Oral anticoagulation and new antiplatelet therapy in acute and chronic cerebral ischemia

Pr. Didier Leys

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Outline

- **Background**
- **Acute stage of cerebral ischaemia**
  - What is proven effective ?
  - Antiplatelet agents
  - Heparin and heparinoids
- **Secondary prevention after cerebral ischaemia**
  - What is proven effective ?
  - Antiplatelet agents
  - Oral anticoagulant
- **Specific issues**
  - Dissections
  - Prevention of DVT and PE
  - Cerebral haemorrhage under anticoagulants / antiplatelet therapy
  - Cerebral ischaemia under anticoagulants / antiplatelet therapy
- **Conclusions**

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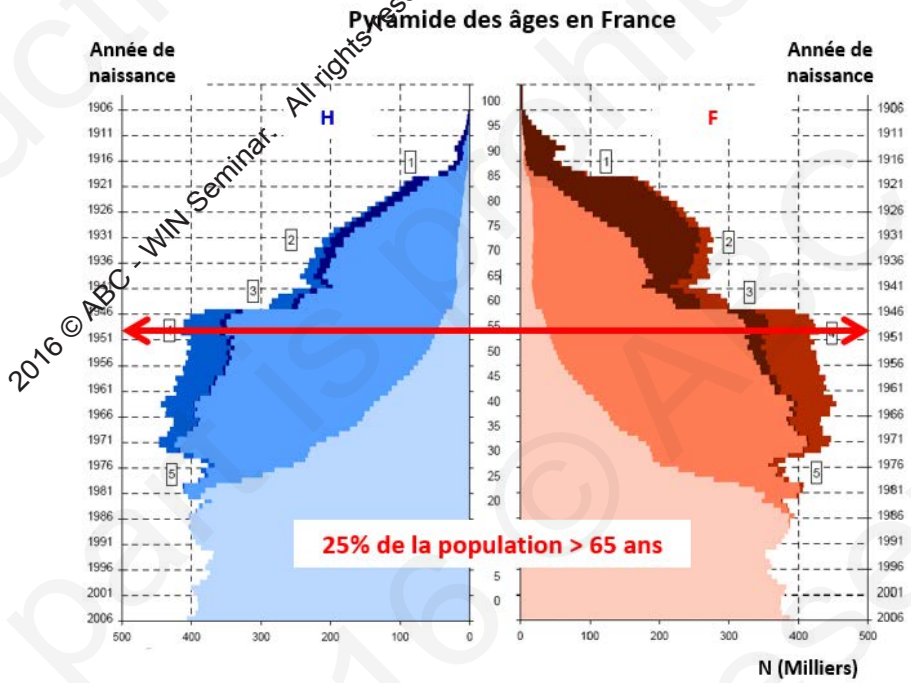
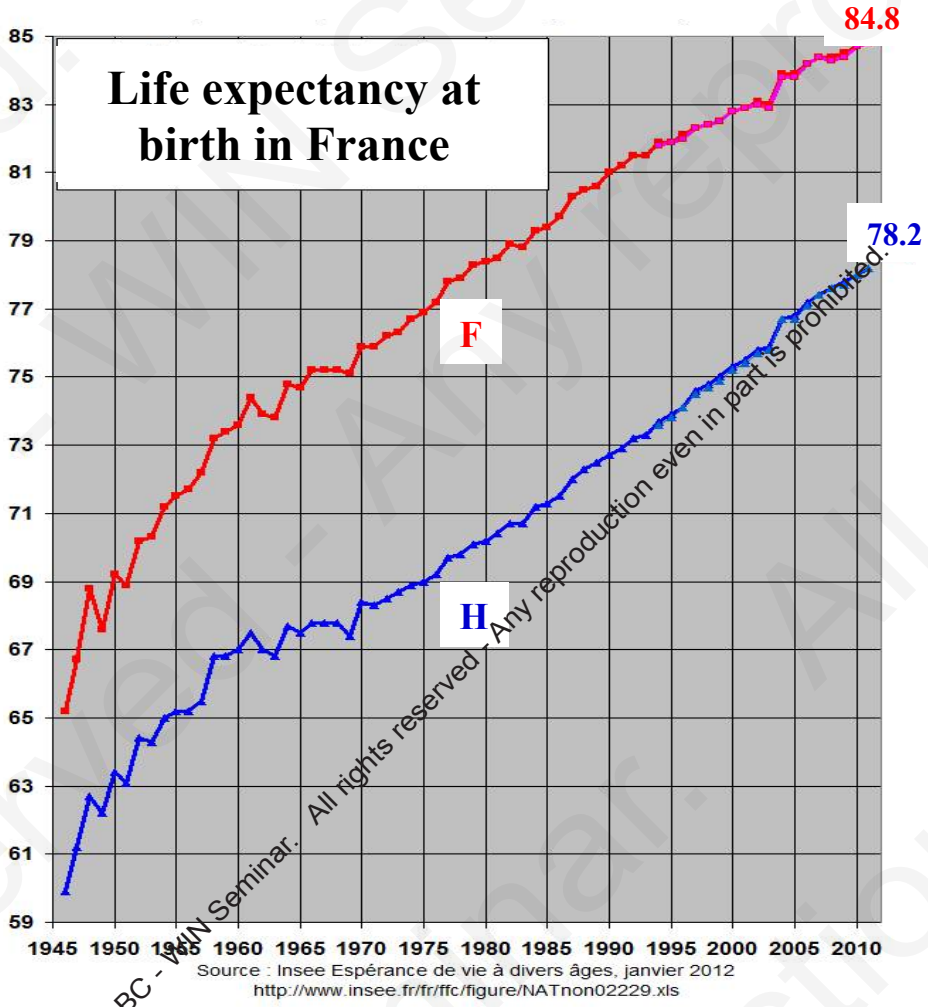
Stroke : a public health issue

- 2400 / million inhabitants / year
- 80-85% ischaemic
- 50% preventable
- Treatable in case of hyperacute management





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Effective therapies in acute cerebral ischaemia

	Level of evidence	Death and handicap prevented for 1,000 patients treated	Target	Death and handicap prevented for 1,000,000 inhabitants
Stroke unit	Several RCTs and meta-analysis	50 (mRS 0-1)	100%	120
Aspirin	Several RCTs and meta-analysis	12 (mRS 0-1)	80%	23
rt-PA < 3 h	Several RCTs and meta-analysis	143 (mRS 0-1)	20%	69
rt-PA 3-4.5h	Several RCTs and meta-analysis	71 (mRS 0-1)	10%	7
Interventional radiology	5** (+1) positive RCTs and meta-analysis of 8* trials	125* to 200** (mRS 0-2)	15%	19 to 30
Hemicraniectomy	Meta-analysis	250 (mRS 0-3)	1%	2 to 3

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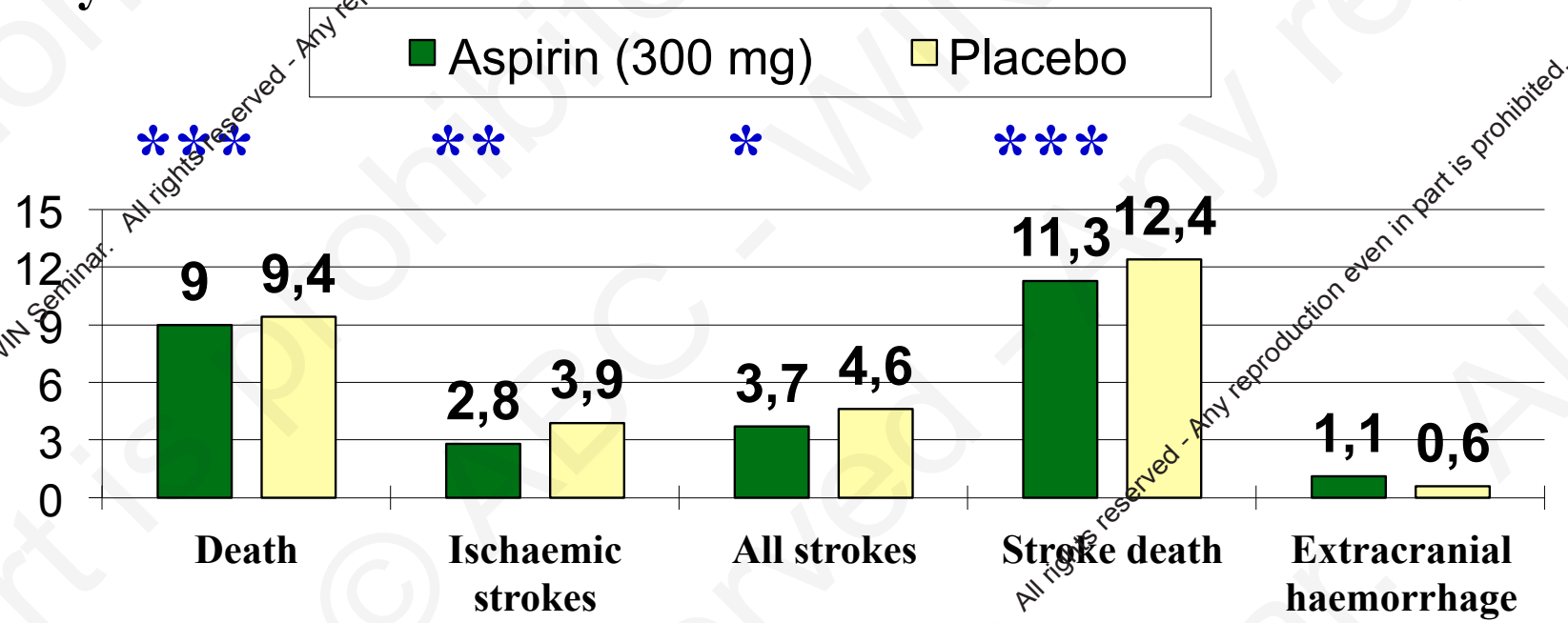
Aspirin

Day 14



IST group, Lancet 1997

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Aspirin vs control

N = 41.325 patients, 8 trials
Aspirin 160 to 300 mg, started < 48h
NEP: number of events prevented

	OR (IC 95%)	NEP / 1000
Under treatment		
- Recurrence of brain ischaemia	0.77 (0.69 – 0.87)	7
- Intracranial haemorrhage	1.23 (1.00 – 1.50)	- 2
- Extracranial haemorrhage	1.68 (1.34 – 2.09)	- 4
- *Deep venous thrombosis*	*0.78 (0.36 – 1.67)*	-
- *Pulmonary embolism*	*0.71 (0.53 – 0.96)*	*1*
End of follow-up (>1 months)		
- Death or dependency	0.94 (0.91 – 0.98)	13
- Complete recovery	1.06 (1.01 – 1.11)	10

Meta-analysis: The Cochrane Library 2004

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FASTER

- N = 392, TIA or minor stroke, < 24h
- Clopidogrel (300 mg then 75mg) or Placebo on top of aspirin
- Prematurely stopped for low inclusion rate
- Stroke at 90 days
  - Clopidogrel 7.1% vs 10.8% RR = 0.7 (0.3 – 1.2)

Kennedy et al, Lancet Neurol 2007

Other antiplatelet agents

- **Ticagrelor tested in SOCRATES**[1]:
  - evaluates whether ticagrelor, (antiplatelet agent that blocks the P2Y12 receptor) reduces the risk of major vascular events compared with aspirin when given within 24 h after symptom onset of a mild ischemic stroke or high-risk transient ischemic attack.

[1]Johnston et al 2015.

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Heparin

- **Potential benefits**
  - Decreases risk of thrombus extension
  - Prevents recurrence of embolic events
  - Prevents DVT and PE
- **Potential risks**
  - Symptomatic intra-cranial haemorrhage
  - Severe extra-cranial haemorrhage
  - Thrombocytopenia

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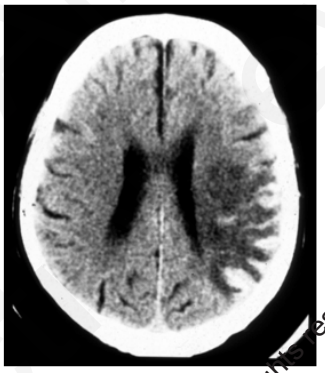
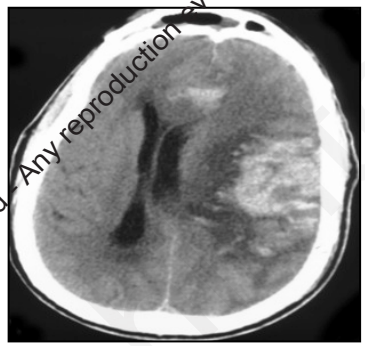
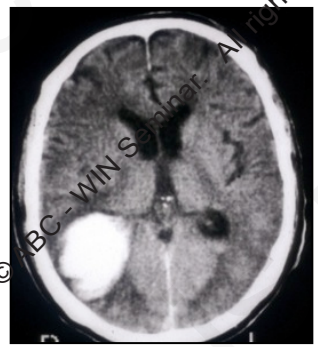
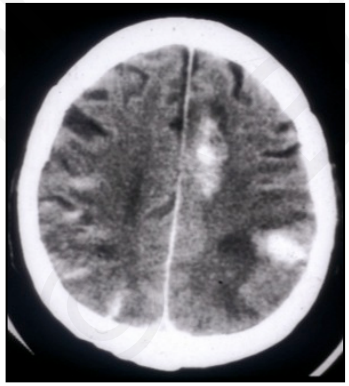
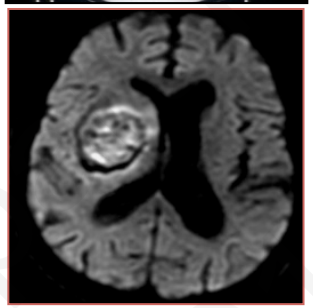
Haemorrhagic transformation











Predictors of HT

- Volume of infarct
- Clinical severity
- Brain oedema
- Early ischaemic signs
- Age
- High Blood pressure
- Cardio-embolic source
- On-going anticoagulant therapy
- Thrombolytic therapy
- Late recanalization

Haemorrhagic transformation

TABLE 1. Rates of HT Among Placebo Groups in Acute Stroke Trials of Intravenous Therapies

	DIAS (Low+High Dose)[22]	AbESTT-I[24]	CLOTBUST-II[73]	NINDS[2]	ECASS-II[25]	ECASS-I[26]	Atlantis-B[74]
Patients, n	27	199	63	312	386	305	275
Baseline, median NIHSSS	12	9	17	15	11	12	10
Time Period	2001–2003	2000–2002	2001–2004	1991–1994	1996–1998	1992–1994	1993–1998
Symptomatic ICH	0	1.0%	4.8%	0.6%	3.4%	6.8% PH	1.3%
Criteria for symptomatic ICH	NIHSSS*	PI†	NIHSSS‡	PI§	PI or NIHSSS¶	N/A	PI‖
Timing of CT	72 hours	36–48 hours	N/A	24 hours	7 days	7 days	10 days
Asymptomatic ICH	18.5%	14.1%	N/A	2.9%	36.8%	29.9% HI	4.7%

*Any ICH associated with a worsening of 4 points or more on the NIHSS and confirmed by CT.

†If neurological deterioration was found and if hemorrhage was detected on brain imaging Causal link required.

‡Hemorrhage with clinical worsening (indicated by an NIHSS score of ≥4) within 72 hours of the onset of stroke.

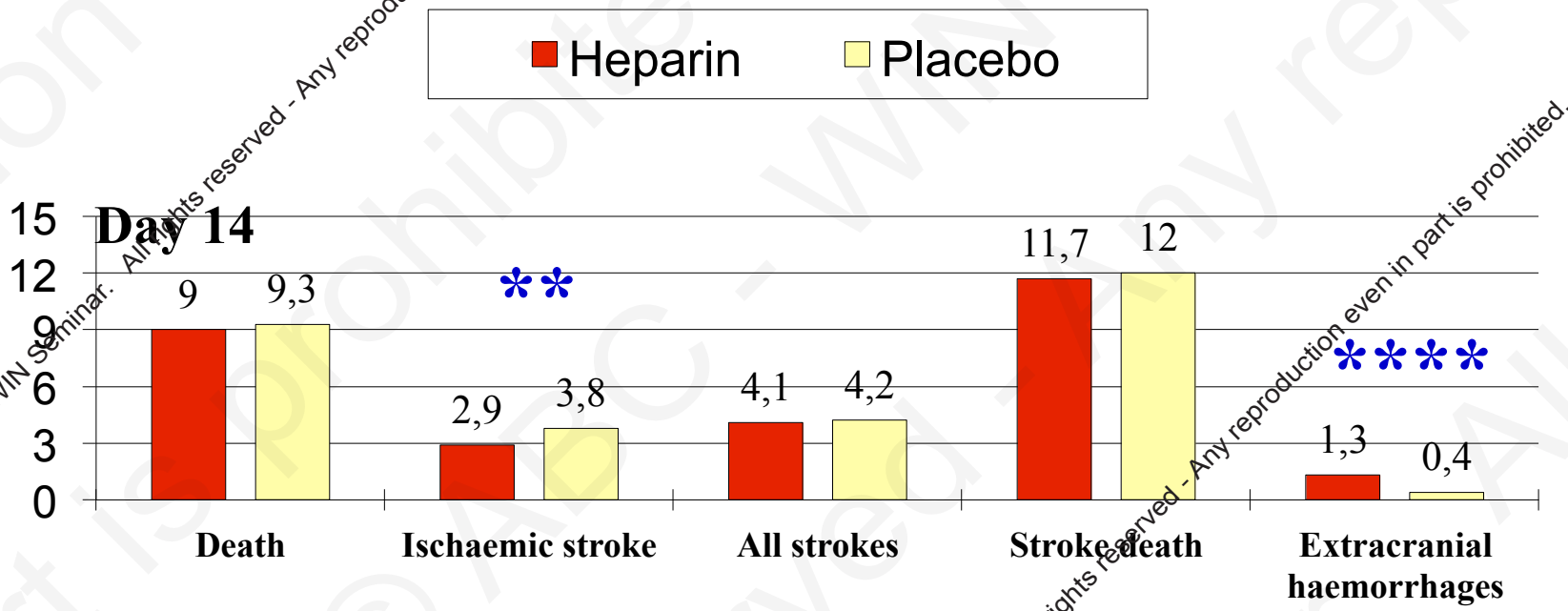
§If not seen on a previous CT scan and there had subsequently been either a suspicion of hemorrhage or any decline in neurological status.

¶Documentation by the investigator of clinical deterioration, or adverse events indicating clinical worsening (eg, drowsiness, increase in hemiparesis) or causing a decreased in the NIHSS score of 4 or more points.

‖Determined by the local investigator.

Khatri et am, Stroke 2007

Heparin



IST group, Lancet 1997

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Anticoagulants vs controls

N = 23.547 patients, 22 trials
Unfractionated heparin, LMWH, heparinoids, VKA, antithrombin.
Started within 14 days
NEP: number of events prevented

	OR (IC 95%)	NEP/ 1000
Under treatment		
- Recurrence brain ischaemia	0.76 (0.65 – 0.88)	9
- Intracranial haemorrhage	2.52 (1.92 – 3.30)	- 9
- Extracranial haemorrhage	2.99 (2.24 – 3.99)	- 9
- *Deep venous thrombosis*	*0.21 (0.15 – 0.29)*	*281*
- *Pulmonary embolism*	*0.60 (0.44 – 0.81)*	*4*
End of follow-up (> 1 month)		
- Death	1.05 (0.98 – 1.12)	-
- Death or dependency	0.99 (0.93 – 1.04)	

Meta-analysis: The Cochrane Library 2004

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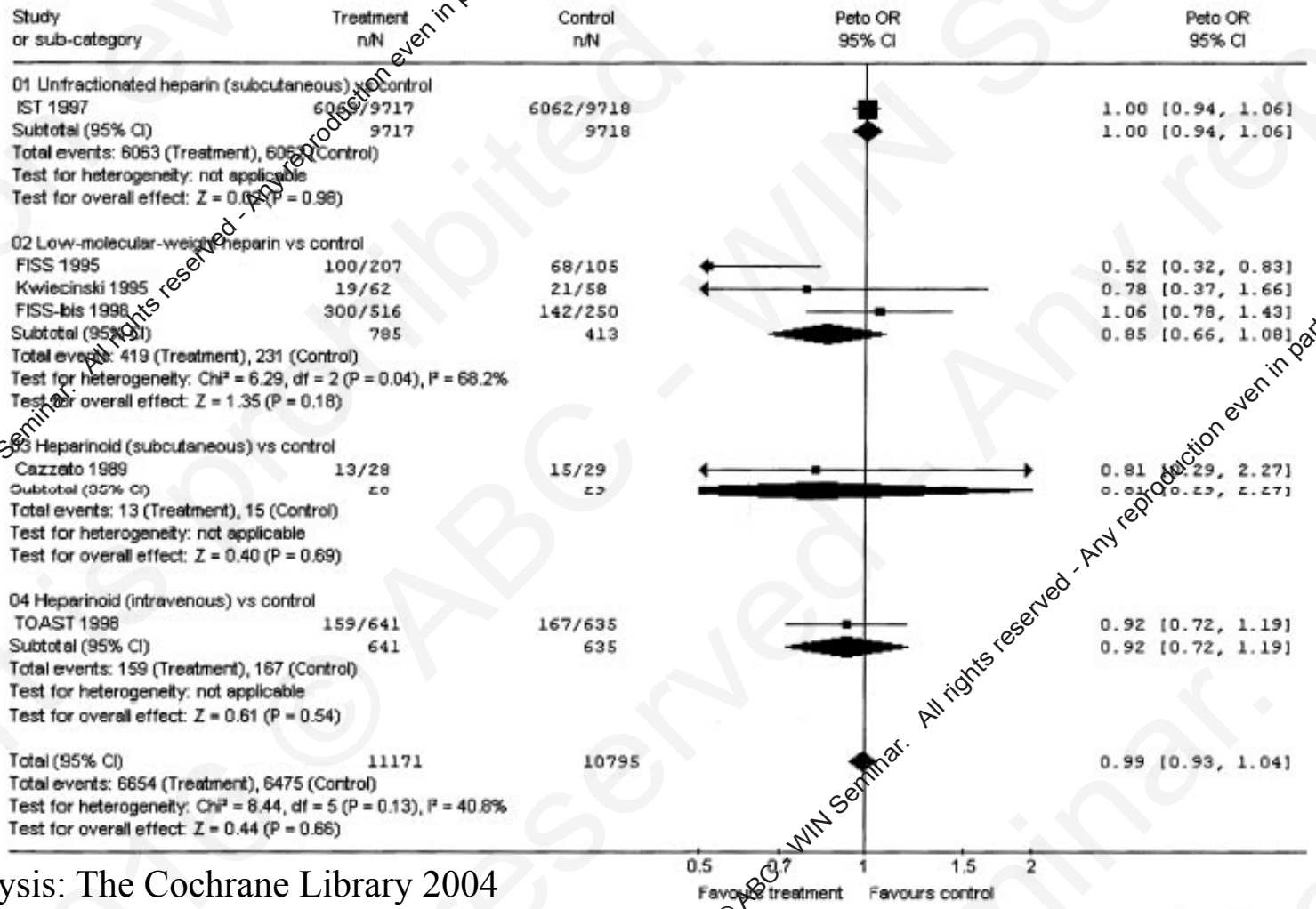
Anticoagulants vs controls



Meta-analysis: The Cochrane Library 2004

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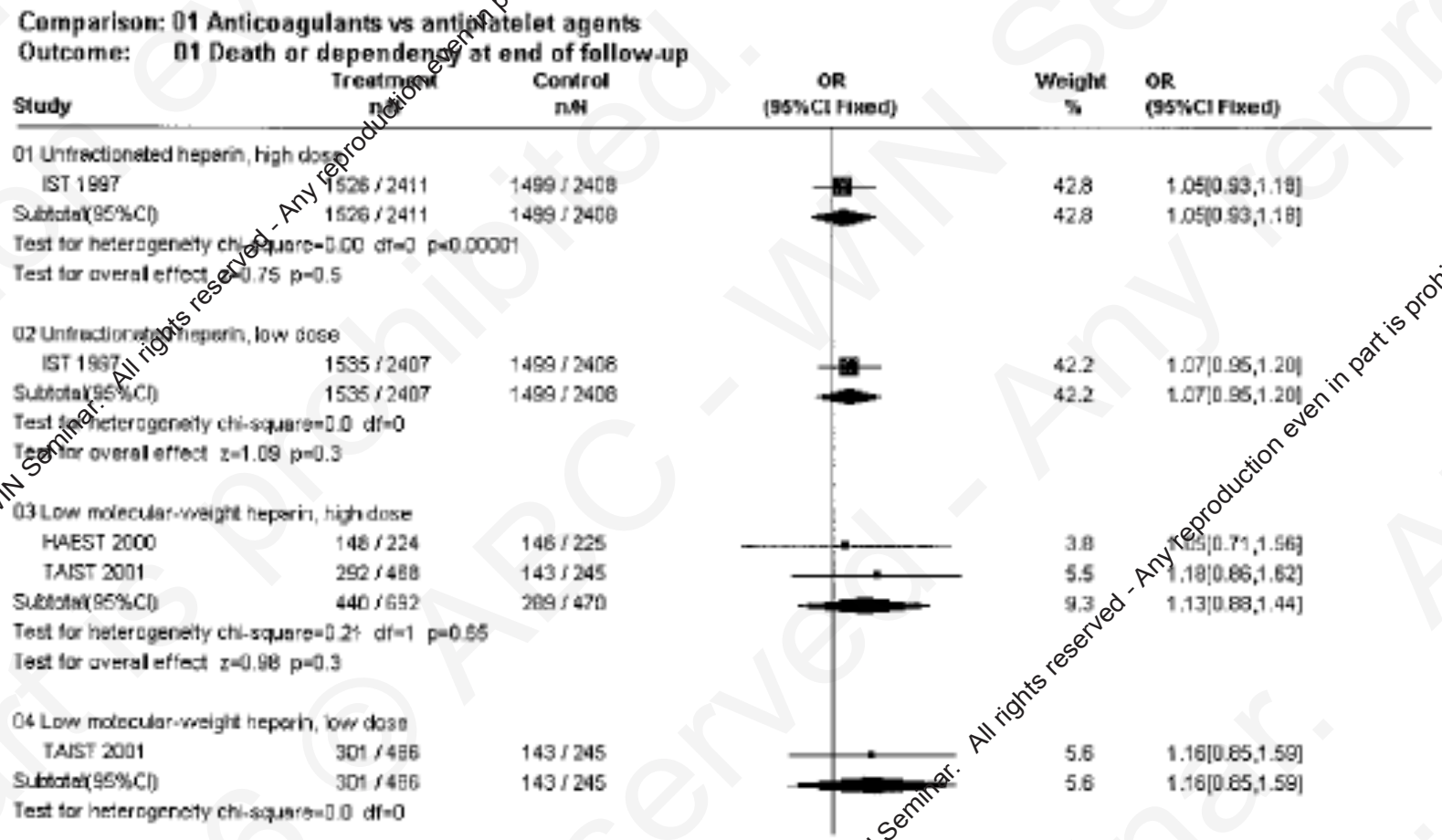
Anticoagulants vs. antiplatelets



Meta-analysis: The Cochrane Library 2004

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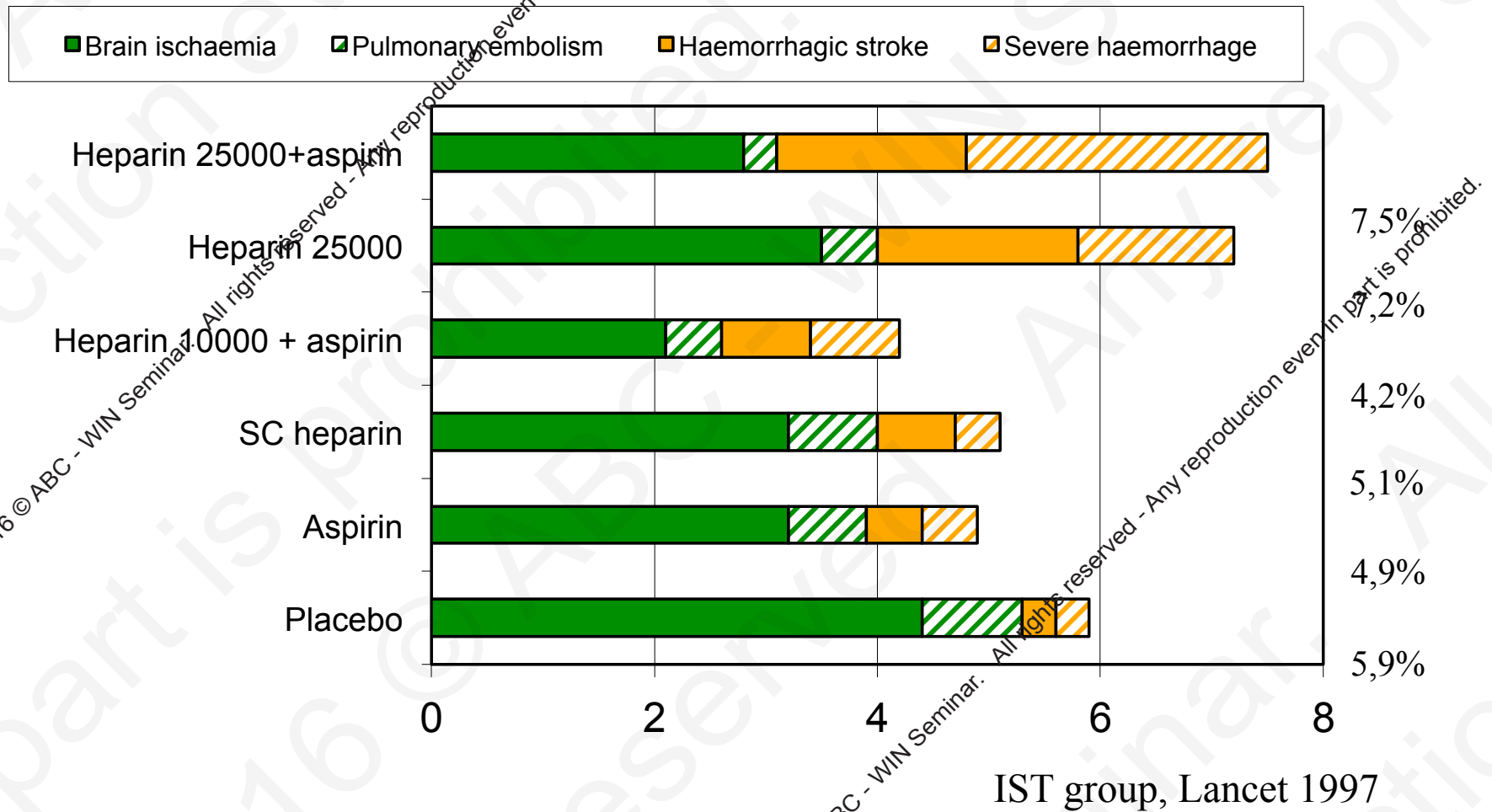
Association anticoagulant + antiplatelets



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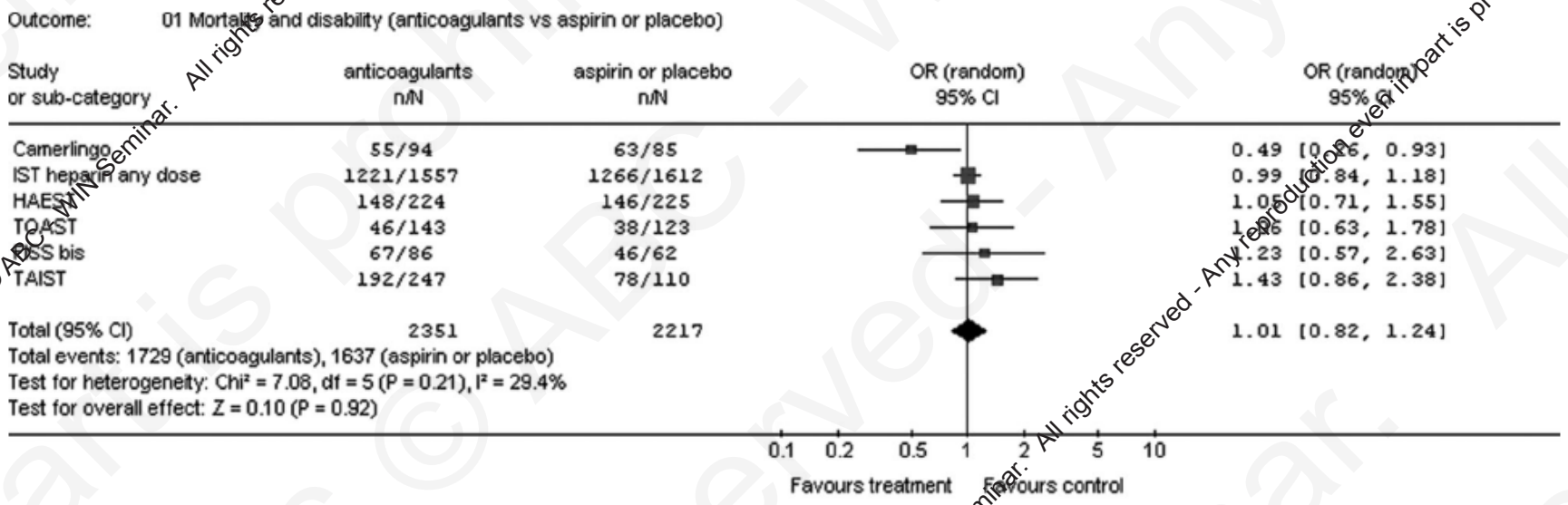
Cardio-embolic ischaemic stroke

7 trials, n = 4624 patients

Recurrent ischaemic stroke: 3% vs 4.9% , OR 0.68 (0.44 – 1.06), p = 0.09, NNT 53

Symptomatic intracanial haem : 2.5% vs 0.7%, OR 2.89 (1.19 – 7.01), p=0.02, NNH 55



Paciaroni et al, Stroke 2007

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ESO 2008

- It is recommended that aspirin (160–325 mg loading dose) be given within 48 h after ischaemic stroke (Class I, Level A)
- It is recommended that if thrombolytic therapy is planned or given, aspirin or other antithrombotic therapy should not be initiated within 24 h (Class IV, GCP)
- The use of other antiplatelet agents (single or combined) is not recommended in the setting of acute ischaemic stroke (Class III, Level C)
- The administration of glycoprotein-IIb-IIIa inhibitors is not recommended (Class I, Level A)
- Early administration of unfractionated heparin (UFH), low molecular weight heparin or heparinoids is not recommended for the treatment of patients with acute ischaemic stroke (Class I, Level A)

When to start OAC in cerebral ischaemia + atrial fibrillation ?

Recommendations	ESO 2008[1]	AHA/ASA 2006[2], ACCP 2008[3]
TIA or minor IS	Immediately	< 2 weeks
Large infarct	Wait 4 weeks	Extra delay (not detailed)

[1]Cerebrovasc Dis 2008;25:457–507; [2]Stroke 2006;37;577-617;
[3]Chest 2008

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Areas of certainty

Table 1. Strategies of Proven Benefit for Secondary Prevention of Stroke.*

Indication and Strategy	Key Trial or Meta-Analysis	
	Study	Results†
Routine‡		
Blood-pressure lowering	PROGRESS[11]: ACE inhibitor plus diuretic vs. placebo; primary end point: total strokes	RRR, 28.0%; ARR, 4.00 percentage points; NNT, 97
Cholesterol lowering (statin)	SPARCL[12]: statin vs. placebo; primary end point: first stroke	RRR, 16.0%; ARR, 2.20 percentage points; NNT, 220
Antiplatelet therapy (unless anticoagulation indicated)		
Aspirin (first-line therapy)	ATTC[13,14]: aspirin vs. placebo; primary end points: nonfatal stroke, nonfatal MI, and death from vascular causes	RRR, 13.0%; ARR, 1.00 percentage points; NNT, 100§
Clopidogrel	CAPRIE[15]: clopidogrel vs. aspirin; primary end points: ischemic stroke, MI, and death from vascular causes	RRR, 8.7%; ARR, 0.51 percentage points; NNT, 196
Aspirin plus dipyridamole	ESPS2[16]: aspirin plus dipyridamole vs. aspirin; primary end point: stroke	RRR, 23.8%; ARR, 2.97 percentage points; NNT, 74
Symptomatic high-grade stenosis: carotid endarterectomy	NASCET[17]: carotid endarterectomy plus medical treatment vs. medical treatment alone; primary end point: any ipsilateral ischemic stroke	RRR, 65.0%; ARR, [illegible] percentage points; NNT, 9
Atrial fibrillation		
Warfarin	EAFT[18]: warfarin vs. placebo; primary end point: all strokes	RRR, 66.0%; ARR, 8.0 percentage points; NNT, 12
Dabigatran	RE-LY[19]: dabigatran vs. warfarin; primary end points: stroke and systemic embolism	RRR, 34.0%; ARR, 0.58 percentage points; NNT, 172¶
Rivaroxaban	ROCKET AF[20]: rivaroxaban vs. warfarin; primary end points: stroke and systemic embolism	RRR, 13.0%; ARR, 0.30 percentage points; NNT, 333
Apixaban	ARISTOTLE[21]: apixaban vs. warfarin; primary end points: stroke and systemic embolism	RRR, 21.0%; ARR, 0.33 percentage points; NNT, 303

From Davis and Donnan, NEJM 2012

Areas of uncertainty

Table 2. Controversial or Investigational Secondary-Prevention Strategies.*

Target	Possible Strategy	Comments
Early recurrent stroke	Combined aspirin and clopidogrel for 90 days from stroke onset	Increased risk with combination therapy vs. aspirin or clopidogrel alone, but meta-analysis suggests possible benefit of combination therapy after a TIA or minor stroke[35]; POINT (NCT00991029): combination therapy vs. aspirin, ongoing
Carotid stenosis	Carotid-artery stenting	Higher risks of periprocedural stroke and death with stenting than with endarterectomy,[36-39] although risks similar with the two treatments among patients 70 years of age or younger[40]
Aortic-arch atheroma	Antiplatelet therapy vs. anticoagulation	Common cause of stroke; most effective treatment unknown; ARCH (NCT00235248)[41]: aspirin plus clopidogrel vs. warfarin, ongoing
Intracranial arterial stenosis	Intracranial stenting	Higher rates of stroke and death with intracranial stenting than with aggressive medical therapy in one trial (SAMMPRIS),[42] but other trials ongoing
Carotid dissection	Antiplatelet therapy vs. anticoagulation	Optimal treatment unclear; CADISS (NCT00238667): aspirin vs. warfarin, ongoing
Patent foramen ovale	Percutaneous closure device vs. medical therapy	No benefit observed with percutaneous closure in CLOSURE I[43]; other trials ongoing

From Davis and Donnan, NEJM 2012

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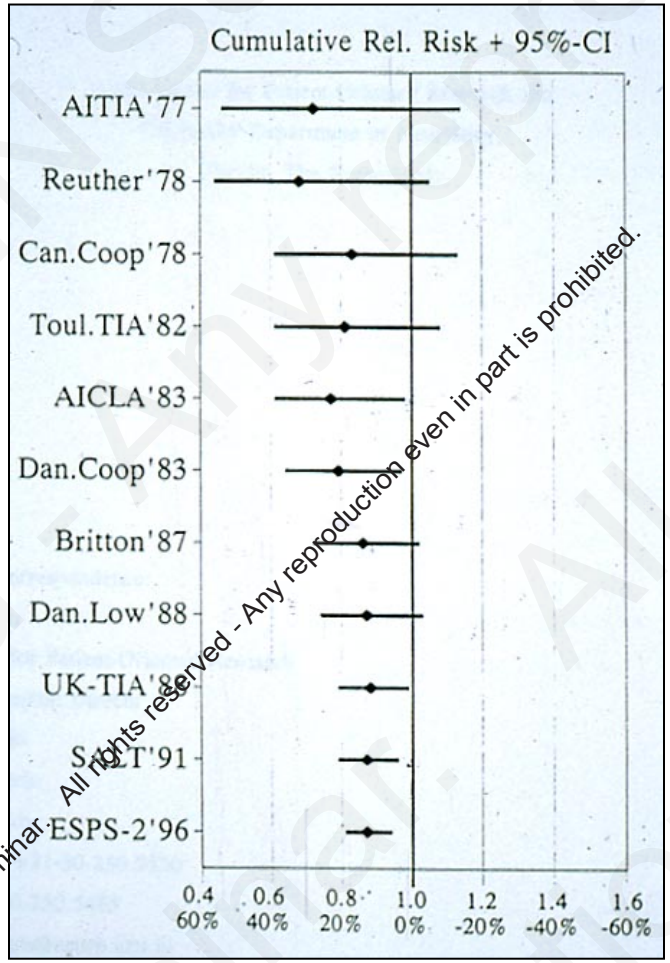
Aspirin

- 13% RRR for major ischemic events after non-selected TIA or ischemic stroke[1]
- Incidence of GI-bleedings: dose-dependent
- No difference of efficacy with the daily dose (< 160 mg / 160 – 325 / >500 mg)



[1]ATT collaboration, 2002; [2]Algra et al, 1996.

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Other antiplatelet agents

- **Clopidogrel**[1] and combination of **aspirin plus dipyridamole**[2] are superior to aspirin, but with very small absolute benefits.
- Comparison of **aspirin plus dipyridamole** with **clopidogrel** : similar outcomes in the two treatment groups. [3]
- No benefit, and increased hemorrhagic risks, with the combined use of clopidogrel and aspirin as compared with clopidogrel alone[4] or aspirin alone[5] for long-term secondary prevention after stroke.

[1]CAPRIE, 1996; [2]Algra et al, 2006; [3]Sacco et al, 2008; [4]Diener et al, 2004; [5]Bhatt et al, 2006.

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Oral anticoagulation

Vitamin K antagonists for secondary prevention in atrial fibrillation.

	N	Target INR	Strokes/patients (anticoagulation *vs* placebo or no treatment)	RRR (%)	ARR (% per year)
AFASAK[17]	671	2·8–4·2	9/335 *vs* 19/336	54	2·6
SPAF-I[18]	421	2·0–4·5	8/210 *vs* 19/211	60	4·7
BAATAF[19]	420	1·5–2·7	3/212 *vs* 13/208	78	2·4
CAFA[20]	378	2·0–3·0	6/187 *vs* 9/191	33	1·2
SPINAF[21]	571	1·4–2·8	7/281 *vs* 23/290	70	3·3
EAFT[22]*	439	2·5–4·0	20/225 *vs* 50/214	68	8
6 trials	2900		53/1450 *vs* 133/1450	64 (95% CI 49–74)	Primary prevention=2·7 Secondary prevention=8·4

*Secondary prevention study. INR=international normalised ratio. RRR=relative risk reduction. ARR=absolute risk reduction. AFASAK=Atrial Fibrillation, Aspirin, Anticoagulation trial. ARR=absolute risk reduction. SPAF=Stroke Prevention in Atrial Fibrillation trial. BAATAF=Boston Area Anticoagulation Trial for Atrial Fibrillation. CAFA=Canadian Atrial Fibrillation Anticoagulation trial. SPINAF=Stroke Prevention in Non-rheumatic Atrial Fibrillation trial. EAFT=European Atrial Fibrillation Trial. Adapted with permission from the American College of Physicians.[23]

Table 1: Adjusted-dose anticoagulation compared with placebo or no treatment

[1]EAFT, 1993

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Oral anticoagulation

- **Vitamin K antagonists for cardio-embolic stroke.**
  - VKAs are also more effective than aspirin alone or combination aspirin plus clopidogrel
  - Aspirin on top of VKAs does not provide any additional benefit and increases the bleeding risk

Antithrombotic agents

- **Vitamin K antagonists for non cardio-embolic stroke.**
  - VKAs are not more effective than aspirin to reduce the risk of recurrent stroke after non cardioembolic strokes and are associated with an increased bleeding risk. [1,2]

[1]Mohr et al, 2001; [2]SPIRIT, 1997

New oral anticoagulant

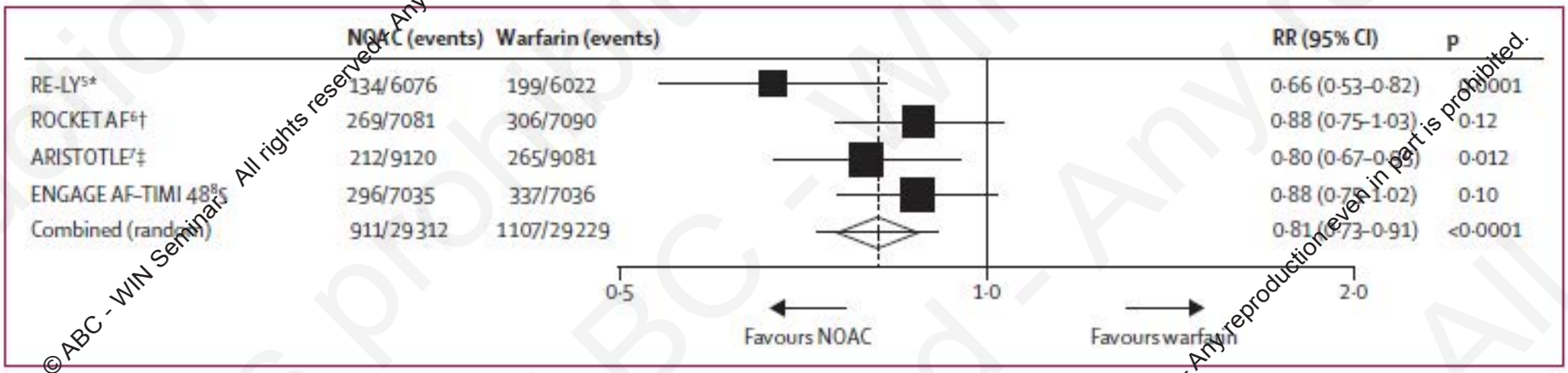

Figure 1: Stroke or systemic embolic events

Data are n/N, unless otherwise indicated. Heterogeneity: I^2=47%; p=0·13. NOAC=new oral anticoagulant. RR=risk ratio. *Dabigatran 150 mg twice daily. †Rivaroxaban 20 mg once daily. ‡Apixaban 5 mg twice daily. §Edoxaban 60 mg once daily.

New oral anticoagulant

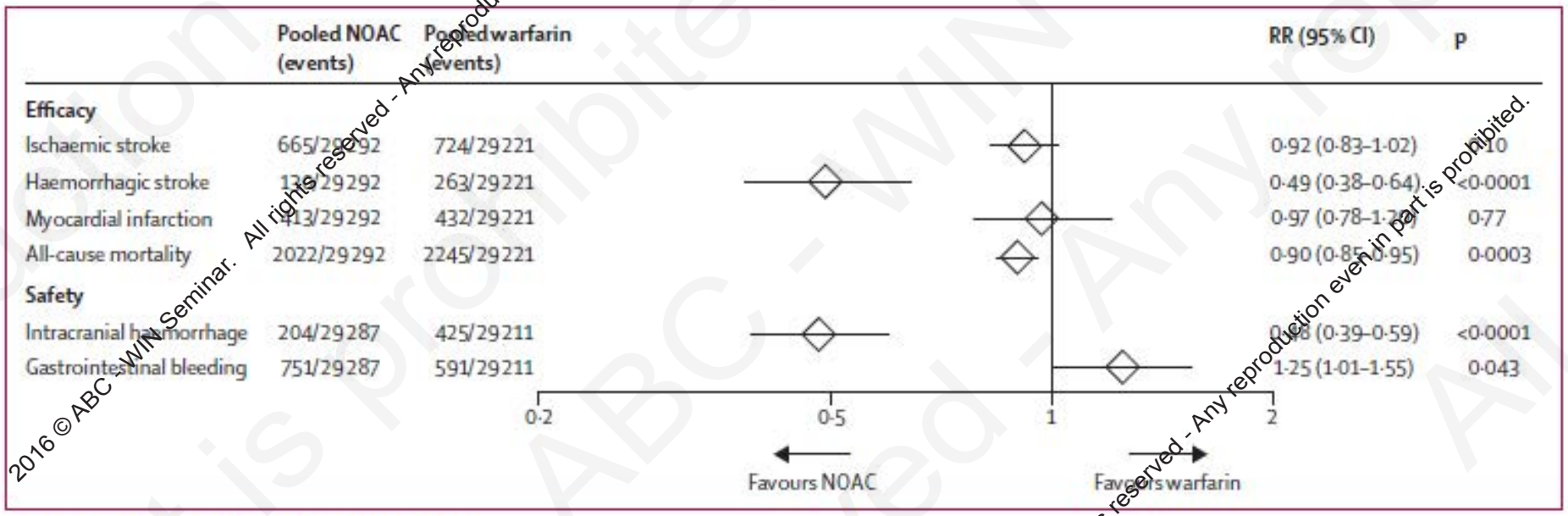

Figure 2: Secondary efficacy and safety outcomes

Data are n/N, unless otherwise indicated. Heterogeneity: ischaemic stroke I^2=32%, p=0·22; haemorrhagic stroke I^2=34%, p=0·21; myocardial infarction I^2=48%, p=0·13; all-cause mortality I^2=0%, p=0·81; intracranial haemorrhage I^2=32%, p=0·22; gastrointestinal bleeding I^2=74%, p=0·009. NOAC=new oral anticoagulant. RR=risk ratio.

New oral anticoagulant

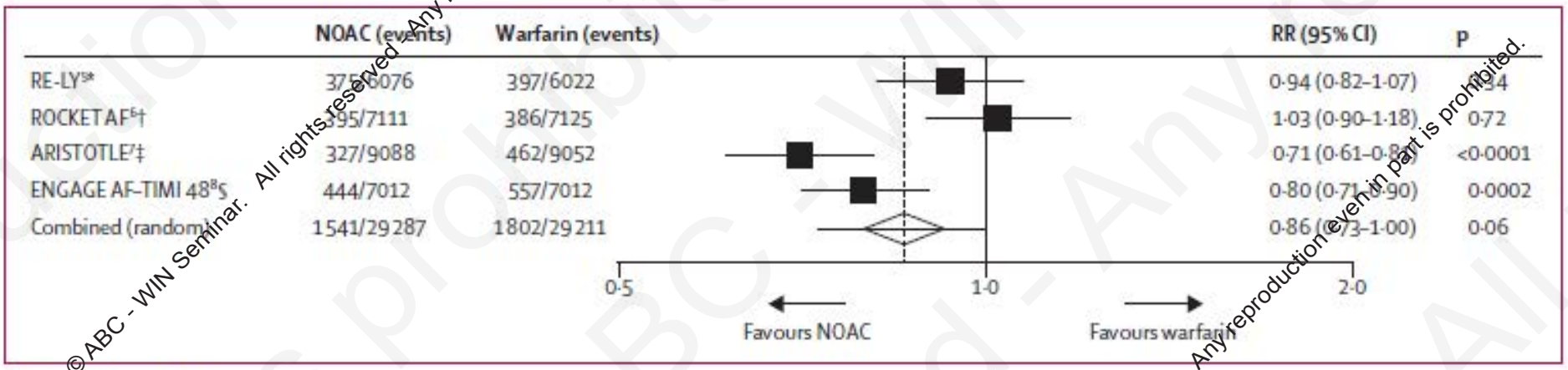

Figure 3: Major bleeding

Data are n/N, unless otherwise indicated. Heterogeneity: I^2=83%; p=0·001. NOAC=new oral anticoagulant. RR=risk ratio. *Dabigatran 150 mg twice daily. †Rivaroxaban 20 mg once daily. ‡Apixaban 5 mg twice daily. §Edoxaban 60 mg once daily.

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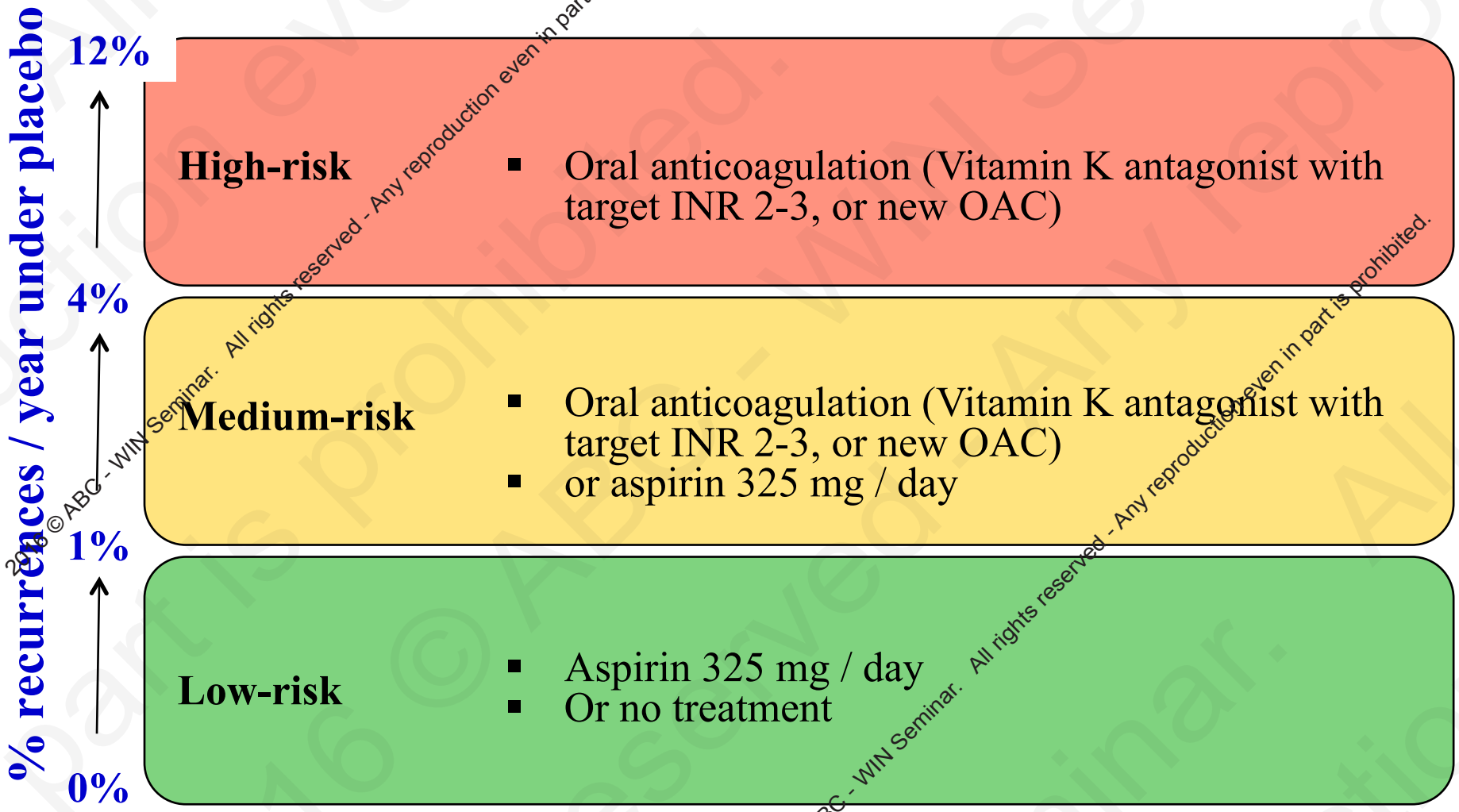
Atrial fibrillation



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- Background
- Acute stage of cerebral ischaemia
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  - Antiplatelet agents
  - Heparin and heparinoids
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- **Specific issues**
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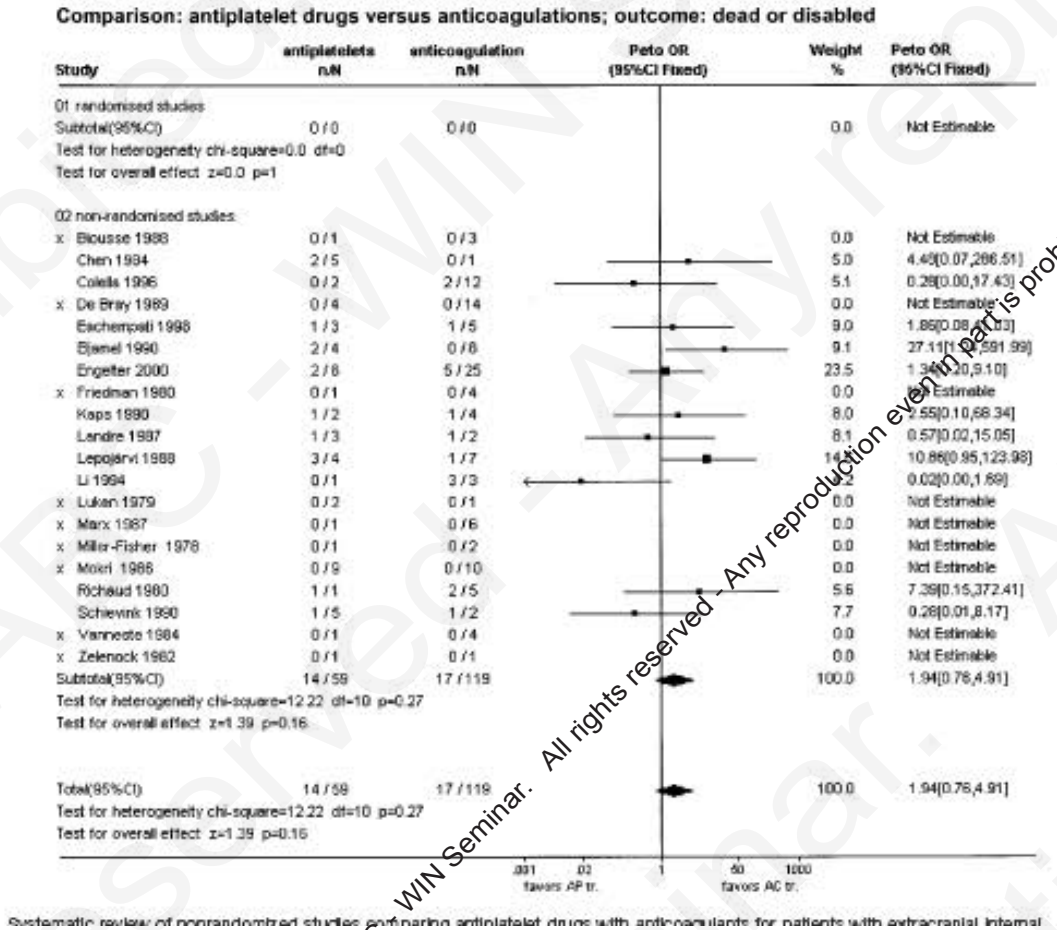
Dissection

Only 1 trial (CADISS) stopped for low recruitment rate.



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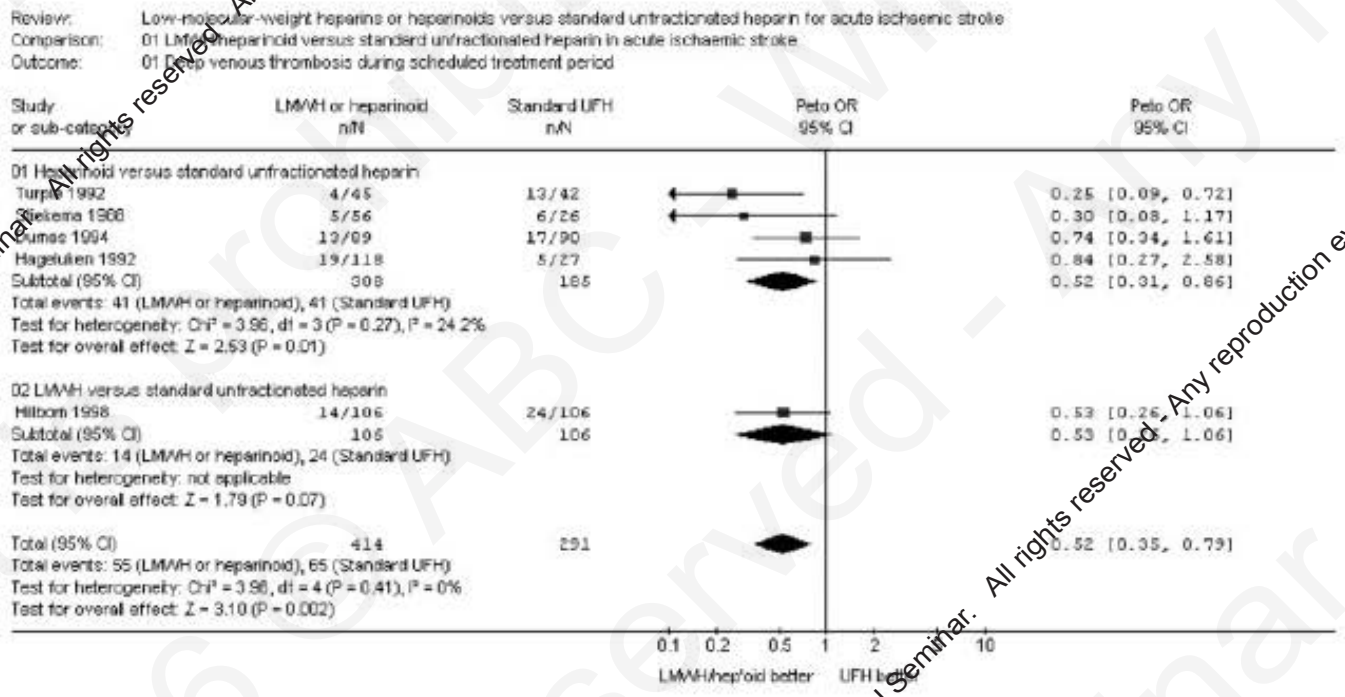
Prevention of DVT and PE

- N = 740 patients, 6 trials
- Les DVT OR = 0.52 (0.56 – 0.79)
- No effect on death



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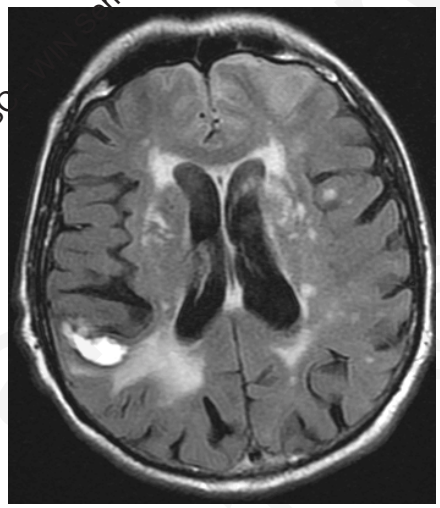
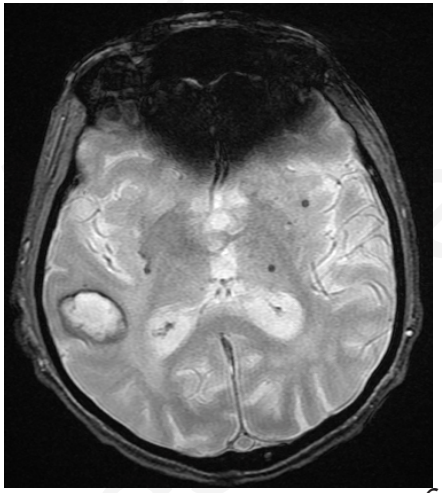
Cerebral haemorrhage under anticoagulant therapy

- Incidence
  - 0.3% - 0.6% / year
- Often leads to death
- Restart AC ?





- Predictors
  - Age > 75 years
  - High BP
  - INR > 4-5
  - Previous stroke
  - Combination with aspirin
  - Lobar ICH
  - White matter changes
  - Microbleeds

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Cerebral haemorrhage under anticoagulant therapy

- **AHA / ASA recommendations (Stroke 2011)**
- For patients who develop ICH, SAH, or SDH, it is reasonable to discontinue all anticoagulants and antiplatelets during the acute period for at least 1 to 2 weeks and reverse any warfarin effect with fresh frozen plasma or prothrombin complex concentrate and vitamin K immediately (Class IIa; Level of Evidence B).
- Protamine sulfate should be used to reverse heparin-associated ICH, with the dose depending on the time from cessation of heparin (Class I; Level of Evidence B). (New recommendation)

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Cerebral ischaemia under anticoagulant therapy

	Proximal occlusion	No Proximal occlusion
INR < 1.7	i.v. rtPA + thrombectomy	i.v. rtPA alone
INR ≥1.7	Thrombectomy alone	Conservative management

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Cerebral ischaemia under antiplatelet therapy

- For patients who have an ischemic stroke while taking aspirin, there is no evidence that increasing the dose of aspirin provides additional benefit. Although alternative antiplatelet agents are often considered, no single agent or combination has been studied in patients who have had an event while receiving aspirin *(Class IIb; Level of Evidence C)*.

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Take home message

- **At the acute stage of cerebral ischaemia**
  - aspirin alone, or combined with clopidogrel for a short period of time, should be given, immediately or after 24 hours in case of thrombolytic therapy
  - Heparin provides no benefit

- **In secondary stroke prevention**
  - Aspirin, or clopidogrel, or the association aspirin plus dipyridamole in indicated except in AF
  - In AF patients should receive OAC, with a new one when possible, otherwise with a VKA and a target INR 2-3