



Apopleksi

Farmakologi

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Apopleksi

Klinisk definition

- Pludseligt opstået
- Fokale neurologiske udfald
- Vaskulær basis (infarkt eller blødning)
- Varige symptomer (> 24 timer)
(*ved varighed < 24 timer = TCI*)^{A,B}

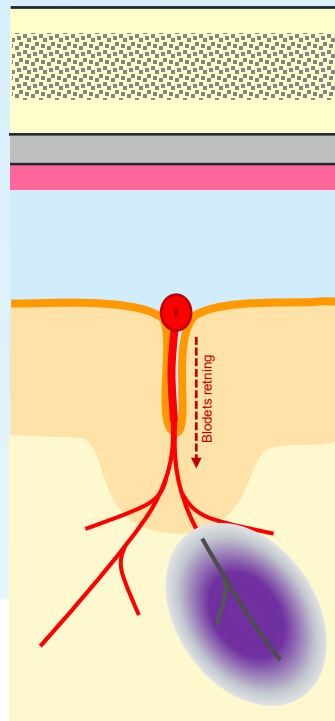
^A Mere end halvdelen har problemer med fatigue og op imod halvdelen har problemer med hukommelse, koncentration og multi-taskning efter tre måneder (Fens *et al.* 2013)

^B 30-50% af patienter med TCI har vævsforandringer på MR DWI (Easton *et al.* 2009)

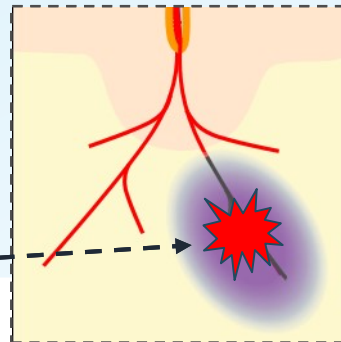
Apopleksi

Iskæmisk apopleksi

Skyldes blodprop
Ca. 90% (9-10.000/år)



Ca. 15% får blødning
i infarkt
(*hæmorrhagisk transformation*)



Hæmorrhagi

Skyldes blødning
Ca. 10% (1000-1500/år)

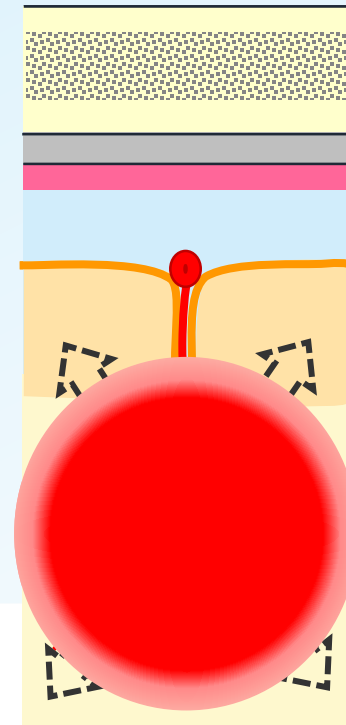
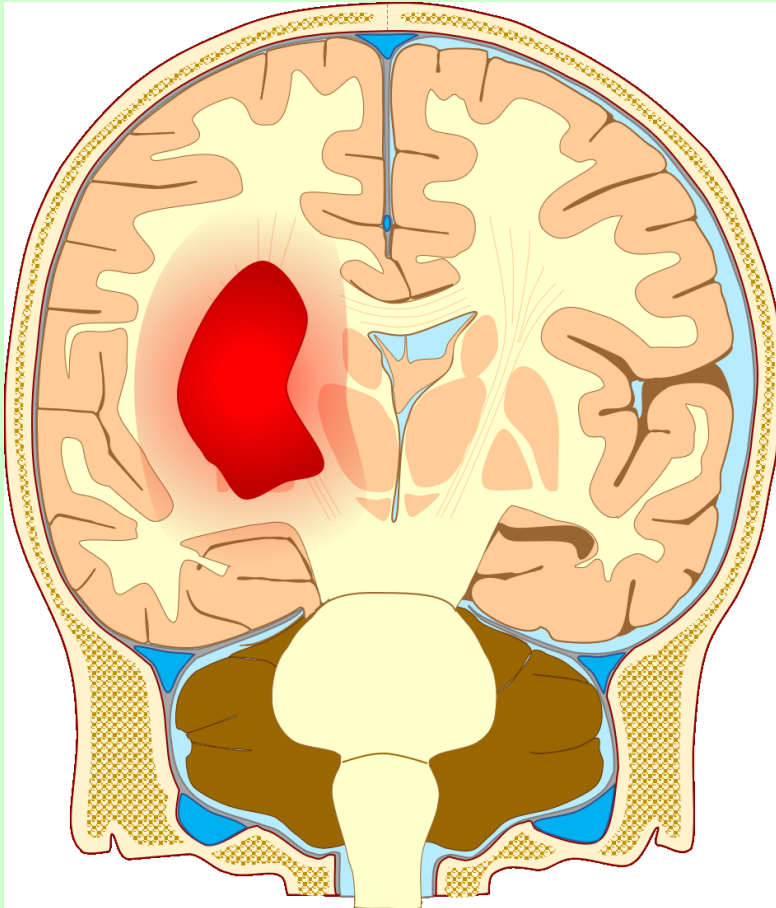


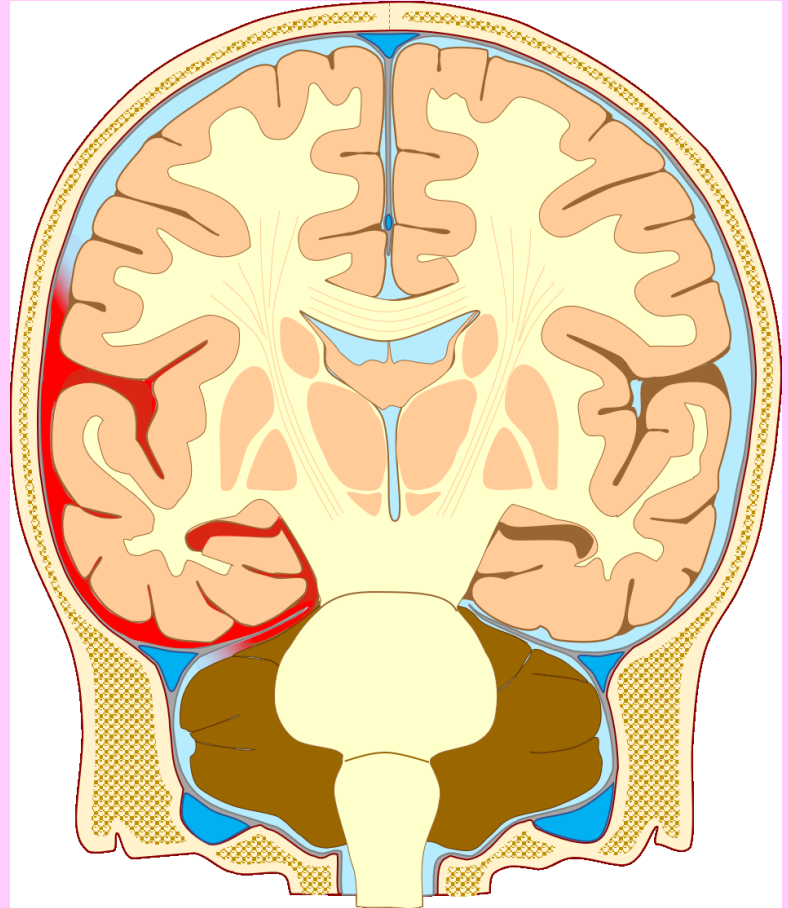
Illustration: Jacob Liljehult 2021

Blødning inde i hjernen



ICH = Apopleksi

Blødning uden på hjernen



SAH ≠ Apopleksi

Neurologiske udfald

De neurologiske udfald
afhænger af:

**Omfanget af
læsionen**

*Hvor stort et
område er ramt?*

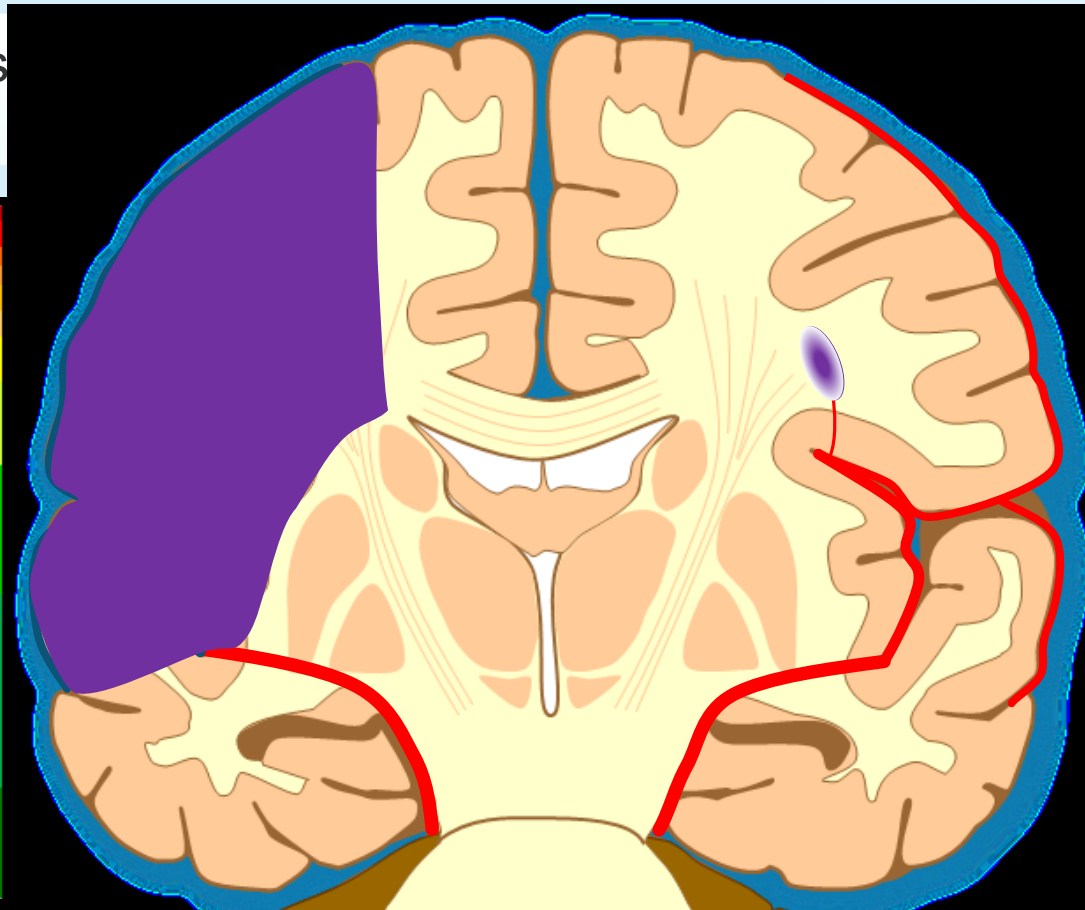
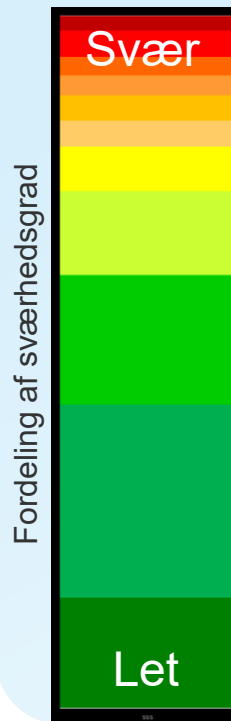
**Placeringen af
læsionen**

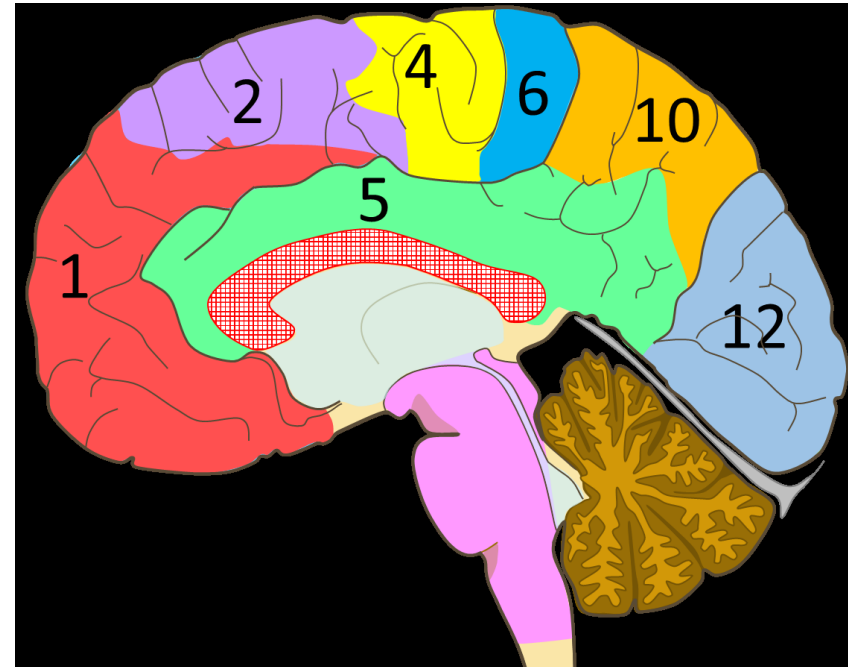
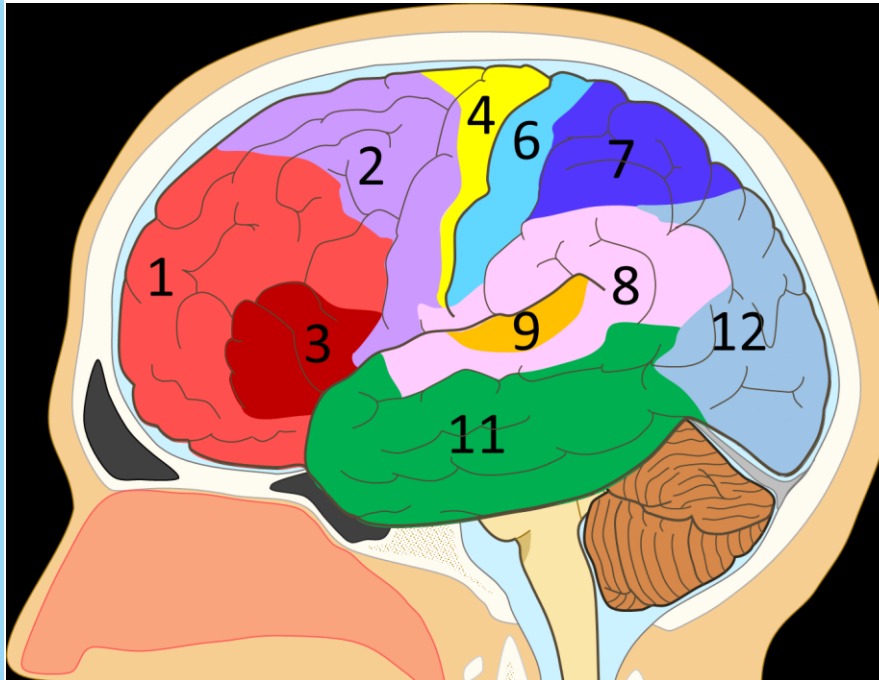
*Hvilket område
er ramt?*

Omfanget af læsionen

Storkars
(a. media

arsinfarkt





1	Højere mentale funktioner Koncentration, planlægning, dømmekraft, impulshæmning, kreativitet
2	Sekundært motorisk område Øjenbevægelser, orientering, skemaer for bevægelser
3	Broca's område Motorisk del af talen
4	Primært motorisk område Initiering af bevægelser

5	Emotionelt område Smerte, sult, "fight & flight"
6	Primært somato-sensorisk område
7	Sekundært somato-sensorisk område Vurdering af tekstur, vægt etc
8	Wernickes område Sprog forståelse
9	Auditorisk område Hørelse

10	Associativt sensorisk område
11	Associativt område Korttidshukommelse, emotioner
12	Visuelt område Syn, objektgenkendelse
13	Cerebellum Balance, kropsholdning, koordination af bevægelser

Illustration: Jacob Liljehult 2020

Hemisfære-lateralisering

Venstre

Højresidige
motoriske og
sensoriske udfald

Højresidige
synsudfald

Sproglige udfald
(*tale, forståelse,
læse, skrive, regne*)

Apraksi

Negativ affekt/
nedsat psyko-
motorisk tempo



Højre

Venstresidige
motoriske og
sensoriske udfald

Venstresidige
synsudfald

Nedsat sygdoms-
erkendelse

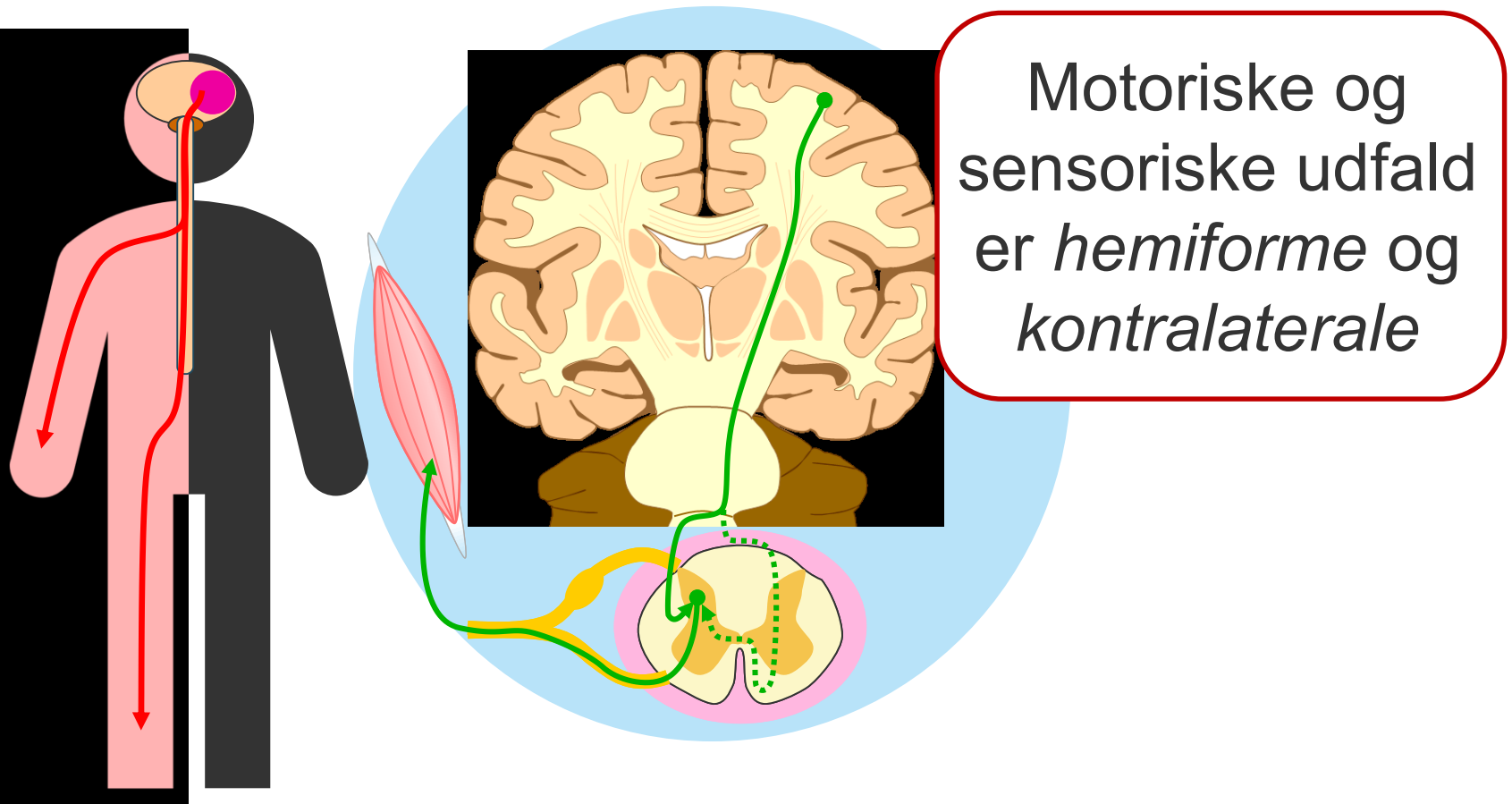
Manglende overblik/
rum/retnings-
forstyrrelser

Neglekt

Positiv affekt/ hurtigt
psyko-motorisk
tempo

Illustration: Jacob Liljehult 2020

Lateraliserede udfald



Symptomer på apopleksi

Diffuse symptomer

Nedsat bevidsthed

Utilpashed

Svimmelhed

Hovedpine

Kramper

Fokale udfald

- Motorisk og somato-sensoriske udfald
- Synsforstyrrelser
- Sproglige og kommunikative problemer
- Visuo-spartielle forstyrrelser
 - *Neglekt og inattention, apraksi*
- Adfærds- og opmærksomhedsforstyrrelser
- Anosognosi

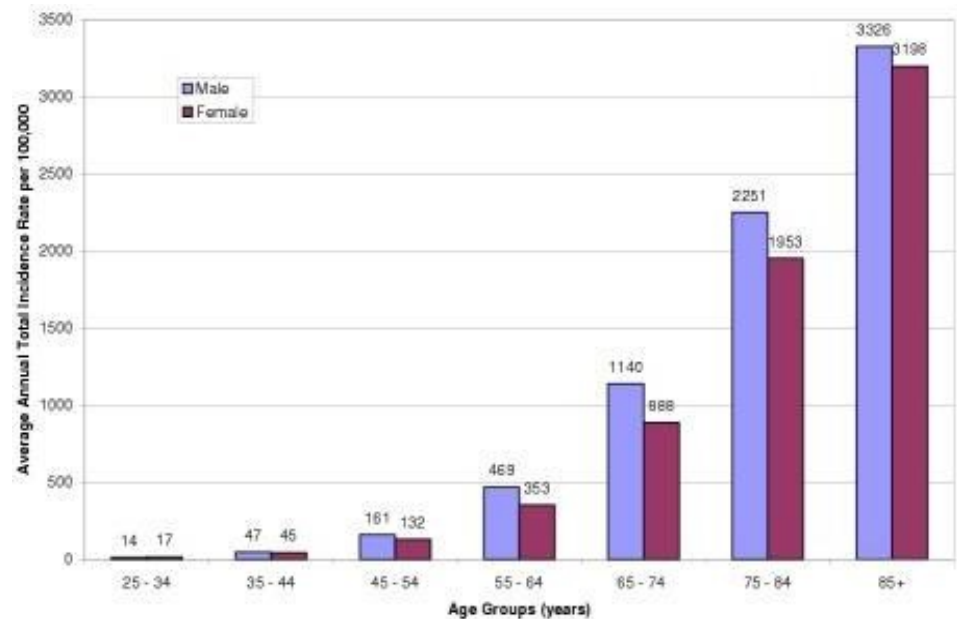
Forekomst

Ca. 12.000 nye
tilfælde om året i DK

Incidensrate 3/1000
per år

Hyppigheden stiger
med alderen

Omkring 40.000
lever med
funktionsnedsættelse
efter apopleksi



Risikofaktorer

Articles

Risk factors for ischaemic and intracerebral haemorrhagic stroke in 22 countries (the INTERSTROKE study): a case-control study

Martin J O'Donnell, Denis Xavier, Lisheng Liu, Hongye Zhang, Siu Lim Chin, Purnima Rao-Melacini, Sumathy Rangarajan, Shafiqul Islam, Prem Pais, Matthew J McQueen, Charles Mondo, Albertino Damasceno, Patricia Lopez-Jaramillo, Graeme J Hankey, Antonio L Dans, Khalid Yusoff, Thomas Truelsen, Hans-Christoph Diener, Ralph L Sacco, Danuta Ryglowicz, Anna Czlonkowska, Christian Weimar, Xingyu Wang, Salim Yusuf, on behalf of the INTERSTROKE investigators*

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See Comment page 74

*Members listed at end of paper

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Institute, Bangalore, India
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Beijing Hypertension League
Institute, Beijing, China
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Mozambique
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Fundacion Oftalmologica de
Santander Clinica Carlos Arandia

Background The contribution of various risk factors to the burden of stroke worldwide is unknown, particularly in countries of low and middle income. We aimed to establish the association of known and emerging risk factors with stroke and its primary subtypes, assess the contribution of these risk factors to the burden of stroke, and explore the differences between risk factors for stroke and myocardial infarction.

Methods We undertook a standardised case-control study in 22 countries worldwide between March 1, 2007, and April 23, 2010. Cases were patients with acute first stroke (within 5 days of symptoms onset and 72 h of hospital admission). Controls had no history of stroke, and were matched with cases for age and sex. All participants completed a structured questionnaire and a physical examination, and most provided blood and urine samples. We calculated odds ratios (ORs) and population-attributable risks (PARs) for the association of all stroke, ischaemic stroke, and intracerebral haemorrhagic stroke with selected risk factors.

Findings In the first 3000 cases (n=2337, 78%, with ischaemic stroke; n=663, 22%, with intracerebral haemorrhagic stroke) and 3000 controls, significant risk factors for all stroke were: history of hypertension (OR 2.64, 99% CI 2.26-3.08; PAR 34.6%; 99% CI 30.4-39.1); current smoking (2.09, 1.75-2.51; 18.9%, 15.3-23.1); waist-to-hip ratio (1.65, 1.36-1.99 for highest vs lowest tertile; 26.5%, 18.8-36.0); diet risk score (1.35, 1.11-1.64 for highest vs lowest tertile; 18.8%, 11.2-29.7); regular physical activity (0.69, 0.53-0.90; 28.5%, 14.5-48.5); diabetes mellitus (1.36, 1.10-1.68; 5.0%, 2.6-9.5); alcohol intake (1.51, 1.18-1.92 for more than 30 drinks per month or binge drinking; 3.8%, 0.9-14.4); psychosocial stress (1.30, 1.06-1.60; 4.6%, 2.1-9.6) and depression (1.35, 1.10-1.66; 5.2%, 2.7-9.8); cardiac causes (2.38, 1.77-3.20; 6.7%, 4.8-9.1); and ratio of apolipoproteins B to A1 (1.89, 1.49-2.40 for highest vs lowest tertile; 24.9%, 15.7-37.1). Collectively, these risk factors accounted for 88.1% (99% CI 82.3-92.2) of the PAR for all stroke. When an alternate definition of hypertension was used (history of hypertension or blood pressure >160/90 mm Hg), the combined PAR was 90.3% (85.3-93.7) for all stroke. These risk factors were all significant for ischaemic stroke, whereas hypertension, smoking, waist-to-hip ratio, diet, and alcohol intake were significant risk factors for intracerebral haemorrhagic stroke.

Interpretation Our findings suggest that ten risk factors are associated with 90% of the risk of stroke. Targeted interventions that reduce blood pressure and smoking, and promote physical activity and a healthy diet, could substantially reduce the burden of stroke.

Hypertension (OR 2.64 [2.26-3.08]*)

Kardielle årsager (OR 2.38 [1.77-3.20]*)

Rygning (OR 2.09 [1.75-2.51]*)

Talje/hofte ratio (OR 1.65 [1.36-1.99]*)

Alkohol (OR 1.51 [1.18-1.92]*)

Fysisk inaktivitet (OR 1.45 [1.11-1.89]*)

Diæt (OR 1.35 [1.11-1.64]*)

Depression (OR 1.35 [1.10-1.66]*)

Stress (OR 1.30 [1.06-1.60]*)

* 99% Konfidensinterval

De mørke områder angiver
population attributional risk

Prognose

Prognosen afhænger af sværhedsgraden

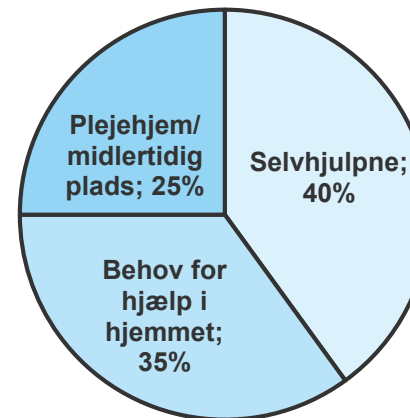
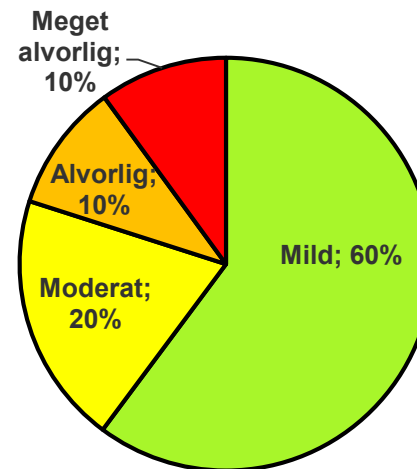
50 % bliver selvhjulpne
10-20 % bliver svært invaliderede

20 % får en ny apopleksi inden for 5 år

9-11 % dør indenfor 30 dage

15-20 % indenfor 1 år

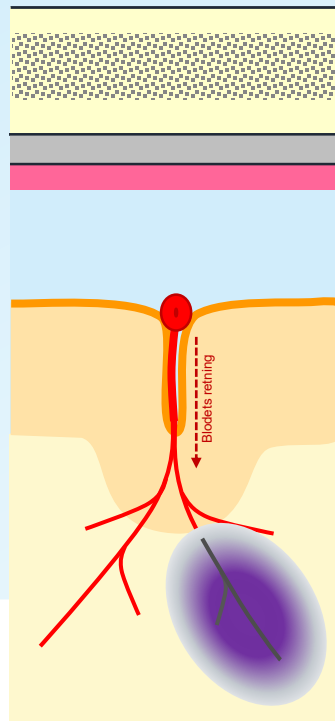
Ca. 10 % udvikler epilepsi



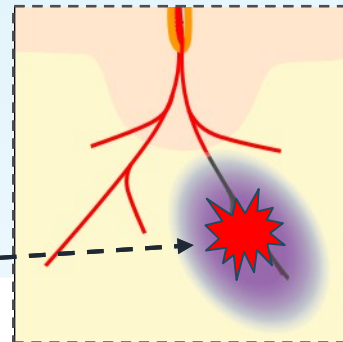
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Hæmorrhagi

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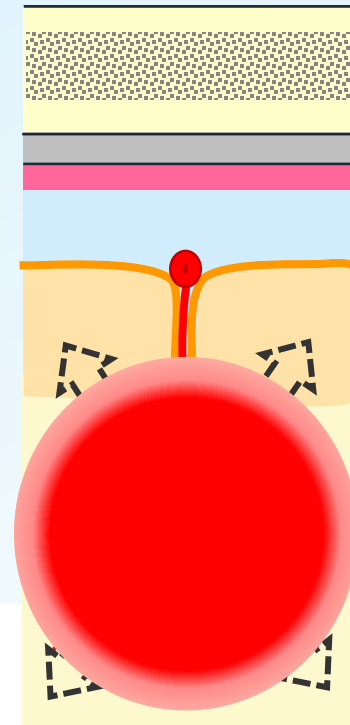


Illustration: Jacob Liljehult 2021

Hæmorrhagisk apopleksi

(Blødning)

Ætiologi

Hæmorrhagi betyder udsivning af blod fra blodbanen til et væv hvor der ikke ellers er blod

- Skyldes en revne på en arterie i hjernen
- Oftest pga. arteriosklerose -> arterierne bliver stive og skrøbelige
- Sjældent pga. aneurisme eller traume.

Hæmorrhagisk apopleksi (Blødning)

Patologi

- 1) **Cellerne i ramte område dør**
 - Direkte skade fra blodkomponenter
 - Blodet koagulerer og hæmmer gasudveksling
- 2) **Blodet fylder og trykker derfor på det omkringliggende hjernevæv**
(Forhøjet intra-kranielt tryk)
- 3) **Ødemdannelse omkring blødningen**
 - Udsivning af plasmaproteiner fra hæmatomet

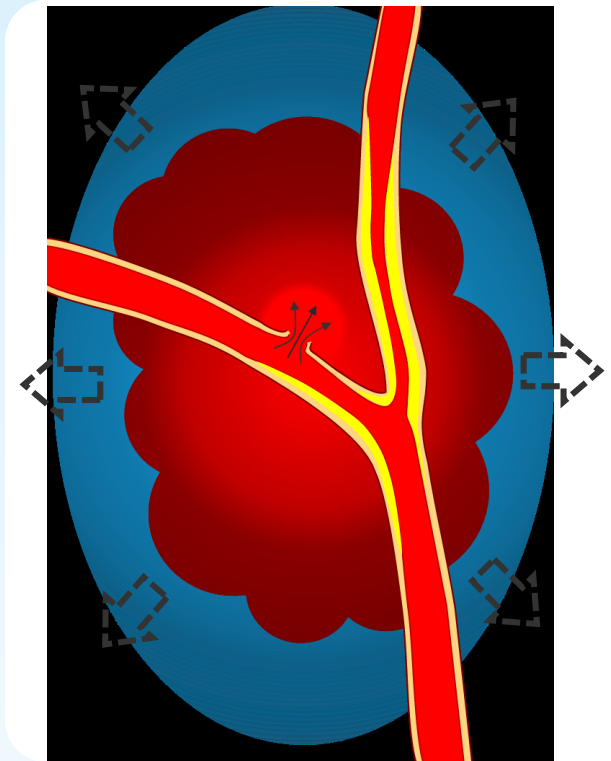
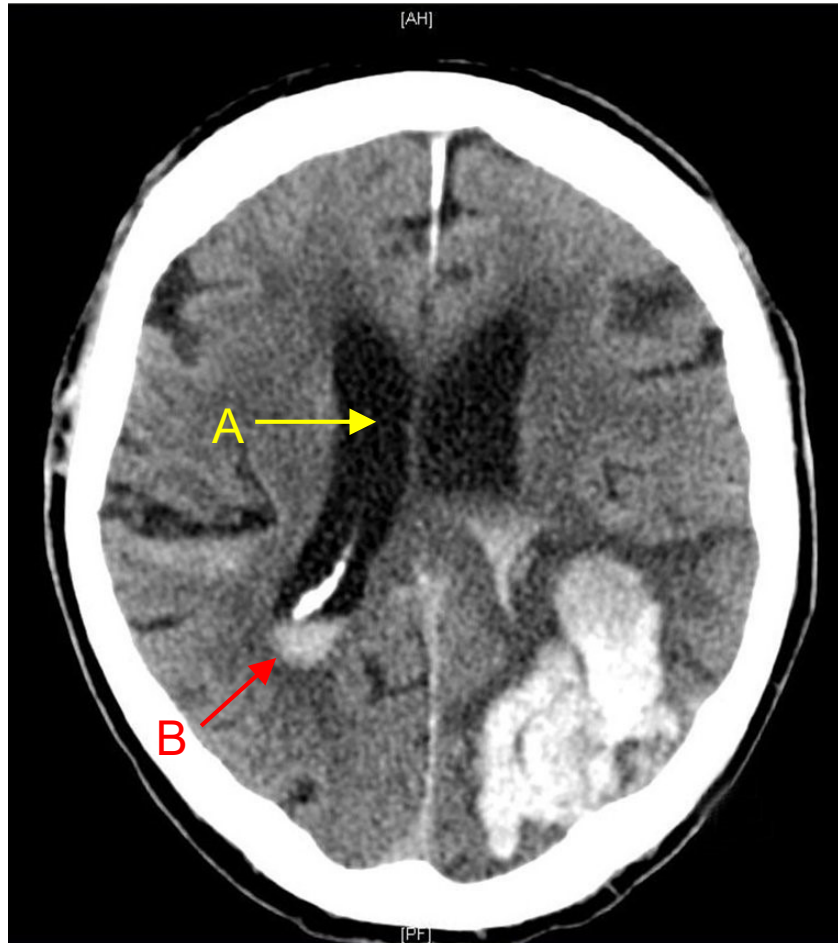
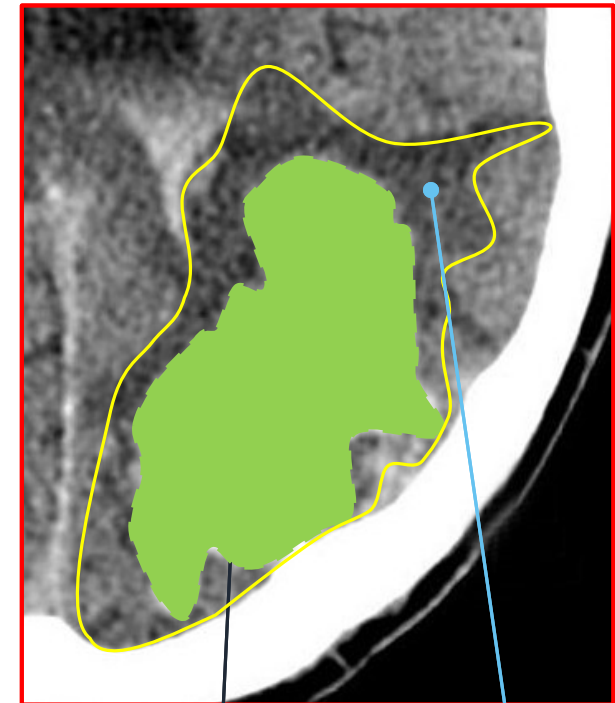


Illustration: Jacob Liljehult 2021

Jacob Mesot Liljehult



A Forskydning af septum over midtlinjen
B Blodrester i lateralventriklen



Blødning

Ødem

Blødning med gennembrud til begge lateral ventrikler

Iskæmisk apopleksi

Iskæmi skyldes en nedsat arteriel blodforsyning til et område af hjernen

Trombe

- Opstår lokalt i et kar i hjernen
- Hyppige årsager: Aterosklerose

Emboli

- Enten fra hjertet eller fra en af de arterier, som forsyner hjernen (aorta, carotis og vertebralis)
- Hyppige årsager: Atrieflimmer, arteriosklerotiske plaques, kardissektion

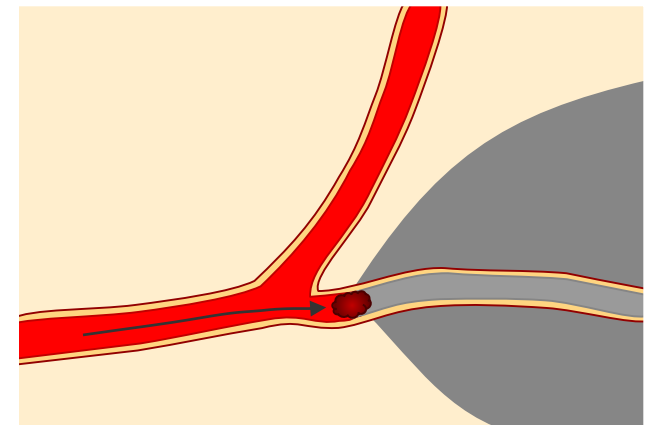
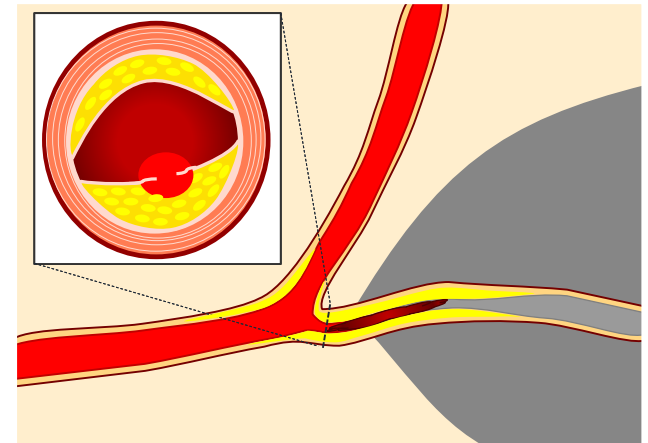


Illustration: Jacob Liljehult 2021

Blodpropper

Venøs

Hjernen
Sinus trombose

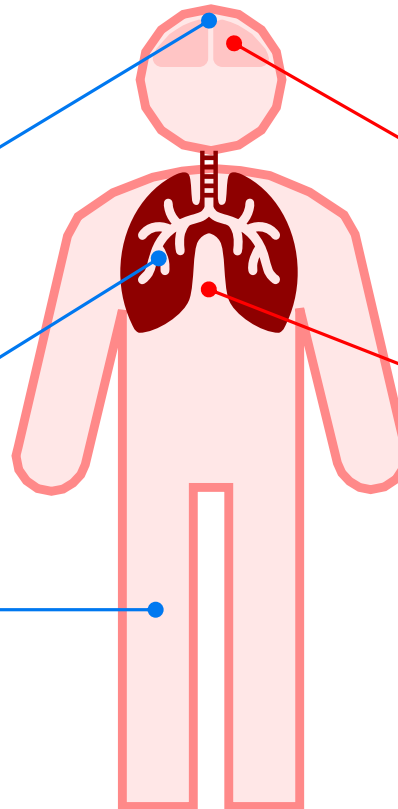
Lunge
Lunge emboli

Ekstremiteter
Dyb venetrombose

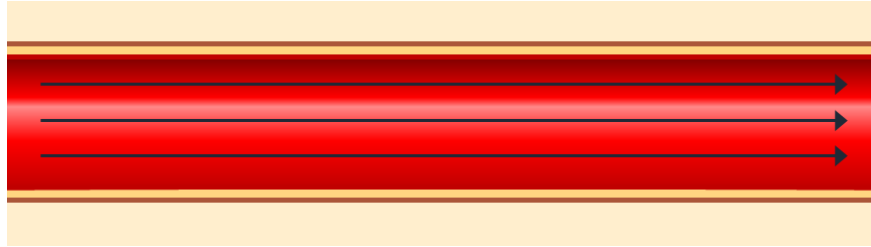
Arteriel

Hjernen
Apopleksi/TCI

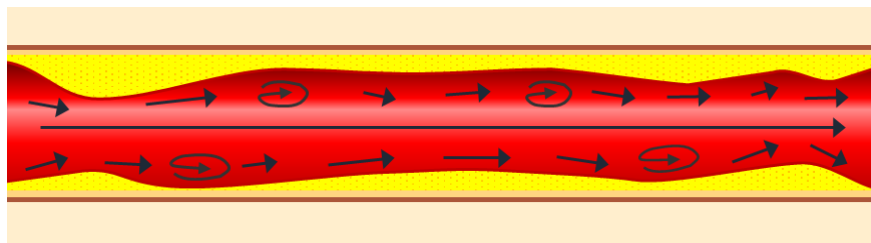
Hjertet
Myokardie infarkt



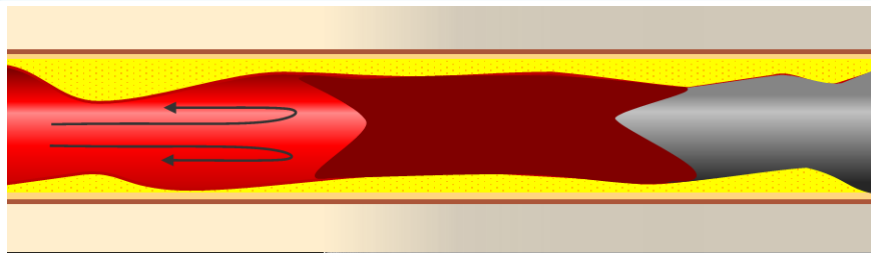
Trombose



Normal arterie
Normalt flow



Arteriosklerotisk arterie
Aflejring af fedt og kalk
Forstyrrelse af blod-flow

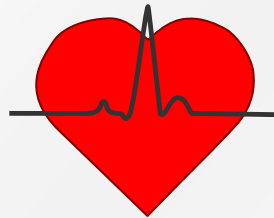


Arteriosklerotisk arterie
Dannelse af trombe

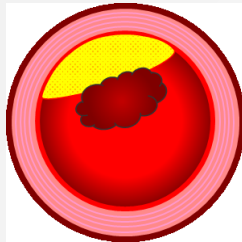
Emboli

Hyppige embolikilder

Hjertet



Arteriosklerose



Dissektion

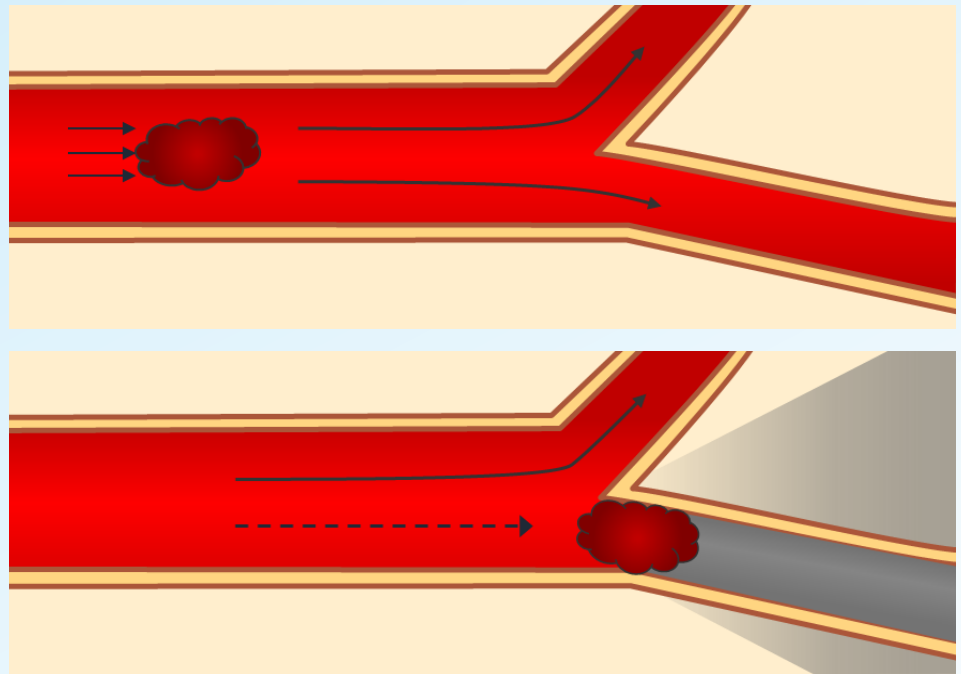
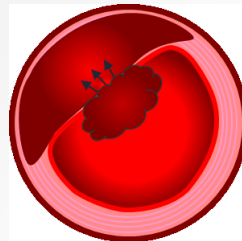


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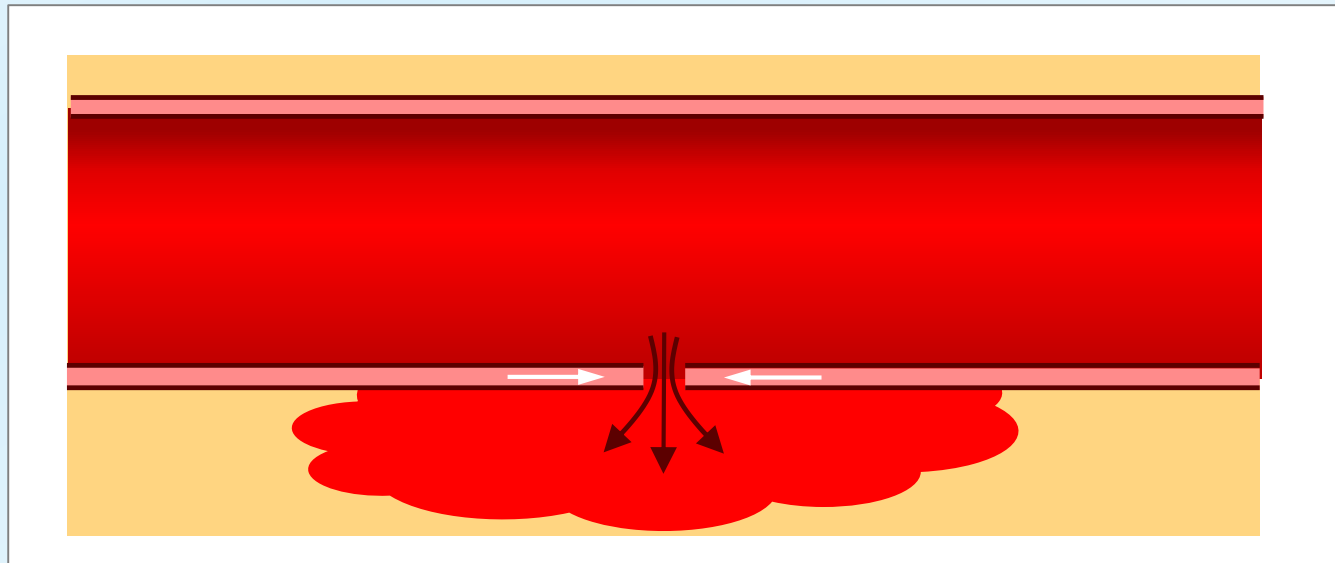
Hæmostase

Kan både aktiveres af faktorer fra *blodet* og faktorer fra *væv*

1. **Reaktion fra karvæggen** → Karret trækker sig sammen
2. **Dannelse af en *pladeprop***
 - Trombocytterne aktiveres → de binder sig fast til karvæggen og til hinanden og danner en *pladeprop*
3. **Dannelse af *fibrin***
 - Koagulation af blodet → dannelse af *fibrin* fibre
4. **Afgrænsning af blodproppen**
 - Fibrinolyse → nedbrydelse af fibrin vha. *plasmin*
 - Inaktivering af koagulationsfaktorer

Hæmostase

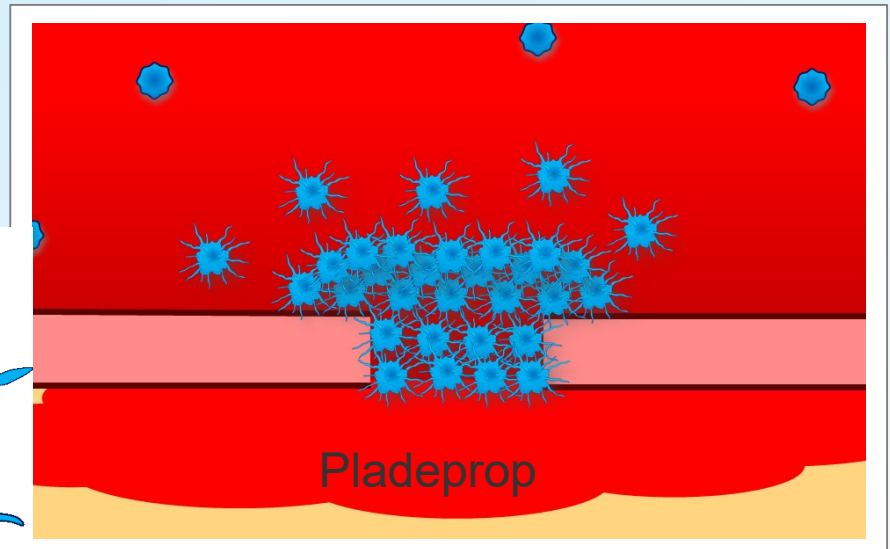
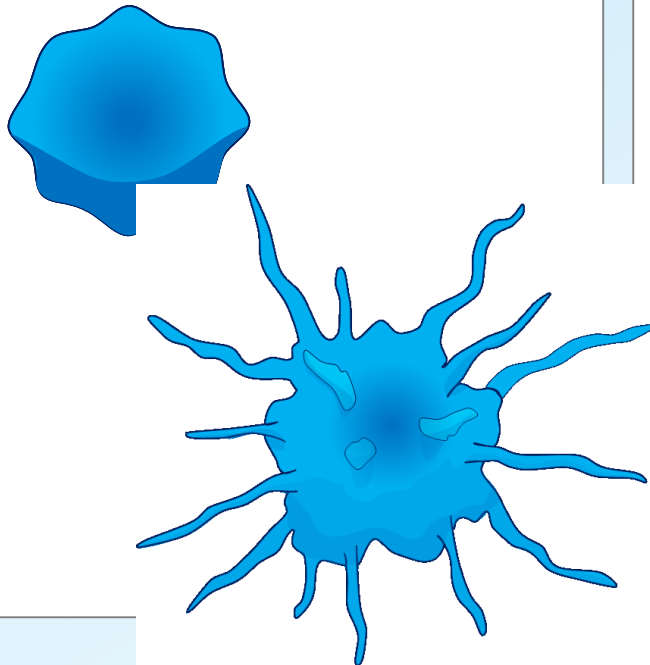
1. **Reaktion fra karvæggen** → Karret trækker sig sammen



Hæmostase

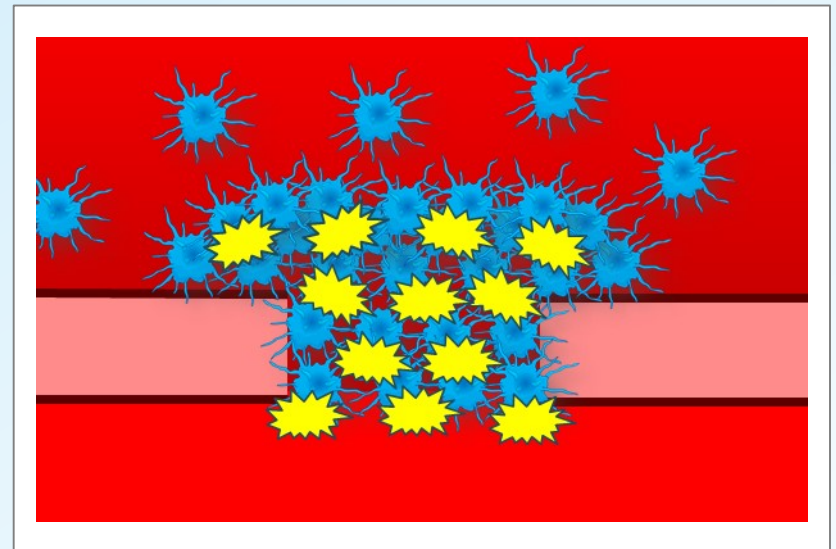
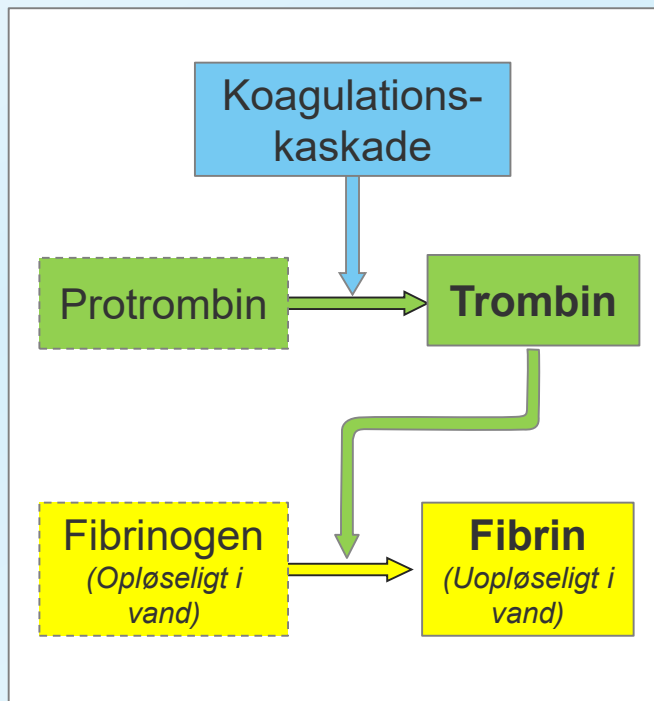
2. Dannelse af en *pladeprop*

Trombocyt aktivering



Hæmostase

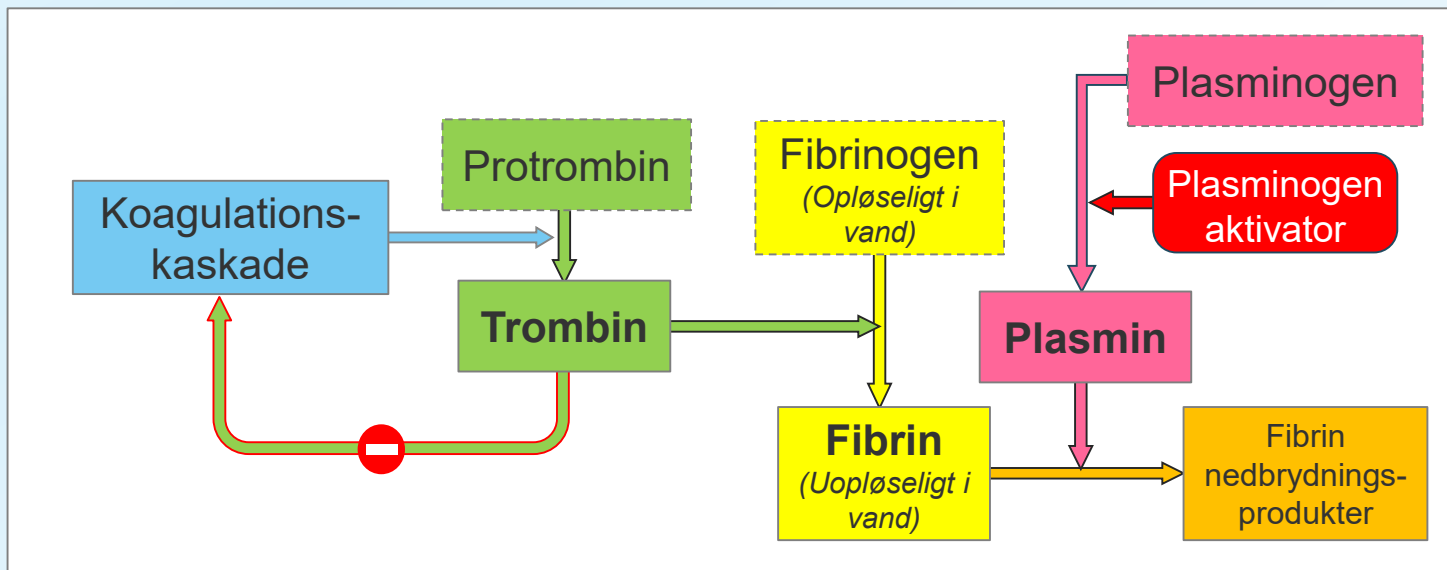
3. Dannelse af *fibrin* (Koagulation)



Hæmostase

4. Afgrænsning af blodproppen

- Fibrinolyse → nedbrydelse af fibrin vha. *plasmin*
- Inaktivering af koagulationsfaktorer



Hæmostase

Kan både aktiveres af faktorer fra *blodet* og faktorer fra *væv*

1. **Reaktion fra karvæggen** → Karret trækker sig sammen

2. **Dannelse af en *pladeprop*** ← Hæmmer processen

- Trombocyterne aktiveres → de binder sig fast til karvæggen og til hinanden og danner en

3. **Dannelse af *fibrin*** ← Hæmmer processen

- Koagulation af blodet → dannelse af *fibrin*

4. **Afgrænsning af blodproppen** ← Fremmer processen

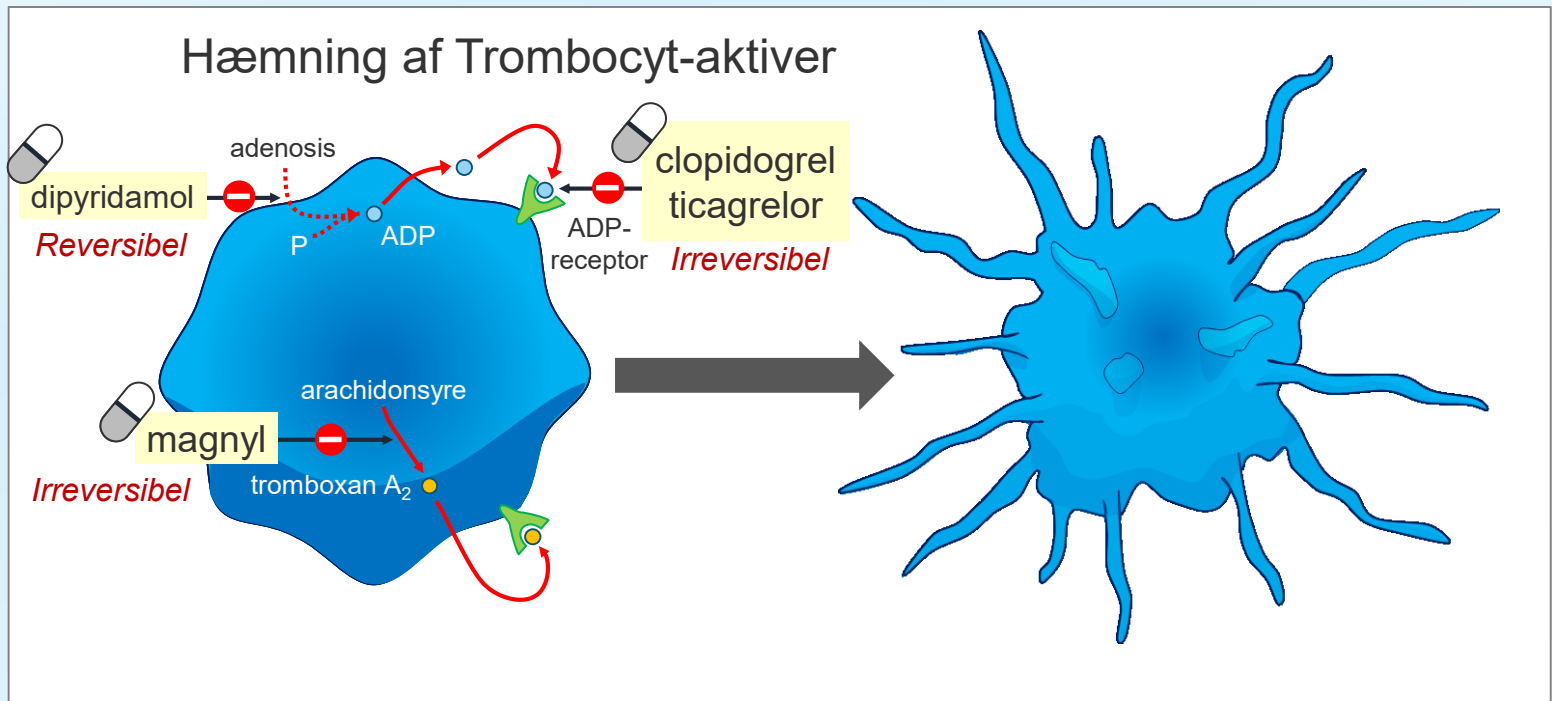
- Fibrinolyse → nedbrydelse af fibrin vha.
- Inaktivering af koagulationsfaktorer

Pladehæmmere
Magnyl, Clopidogrel,
Brilique

AK: Marevan
NOAK: Eliquis,
Xarelto, Pradaxa
(Hepariner)

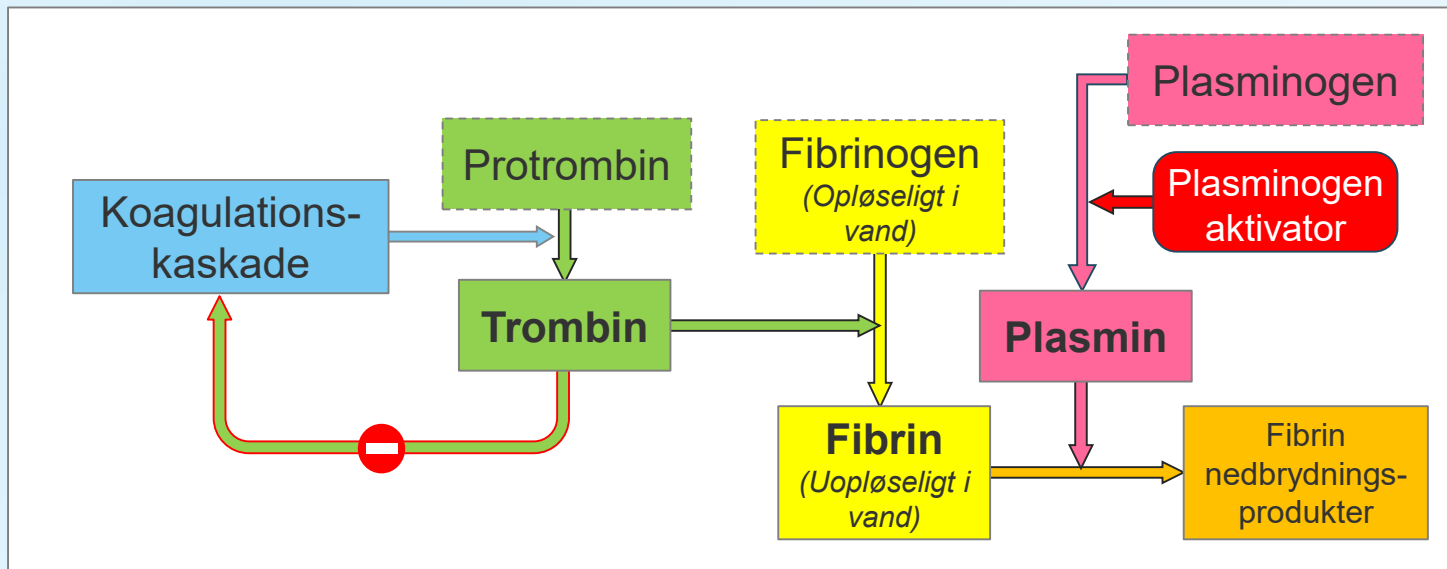
Trombolyse
Actilyse (Alteplase)

Tranexamsyre

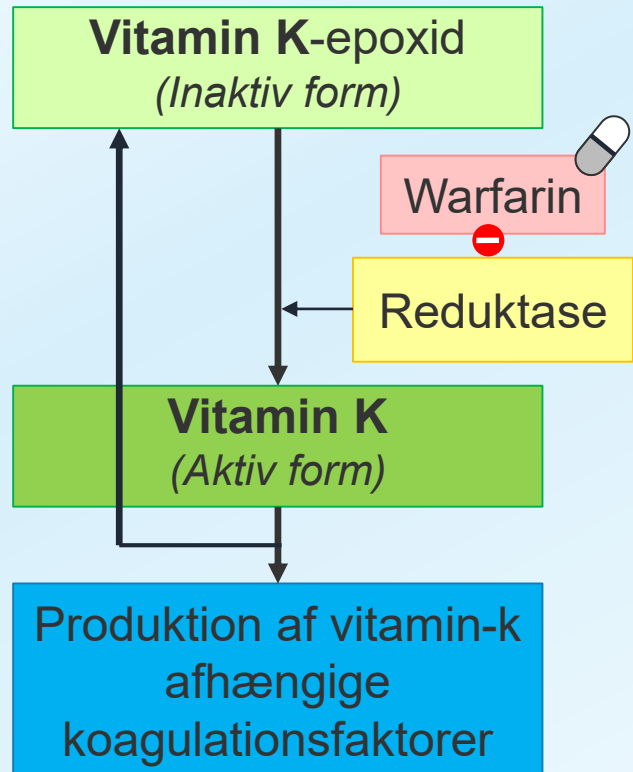


Antikoagulation (AK)-behandling

- Indirekte effekt (Warfarin)
- Direkte effekt (DOAK)
- Antitrombin III (Heparin)

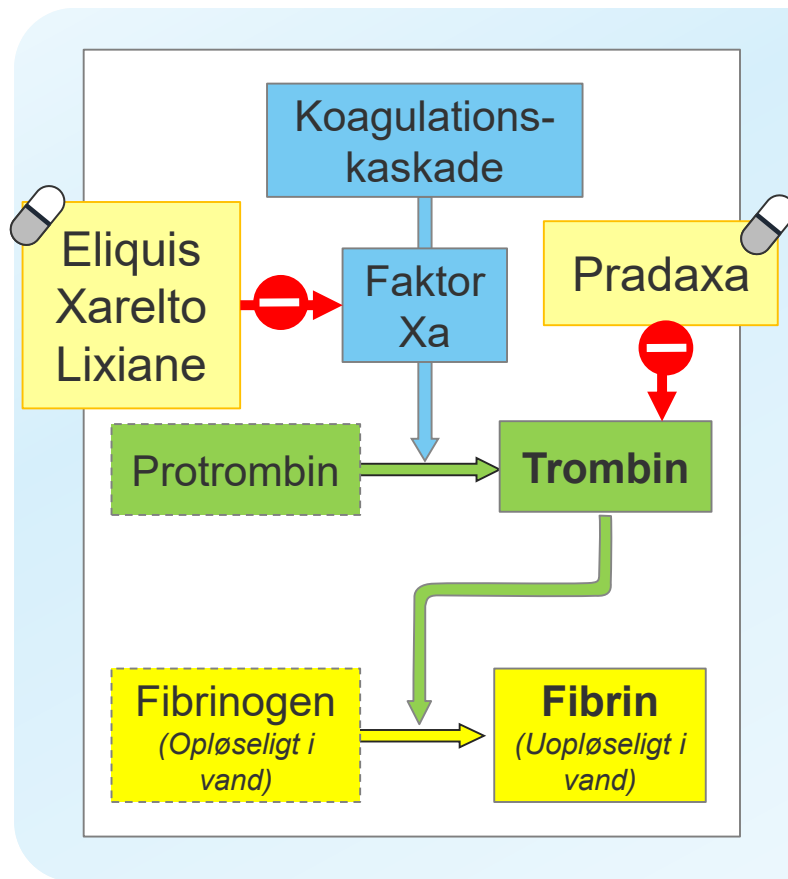


K-vitamin antagonister



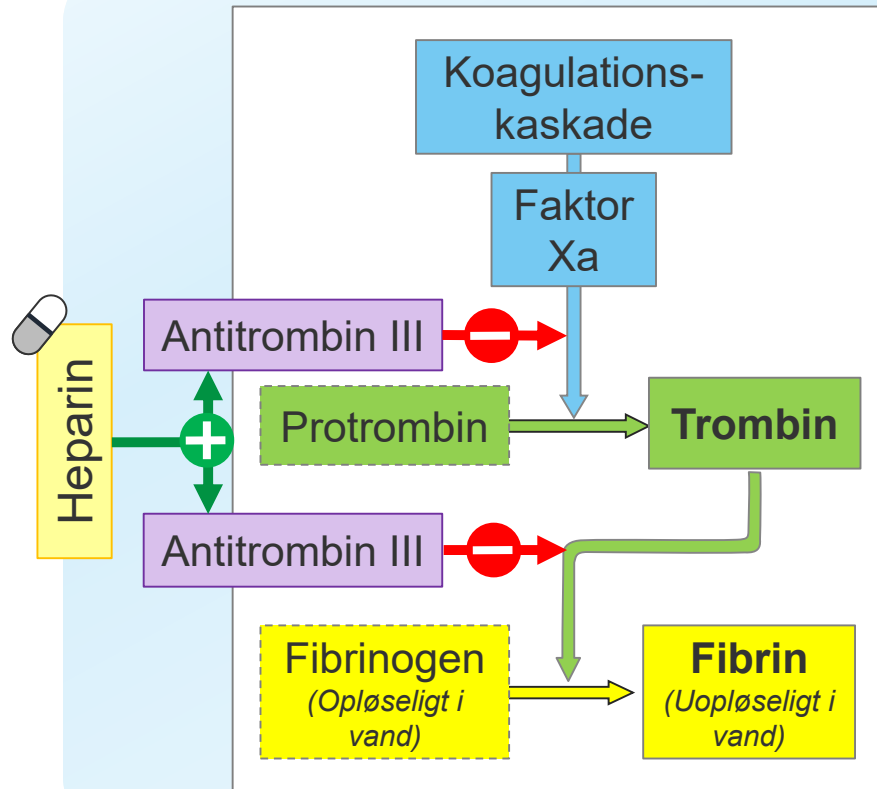
- Koagulationsfaktorerne produceres i leveren
- KF 2, 7, 9 og 10 kan kun produceres ved hjælp af aktivt Vitamin K
- Warfarin hæmmer aktiveringen af Vitamin K epoxid ved at hæmme enzymet *reduktase*
- Derved reduceres mængden af KF

Direkte Oral antikoagulation (DOAK)



- DOAK hæmmer koagulation ved direkte at hæmme enten Trombin eller Xa (Aktiveret Faktor 10)
- Virkningen er reversibel

Hepariner



- Hepariner virker ved at forstærke effekten af Antitrombin III
- Antitrombin III hæmmer både effekten af KF Xa og Trombin (KF IIa)

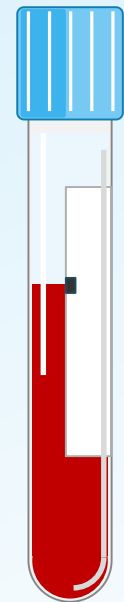
Marevan

DOAK

Effekt	Effekt omtrent ens, dog lidt færre bivirkninger ved DOAK	
Dosis	Variabel	Fast
Kost	Interaktion med vitamin-K- holdige fødevarer	Ingen interaktion Pradaxa kan ikke gives via sonde
Forsigtighed	Obs compliance og ændringer i kostindtag Interaktion med kosttilskud	Nedsat nyrefunktion, leversygdom, koagulationsforstyrrelser
Opfølgning	Behov for blodprøver og dosisjustering	Ingen
Forgiftning	Octaplex (Protrombin) IV vitamin-K og frisk frossen plasma	Pradaxa -> PraxBind Aktuelt ingen antidot for Xa-hæmmerne

Biokemi

- **PP** (P-koagulationsfactor 2, 7, 10)
 - Måler indhold/effekt af KF 2, 7 og 10 i blodet
- **INR** | International Normalised Ratio
 - Standardiseret omregning af PP
 - Anvendes til regulering af Marevan/Marcoumar dosis
- **APTT** (Aktiveret partiel tromboplastin tid)
 - Måler effekten af KF 1, 2, 5, 8, 9, 10, 11 og 12



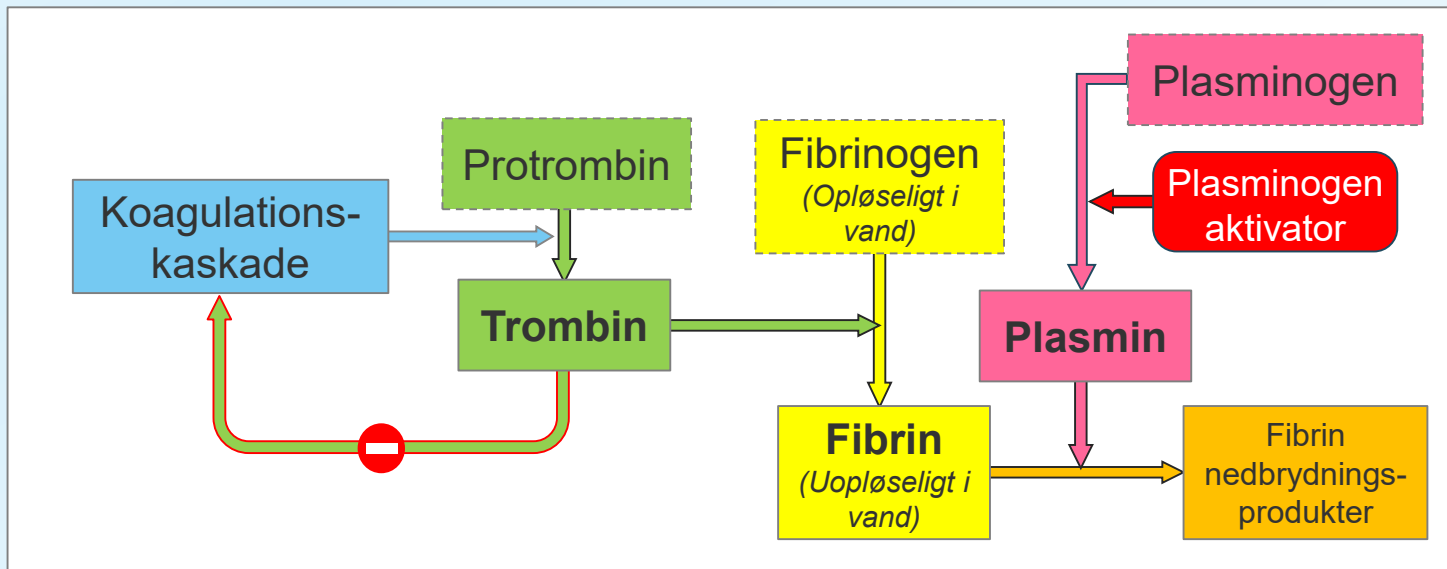
Tromboprofylakse ved iskæmisk apopleksi

Apopleksi	Loading dosis		Fast dosis
TCl/minor stroke	300 mg Clopidogrel eller 300 mg Magnyl		75 mg Clopidogrel eller 75 mg Magnyl
TCl/minor stroke + øget risiko	300 mg Clopidogrel <u>og</u> 300 mg Magnyl	75 mg Clopidogrel <u>og</u> 75 mg Magnyl i 3 uger	75 mg Clopidogrel eller 75 mg Magnyl
Storkarssygdom	300 mg Clopidogrel <u>og</u> 300 mg Magnyl	75 mg Clopidogrel <u>og</u> 75 mg Magnyl i 3-12 uger	75 mg Clopidogrel eller 75 mg Magnyl
Kardioemboli	300 mg Clopidogrel eller 300 mg Magnyl		DOAK eller Marevan (INR 2-3)
Emboli af anden årsag	300 mg Clopidogrel og/eller 300 mg Magnyl	Eventuelt LMWH	Marevan

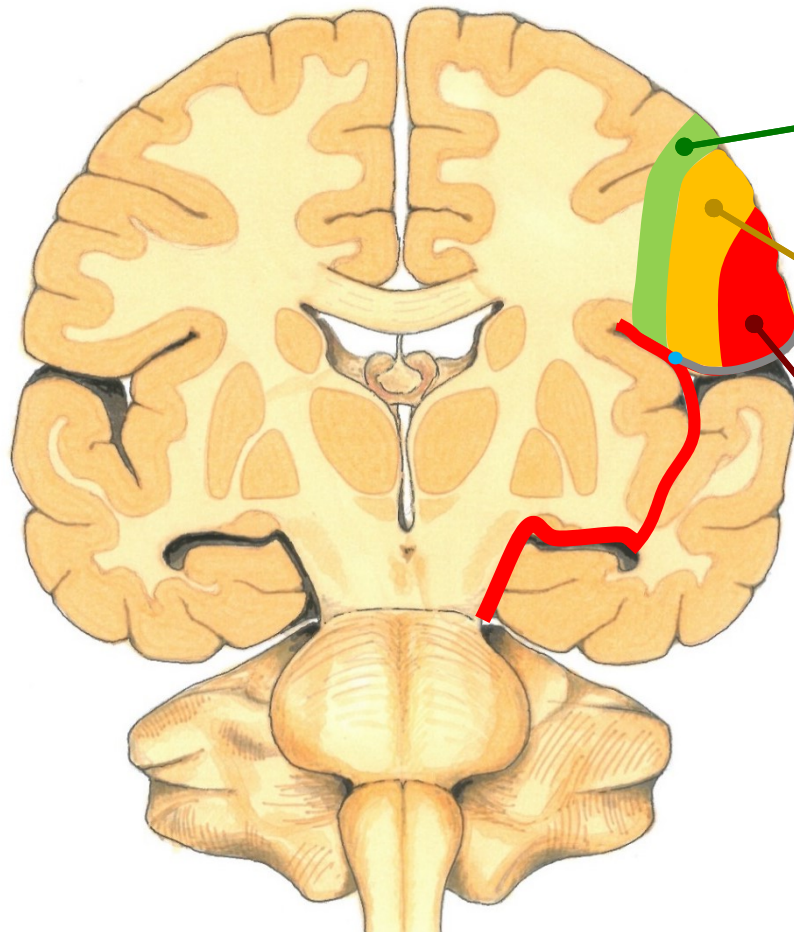
Trombolyse

Alteplase | Human vævsplasminogenaktivator (rt-PA)

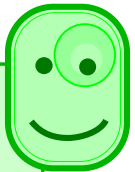
Aktivering af plasmin spalter fibrin-netværket i blodproppen, så blodproppen går i stykker



Hvad sker der i vævet?



Perfusion 100-50 %: Normal funktion



Perfusion 50-20 %: **Penumbra**

- Skift fra aerob til anaerob metabolisme
- Nedsat funktion af vævet, men cellerne kan overleve i noget tid



Perfusion <20 %: **Infarkt**

- ATP bliver brugt op i løbet af få minutter
- Alle ATP-afhængige processer ophører
- Cellerne dør



Illustration: Jacob Liljehult 2021

Kapløb med tiden

Articles

Time to treatment with intravenous alteplase and outcome in stroke: an updated pooled analysis of ECASS, ATLANTIS, NINDS, and EPITHET trials

Kennedy Ryan, Josh Bivard, Bridger van Kesteren, Thomas G Brott, Danilo Toni, James Grotts, Gregory M Albers, Mark Lofgren, John Malters, Scott Alexander, Barbara C Fling, Stephen M Davis, Geoffrey Desha, Wataru Hara, Jeyaraj G G, GILBERT, MICHEL, and EPITHET n 39 Study Group Investigators

Summary Background Early administration of intravenous recombinant tissue plasminogen activator (rt-PA) after ischaemic stroke improves outcomes. Previous analysis of combined data from individual patients suggested potential benefit beyond 3 h from stroke onset. We re-examined the effect of time to treatment with intravenous rt-PA (altered on therapeutic benefit and clinical risk) by adding recent trial data to the analysis.

Methods We added data from ECASS III (821 patients) and EPITHET (800 patients) to a pool of common data from three other trials of alteplase for acute stroke (2775 patients). We used multivariate logistic regression to assess the relation of stroke onset to time to treatment (OTT) with treatment on favourable 3-month outcome (defined as modified Rankin score 0–1), mortality, and occurrence and measures of clinically relevant parenchymal haemorrhage. The presence of an arterial occlusion was inferred from the patient's symptoms and absence of haemorrhage or other causes of ischaemic stroke. Vascular imaging was used as a supplement in the trials. All patients with confirmed OTT within 360 min were included in the analysis.

Findings Treatment was started within 360 min of stroke onset in 3670 patients randomly allocated to alteplase (n=2056) or no alteplase (n=1614). Odds of a favourable 3-month outcome increased as OTT decreased (p<0.001) and no benefit of alteplase treatment was seen after around 270 min. Adjusted odds of a favourable 3-month outcome were 1.55 (95% CI 1.44–1.67) for 0–30 min, 1.44 (1.32–1.57) for 30–60 min, 1.14 (1.04–1.25) for 60–90 min, 1.12 (1.02–1.23) for 90–120 min, and 1.22 (1.12–1.33) for 120–150 min in favour of the alteplase group. Large parenchymal haemorrhage was seen in 76 (5.2%) of 1456 patients assigned to alteplase and 11 (0.7%) of 1614 controls, with no clear relation to OTT (p=0.416). Adjusted odds of mortality increased with OTT (p<0.001) and were 0.78 (0.63–0.97) for 0–30 min, 1.12 (0.98–1.27) for 30–60 min, 1.22 (1.07–1.39) for 60–90 min, and 1.40 (1.25–1.57) for 90–120 min.

Interpretation Patients with ischaemic stroke selected by clinical symptoms and CT benefits from intravenous alteplase when treated up to 6 h. To increase benefit as a treatment, more often should be taken to shorten delay to initiation of treatment. But and 4–5 h, risk might outweigh benefits.

Funding Notes

Introduction The alteplase-based study has shown a subsequent benefit of early treatment with intravenous recombinant tissue plasminogen activator (rt-PA) in patients with acute ischaemic stroke. The National Institutes of Neurological Disorders and Stroke 2 (NINDS) and the USA, which started treatment within 3 h of stroke onset, and the European Cooperative Acute Stroke Study (ECASS) III trial in Europe, which started treatment 3–4 h after stroke onset. This study showed, independently, no conclusive benefit of early rt-PA treatment.^{1,2} Analysis of the pooled data suggested that benefit from treatment decreased as time from stroke onset to start of treatment increased.³ Thus, risk-benefit might change as the interval between stroke onset and treatment lengthens. Stroke registries have confirmed that some patients are treated with rt-PA beyond the currently approved time of 3 h from stroke onset.⁴ This approach might become more frequent because evidence from ECASS III suggests that treatment initiated at 3–4 h is safe and effective when patients with evidence of ischaemic brain injury on CT scan are included.⁵

Since the first trials were designed, investigators have cooperated to ensure that important common data elements were gathered to pooled trials of rt-PA for acute stroke. In this updated pooled analysis, we aimed to assess the effect of time to treatment with the intravenous rt-PA alteplase on therapeutic benefit and clinical risk. In particular, we postulated that the benefit of rt-PA would be smaller and the risk greater in patients who were treated at later times from stroke onset. We also aimed to assess the effect of reduced recovery of brain function after reperfusion and increased risk of death and brain haemorrhage.

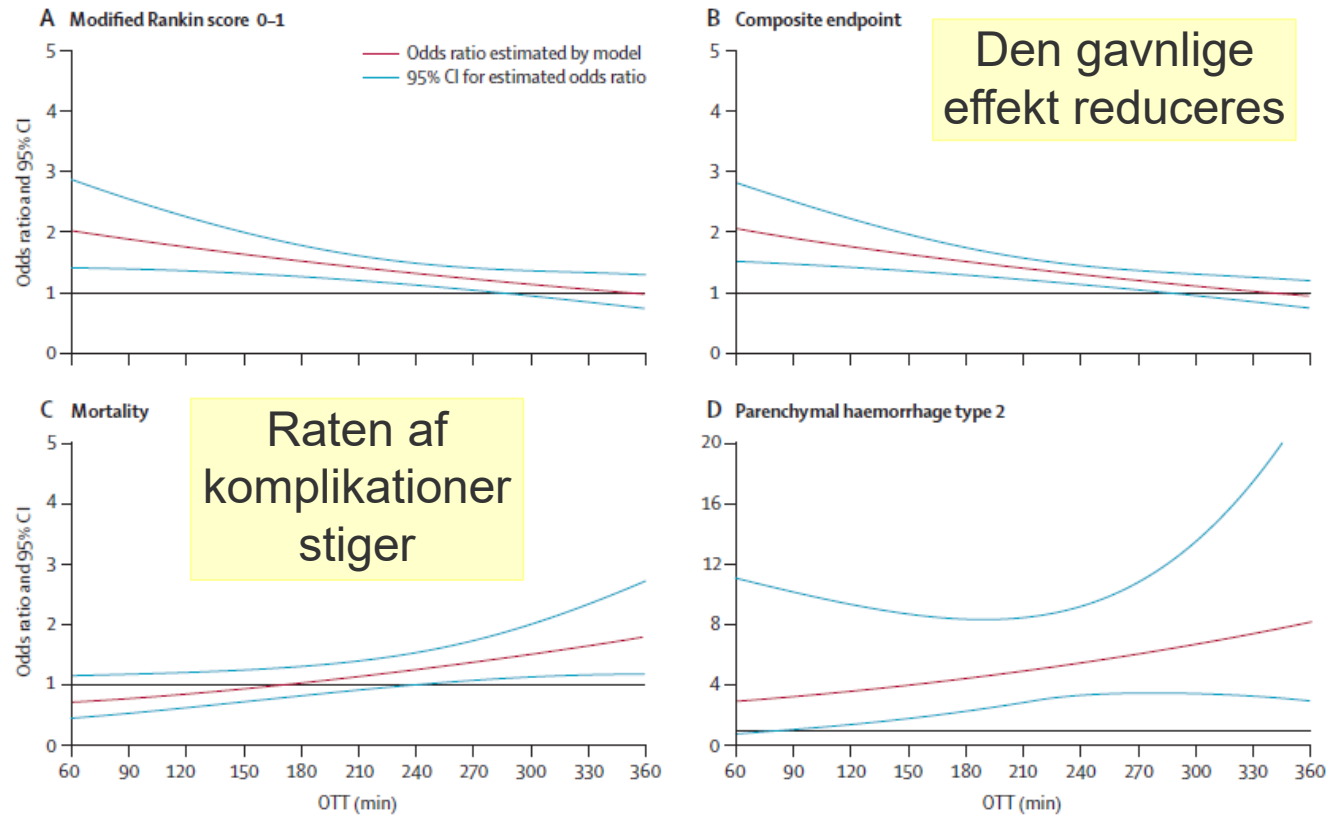
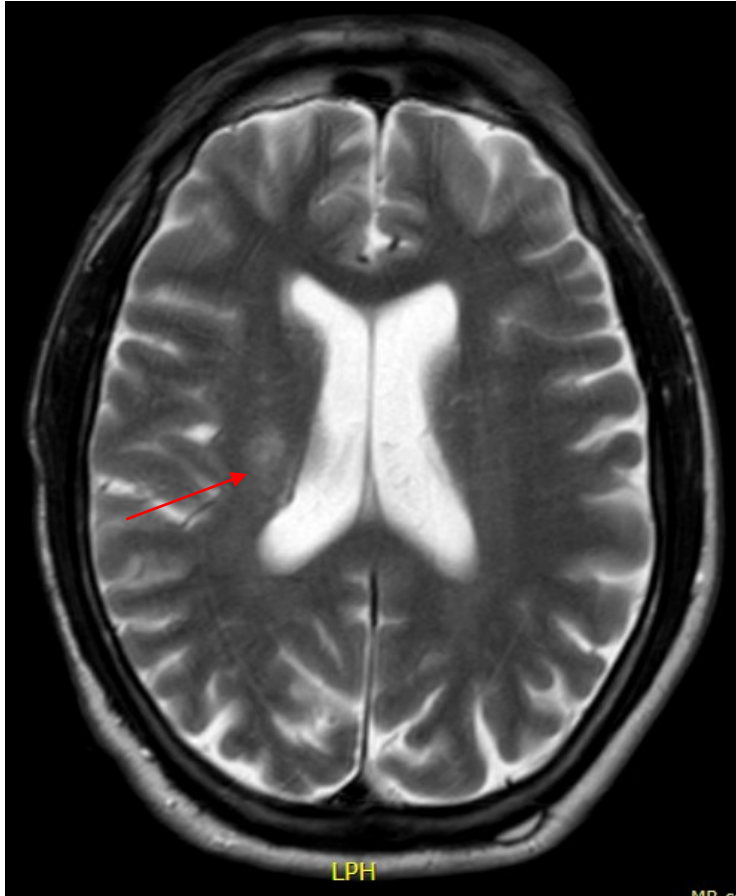


Figure 1: Relation of onset to treatment delay with treatment effect

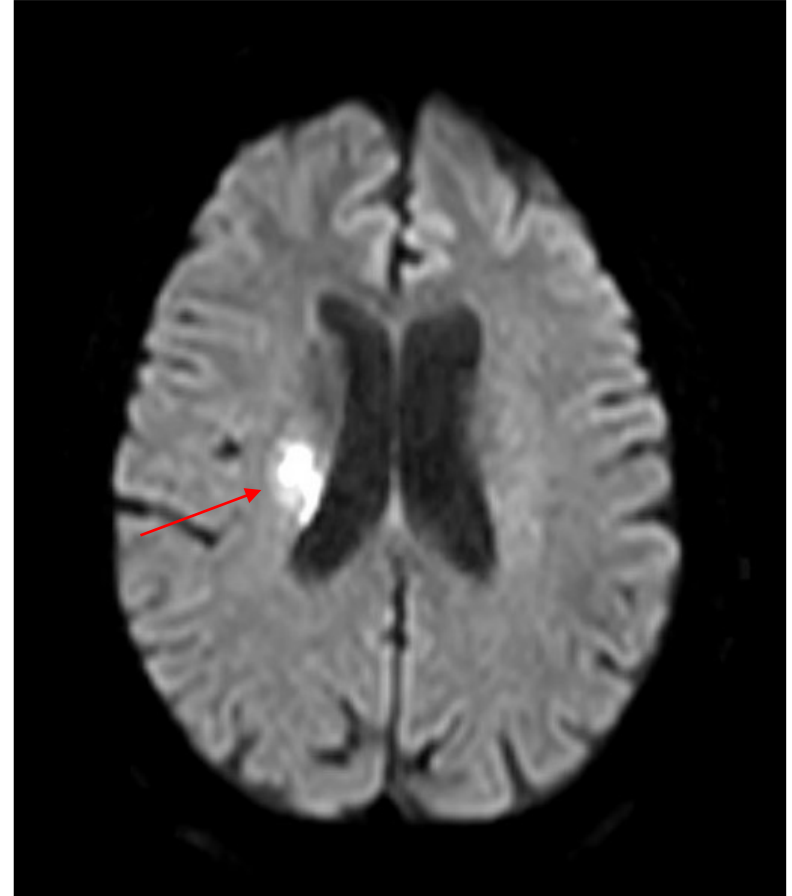
Den gavnlige effekt reduceres

Raten af komplikationer stiger

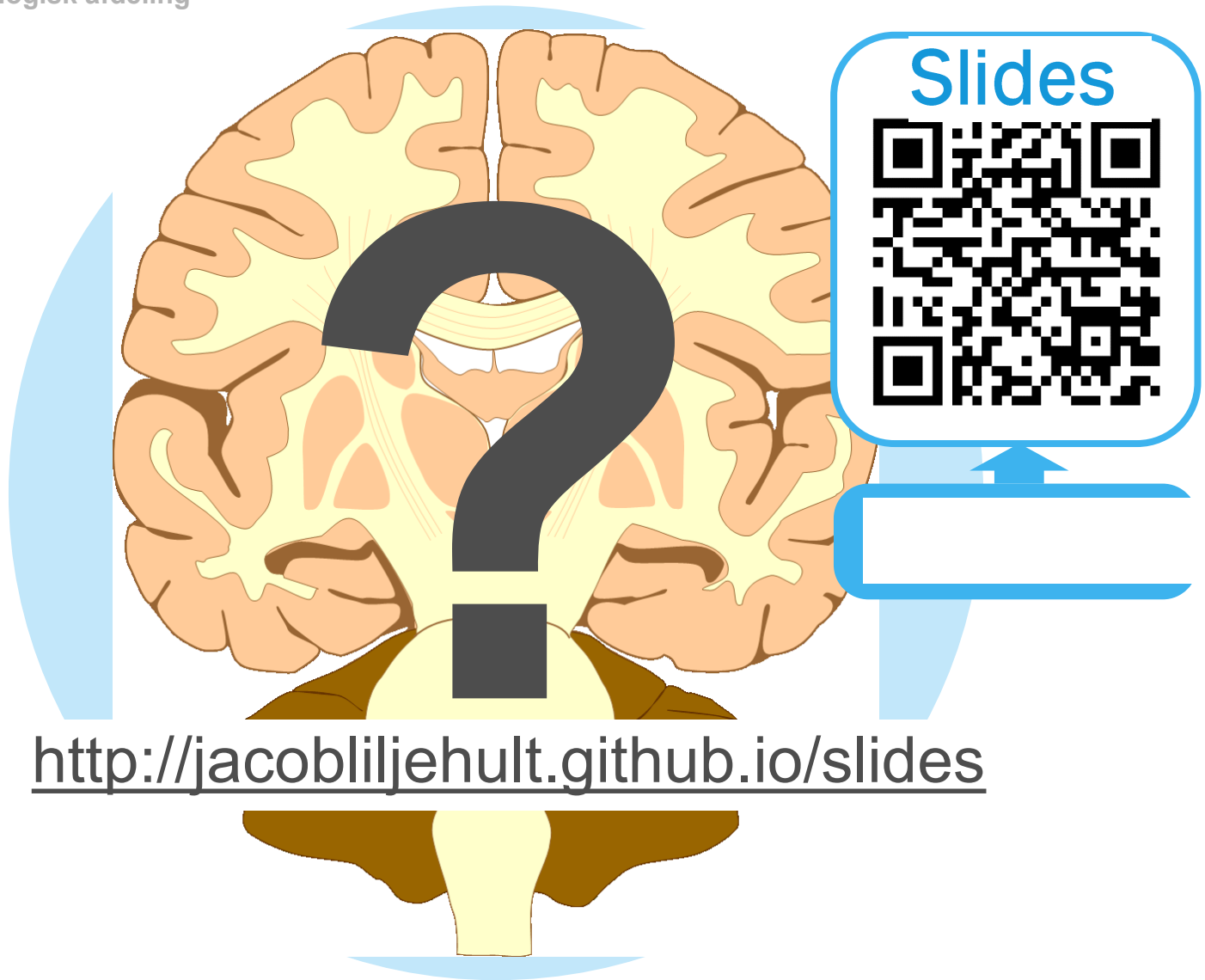
MR



T2-vægtet



Diffusionsvægtet (DWI)



<http://jacobliljehult.github.io/slides>

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