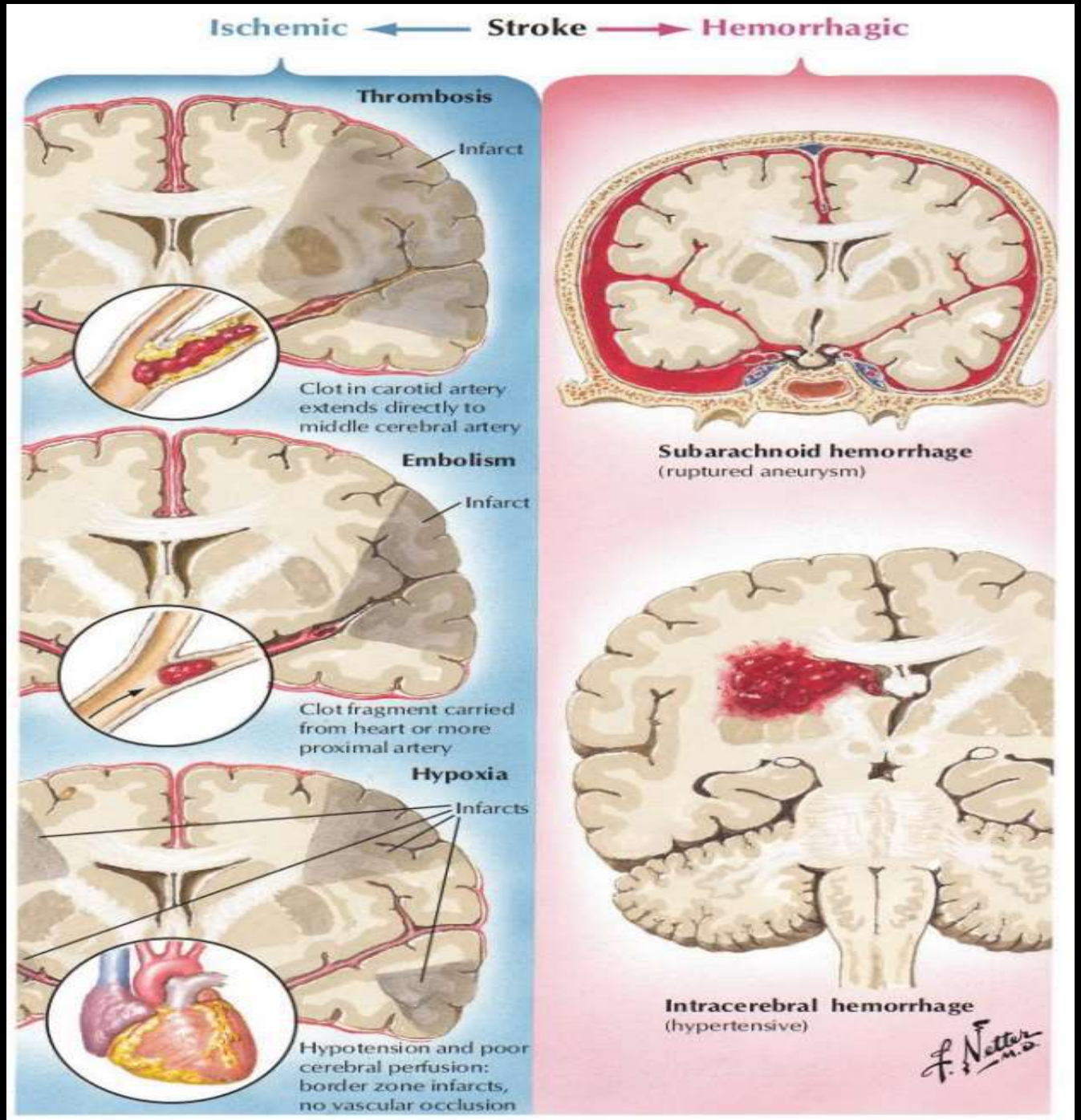
OBAT STROKE

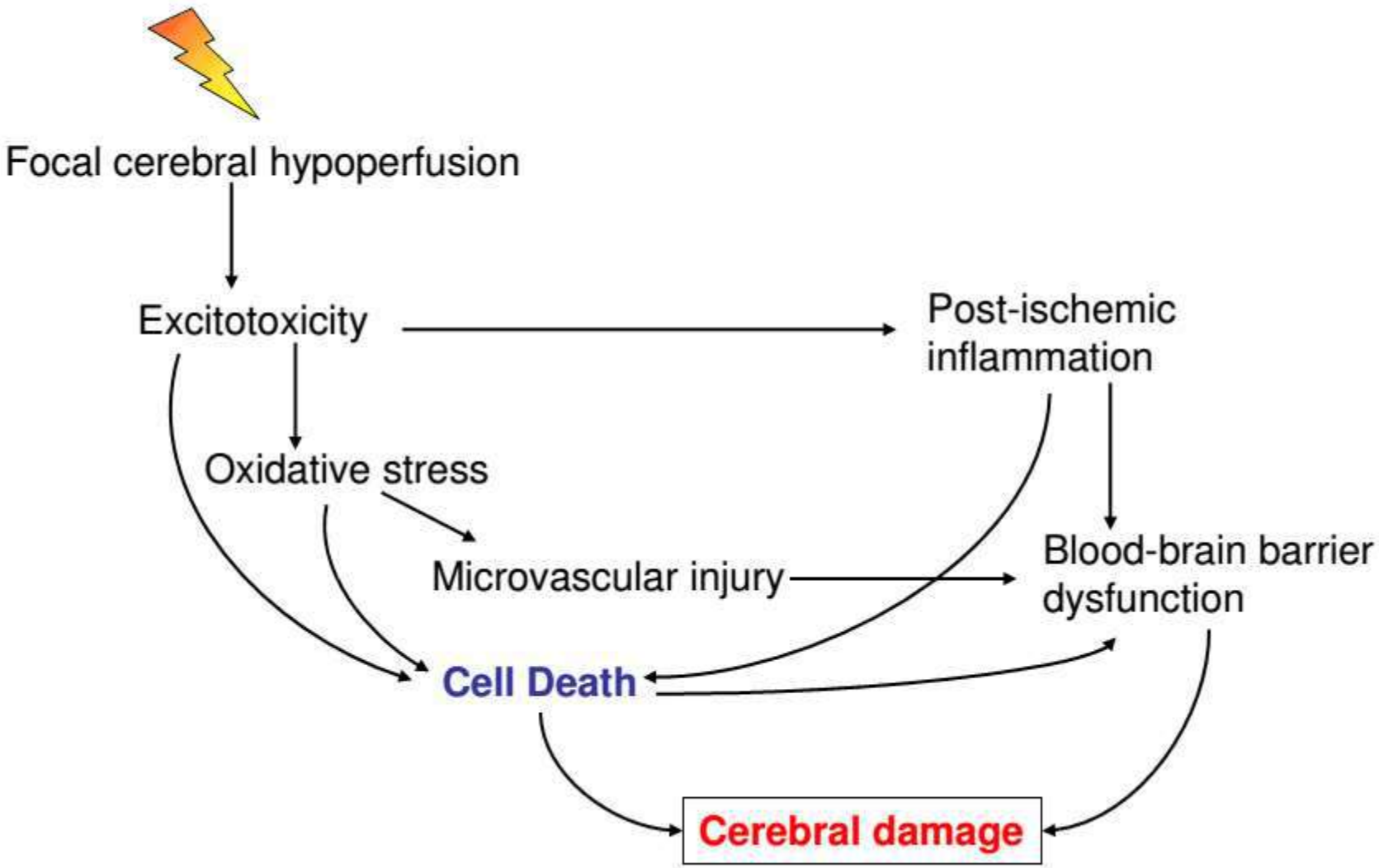
Fathiyah Safithri

Definisi

- Stroke adalah sindroma klinis yang ditandai oleh **disfungsi cerebral fokal atau global** yang berlangsung **24 jam atau lebih**, yang dapat menyebabkan disabilitas atau kematian yang disebabkan oleh perdarahan spontan atau suplai darah yang tidak adekuat pada jaringan otak.

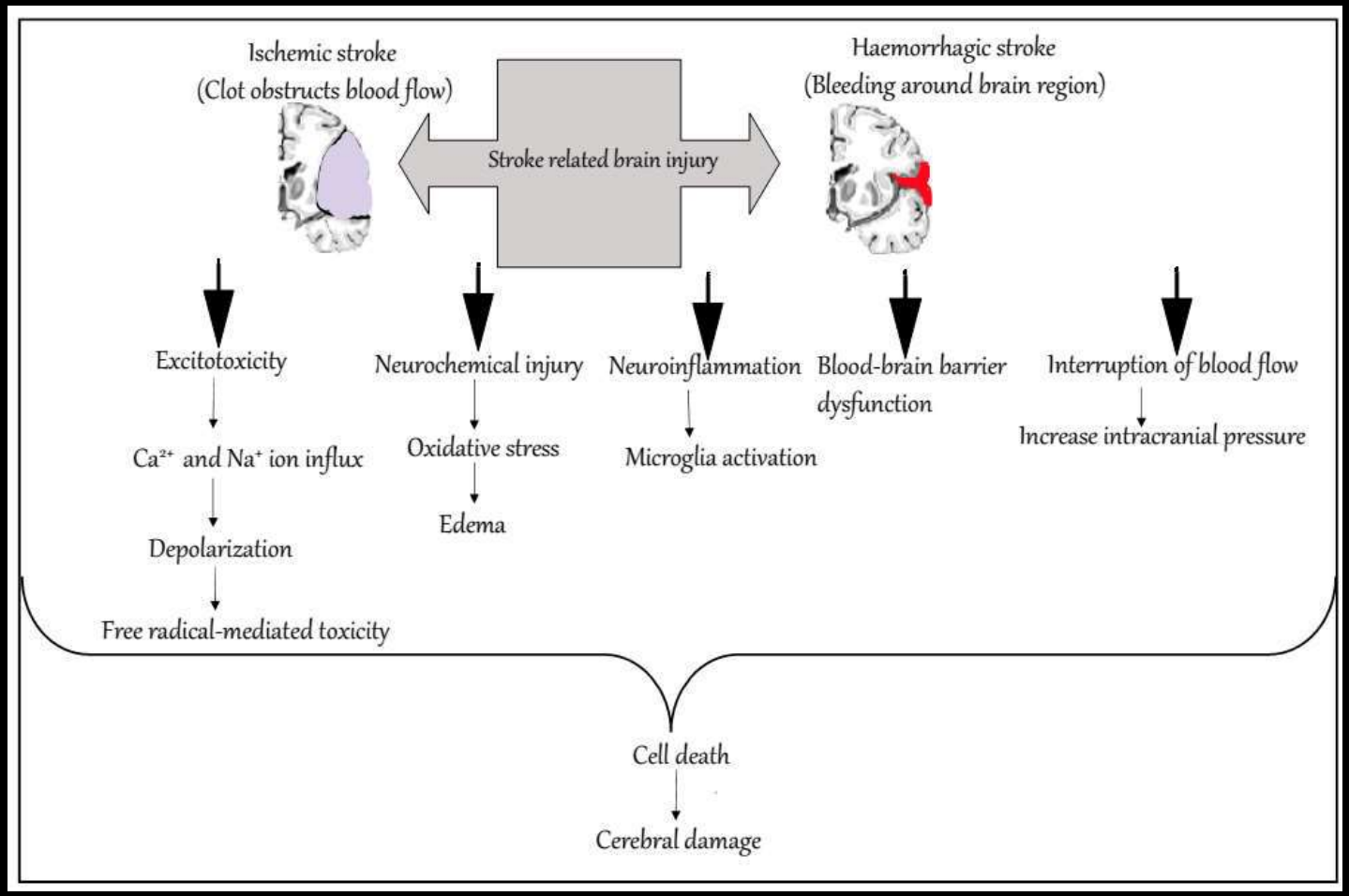

Ischemic
Stroke
Hemorrhagic
Thrombosis
Infarct
Clot in carotid artery extends directly to middle cerebral artery
Embolism
Infarct
Clot fragment carried from heart or more proximal artery
Hypoxia
Infarcts
Hypotension and poor cerebral perfusion: border zone infarcts, no vascular occlusion
Subarachnoid hemorrhage
(ruptured aneurysm)
Intracerebral hemorrhage
(hypertensive)
F. Netter M.D.

Stroke



Journal of Translational Medicine 2009, **7**:97

Molecular mechanism of stroke



Int. J. Mol. Sci. **2020**, *21*, 7609

FAKTOR RESIKO STROKE

Modifiable	Non-modifiable
Hipertensi	Usia – resiko meningkat dua kali lipat setiap dekade setelah usia 55 tahun
Kolesterol meningkat (statin menurunkan resiko 30%)	Sex – laki-laki memiliki resiko lebih besar namun wanita hidup lebih lama; lebih banyak wanita yang meninggal karena stroke (60% dari seluruh kematian stroke)
Diabetes mellitus (faktor resiko independen)	Ras: African-American, Asian dan Hispanik memiliki resiko lebih besar, diperkirakan akibat hipertensi
Penyakit jantung (penyakit katup atau pengganti katup, faktor yang menurunkan kontraksi ventrikel)	Diabetes Mellitus – diperparah oleh hipertensi atau kontrol glukosa yang rendah.
Atrial fibrilasi (3-4x resiko)	Riwayat keluarga dengan stroke atau TIA
Stroke sebelumnya	
Obesitas	
Alkohol berlebih	
Merokok (2x resiko iskemik meningkat, 4x resiko hemoragik meningkat)	
Kontrasepsi oral/Hormone replacement therapy	

Stroke Iskemik

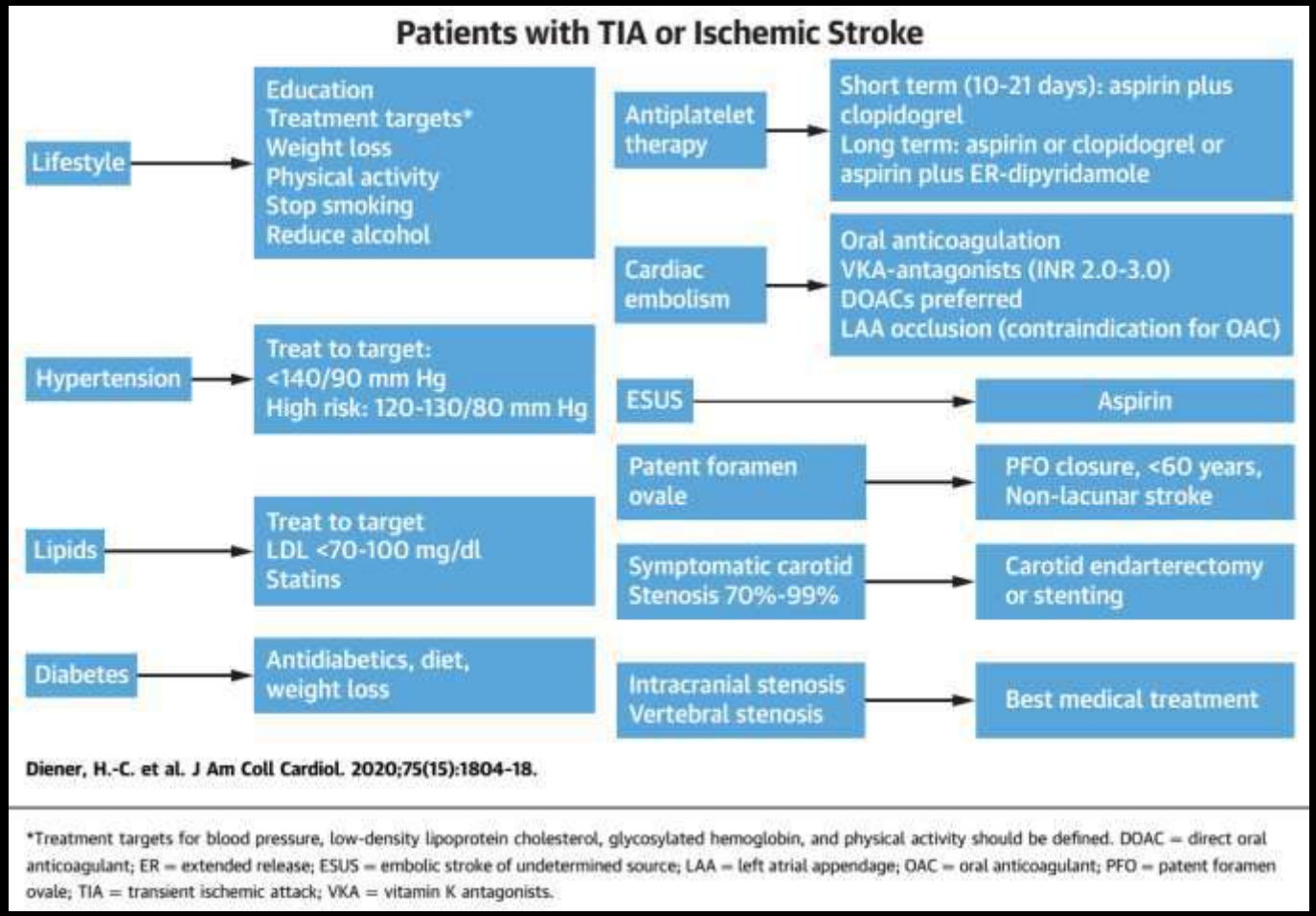
- merupakan disfungsi neurologis yang disebabkan oleh infark fokal **serebral**, **spinal** maupun **retinal**.
- ditandai : hilangnya sirkulasi darah tiba-tiba pada suatu area otak,
  dan secara klinis menyebabkan hilangnya fungsi neurologis dari area tersebut.
- disebabkan oleh thrombosis atau emboli pada arteri cerebral
- stroke iskemik lebih sering terjadi daripada stroke hemoragik

Recommendations for Pharmacotherapy of Ischemic Stroke

	Primary Agents	Alternatives
Acute Treatment	tPA 0.9 mg/kg IV[6,17] (maximum 90 kg) over 1 hour in selected patients within 3 hours of onset. ASA 160–325 mg daily[6,17] started within 48 hours of onset	tPA (various doses) intraarterially up to 6 hours after onset in selected patients
Secondary Prevention		
Noncardioembolic	Aspirin 50–325 mg daily[6] Clopidogrel 75 mg daily[6] Asprin 25 mg + extended-release dipyridamole 200 mg twice daily[6]	Ticlopidine 250 mg twice daily[6]
Cardioembolic (esp. atrial fibrillation)	Warfarin (INR = 2.5)[6]	
All	ACE inhibitor + diuretic or ARB[45] blood pressure lowering[33,34] Statin[39]	➔Stl 7hr fase akut

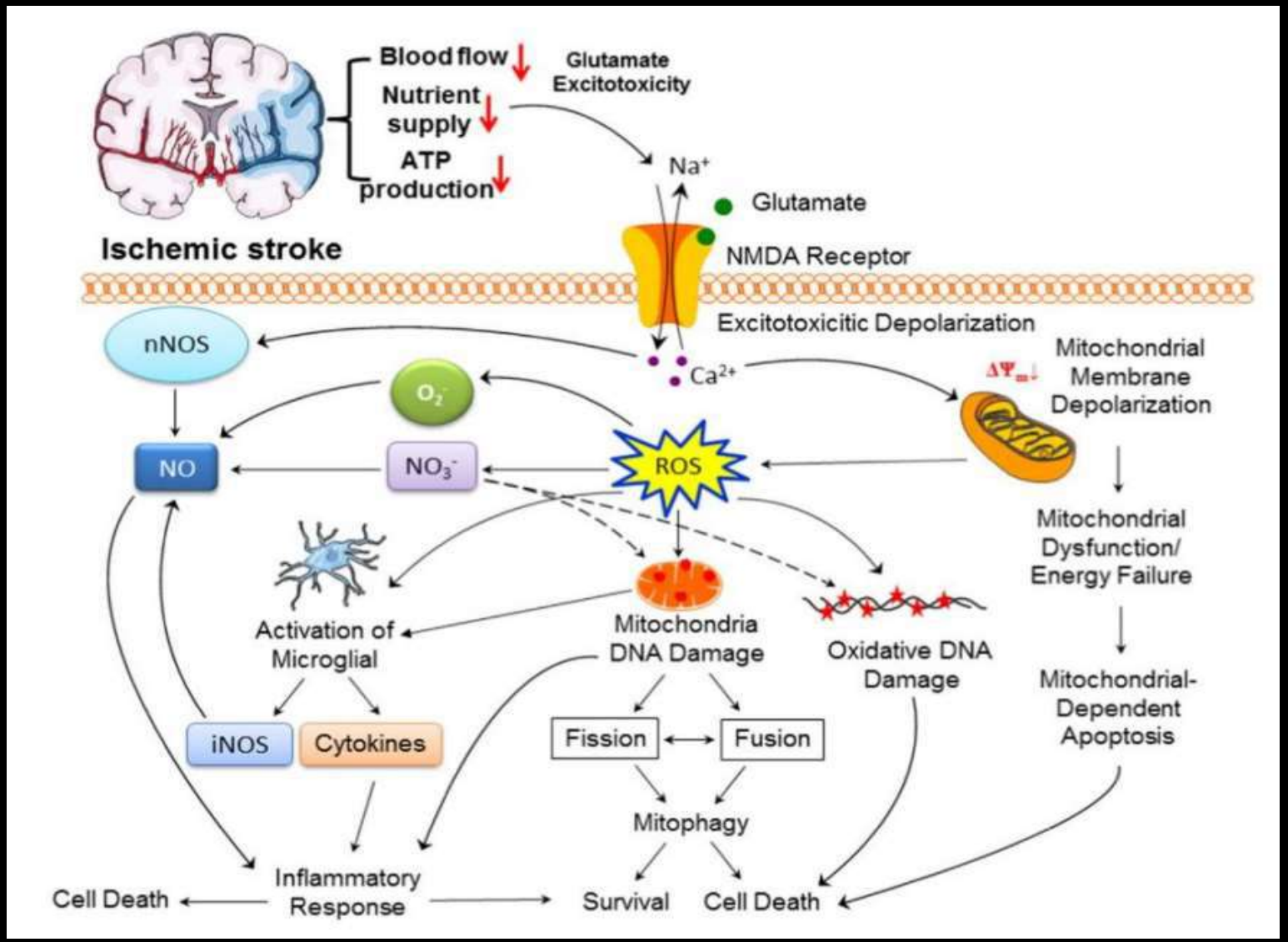
diambil dari Pharmacotheraphy-Pathophysiologic –Dipiro-2005

Secondary Prevention



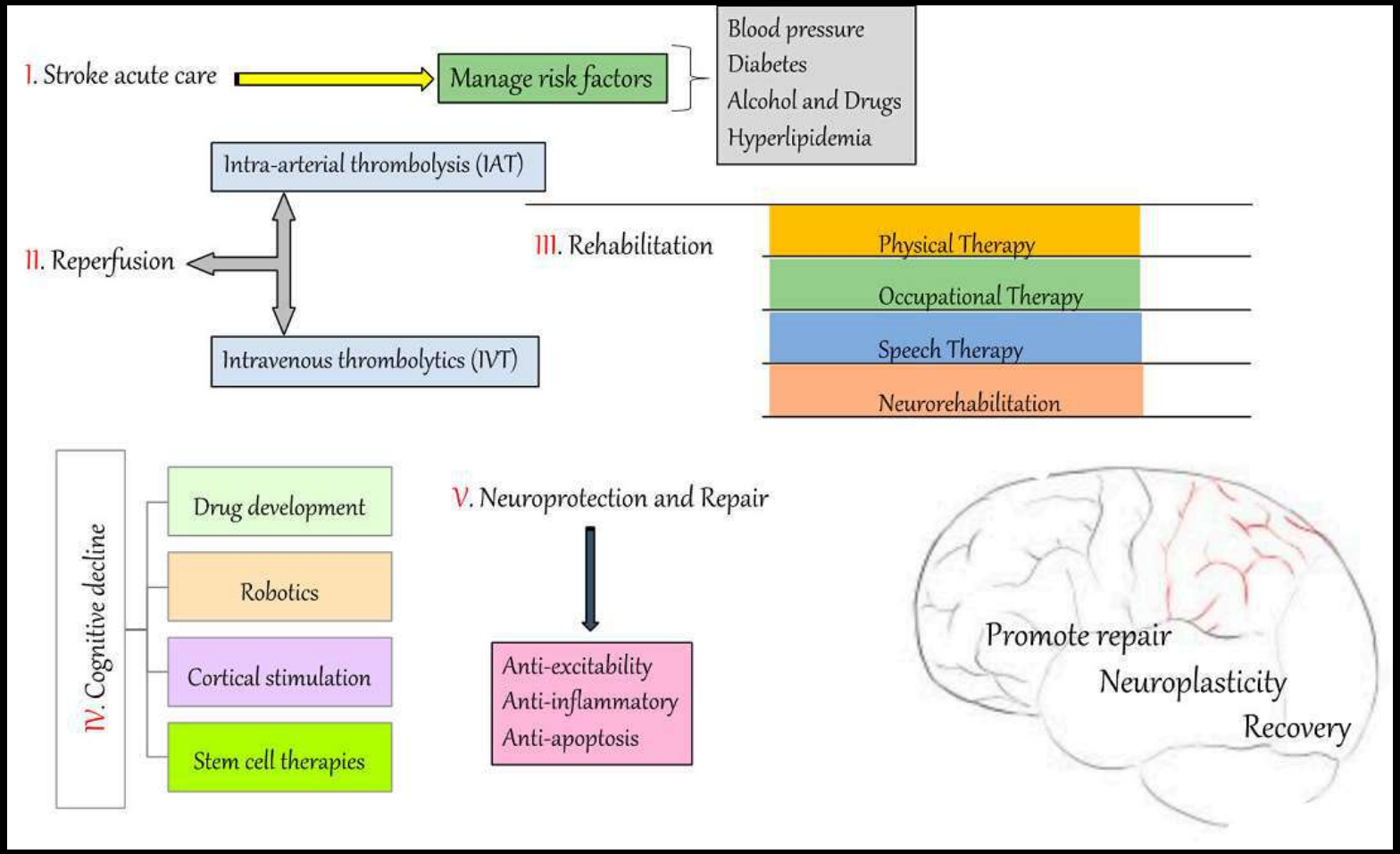
JACC VOL. 75, NO. 15, 2020
APRIL 21, 2020:1804-18

Kaskade iskemik setelah stroke



(Yang et al., 2018)

Stroke management strategis



STROKE ISKEMIK

Tujuan terapi pd Stroke Iskemik akut :

- Meminimalisir volume jaringan otak yg infark (irreversibel)
  - ➔Tx REPERFUSI
  - ➔Tx NEUROPROTEKSI
- Mencegah komplikasi
- Mencegah kecacatan
- Mencegah STROKE ULANG

STROKE ISKEMIK

- REPERFUSI

= memperbaiki aliran darah ke daerah iskemi sesegera mungkin

- NEUROPROTEKSI

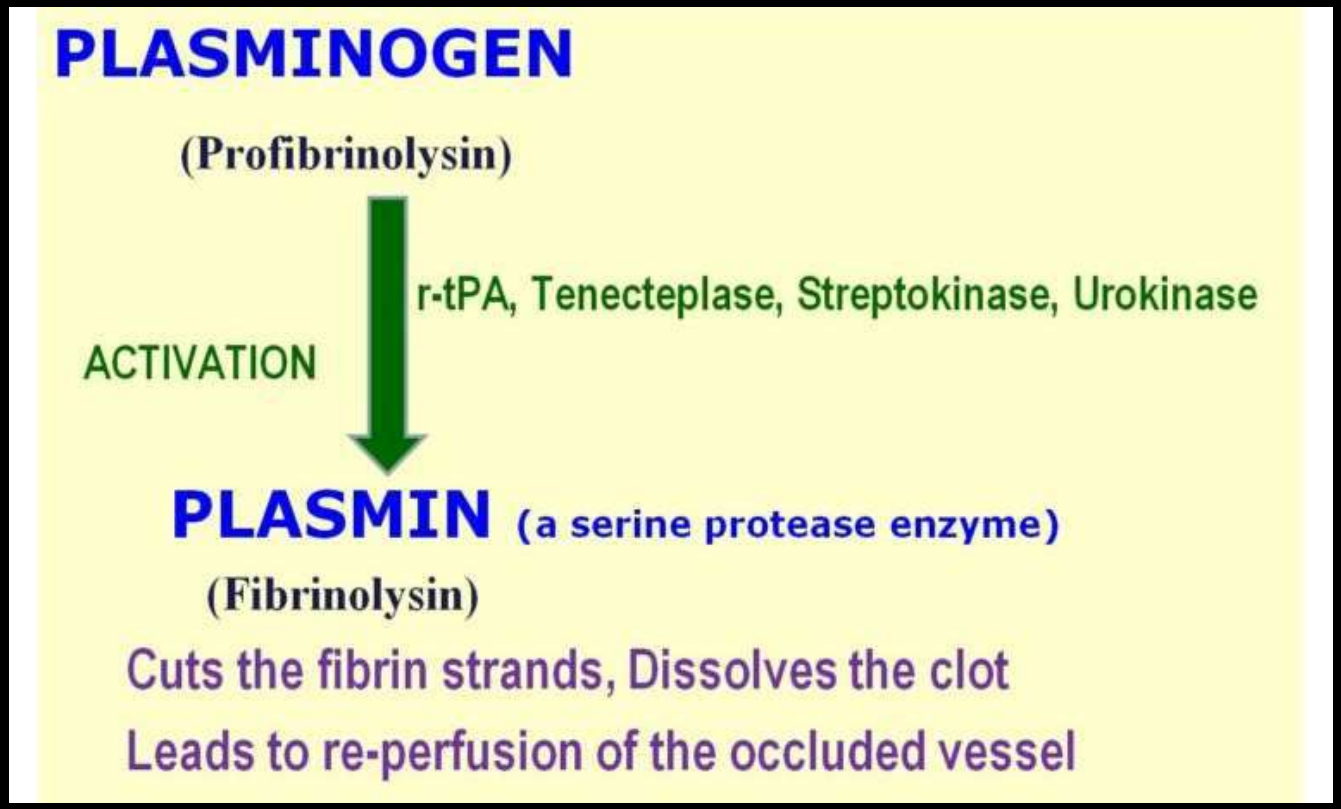
= melindungi sel dari kerusakan akibat iskemi (mencegah injury irreversible pada area iskemik penumbra)

OBAT UTK REPERFUSI

1. Menghancurkan trombus (Reperfusi dini, onset < 3 jam)
   ➔**Trombolitik**
2. Mencegah bekerjanya faktor2 koagulan (pd atrial fibrillasi, resiko emboli >>, antiplatelet tdk efektif cegah stroke ulang meski tdk ada risk emboli)
   ➔ **Antikoagulan**
3. Menghambat aggregasi platelet (stl 48 j fase akut, preventif sekunder)
   ➔**Antitrombotik / antiplatelet**

THROMBOLYTIC / FIBRINOLYTIC THERAPHY

TROMBOLITIK



Penggolongan

Golongan	Nama Obat	
Generasi I	Streptokinase Urokinase	Alami, tdk digunakan lg
Generasi II Tissue plasminogen activator (t-PA)	Alteplase Reteplase	Alami. Waktu paruh 3-4 menit
Generasi III recombinan-Plasminogen activator (r-PA)	Tenecteplase	bioengineered variant of alteplase with 80-fold larger resistance to inactivation by plasminogen activator inhibitor-1 and longer half-life **(14-45 menit)**
Generasi IV	desmoteplase	Uji klinik fase III

The specificity for bound plasmin enhance from first to fourth generation. Moreover, the more fibrin-selective the protease is the higher is the probability that it stimulate the clot-bound rather than the circulating plasminogen.

Alteplase

- **Intravenous Thrombolysis**
  - IV r-tPA was a major milestone in stroke treatment, as the first disease-modifying therapy for Acute Ischemic Stroke (AIS)
  - Recommended (AHA/ASA): 3 to 4.5 hr of symptom
    onset, no hemorrhagic (CT scan)
  - Limitation: unresponsiveness to large thrombi
- **Intra-arterial Thrombolysis**
  - using catheters that are delivered intra-arterially (IA) to the site of the intracranial clot to recanalize the occluded vessel
  - Recommended : 6 hr of symptom onset

Kriteria Indikasi dan Kontraindikasi Pasien Stroke Iskemik Akut yang Dapat Menggunakan rtPA dalam 3 jam Setelah Onset

Indikasi	Kontraindikasi	Kontraindikasi relatif*
• Diagnosis stroke iskemik dengan gangguan neurologis yang terukur • Usia ≥ 18 tahun	• Riwayat stroke atau trauma kepala dalam 3 bulan terakhir • Adanya gejala pendarahan subaraknoid • Riwayat pengambilan sampel darah pada arteri yang tidak terkompresi dalam 7 hari terakhir • Riwayat pendarahan intrakranial • Neoplasma intrakranial, malformasi arteriovena, atau aneurisma • Riwayat operasi intrakranial atau intraspinal dalam jangka waktu dekat • Tekanan darah sistolik >185 mmHg atau diastolik >110 mmHg • Pendarahan internal aktif • Trombosit < 100.000/mm^3 • Riwayat penggunaan heparin dalam 48 jam, dengan adanya peningkatan aPTT lebih dari angka normal • Menggunakan antikoagulan dengan INR >1,7 atau PT >15 detik • Menggunakan *direct thrombin inhibitor* atau *direct factor Xa inhibitor* dengan peningkatan parameter laboratorium seperti (aPTT, INR, trombosit, ECT, TT) • Gula darah < 50mg/dL • CT menunjukkan infark multilobar	• Perbaikan gejala stroke yang cepat • Kehamilan • Kejang • Operasi besar atau trauma dalam 14 hari terakhir • Riwayat pendarahan pada saluran cerna atau saluran kencing dalam 21 hari terakhir • Riwayat infark miokard dalam 3 bulan terakhir

*memerlukan pertimbangan *risk to benefit* untuk pemberian fibrinolitik pada pasien dengan kondisi tersebut. aPTT (*activated partial thromboplastin time*); CT (*computed tomography*); ECT (*ecarin clotting time*), PT (*partial thromboplastin*); INR (*international normalized ratio*); rtPA (*recombinant tissue plasminogen activator*); TT (*thrombin time*)

Jauch EC, Saver JL, Adams HP Jr, Bruno A, Connors JJ, Demaerschalk BM, et al. Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2013 Mar;44(3):870-947.

Kriteria Tambahan Indikasi Dan Kontraindikasi Pasien Stroke Iskemik Akut yang dapat menggunakan rtPA 3 – 4,5 Jam Setelah Onset

Indikasi	Kontraindikasi relatif*
• Diagnosis stroke iskemik dengan gangguan neurologis yang terukur	• Usia > 80 tahun • Stroke berat (NHSS>25) • Menggunakan antikoagulan oral tanpa memperhatikan nilai INRnya • Riwayat stroke iskemik dan diabetes

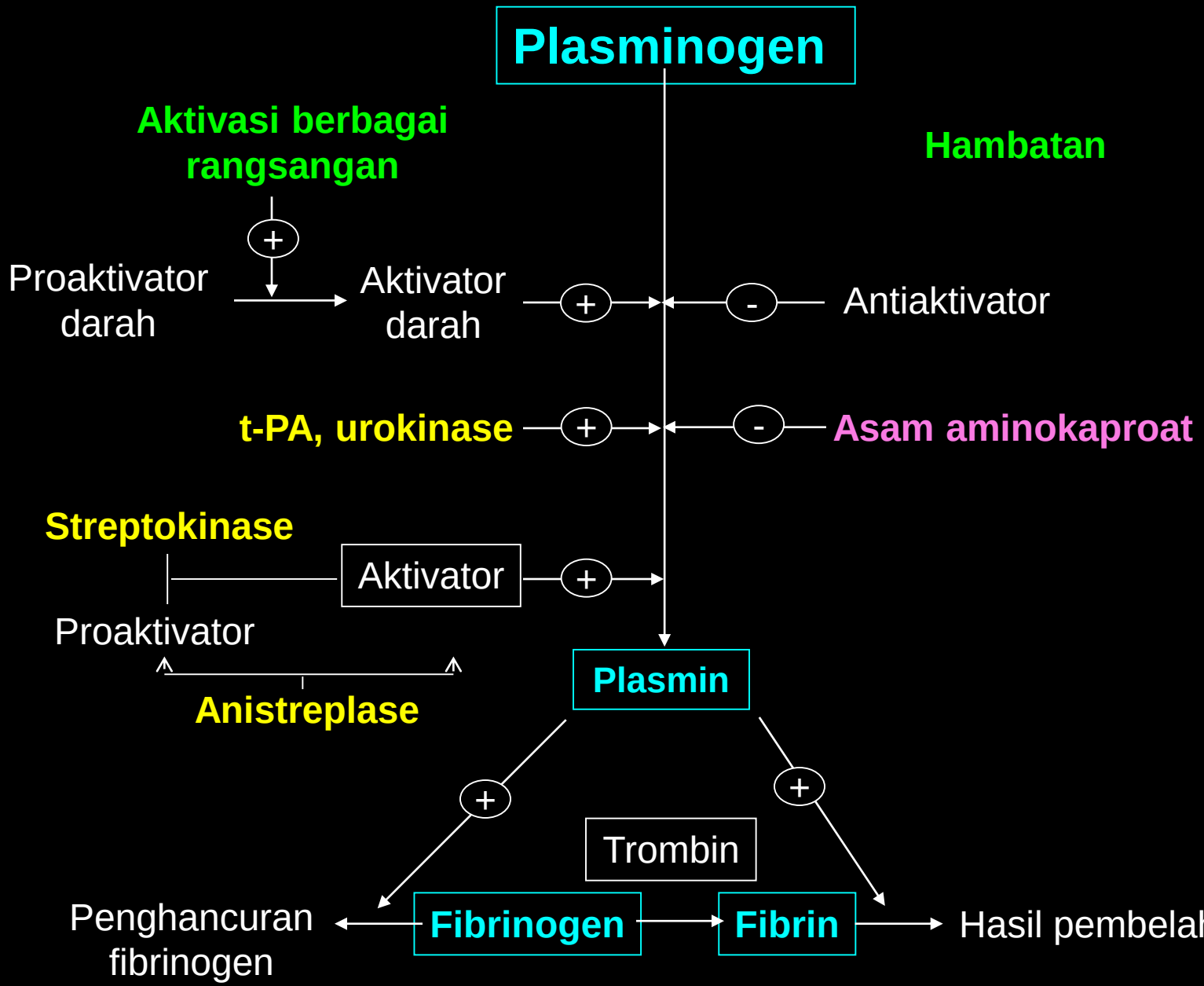
*memerlukan pertimbangan *risk to benefit* untuk pemberian fibrinolitik pada pasien dengan kondisi tersebut. INR (*international normalized ratio*); NHSS (*National Institutes of Health Stroke Scale*); rtPA (*recombinant tissue plasminogen activator*)

Jauch EC, Saver JL, Adams HP Jr, Bruno A, Connors JJ, Demaerschalk BM, et al. Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2013 Mar;44(3):870-947.

Aturan Penggunaan rtPA (alteplase)

- Infus 0.9 mg/kg IV (maksimal dosis 90 mg) selama 60 menit, dengan 10% dosis diberikan bolus selama 1 menit.[8,9]
- Untuk memudahkan proses monitoring pasien dirawat di ICU atau stroke unit
- Hentikan infus rtPA apabila pasien mengeluhkan nyeri kepala yang berat, hipertensi akut, mual, muntah atau terjadi perburukan pada pemeriksaan neurologis
- Monitor tekanan darah dan penilaian neurologis disarankan tiap 15 menit selama dan setelah terapi IV rtPA selama 2 jam, kemudian tiap 30 menit selama 6 jam, kemudian tiap jam selama 24 jam setelah terapi rtPA
- *Follow up* CT scan dan MRI scan 24 jam setelah terapi rtPA, tetapi sebelum memulai terapi antikoagulan atau antiplatelet

Skema Mekanisme Kerja Trombolitik



Mekanisme Kerja Trombolitik

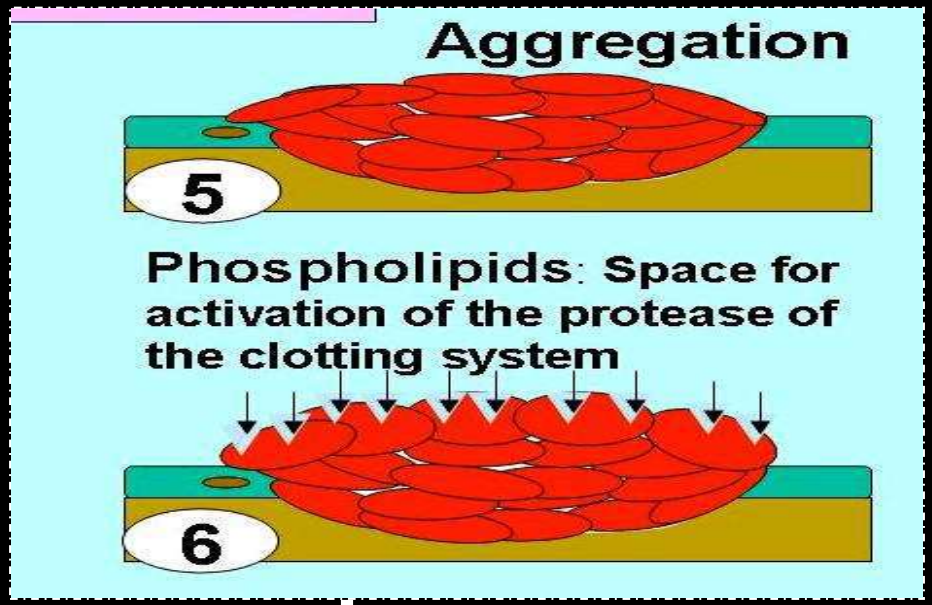
Streptokinase (dr Streptokokkus)	Bergabung dgn plasminogen & membentuk kompleks aktivator → kompleks aktivator mengkatalisa perub plasminogen menjadi plasmin →hidrolisa fibrin plug, fibrinogen & fakt V & VII →clot hancur
Urokinase (dr sel ginjal mns)	•Sec langsung mengubah plasminogen menjadi plasmin dg memotong ikatan arginin-valin pd plasminogen • sec langs merusak fibrin & fibrinogen
Alteplase / Recombinant Tissue plasminogen activator (rt-PA)	Aktivitas enz tgt ada/tdknya fibrin. Sec cepat mengaktivasi plasminogen yg terikat pd fibrin. Kurang mempengaruhi plasminogen yg bebas → ES bleeding sistemik << (teori), klinik : induksi sistem lisis → bleeding

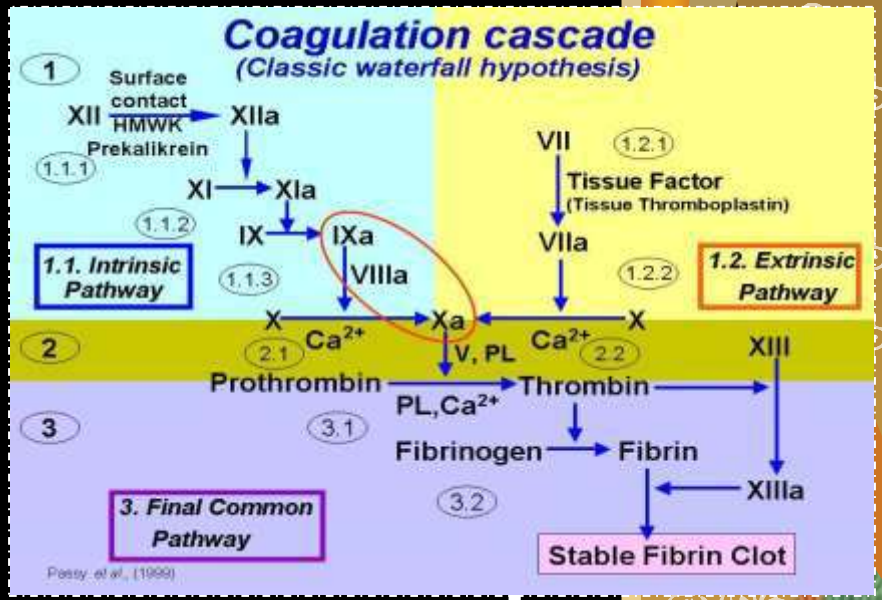
Table 8. Eligibility Recommendations for IV Alteplase in Patients With AIS

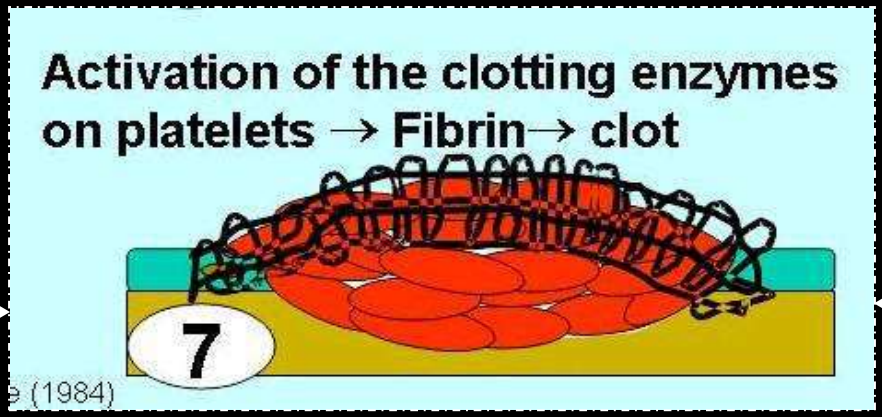
Indications (COR I)	
3–4.5 h–Age	IV alteplase treatment in the 3- to 4.5-h time window is recommended for those patients ≤80 y of age, without a history of both diabetes mellitus and prior stroke, NIHSS score ≤25, not taking any OACs, and without imaging evidence of ischemic injury involving more than one-third of the MCA territory.† *(COR I; LOE B-R)*§
Urgency	Treatment should be initiated as quickly as possible within the above-listed time frames because time to treatment is strongly associated with outcomes.† *(COR I; LOE A)*
BP	IV alteplase is recommended in patients with BP <185/110 mm Hg and in those patients whose BP can be lowered safely to this level with antihypertensive agents, with the physician assessing the stability of the BP before starting IV alteplase.† *(COR I; LOE B-NR)*§
Blood glucose	IV alteplase is recommended in otherwise eligible patients with initial glucose levels >50 mg/dL.† *(COR I; LOE A)*
CT	IV alteplase administration is recommended in the setting of early ischemic changes on NCCT of mild to moderate extent (other than frank hypodensity).† *(COR I; LOE A)*

ANTICOAGULANT THERAPHY

FASE KOAGULASI







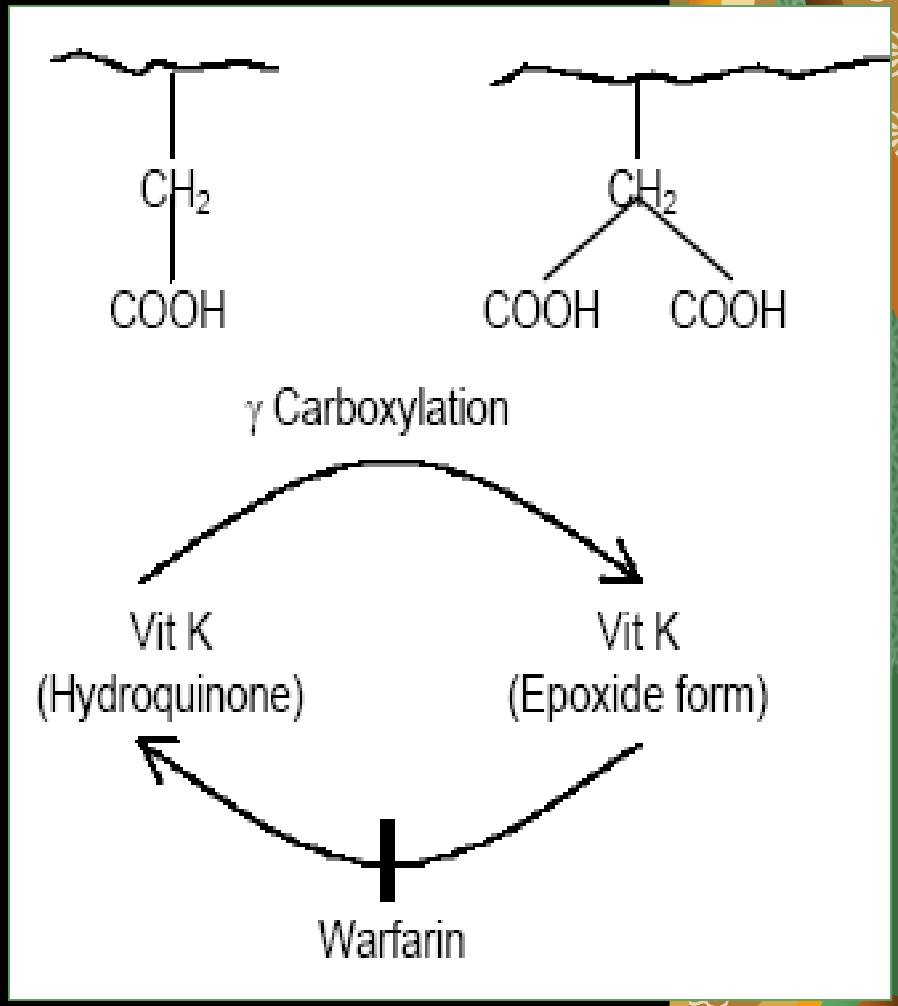
Goal : Stop bleeding (fibrin-clot formation)
Components : clotting-coagulation factors
Process : secondary hemostatic plug formation (fibrin-clot formation)

Mekanisme Kerja Antikoagulan

Heparin Enoxaparin	Berikatan dgn AT III → me↑ aksi ATIII → AT III hambat protease fak. pembekuan (fak. IIa, Xa, IXa) → hambat proses pembekuan darah **Tdk digunakan pada stroke akut, beresiko tjd transformasi hemorrhagic**
Warfarin (Antikoagulan oral)	Cegah reduksi vit. K teroksidasi → aktivasi fak.koagulasi (II, VII, IX, X, prot C & prot S) di hepar terganggu

WARFARIN

- Mek kerja : hamb enz vit- K epoxide reductase → me ↓ prod vit K yg aktif (reduced hydroquinone), yg diperlukan sbg cofaktor proses γ-karboksilasi u/ aktivasi fakt koagulan yg dependen vit K (fakt II, VII, IX, X, prot C dan S
- Efek antikoagulan timbul stl proses karboksilasi tdk terjadi →Efek antitrombotik tampak stl Tx hr ke-5
- Paling efektif mencegah stroke pd pt atrial fibrillasi
- Long half life, slow onset
- ES : bleeding
- KI : ibu hamil (teratogenik)



Faktor yg mempengaruhi Effikasi Warfarin

Faktor pasien

- Effikasi me ↑: pe ↓ BB, usia > 80th, akut illness, ggn fs hepar, gagal jantung, gagal ginjal, peminum alkohol]
- Effikasi me ↓ : pe ↑BB, diare & vomit, usia< 40th,

Interaksi Obat

- me ↓ ikatan prot :aspirin, fenilbutazon, CPZ, sulfinpirazon
- Hamb metab warfarin :simetidin, eritromisin, Na valproat
- me ↑metab warfarin: fenitoin, barbiturat, karbamazepin
- me ↓ sintesa fakt II, VII, IX, X : fenitoin, salisilat
- me ↓absorbsi vit K : AB broad spektrum, laxative
- me ↑resiko ulkus peptik: NSAID, Steroid
- Trombolitik : tPA, Streptokinase
- Antiplatelet drug : Aspirin, NSAID

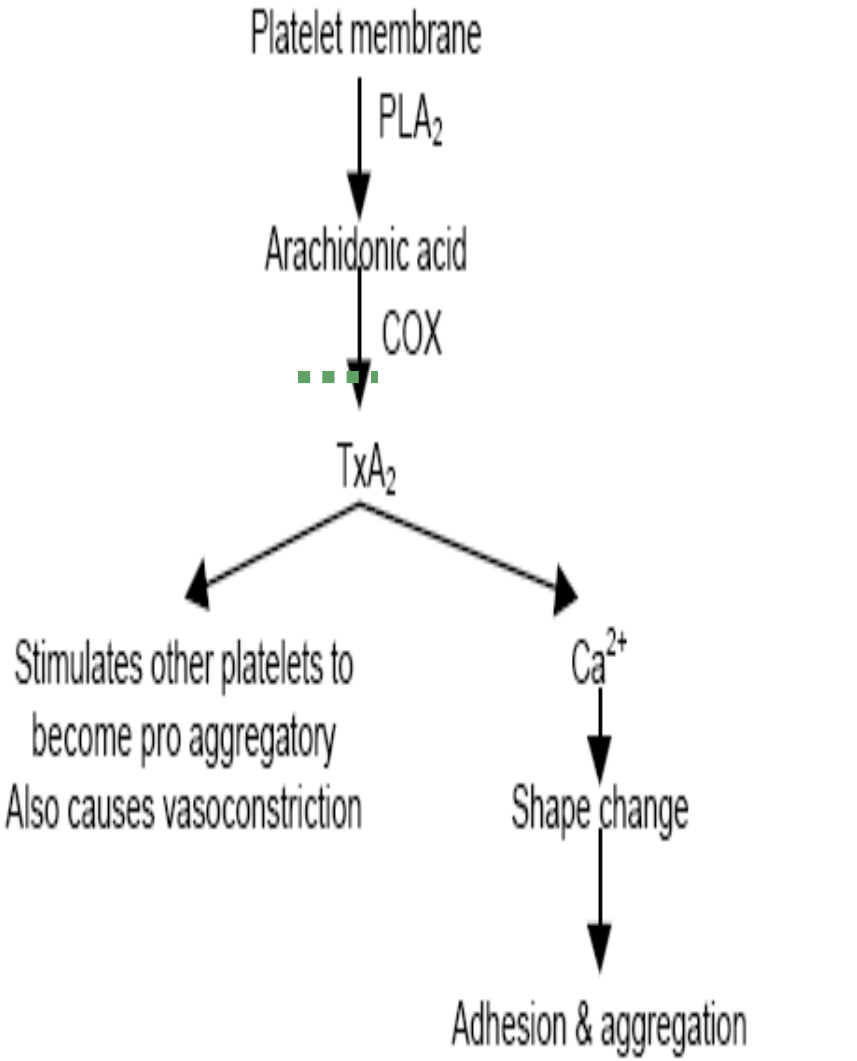
ANTITROMBOTIK

= Menghambat aggregasi platelet & pembent trombus

a.Menghambat sintesa TXA2 : **aspirin**

b.Antagonis reseptor ADP (adenosin diphosphate) : **ticlopidine, clopidogrel**

ASPIRIN



- ✓ **Mek kerja : Menghambat enz COX1 ➔ perub AA menj PGH2↓ ➔produksi TXA2 ↓ & PGI2 ↓**
- ✓ **Relatif selektif thd COX-1 (hamb thd COX1>200x diband COX2)➔pd dosis kecil cend bekerja pd COX1**
- ✓ **Supresi agregasi platelet selama 7-10 hr (=ms hidup platelet). COX1 diasetilasi o/ aspirin sec irreversibel & tdk dpt diresintesa oleh platelet ok tdk punya nuklei**

ASPIRIN (lanj)

- ✓ Cepat diabsorbsi di GIT
- ✓ Sebag alami first pass di hepar menj salisilat
- ✓ Distribusi luas
- ✓ Hemostasis kembali normal stl 36 jam (Sutul release platelet baru)
- ✓ Efektifitas dlm me↓ mortalitas IMA hampir sama dg Streptokinase
- ✓ ES : iritasi GIT, me↑resiko perdrhan otak, bronkokonstriksi

- ✓ **Penggunaan:**
  - a. unstable angina
  - b. non-Q-wave myocard infark
  - c. mencegah re-infark pd MI, stroke
  - d. mencegah rekkuren TIA & me ↓ resiko stroke pd pasien TIA
  - e. me ↓ resiko arterial trombosis pd kateterisasi koroner, balloon angioplasti, bedah vaskuler
- ✓ **Pemakaian pd sindr koroner akut :**
  - loading dose 325 aspirin chewable, selama MRS 160-325mg/hr, maintenance 80mg/hr

TICLOPIDINE, CLOPIDOGREL

Mek kerja :

- blok ADP yg release oleh platelet yg teraktivasi → hamb rekruitment & aktivasi platelet lbh lanj →platelet yg tdk teraktivasi, tdk terj perub konformasi R/GPIIb/IIIa→ hamb ikatan fibrinogen dg R/GP IIb/IIIa
- Mempengaruhi ikatan vwF (yg direlease kollagen p.d) thd R/GP1b →hamb adhesi & agregasi platelet
- Hambatan thd agregasi bersifat irreversibel

- Peak effect 2j, efek inhibisi thd platelet stl hr ke 4, steady state stl hari ke 14-21
- prodrug →metab di hepar →drug aktif
- Penggunaan :
  - ✓ Preventif rekurrren trombosis pd stroke&TIA (affikasi>aspirin)
  - ✓ Unstable angina. Loading dose 2x250 slm 3 hr
  - ✓ Tdk dipakai pd kasus yg perlu efek antitrombotik segera
- ES : purpura, bleeding GIT (<< dp ASA), jarang supresi sutul (netropeni, agranulositosis)
- Clopidogrel, depresi sutul <, gangg GIT > dp Ticlopidine

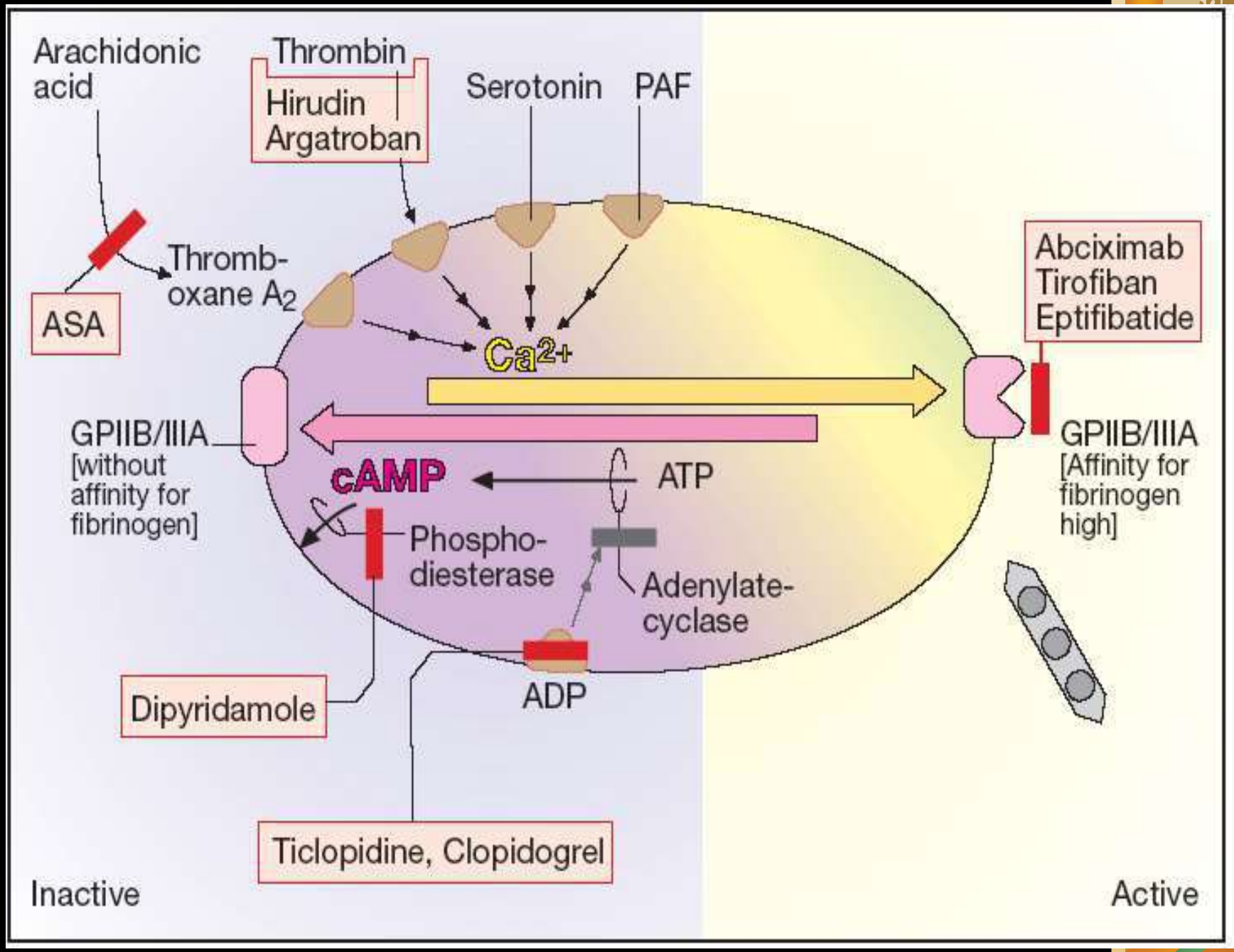
DIPYRIDAMOLE

Mekanisme kerja :

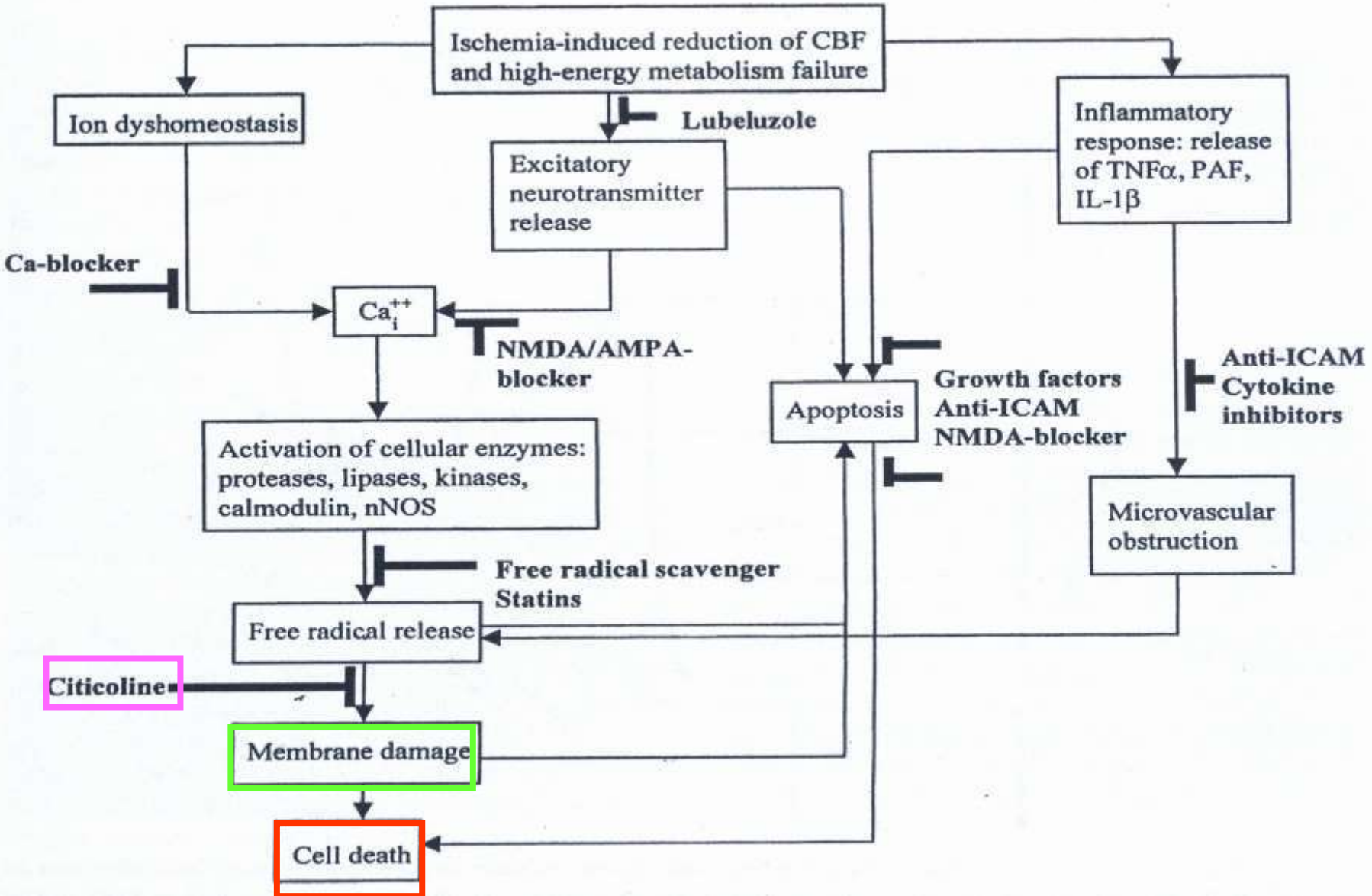
- ✓ Hamb enz PDE ➔me ↑ cAMP ➔ Vasodilator koroner
- ✓ Hamb sintesa TXA2, potensiasi efek PGI2 dlm me ↓ adhesi platelet ➔efek antiplatelet
- ✓ Blok uptake adenosin pd RBC ➔me ↑ kdr adenosin di plasma ➔me↑ efek vasodilator & antiplatelet

Penggunaan :

- Kombinasi dg aspirin : me↓ resiko stroke 16-37%
- Kombinasi dg warfarin ➔hamb embolisasi pd katub jant buatan


Arachidonic acid
Thrombin
Hirudin
Argatroban
Serotonin
PAF
Thromb-oxane A_2
ASA
Ca^{2+}
Abciximab
Tirofiban
Eptifibatide
GPIIB/IIIA [without affinity for fibrinogen]
cAMP
ATP
GPIIB/IIIA [Affinity for fibrinogen high]
Phospho-diesterase
Adenylate-cyclase
Dipyridamole
ADP
Ticlopidine, Clopidogrel
Inactive
Active

BLOCKAGE OF KEY PATHWAYS IN THE ISCHEMIC CASCADE BY AVAILABLE NEUROPROTECTIVE AGENTS



OBAT UNTUK NEUROPROTEKSI

- **PIRACETAM** (Noothropil)
- **PENTOKSIFILIN**
- **CITICOLIN**

PIRACETAM

- acts on the CNS and has been described as a nootropic;
- to protect the cerebral cortex against hypoxia.
- to inhibit platelet aggregation and reduce blood viscosity at high doses
- did not influence the outcome if given within 12 hours of the onset of acute ischaemic stroke. The data did not support routine use of **piracetam** in acute ischaemic stroke
- ES : Anxietas, Irritabilitas,Headache, Agitasi, Tremor,Nervousness
- Indikasi : Stroke, ischemia and symptoms, adjunct to intensive speech therapy in improving aphasia following stroke

PENTOKSIFILIN

- xanthine derivative used in the treatment of peripheral vascular disease
- often classified as a vasodilator, its primary action seems to be a reduction in blood viscosity, probably by effects on erythrocyte deformability and platelet adhesion and aggregation
- increase blood flow to ischaemic tissues and improve tissue oxygenation in patients with peripheral vascular disease and to increase oxygen tension in the cerebral cortex and in the cerebrospinal fluid
- inhibits production of the cytokine, tumour necrosis factor alpha (TNFα),
- Meningkatkan fungsi neurotransmitter Ach melalui reseptor muscarinik cholinergic yang mencakup proses memori.
- Aktivasi metabolik peredaran darah otak meningkatkan kecepatan metabolik serebral oksigen dan glukosa regional menormalkan aliran darah ke daerah iskemik, dengan sekunder menurunkan rasio laktat/piruvat.

SITIKOLIN

- derivative of choline and cytidine that is involved in the biosynthesis of lecithin. It is claimed to increase blood flow and oxygen consumption in the brain
- meningkatkan norepinephrine and dopamine di CNS → pada kondisi aneuroprotective and ischemic
- menurunkan volume lesi iskemik
- restore the activity of mitochondrial ATPase and membrane Na+/K+ATPase, untuk menghambat aktivasi phospholipases, dan mempercepat reabsorbsi cerebral edema.
- Menghambat terjadinya apoptosis yang berhubungan dengan terjadinya cerebral iskemik, neurodegeneration

Antihipertensi utk stroke iskemik akut

Pilihan Obat	Tekanan Darah
Pasien dapat menerima rtPA namun tekanan darah > 185/110 mmHg, maka pilihan terapi: • **Labetalol 10-20 mg IV selama 1-2 menit, dapat diulang 1 kali, atau** • **Nikardipin 5 mg/jam IV, titrasi sampai 2,5 mg/jam tiap 5-15 menit, maksimum 15 mg/jam; setelah tercapai target maka dapat disesuaikan sesuai nilai tekanan darah.**	• Apabila tekanan darah tidak tercapai ≤ 185/110 mmHg, maka jangan berikan rtPA
Pasien sudah mendapat rtPA, namun tekanan darah sistolik >180-230 mmHg atau diastolik >105-120 mmHg, maka pilihan terapi: • **Labetalol 10 mg IV, kemudian infus IV kontinu 2-8 mg/menit, atau** • **Nikardipin 5 mg/jam IV, titrasi sampai 2,5 mg/jam tiap 5-15 menit, maksimum 15 mg/jam.**	• Tekanan darah selama dan setelah rtPA ≤ 180/105 mmHg, monitor tiap 15 menit selama 2 jam dari dimulainya rtPA, lalu tiap 30 menit selama 6 jam dan kemudian tiap jam selama 16 jam

STATIN – pleiotropic effect in stroke

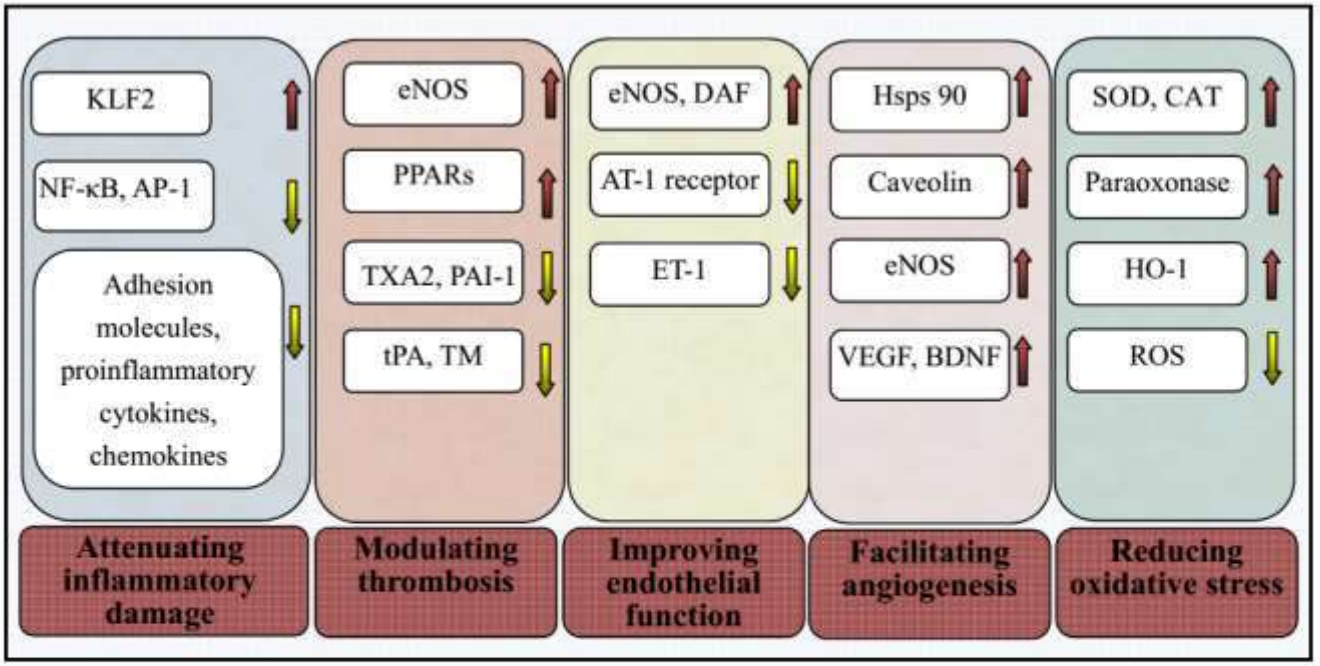
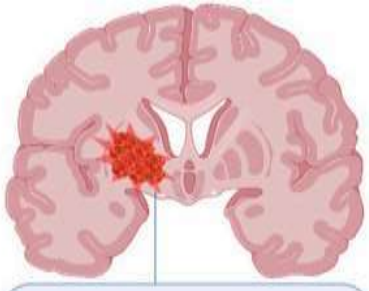


Fig. (1). Many roles of statins beyond lowering cholesterol. The pleiotropic effects and the underlying associated mechanisms of statins beyond lowering cholesterol, including improving endothelial function, modulating thrombogenesis, attenuating inflammatory and oxidative stress damage, and facilitating angiogenesis. NF-κB = nuclear factor-κB; AP-1 = activatorprotein-1; PPARs = peroxisome proliferator-activated receptors; KLF2 = Kruppel-like factor-2; TXA2 = thromboxane A2; PAI-1 = plasminogen activator inhibitor-1; tPA = tissue plasminogen activator; TM = thrombomodulin; ET-1 = endothelin-1; AT-1 = angiotensin II type 1; eNOS = endothelial nitric oxide synthase; VEGF = vascular endothelial growth factor; BDNF = brain-derived neurotrophic factor; Hsp90 = heat-shock protein 90; ROS = reactive oxygen species.

STROKE PERDARAHAN



Intracerebral Hemorrhage

Primary Brain Injury

Hematoma mass expansion

↓

Brain parenchyma mechanical compression

↓

Increase of intracranial pressure

↓

* Decrease of blood flow
* Brain deformation
* Release of neurotransmitters
* Depolarization of membrane potential
* Dysfunction of mitochondria

↓

Inflammation / Edema

Secondary Brain Injury

Thrombin

↓

* CNS microglial activation
* Src kinase activation
* Complement pathway activation
* Protease activated receptors (PARs) activation

↓

Inflammation

↓

* Activation of resident microglia
* Infiltration of immune cells
* Increase of local cytokines
* Increase of ROS

↓

Apoptosis & Necrosis

↓ BBB breakdown + edema

↓ Neuronal damage

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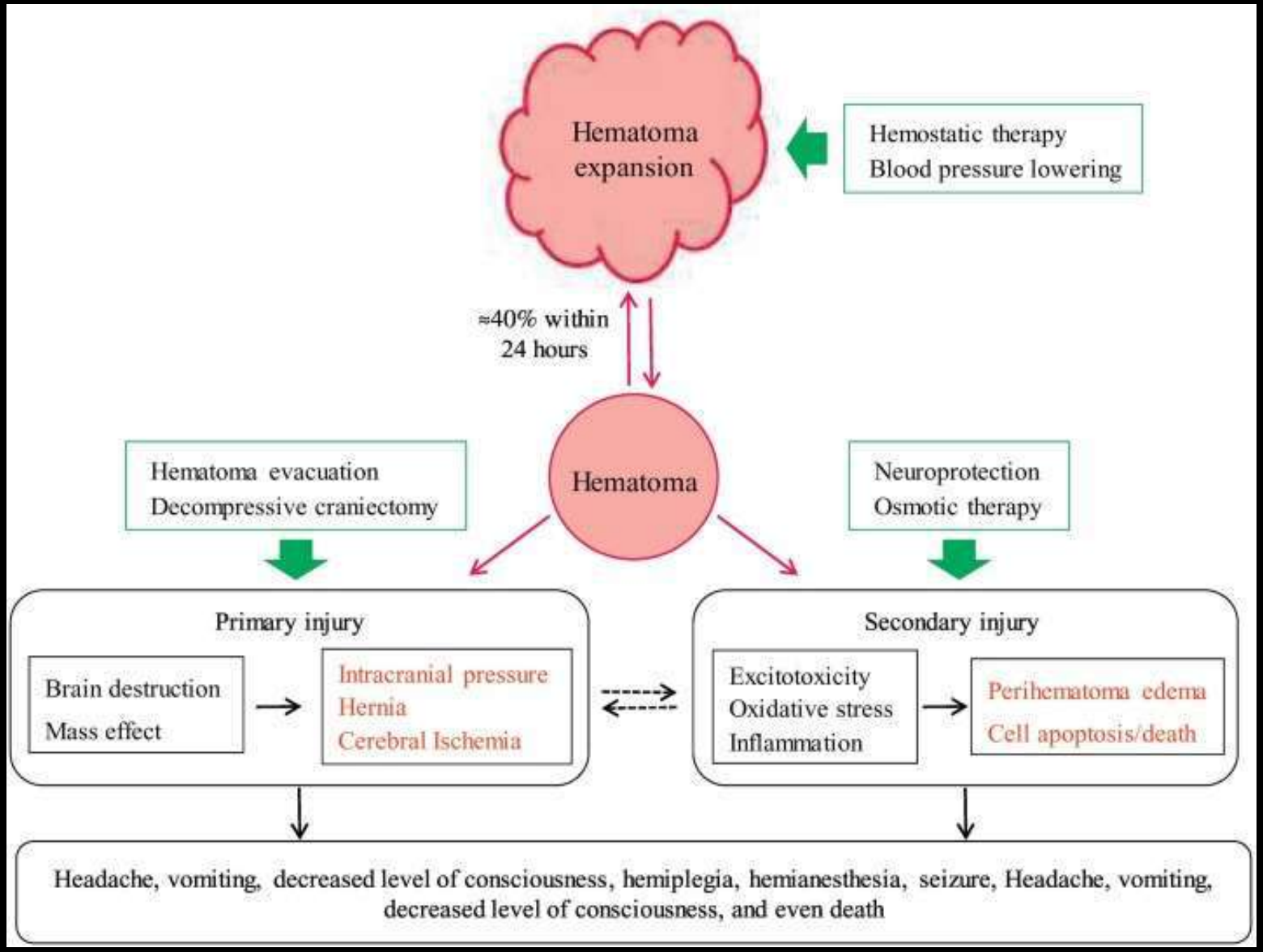

DOI:https://doi.org/10.1016/j.jns.2020.117020

Antihipertensi utk stroke perdarahan (ICH)

Drug	Mechanism	Dose	Cautions
Labetalol	Alpha-1, beta-1, beta-2 receptor antagonist	20-80 mg bolus every 10 minutes, up to 300 mg; 0.5 to 2.0 mg/minute infusion	Bradycardia, congestive heart failure, bronchospasm, hypotension
Esmolol	Beta-1 receptor antagonist	0.5 mg/kg bolus; 50 to 300 µg/kg/minute	Bradycardia, congestive heart failure, bronchospasm
Nicardipine	L-type calcium channel blocker (dihydropyridine)	5 to 15 mg/h infusion	Severe aortic stenosis, myocardial ischemia, hypotension
Enalaprilat	ACE inhibitor	0.625 mg bolus; 1.25 to 5 mg every 6 h	Variable response, precipitous fall in blood pressure with high-renin states
Fenoldopam	Dopamine-1 receptor agonist	0.1 to 0.3 µg/kg/minute	Tachycardia, headache, nausea, flushing, glaucoma, portal hypertension
Nitroprusside*	Nitrovasodilator (arterial and venous)	0.25 to 10 µg/kg/minute	Increased intracranial pressure, variable response, myocardial ischemia, thiocyanate and cyanide toxicity, hypotension

*Nitroprusside is not recommended for use in acute intracerebral hemorrhage because of its tendency to increase intracranial pressure. Modified with permission from Mayer SA, Rincon F: Management of intracerebral hemorrhage. *Lancet Neurol* 2005, **4**:662-672. ACE, angiotensin-converting enzyme.

Critical Care 2008, **12**:237 (doi:10.1186/cc7092)

ε-Aminocaproic acid (EACA),
(Tranexamic acid)

- Antifibrinolitik dg blok tempat ikatan fibrin pd plasminogen → hamb aktivasi plasminogen menj plasmin
- ES : trombosis intravasc(ok hamb aktivasi plasminogen), hipotensi, miopati, diare.

Kronologi Edema Cerebri

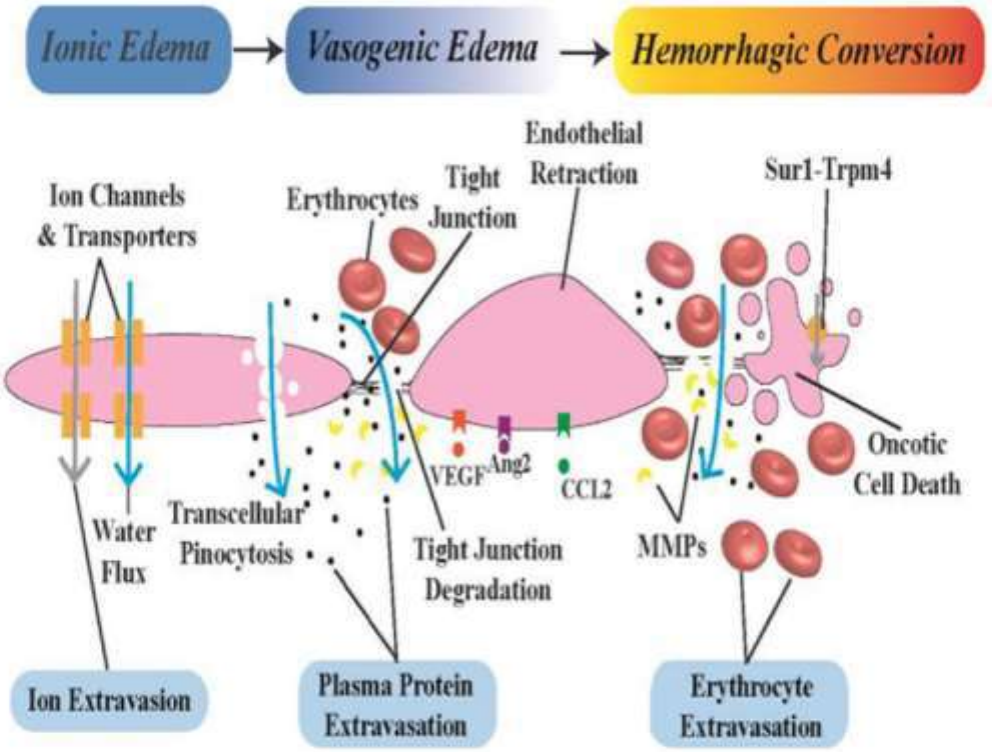

Fig. 1. Ionic brain edema: In the ionic edema (Ionic Edema) phase, water flux (blue arrow) and ion flux (gray arrow) are mediated by plasma membrane channels and transporters; Vasogenic Edema, by plasma Protein (except red blood cells) extravasation is involved in trans-cell channel transport, as well as tightly linked MMP degradation and endothelial retraction between cells, and can also be triggered by VEGF, Ang2 and CCL2 signaling; Hemorrhagic conversion is Occurred by structural disintegration of blood vessels, driven by tightly linked complete egradation or Sur1-Trpm4-mediated swelling and apoptosis of endothelial cells.[3]

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Mannitol- menurunkan TIK

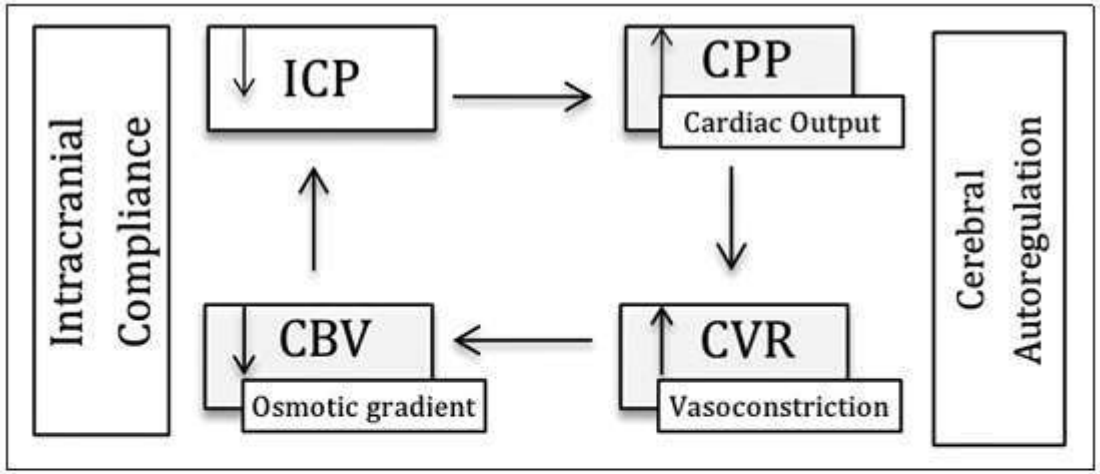

Figure 3: Three proposed mechanisms of mannitol for lowering the intracranial pressure. First, it improves the cerebral perfusion pressure, as a result of the transient increase of the cardiac output. When cerebral autoregulation is preserved, this improvement causes reflex cerebral vasoconstriction, leading to an increase of the cerebrovascular resistance. Finally, the osmotic gradient generated diminishes the cerebral blood volume and improves the intracranial compliance. All these changes lead to a consistent improvement of the intracranial pressure

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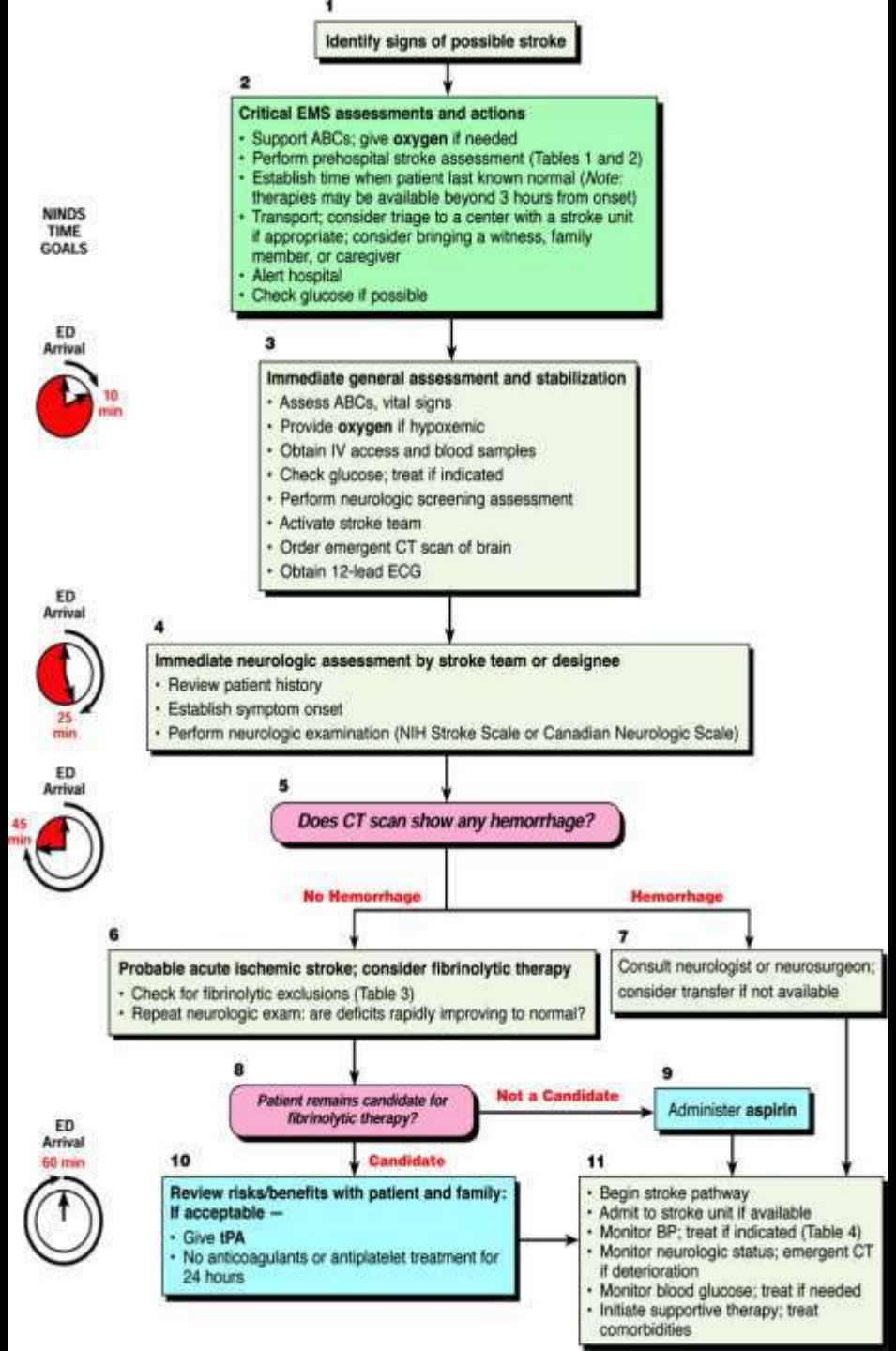

Perspective: Strokes, Part III: What is the standard of care?

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Terima kasih perhatiannya…..