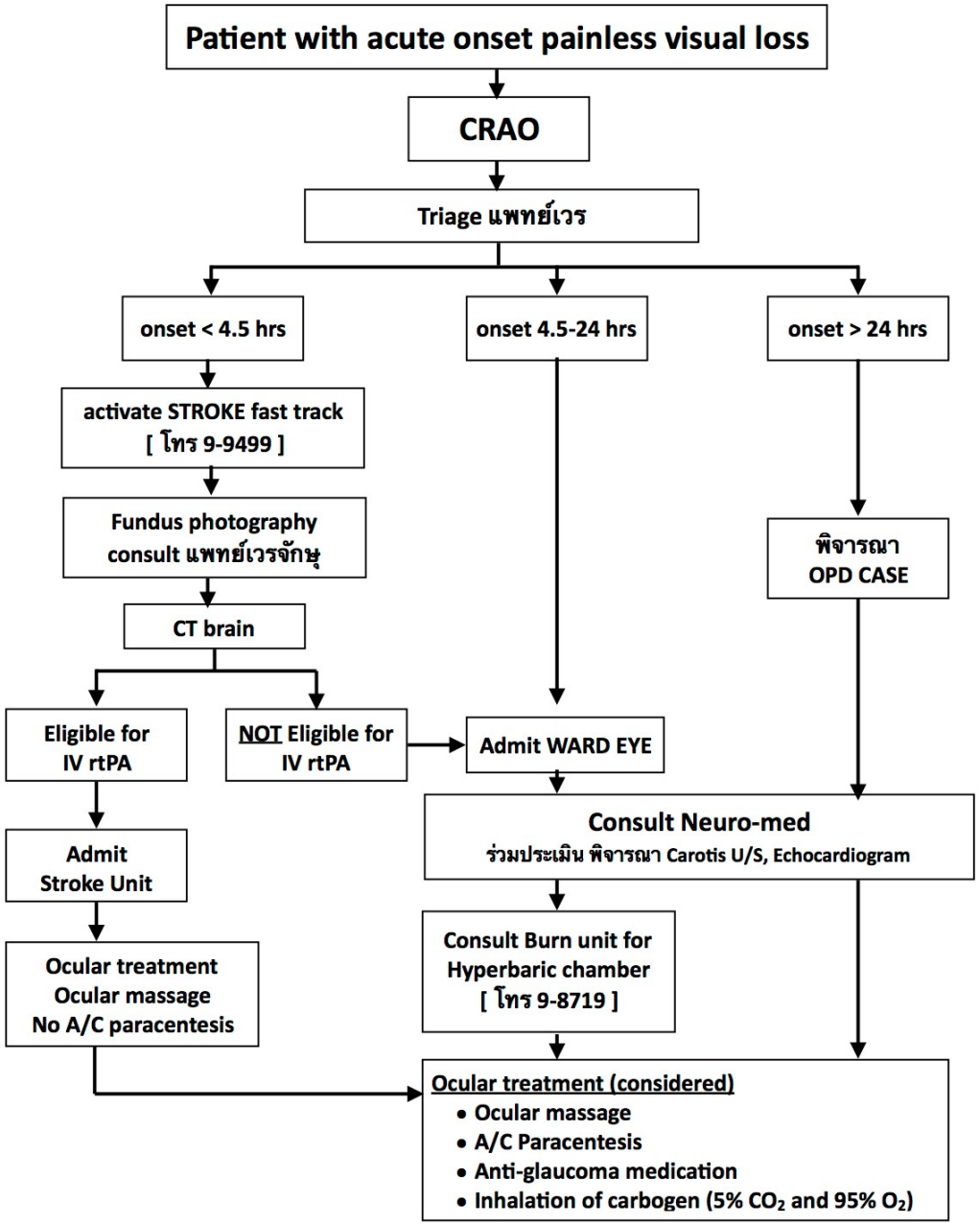
Table 1 Continued

Authors, year	No. of patients	Study type	Fibrinolytic agent	Time to treatment	Pretreatment VA	Post-treatment VA	Angiographically confirmed?	Comments
Schmidt *et al*, 2002[11]	62	Cohort	Urokinase or rtPA	9 h	Diminished, highly reduced, or no LP	Overall improvement in 58% (36/62) vs 29% (34/116) in the control group ($p = 0.0022$) Distinct or partial improvement in 80% (8/10) with incomplete CRAO vs 66% (19/29) in the control group, 51% (24/47) with subtotal CRAO vs 18% (15/83) in the control group, 80% (4/5) with total CRAO vs 0% (0/4) in the control group No change or deterioration in 20% (2/10) with incomplete CRAO vs 34% (10/29) in the control group, 49% (23/47) with subtotal CRAO vs 82% (68/83) in the control group, 20% (1/5) with total CRAO vs 100% (4/4) in the control group	Yes	Continuation of data from Schumacher *et al*, 1991,[16] 1993[18] and Schmidt *et al*, 1992[17]
Fernandez *et al*, 2002[41]	5	Case series	Urokinase	11 h	NA	5/5 (100%) showed improvement in perfusion of retinal arteries 4/5 (80%) showed improvement in VA	NA	Spanish
Butz *et al*, 2003[23]	22	Case series	Urokinase (n = 7), rtPA (n = 15)	7.6 h (1.8) h	HM or worse in 77% (17/22)	20/20 in 5% (1/22) HM to 20/32 in 36% (8/22) No change in 59% (13/22)	No	
Diaconu *et al*, 2004[42]	1	Case report	NA	NA	NA	NA	NA	Romanian
Arnold *et al*, 2005[12]	37	Case-control study	Urokinase	4 h	<0.01 in 57% (21/37) 0.01 to 0.05 in 43% (16/37) >0.05 in 0% (0/37)	>0.6 logMAR in 22% (8/37) vs 0% (0/19) in the control group, $p = 0.04$	No	
Plant and Landau, 2005[43]	NA	Editorial commentary	NA	NA	NA	NA	NA	
Pettersen *et al*, 2005[24]	6	Case series	rtPA			Improvement by two or more lines in 50% (3/6) Improvement by one line in 50% (3/6) 20/300 or better achieved in 0% (0/6)		

CRAO, central retinal artery occlusion; FC, finger counting; HM, hand movements; LP, light perception; rtPA, recombinant tissue plasminogen activator; VA, visual acuity.

CRAO algorithm treatment

Department of Ophthalmology, Siriraj hospital



conclusion

- WHY CRAO/ CRVO?
- What evidence do we have?
- How do we treat?
  - What is our current practice?
  - Is our best good enough?
- How can we make a different?
  - Eye Stroke Initiative
  - The LIRIC Study