

Modifiers of the clinical course of infective endocarditis

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Infective endocarditis : modifiers

- **Clinical course without intervention**
- Antibiotics
- Surgery
- Embolic modifiers

Infective endocarditis : modifiers

- Hemodynamic damage of the valvular endocardium
 - Formation of a coagulum
 - Transient bactremia (oral, skin, GI)
- Vegetation
 - Focal agranulocytosis
 - Continuous bactremia
- Valvular destruction
- Embolization

Infective endocarditis : no intervention

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Mortality 100%

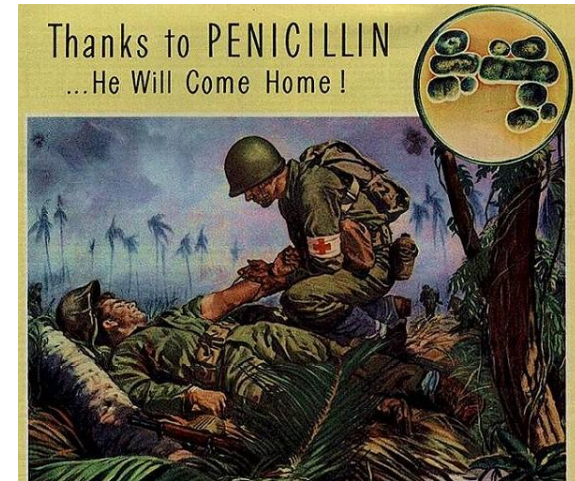
Infective endocarditis : modifiers

- Clinical course without intervention
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Infective endocarditis : antibiotics

- Antibiotics
 - 4-6 weeks
 - Parenterally

➔ Mortality \approx 50%



Infective endocarditis : epidemiology

- Antibiotics (4-6 w, iv) mortality \approx 50%

- **Change in epidemiology:**

Etiologic shift towards staphylococci

Shorter delay

Older patients

Degenerative valve disease

Prosthetic valve

Health care associated infections

Infective endocarditis : modifiers

- Clinical course without intervention
- Antibiotics
- **Surgery**
- Embolic modifiers

Infective endocarditis : surgery

Surgery 1960's

- Mortality ↓

Bannay et al. Eur Heart J 2009

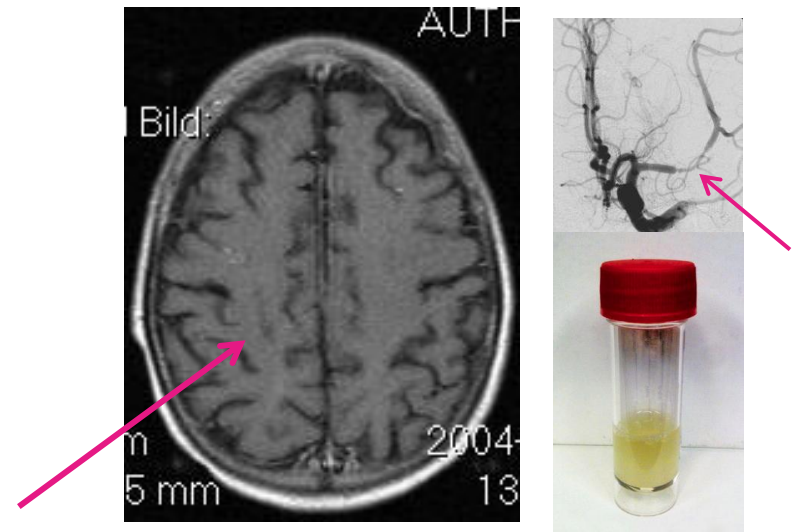
15 - 20% during the last two decades

- Cardiac sequelae ↓

- Cerebral complications →

Neurologic sequelae

Neurologic death



| Author | N | Symptomatic CNS complication % | Ischemia % | Hemorrhage % | Meningitis % | Mortality +/- CNS complication % |
|-------------------|------------|--------------------------------|-----------------|--------------|----------------|----------------------------------|
| Harrison -67 | 116 | 28 | 22 | - | 19 | 67 / 44 |
| Pruitt -78 | 218 | 39 | 28 (17) | 7 | 16 | 58 / 20 |
| Hart -90 | 133 NVE | 23 | 19 | 7 | - | - |
| Kanter -91 | 166 | 35 | 20 ^a | | 5 | 35 / 19 |
| Pruitt -96 | 144 | 29 | 18 | | 4 | 32 / 13 |
| Heiro -00 | 218 | 25 | 11 | 2 | 4 | 24 / 10 |
| Anderson -03 | 770 | 14 | 7 | 2 | | ns |
| Corral - 07 | 550 | 13 | 8 | 3 | 2 | 34 / 11 |
| Thuny -07 | 496 | 18 (22 ^b) | 16 ^c | 4 | | 1 y: 25 / 19 (ns) |
| Dickerman -07 | 1437 | 15 | 15 ^a | | | - |
| Snygg-Martin -10 | 684 | 25 | 20 ^c | 2 | 6 | 27 / 10 |
| Garcia-Cabrero-13 | 1345 | 25 | 14 | 5 | 6 ^d | 45/24 |

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20 – 25 %

Infective endocarditis : modifiers

- Clinical course without intervention
- Antibiotics
- Surgery
- **Modifiers of embolic risk**

Embolic complications: predictors

- *Microorganism: S. aureus*
- Vegetation length > 10 mm
- Mitral valve endocarditis
- Native valve endocarditis
- Previous embolic event

Cerebral complications: predictors

- *Microorganism: S. aureus*
- Vegetation length > 10 mm
- IE location: Mitral valve IE
- Native valve IE
- Previous embolic event

Younger age

CRP level

Platelet volume

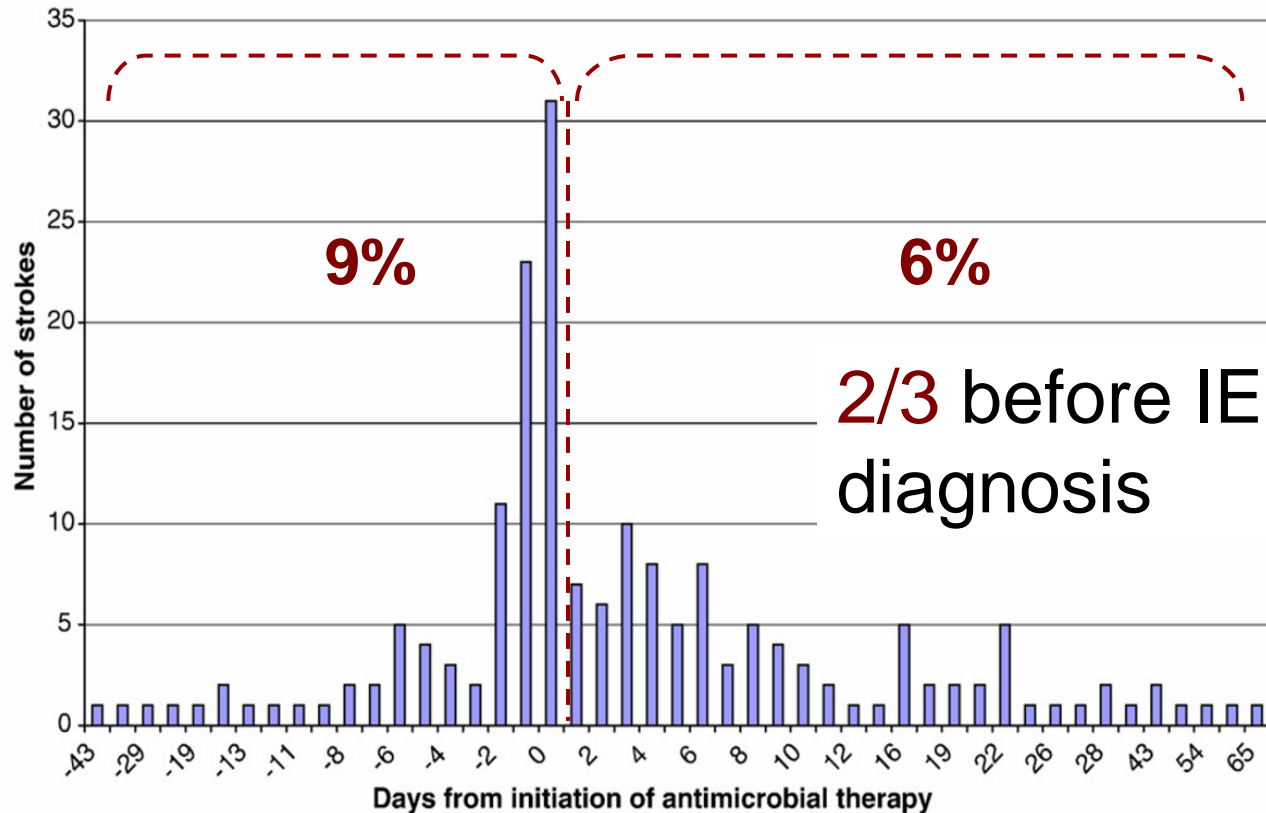
Procoagulant changes

Autoantibodies

Fungal endocarditis

Infective endocarditis : embolic modifiers

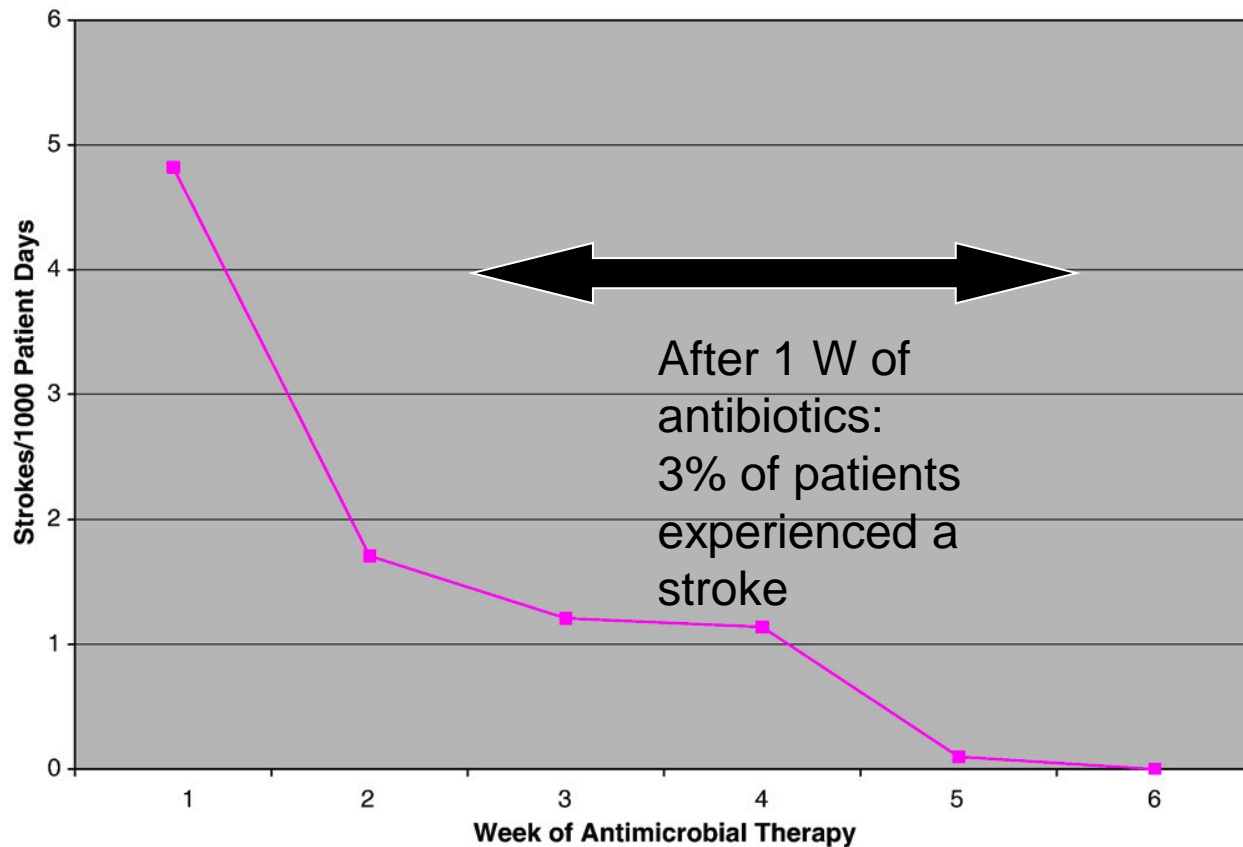
➤ Early diagnosis



Daily incidence of stroke in ICE cohort.

Infective endocarditis : embolic modifiers

➤ Effective antibiotics!!



Infective endocarditis : embolic modifiers

Early surgery in selected cases

| C - PREVENTION OF EMBOLISM | | | |
|--|--------|-----|---|
| Aortic or mitral IE with large vegetations (> 10 mm) following one or more embolic episodes despite appropriate antibiotic therapy | Urgent | I | B |
| Aortic or mitral IE with large vegetations (> 10 mm) and other predictors of complicated course (heart failure, persistent infection, abscess) | Urgent | I | C |
| Isolated very large vegetations (> 15 mm) [#] | Urgent | IIb | C |

Infective endocarditis : embolic modifiers

Adjunctive treatment with platelet inhibitors?

- Inhibition of vegetation formation
- Direct bactericidal effect?
- Animal models
- Case report series

Infective endocarditis : embolic modifiers

Multi-Centre Aspirin Trial in Infective Endocarditis

- RCT
 - Four years, 115 p randomized in, 19 centers
 - No reduced rate of embolism
 - Increased risk of bleeding (GI)

“Aspirin does not reduce embolic risk in stable patients with endocarditis”

Chan KL et al. J Am Coll Cardiol 2003

Infective endocarditis : embolic modifiers

On-going platelet inhibitors:

Cohort studies, Post-hoc

- Conflicting

es

Addition of antiplatelet therapy not indicated in endocarditis.

No risk with on-going therapy

in S aureus bactremia?

Anawekar C et al. CID 2007; Pepiin et al. 2009 Clin Micro Inf
Chan KL et a. CID 2008, Snygg-Martin et al . SCJID 2011

Infective endocarditis : embolic modifiers

Additional treatment with anticoagulants?

- Older studies: cerebral bleeding
- Poor prognosis

Endocarditis per se is not an indication for anticoagulant therapy

Infective endocarditis : embolic modifiers

On-going oral anticoagulants:

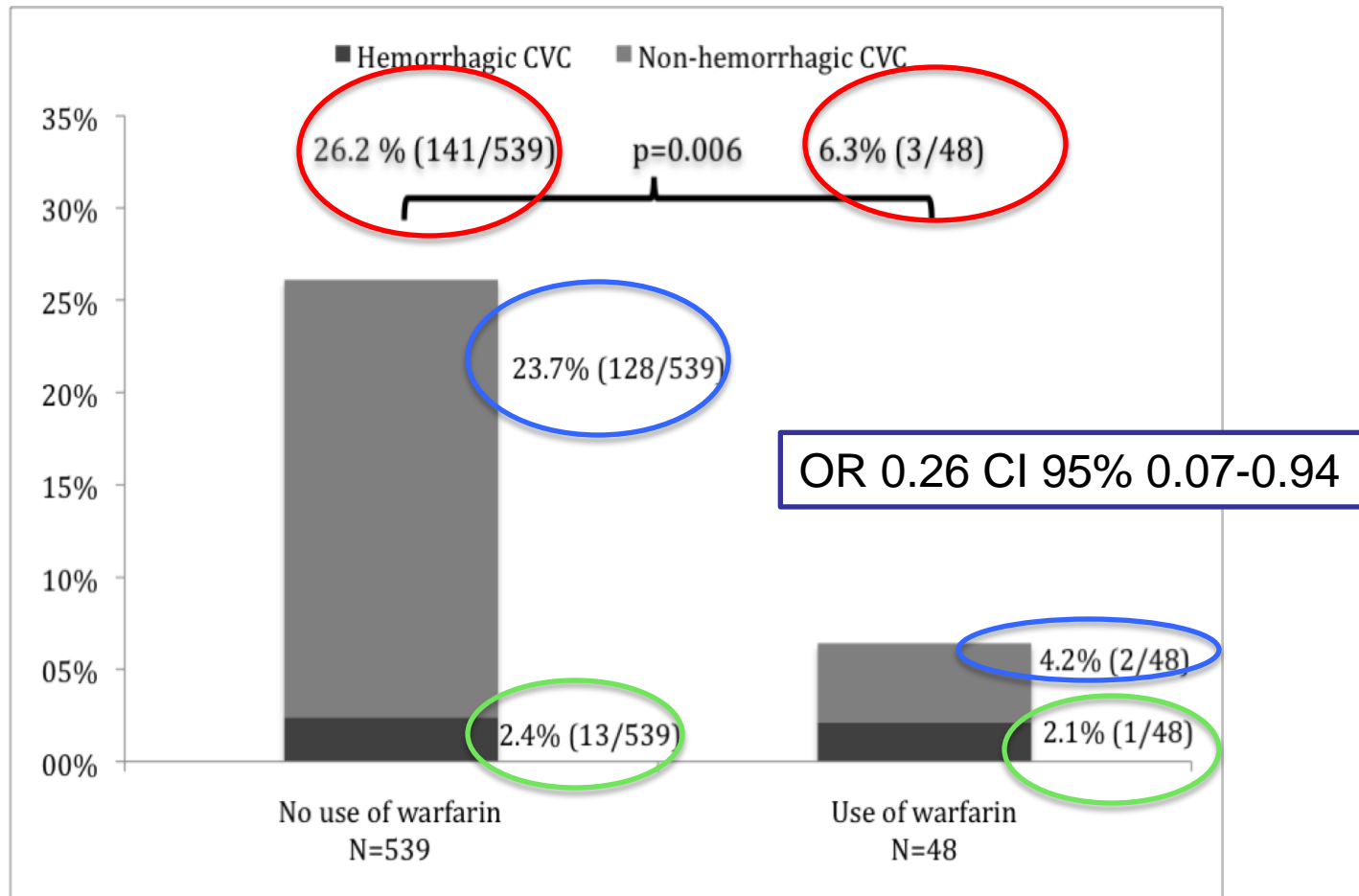
- Increased risk for cerebral bleeding

Tornos P et al. Arch Intern Med. 1999
Garcia-Cabrera E et al. Circulation 2013

- Decreased frequency ischemic lesions

Rasmussen RV et al Cardiology 2009,
Snygg-Martin U et al. Eur J Clin Microbiol Infect Dis 2010

Cerebral complications in patients with/without warfarin at IE presentation



Snygg-Martin U et al. Eur J Clin Microbiol Infect Dis 2010

Table 21 Management of antithrombotic therapy in infective endocarditis

| Recommendations: antithrombotic therapy | Class ^a | Level ^b |
|---|--------------------|--------------------|
| Interruption of antiplatelet therapy is only recommended in the presence of major bleeding | I | B |
| In ischaemic stroke without cerebral haemorrhage, replacement of oral anticoagulant therapy by unfractionated heparin for 2 weeks is indicated with a close monitoring of activated partial thromboplastin or the activated cephalin clotting time | I | C |
| In intracranial haemorrhage, interruption of all anticoagulation is recommended | I | C |
| In patients with intracranial haemorrhage and a mechanical valve, unfractionated heparin should be reinitiated as soon as possible (with close monitoring of activated partial thromboplastin or activated cephalin clotting time) following multidisciplinary discussion | IIa | C |
| In the absence of stroke, replacement of oral anticoagulant therapy by unfractionated heparin during 2 weeks may be considered in case of <i>S.aureus</i> IE with a close monitoring of activated partial thromboplastin or the activated cephalin clotting time | IIb | C |

^aClass of recommendation.

^bLevel of evidence.

Infective endocarditis : embolic modifiers

Other pharmacological possibilities, statins?

TABLE 4. Association of Antiplatelet and Statin Therapy With Outcomes

| Treatment | Adjusting model | Outcome | |
|------------------|---|-------------------------|--------------------------------|
| | | Embolism ^a | 6-Month mortality ^b |
| Antiplatelet use | Univariate | 0.49 (0.29-0.82) [.007] | 0.96 (0.61-1.53) [.87] |
| | Propensity score | 0.71 (0.37-1.36) [.30] | 0.97 (0.55-1.69) [.91] |
| | Propensity score + risk factors ^c | 0.82 (0.41-1.65) [.58] | 0.66 (0.35-1.26) [.21] |
| | Propensity score + risk factors ^c + statins | 0.94 (0.46-1.92) [.86] | 0.64 (0.33-1.24) [.18] |
| Statin therapy | Univariate | 0.35 (0.18-0.67) [.001] | 0.95 (0.57-1.59) [.85] |
| | Propensity score | 0.30 (0.14-0.62) [.001] | 1.05 (0.57-1.93) [.87] |
| | Propensity score + risk factors ^c | 0.40 (0.15-1.04) [.06] | 1.19 (0.59-2.42) [.62] |
| | Propensity score + risk factors ^c + acetylsalicylic acid | 0.42 (0.16-1.13) [.08] | 1.34 (0.64-2.79) [.44] |

Anawekar et al. 2011 Mayo Clin Proc

Infective endocarditis : embolic modifiers

- “Statins can have pleiotropic effects including inhibition of platelet function and immunomodulatory effects...”

Anawekar et al. 2011 Mayo Clin Proc

Further investigation in other patient populations needed

Infective endocarditis : modifiers of clinical course

- Find the endocarditis
- Give proper antibiotics
- Consider surgery early and often
- No additional pharmacologic treatment shown to be effective
- Antiplatelet and anticoagulant therapy have been studied with pros and cons
- Statins need further investigation