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OBAT ANTI HIPERTENSI

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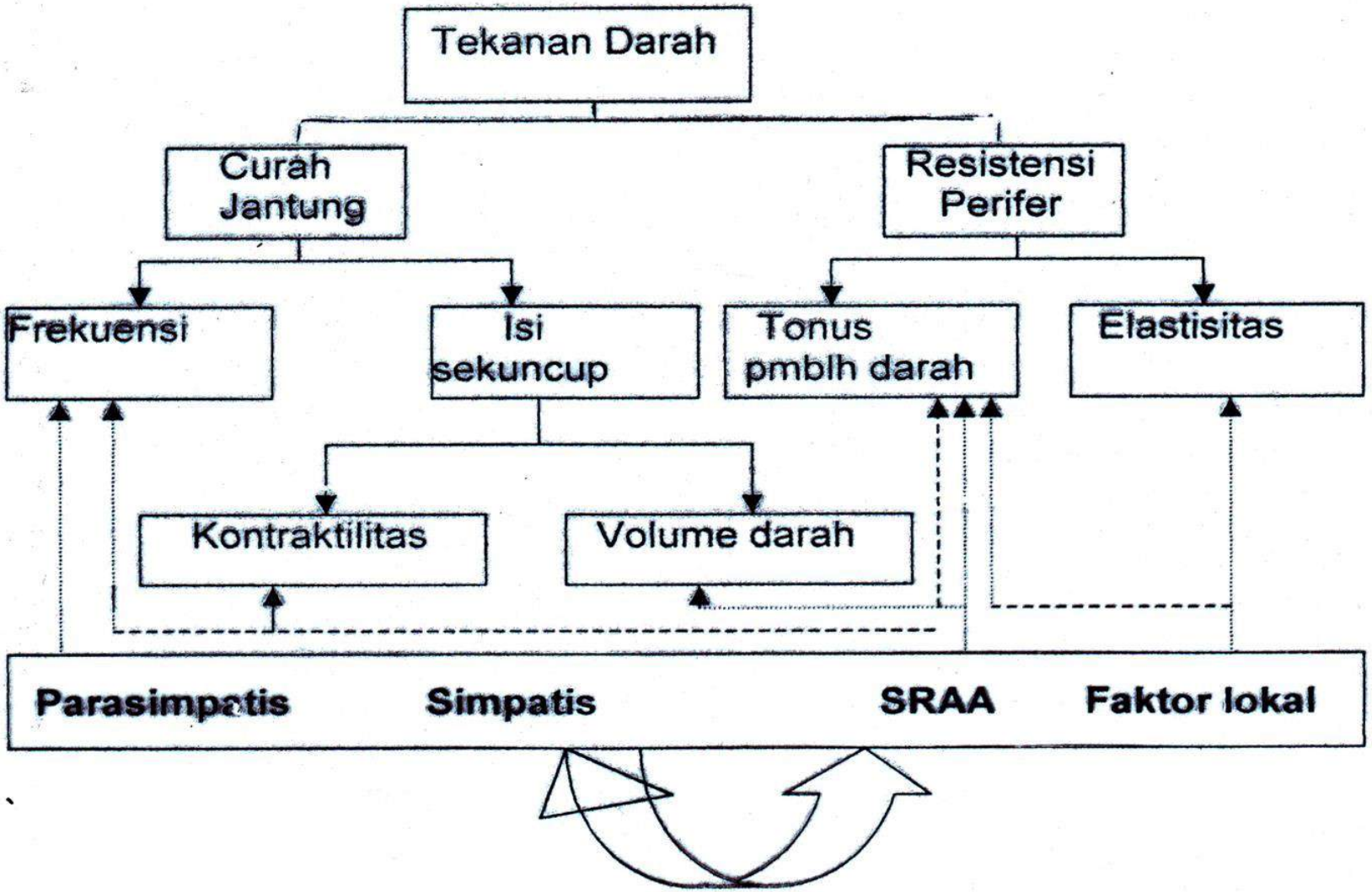
Kemampuan akhir yang diharapkan

- Mahasiswa mampu menguraikan tentang Obat antihipertensi

MEKANISME PENGATURAN TEKANAN DARAH



Volume darah diatur oleh :

- Sistem renin angiotensin aldosteron (SRAA)
- Ginjal : mekanisme pressure natriuresis

  TD ↑ → eksresi Na dan H2O ↑ → TD ↓
- Atrial natriuretic factor (atriopeptin)

  - Hormon yang diproduksi terutama oleh atrium
  - Vasodilator
  - Natriuresis & diuresis

Faktor lokal : substansi yg dihasilkan oleh endotelium pembuluh darah

A. Vasokonstriktor

- Endotelin
- Angiotensin II
- Tromboksan AII

B. Vasodilator

- Prostasiklin (PGI2)
- Nitrit oxide (NO = EDRF)

EDRF (Endotelium Derived Releasing Factor)

- Vasodilator
- Antiagregasi trombosit
- Antileucocyte adherence
- Antiproliferatif (jangka panjang)

Klasifikasi Hipertensi

1. Berdasarkan berat ringannya

	Diastole	systole
Normal	<85	<130
Normal Tinggi	85-89 mm Hg	130-139
Hipertensi		
- Ringan	90-99	140-159
- Sedang	100-109	160-179
- Berat	110-119	180-209
- Sangat berat	>120	>210

2. Berdasarkan Penyebabnya

a. HT essensial/primer/idiopatik
   ± 95 % kasus

b. HT sekunder :
   - HT renal
   - HT endokrin
   - HT karena penyakit lain
   - HT karena obat

Faktor risiko

- Genetik
- Umur
- Jenis kelamin
- Berat badan
- Merokok dan alkohol
- Stres
- Profil lipid darah

Komplikasi

- Stroke
- Gagal ginjal
- Gagal jantung
- Aneurisme aorta

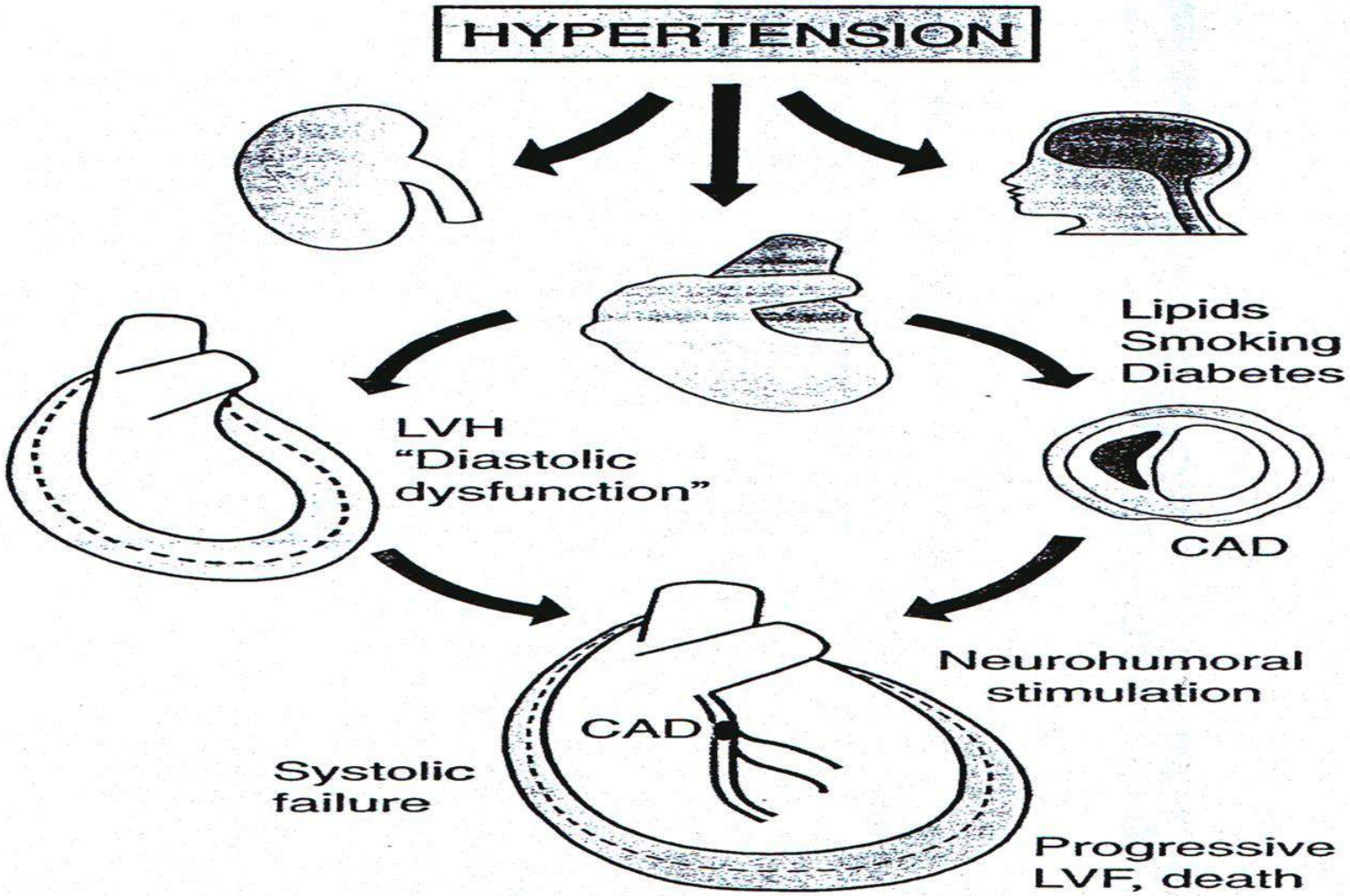
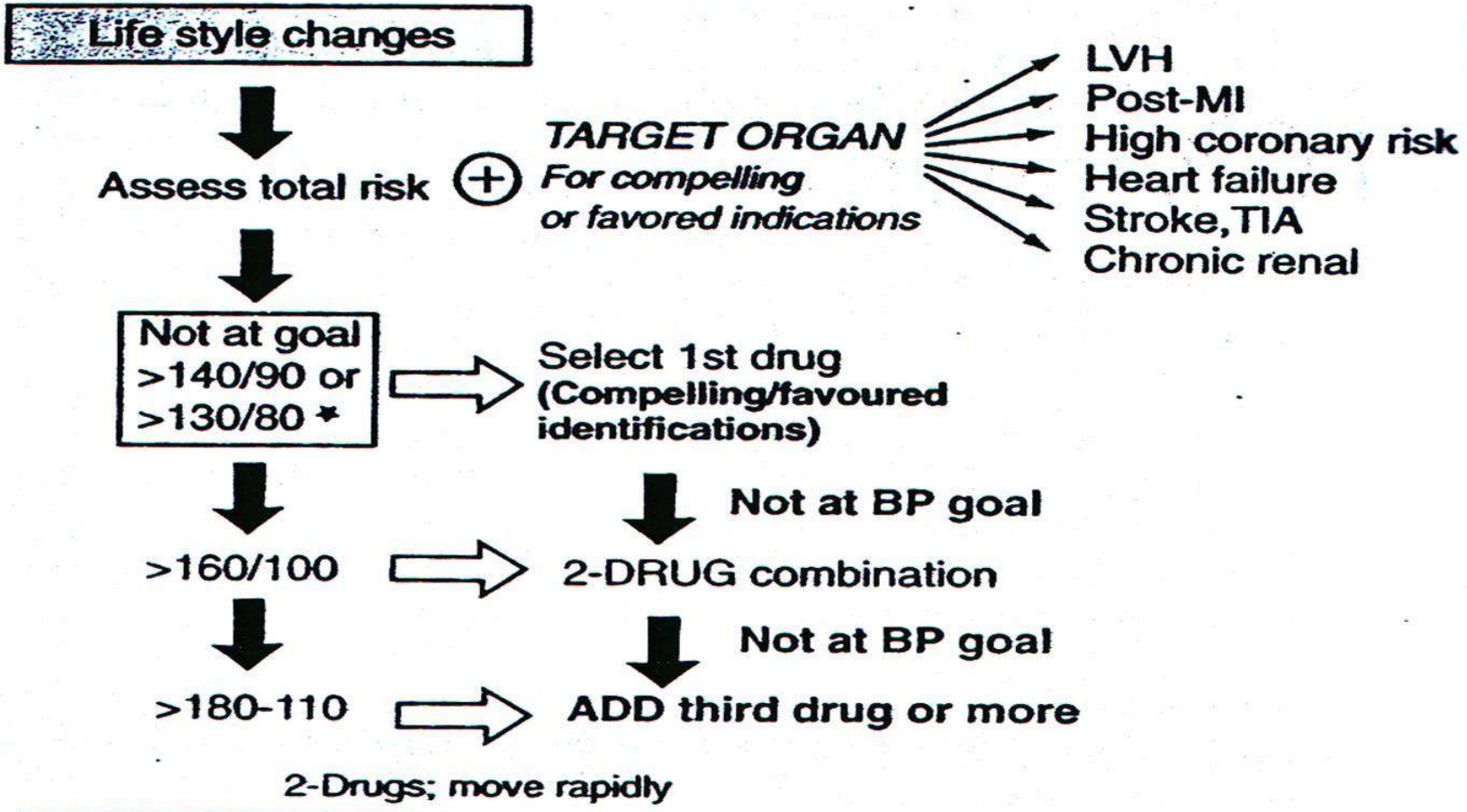


Figure 7-2 In hypertension, cardiac complications are the most common cause of death. Hypertension also kills by renal and cerebral complications. The two major cardiac events are left ventricular hypertrophy *(LVH)* and promotion of coronary artery disease *(CAD)*. The end result of LVH and CAD is left ventricular systolic failure *(LVF)* which, if progresses, can lead to death. (*Figure © LH Opie, 2005.*)

BP MANAGEMENT



* Diabetes; chronic renal disease; or very high CV risk

Figure 7-4 Proposed simplified treatment algorithm for hypertension, based on JNC 7[11,12] and European Society recommendations.[21]

Obat antihipertensi

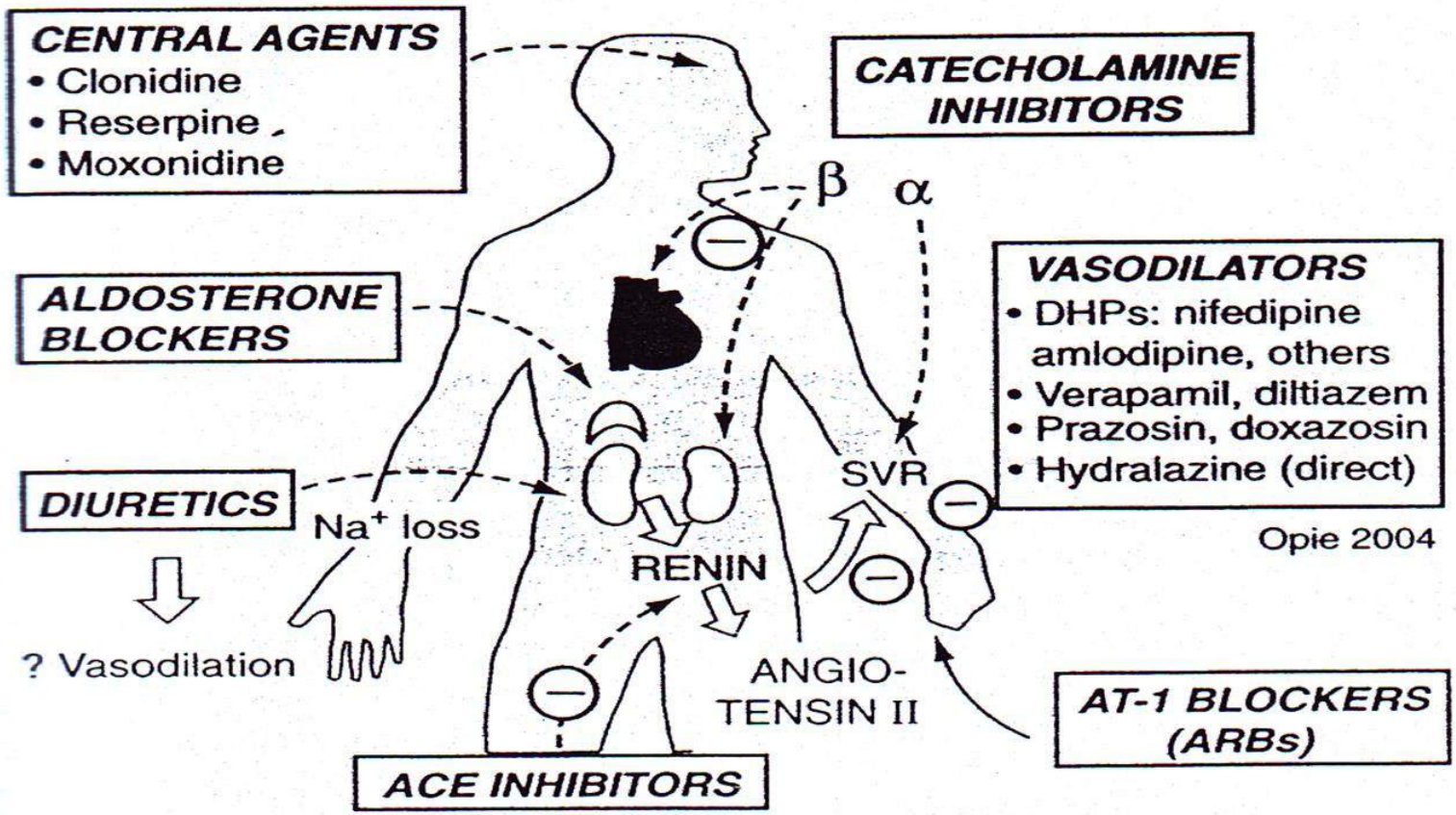


Figure 7-1 Different types of antihypertensive agents act at different sites. Because hypertension is frequently multifactorial in origin, it may be difficult to find the ideal drug for a given patient and drug combinations are often used. *ARBs* = angiotensin receptor blockers; *AT-1* = angiotensin II subtype 1; *DHPs* = dihydropyridines; *SVR* = systemic vascular resistance. (*Figure © LH Opie, 2005.*)

Table 7-3 Guidelines for Selecting Drug Treatment for Hypertension

Class of Drug	Favored Indications	Possible Indications	Compelling Contraindications	Possible Contraindications
Diuretics (low-dose thiazides)	Congestive heart failure; Elderly hypertensive patients; Systolic hypertension; African origin subjects	Obesity	Gout	Pregnancy; Dyslipidemia; Metabolic syndrome; Sexually active men
Diuretics (loop)	Congestive heart failure; Renal failure		Hypokalemia	
Diuretics (antialdo)	Congestive heart failure; Postinfarct; Aldosteronism (1° or 2°)	Refractory hypertension	Hyperkalemia; Renal failure	Diabetic renal disease
β-Blockers	Angina; Tachyarrhythmias; Post-MI Heart failure (up-titrate)	Pregnancy; Diabetes	Asthma, severe COPD Heart block*	Metabolic syndrome; Athletes and exercising patients; Erectile dysfunction; Peripheral vascular disease
ACE inhibitors	Left ventricular dysfunction or failure; Postinfarct; Nephropathy, type 1; Diabetic or nondiabetic proteinuria	CV protection (BP already controlled); type 2 nephropathy	Pregnancy; Hyperkalemia; Bilateral renal artery stenosis	Severe cough; Severe aortic stenosis
Angiotensin-II antagonists (ARBs)	ACE inhibitor cough; Diabetes type 2 nephropathy including microalbuminuria; LVH; Heart failure	Postinfarct	Pregnancy; Bilateral renal artery stenosis Hyperkalemia	Severe aortic stenosis
Calcium antagonists (CCBs)	Angina, effort; Elderly patients; Systolic hypertension; Supraventricular tachycardias‡; Carotid atherosclerosis	Peripheral vascular disease; Diabetes; African origin; Pregnancy	Heart block†; Clinical heart failure (possible exception: amlodipine, but needs care)	Early heart failure

*Grade 2 or 3 atrioventricular block.

†Grade 2 or 3 atrioventricular block with verapamil or diltiazem.

‡Verapamil or diltiazem.

ACE = angiotensin converting enzyme; Aldo = aldosterone; CV = cardiovascular; COPD = chronic obstructive pulmonary disease.

Modified from the report of the European Societies.[21]

I. Diuretik

Mekanisme antihipertensi

- Diuresis } volume darah ↓
- Natriuresis } curah jantung ↓
- Me ↓ resistensi perifer (karena adaptasi pembuluh darah atau efek langsung thiazid)

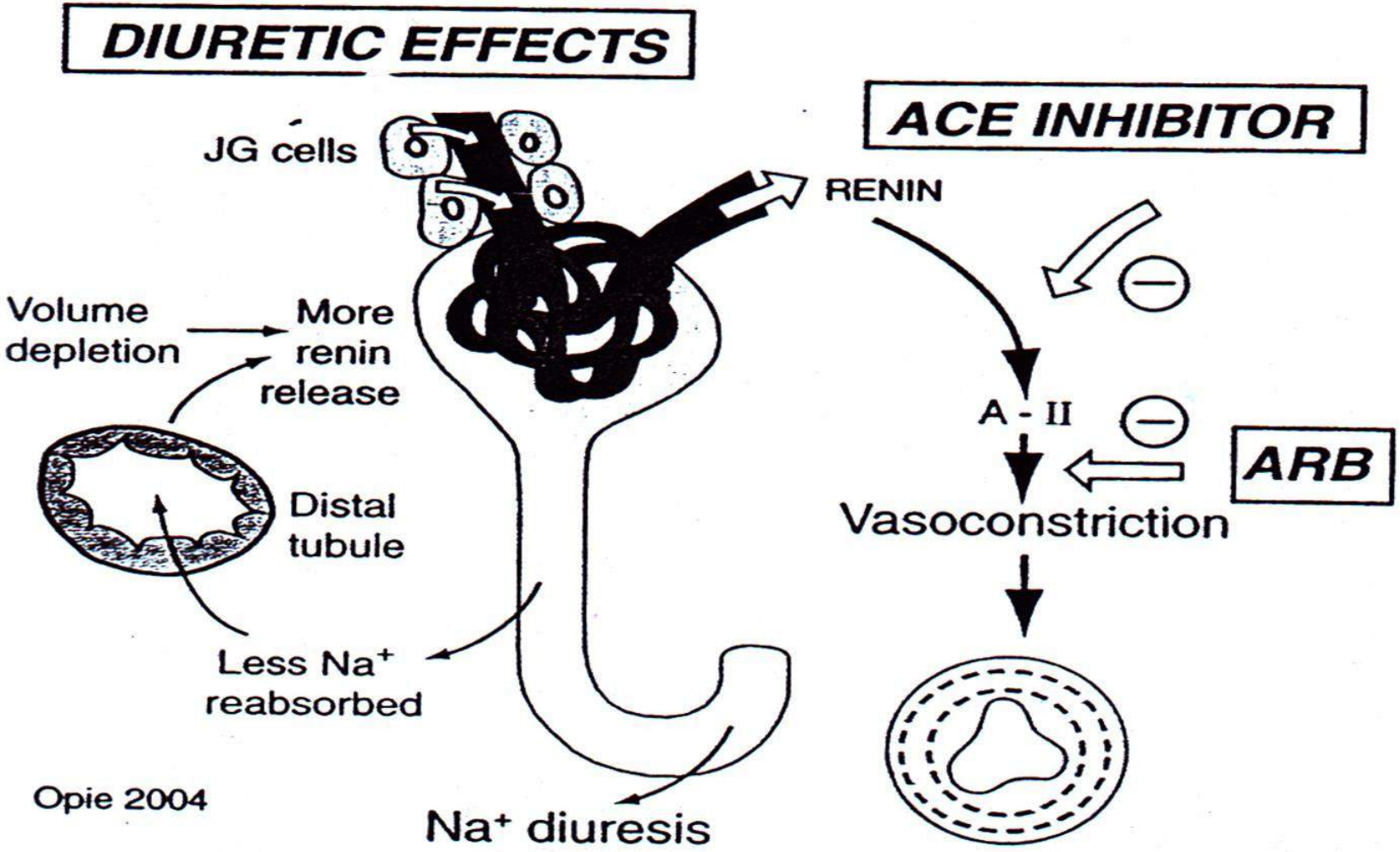


Figure 7-5 Diuretic mechanisms in hypertension. Note self-limiting sequence whereby sodium loss and volume depletion stimulate renin release to promote vasoconstriction. The latter effect is alleviated by concurrent therapy with an ACE inhibitor or an angiotensin receptor blocker (*ARB*). *JG* = juxtaglomerular. (*Figure © LH Opie, 2005.*)

I. Diuretik Thiazid : HCT, bendro flumethiazid, klortalidon, indapamid

- Mula kerja : 2- 3 hari
- Efek maksimum : 2 -4 minggu
- **Penggunaan :**
  - Pilihan utama pada HT ringan & sedang
  - Fungsi ginjal harus baik
  - Dalam kombinasi : me ↑ AH lain & mencegah retensi cairan oleh AH lain
  - Terutama untuk HT dg PRA rendah (usia lanjut)

Efek samping

- Hipokalemia →toksisitas digitalis ↑
- Hipomagnesemia, hiponatremia
- Hiperurisemia → hati-hati pada Gout akut
- Hiperkolesterolemia, hipertrigliseridemia
- Gangguan fungsi seksual
- Hiperkalsemia

Kontra Indikasi& interaksi

- KI : Gagal ginjal
- Interaksi : AINS & diet garam tinggi
  $\rightarrow$ aktivitas thiazid $\downarrow$

2. Diuretik Kuat : Furosemid

- Mekanisme kerja = thiazid
- Kerja cepat
- Efektif untuk HT dengan ganggaun fungsi ginjal & gagal jantung
- Efek samping = thiazid kecuali hiperkalsemia

3. Diuretik Hemat Kalium : Triamteren, Amilorid, Triamteren

- Merupakan diuretic lemah
- Sering dikombinasikan dengan diuretik lain (mengurangi hipokalemia)
- Dapat menimbulkan hiperkalemia :
  - Pada gagal ginjal
  - Kombinasi dengan AINS dan ACE inhibitor

II. Penghambat Adrenergik
2.1. Beta blocker

Mekanisme : hambatan reseptor beta 1

- Kontraktilitas miokard ↓ → curah jantung ↓
- Sekresi renin ↓ → resistensi perifer ↓

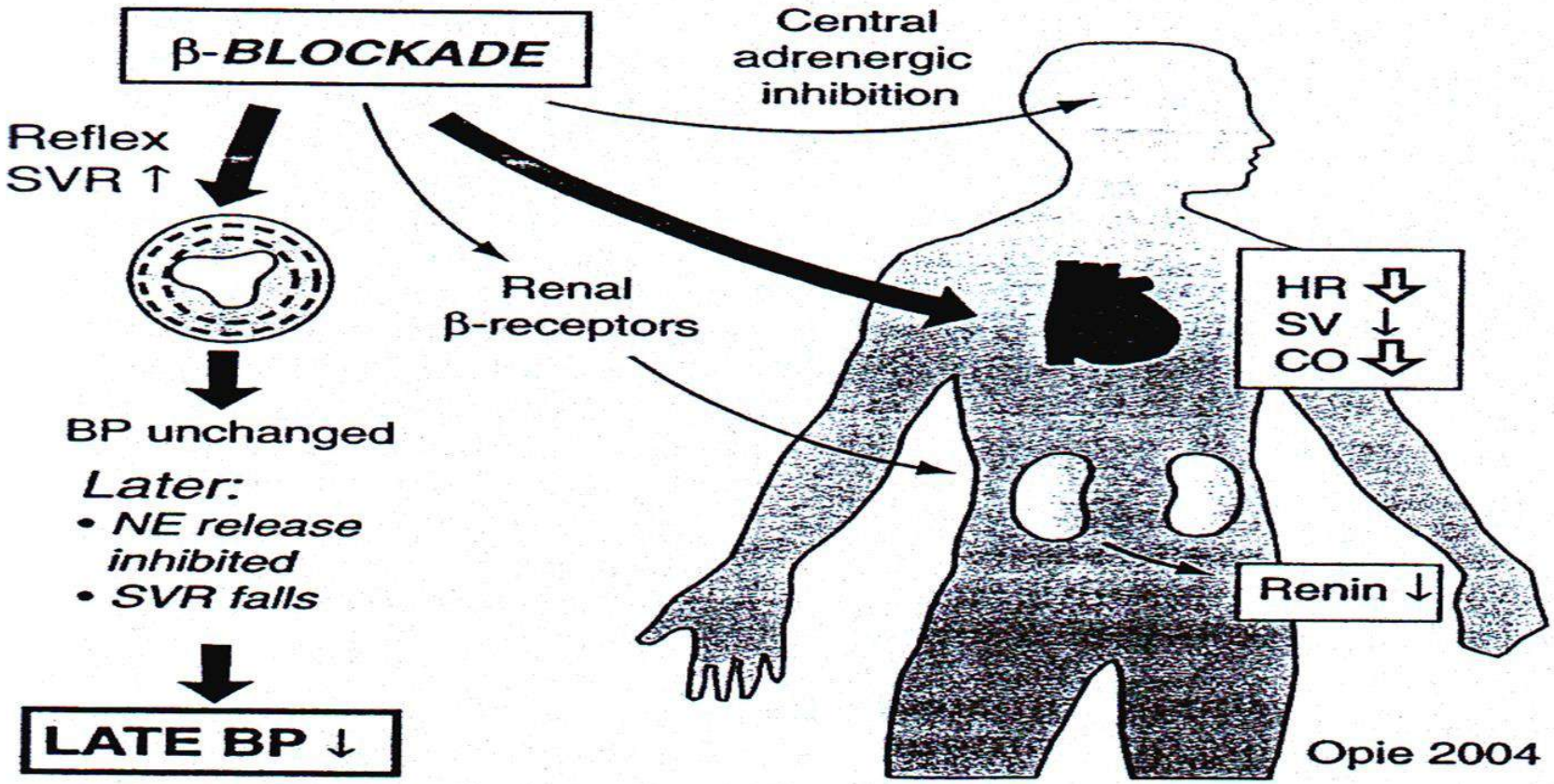


Figure 7-7 Proposed antihypertensive mechanisms of β-blockade. An early fall in heart rate *(HR)*, stroke volume *(SV)*, and cardiac output *(CO)* does not lead to a corresponding fall in blood pressure because of baroreflex-mediated increased peripheral α-adrenergic vasoconstriction, with a rise in systemic vascular resistance. Within a few days β-blockade of prejunctional receptors on the terminal neuron with consequent inhibition of release of norepinephrine *(NE)*, which may explain why the SVR falls to normal. The blood pressure now falls. In the case of vasodilatory β-blockers, with added α-blockade, there is an early decrease in SVR and a rapid fall in BP.[113] (*Figure © LH Opie, 2005.*)

Penggunaan

- Obat tahap I untuk HT ringan dan sedang
- HT dengan penyakit jantung koroner
- HT dengan aritmia supraventrikular
- HT hiperdinamik

Efek Samping

- Bronkospasme, KI : ashma, PPOM
- Gangguan sirkulasi perifer, KI : peny vaskular perifer, DM, Sick sinus syndrome, block AV derajat 2 dan 3
- Hipertrigleridemia
- Perburukan fungsi ginjal

2.2 Alfa blocker: prazosin, Terazosin, bunazosin, doksazosin

- Mekanisme : hambatan reseptor alfa 1
- Efek positif terhadap lipid darah→ LDL ↓, HDL ↑
- Mengurangi resistensi insulin
- Tidak berinteraksi dg AINS

Penggunaan alfa blocker

- AH tahap I untuk HT ringan dan sedang
- HT dengan dislipidemia
- HT dengan DM
- HT dengan gangguan sirkulasi perifer, perokok
- HT dengan hipertrophi prostat

Efek samping

- Hipotensi ortostatik (fenomena dosis pertama) ; sering terjadi pada prazosin
  - Berikan dosis awal serendah mungkin
  - Sebelum tidur
  - Peningkatan dosis scr bertahap
- Sakit Kepala
- Palpitasi
- Takikardi & Udem perifer

2.3. Adrenolitik Sentral : klonidin, metildopa, guanfasin, guanabenz

Mekanisme kerja : **alfa 2 agonist**

- Symphatetic outflow ↓
- Curah jantung ↓ → kembali normal
- Resistensi perifer ↓

Efek samping

- Mulut kering, sedasi, pusing
- Konstipasi, mual
- Impotensi
- Retensi cairan → kombinasi dengan diuretik
- Reaksi putus obat → krisis hipertensi (jika terjadi beri obat kembali)
- Jangan diberikan pada pasien yg tidak patuh

Penggunaan

- AH tahap 2 atau 3
- Metildopa : Terpilih untuk HT pada kehamilan
- Interaksi :
  - diuretik $\rightarrow \uparrow$ efek AH lain $\uparrow$
  - Antidepresan trisiklik (ADTs) $\rightarrow$ efek AH $\downarrow$
  - Amin simpatomimetik $\rightarrow$ efek AH $\downarrow$

2.4. Penghambat saraf adrenergik: reserpin, guanetidin

Mekanisme :

- Reserpin : menghambat transport NE ke dalam vesikel
- Guanetidin : Mencegah NE keluar vesikel $\rightarrow$ NE dipecah oleh MAO

Indikasi Reserpin

- AH tahap I
- Kombinasi dengan thiazid : terpilih untuk golongan ekonomi lemah
- Harga murah
- Efektif
- Cukup aman (pada dosis terapi)

Efek samping

- Sedasi, gangguan konsentrasi
- Depresi
- Kongesti nasal
- Ulkus peptikum

2.5. Penghambat Ganglion: trimetafan

- Untuk krisis hipertensi
- Kerja sangat cepat & singkat
- Sudah jarang/ tidak digunakan

III. Vasodilator
3.1 . Natrium nitroprusid

- Merupakan donor NO
- Kerja sangat cepat & singkat
- Hanya diberikan IV (infus kontinyu)

Indikasi

- Krisis hipertensi
- Pengendalian tekanan darah pada oprasi besar

Efek samping

- Takikardi
- Serangan angina pektoris
- Rebound fenomena
- Dosis toksik (> 2 μg/ kg/ min) → met Hb (terbentuk sianida & tiosianat)

3.2. Hidralazin

- Vasodilator arteriol
- Mekanisme : lewat adenosin ? Lewat NO?
- Kinetik :
  - Abs oral cepat & sempurna
  - Mengalami metabolisme lintas I
  - Pada asetilator cepat : kadar ↑

Penggunaan

- Obat ke 3 setelah diuretik & betablocker
- Intravena
  - HT darurat
  - HT pada glomerulonefritis
  - HT pada eklampsia

Efek samping

- Takikardi
- Retensi cairan
- Lupus like syndrome
- Angina pectoris (karena penurunan perfusi jantung)
- KI : Dissecting aortic aneurisme

3.3. Pembuka kanal kalium : minoksidil, diaksozid

Membuka kanal kalium → K keluar sel

- Hiperpolarisasi membran
- Vasodilatasi terutama arteriol

Penggunaan

- HT akselerasi / maligna
- HT dengan peny ginjal (GGA, GGK)
- HT ensefalopati)

Efek samping

Minoksidil :

- Retensi cairan
- Takikartdi
- Hipertrikosis
- Efusi pleura
- Hipertensi rebound

Efek samping

Diaksozid

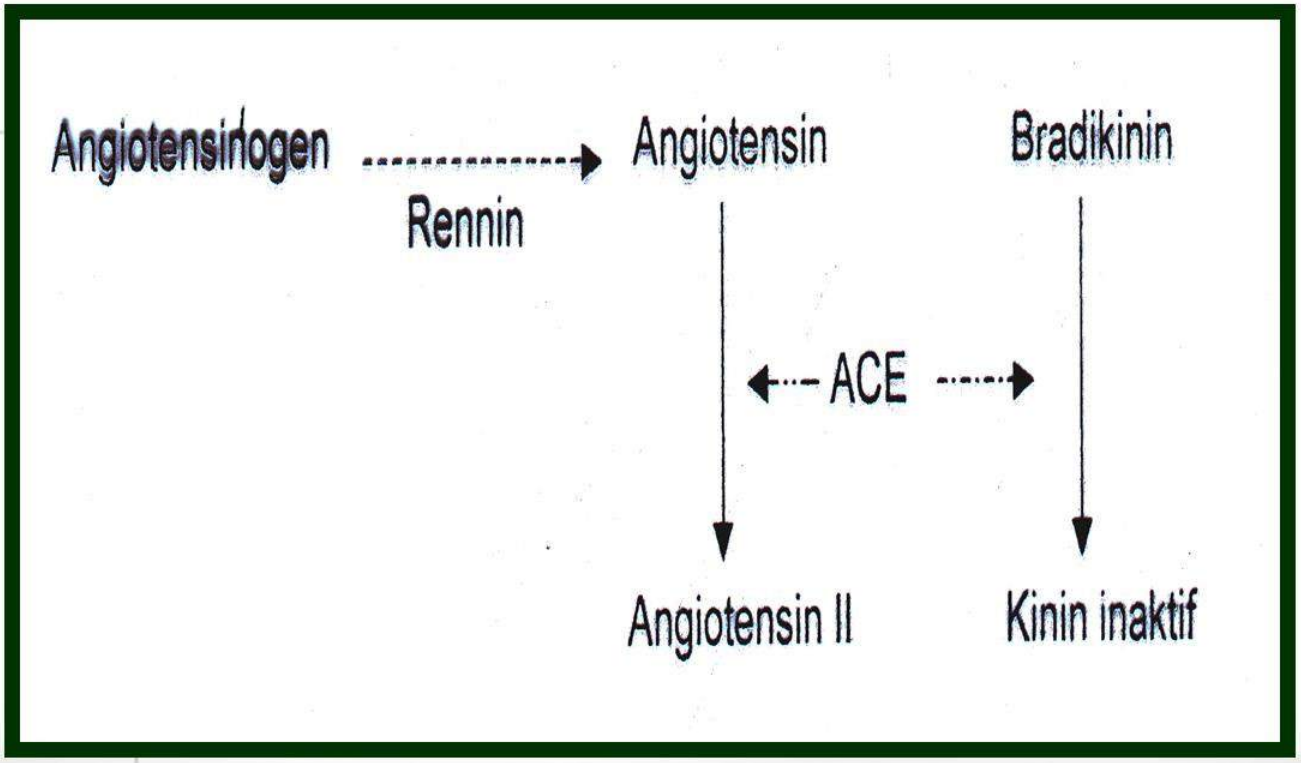
- Retensi cairan
- Takikardi
- Hiperglikemia
- Gangguan persalinan

T1/2 : minoksidil : 4.2 jam, diaksozid : 20-60 jam

Masa kerja : minoksidil : 24 jam, diazoksid

IV. ACE inhibitor

Sistem Renin Angiotensin Aldosteron (SRAA)



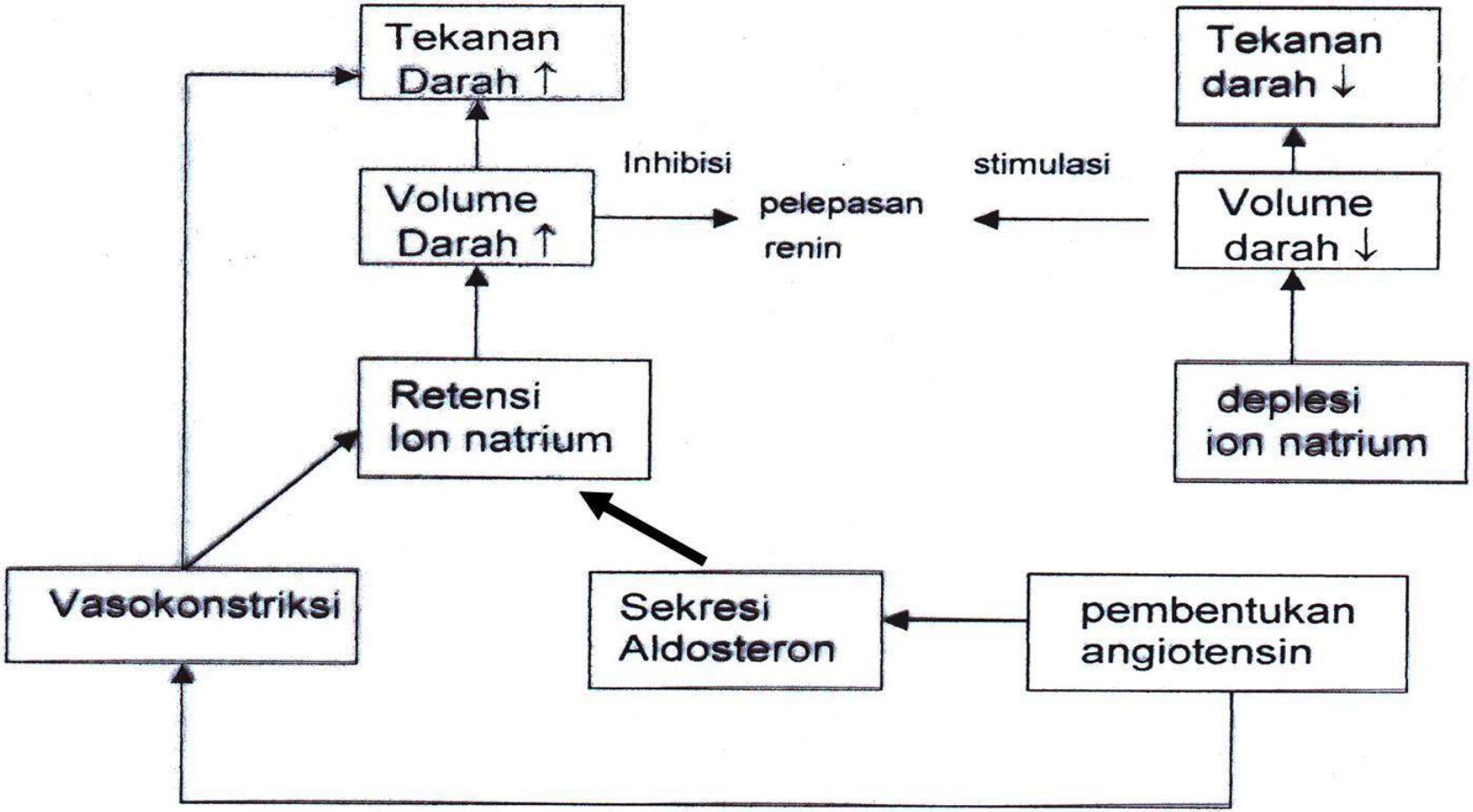
Renin

- Enzim yang mengkatalisis pembentukan angiotensin II

  Angiotensin I $\xrightarrow{\text{renin}}$ Angiotensin 2

- Renin disintesis, disimpan dan disekresi oleh sel jukstaglomerulus ginjal yg terdapat pd dinding arteriol aferen
- Kontrol sekresi : pada ginjal (jalur makula densa, SSP (jalur reseptor beta adrenergik)dan lewat mekanisme umpan balik negatif

Gambar : skema peranan SRA



MECHANISM

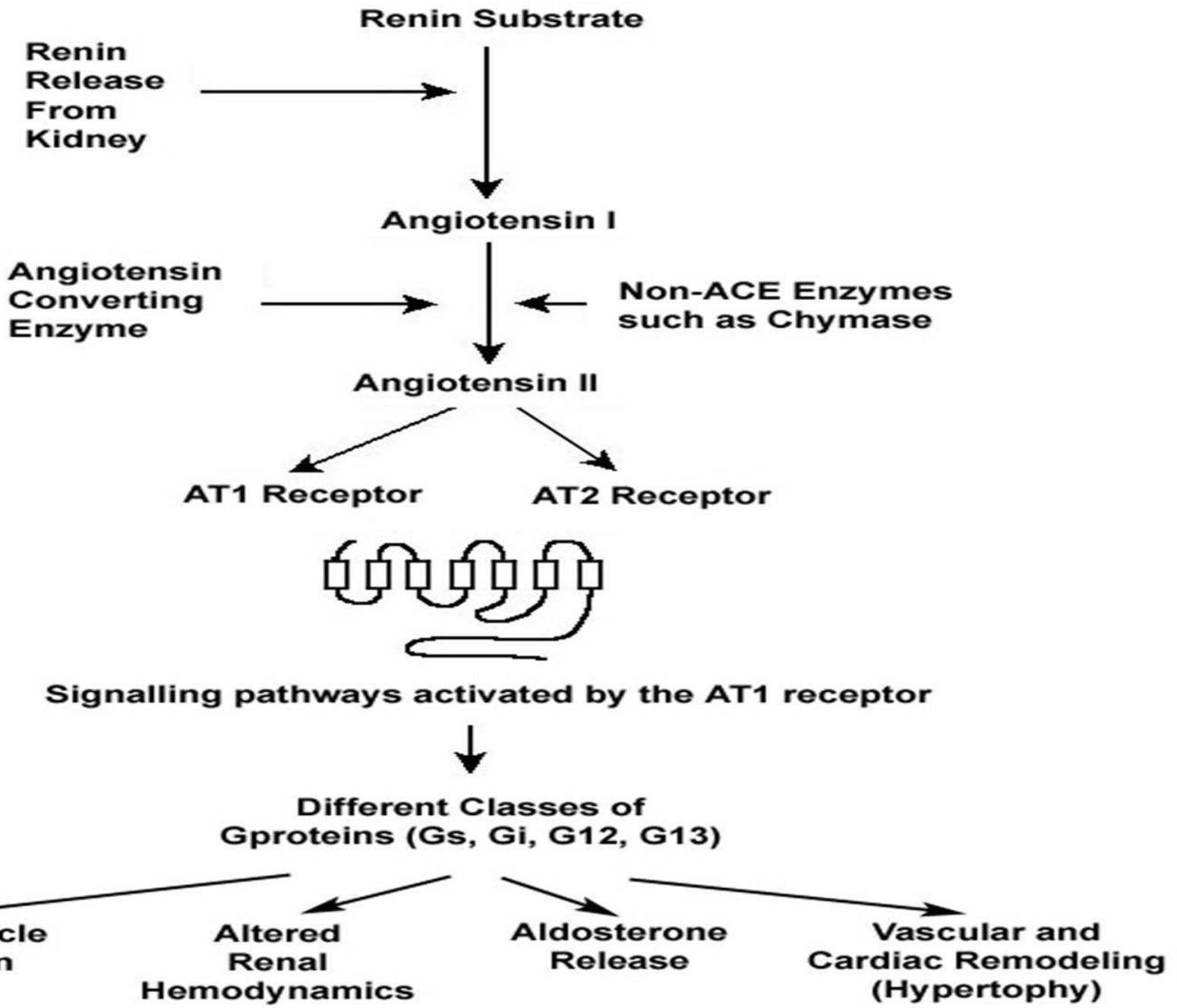

Renin Substrate
Renin Release From Kidney
Angiotensin I
Angiotensin Converting Enzyme
Non-ACE Enzymes such as Chymase
Angiotensin II
AT1 Receptor
AT2 Receptor
Signalling pathways activated by the AT1 receptor
Different Classes of Gproteins (Gs, Gi, G12, G13)
Smooth Muscle Contraction
Altered Renal Hemodynamics
Aldosterone Release
Vascular and Cardiac Remodeling (Hypertophy)

Table 5-1 Potential Pathogenic Properties of Angiotensin II

Heart

Myocardial hypertrophy
Interstitial fibrosis

Coronary Arteries

Endothelial dysfunction with deceased release of nitric oxide
Coronary constriction via release of norepinephrine
Increased oxidative stress; oxygen-derived free radicals formed via NADH oxidase
Promotion of inflammatory response and atheroma
Promotion of LDL-cholesterol uptake

Kidneys

Increased intraglomerular pressure
Increased protein leak
Glomerular growth and fibrosis
Increased sodium reabsorption

Adrenals

Increased formation of aldosterone

Coagulation System

Increased fibrinogen
Increased PAI-1 relative to tissue plasminogen factor

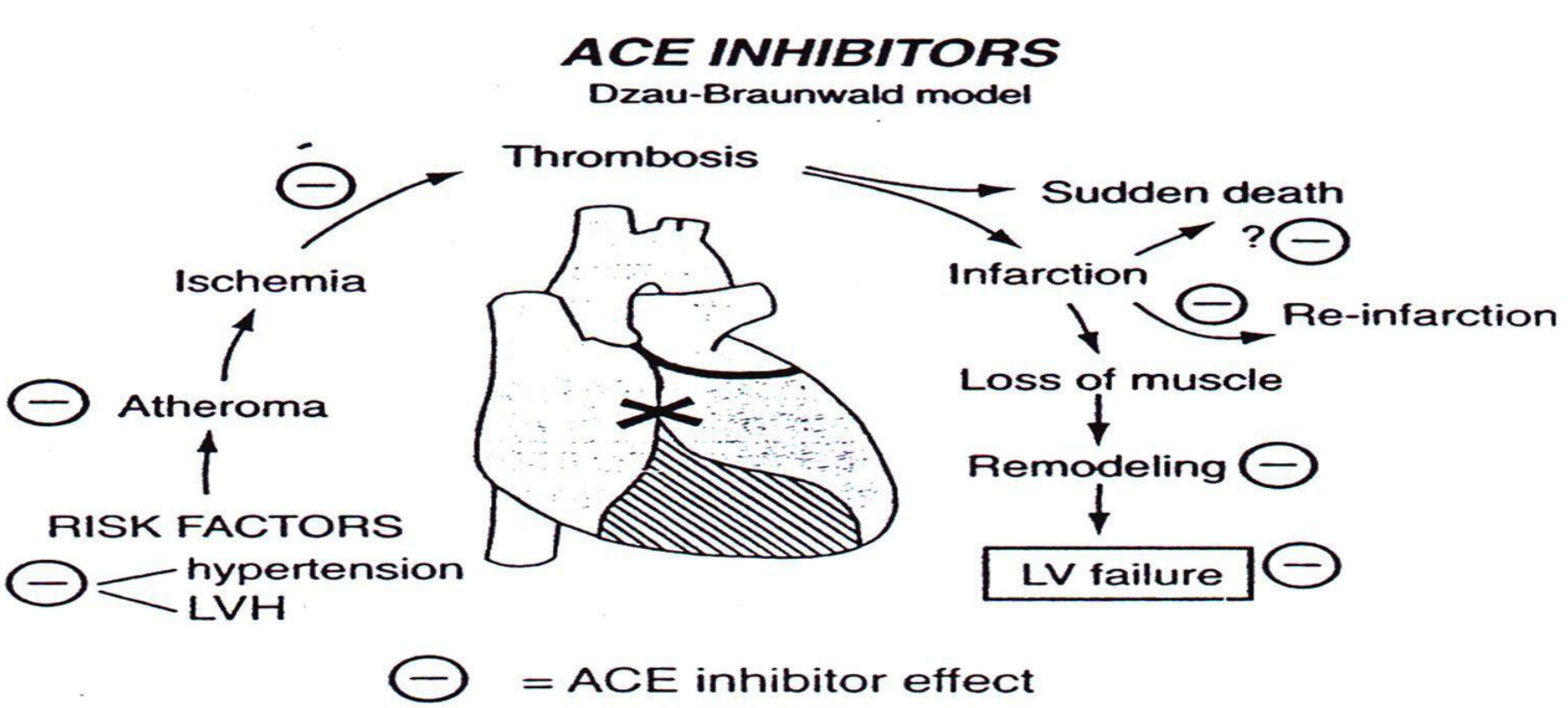


Figure 5-1 Dual role of ACE inhibitors, both preventing and treating cardiovascular disease. Note multiple sites of action in both primary and secondary prevention. ACE inhibitors have an indirect effect in primary prevention by lessening hypertension and by decreasing left ventricular hypertrophy. They protect the blood vessels indirectly by an antihypertensive effect, and directly inhibit carotid atherogenesis and thrombogenesis. Given at the start of myocardial infarction, they improve mortality in high-risk patients. By an antiarrhythmic effect, they may act to prevent postinfarct sudden death. By lessening wall stress, they beneficially improve postinfarct remodeling and decrease the incidence of left ventricular failure. The concept of sequential changes leading to a chain of events from risk factors to left ventricular failure is based on Dzau and Braunwald.[126] *LVH* = left ventricular hypertrophy. (*Figure © LH Opie, 2005.*)

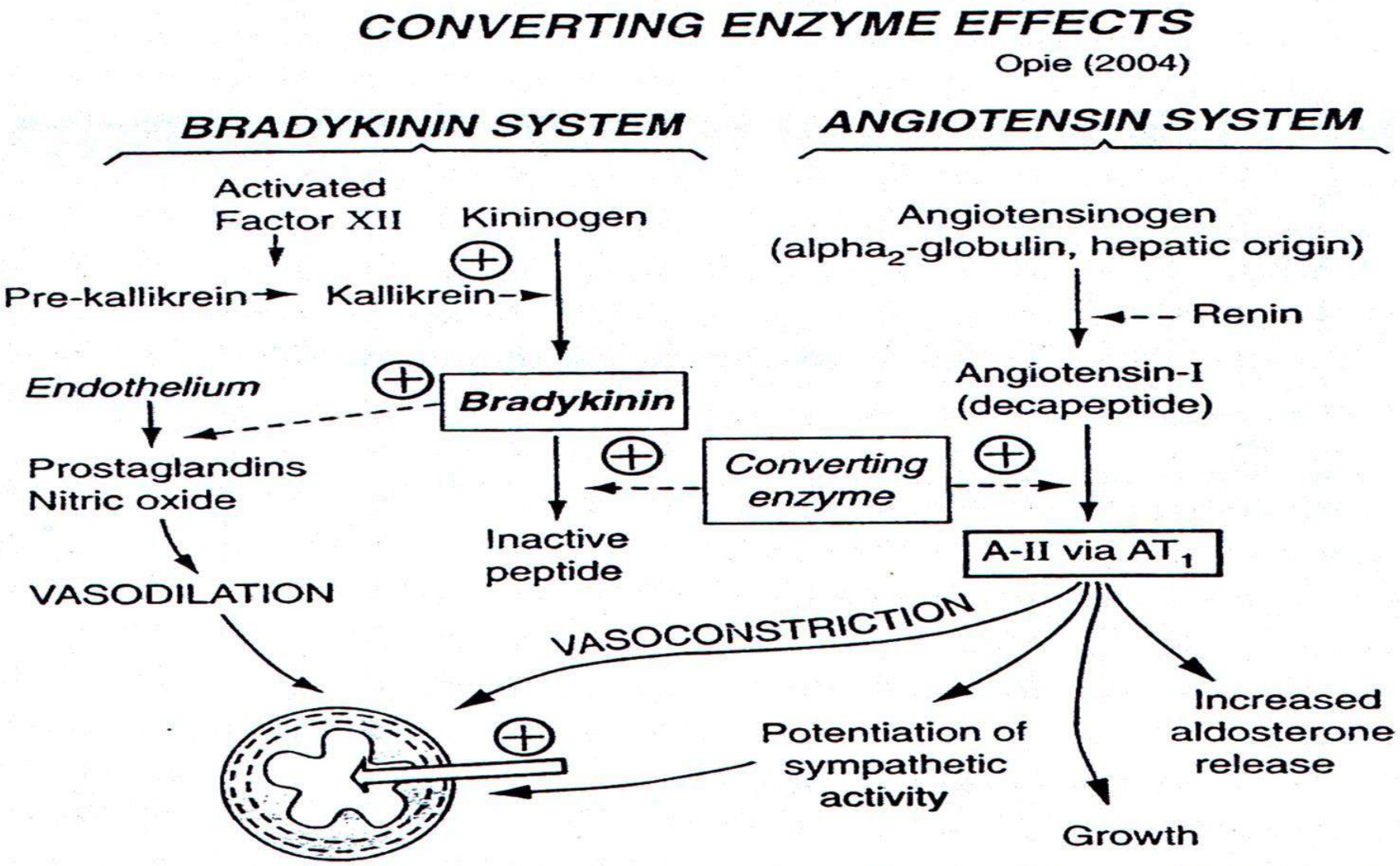


Figure 5-2 ACE inhibitors have dual vasodilatory actions, chiefly on the renin-angiotensin system with ancillary effects on the breakdown of bradykinin. The result of the former action is the inhibition of the vasoconstrictory systems and the result of the latter is the formation of vasodilatory nitric oxide and prostacyclin. These effects of bradykinin may protect the endothelium. (*Figure © LH Opie, 2005.*)

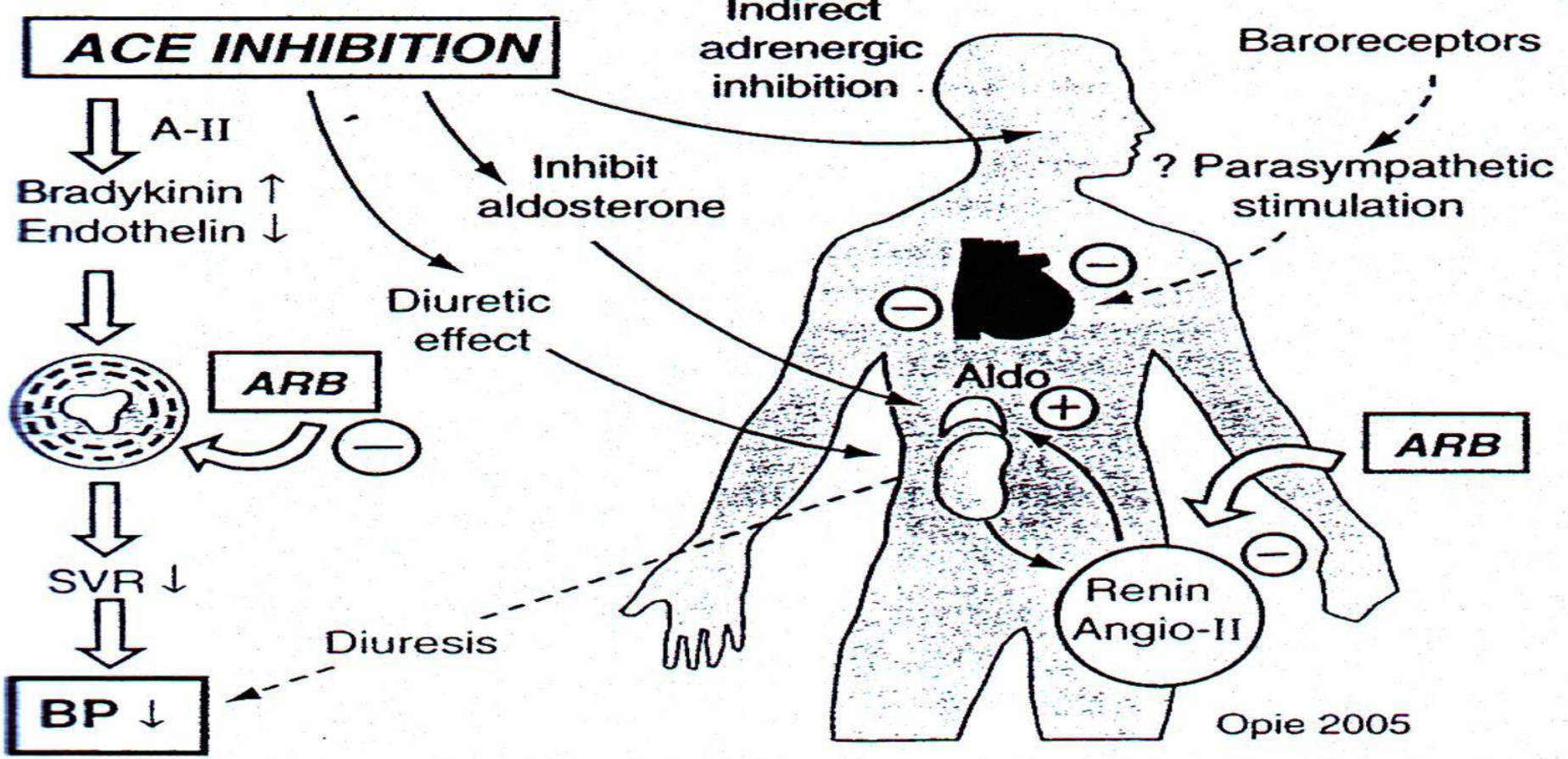


Figure 7-9 Proposed mechanisms whereby ACE inhibitors and angiotensin receptor blockers *(ARBs)* may have their antihypertensive effects. Note that the major effect is on the peripheral arterioles causing vasodilation and a fall in the systemic vascular resistance *(SVR)*, also called the peripheral vascular resistance. Indirect inhibition of adrenergic activity also promotes arteriolar dilation. Decreased angiotensin-II *(A-II)* levels may also act by increased formation of bradykinin and decreased formation of endothelin, as well as by inhibition of central effects of angiotensin-II with indirect adrenergic inhibition, thereby differing from the vasodilation induced by CCBs (see Fig. 7-8). Parasympathetic activity is also stimulated. *Aldo* = aldosterone. (*Figure © LH Opie, 2005.*)

Penggunaan ACE Inhibitor

- AH Tahap I untuk HT ringan, sedang dan berat'
- Untuk HT dengan gagal jantung
- Mengurangi resistensi terhadap insulin
- Terpilih untuk HT dengan dislipidemia, DM dan nefrophati DM
- Efektif untuk HT dengan PRA tinggi , sedang & rendah (krn efeknya pada ang II tissulaire & inhibisi simpatis)
- Pemberian kronis : kardioprotektif

Efek samping

- Batuk kering
- Angioneurotik udem
- Skin rash dan gangguan pengecapan

Kontraindikasi

- Kehamilan (risiko gagal ginjal pada janin)
- Stenosis arteri renalis bilateral (risiko gagal ginjal)

Sediaan

- Kaptopril
- Enalapril

2-3 kali sehari

- Fosinopril
- Lisinopril
- Perindopril
- Quinapril
- Ramipril
- Trandolapril

1 kali sehari

Antagonis kalsium (CCB)

Mekanisme :

- Blokade influk ion kalsium lewat voltage operated channel (VOC) → vasodilatasi →TD ↓
- Di ginjal : RBF ↑ → diuresis ↑

Klasifikasi berdasarkan struktur kimia :

1. Fenilalkilamin, misal : verapamil (V), galopamil, tiapamil
2. Benzotiazepin, misal diltiazem (D)
3. Dihidropiridin (DHP), misal : nifedipin (N), nitrandipin (Nt), nikardipin (Nk), nimodipin, nisoldipin, niludipin, isradipin (I), felodipin (F) dan amlodipin (A)
4. Piperazin , misal : sinarizin, flunarizin , lidoflazin

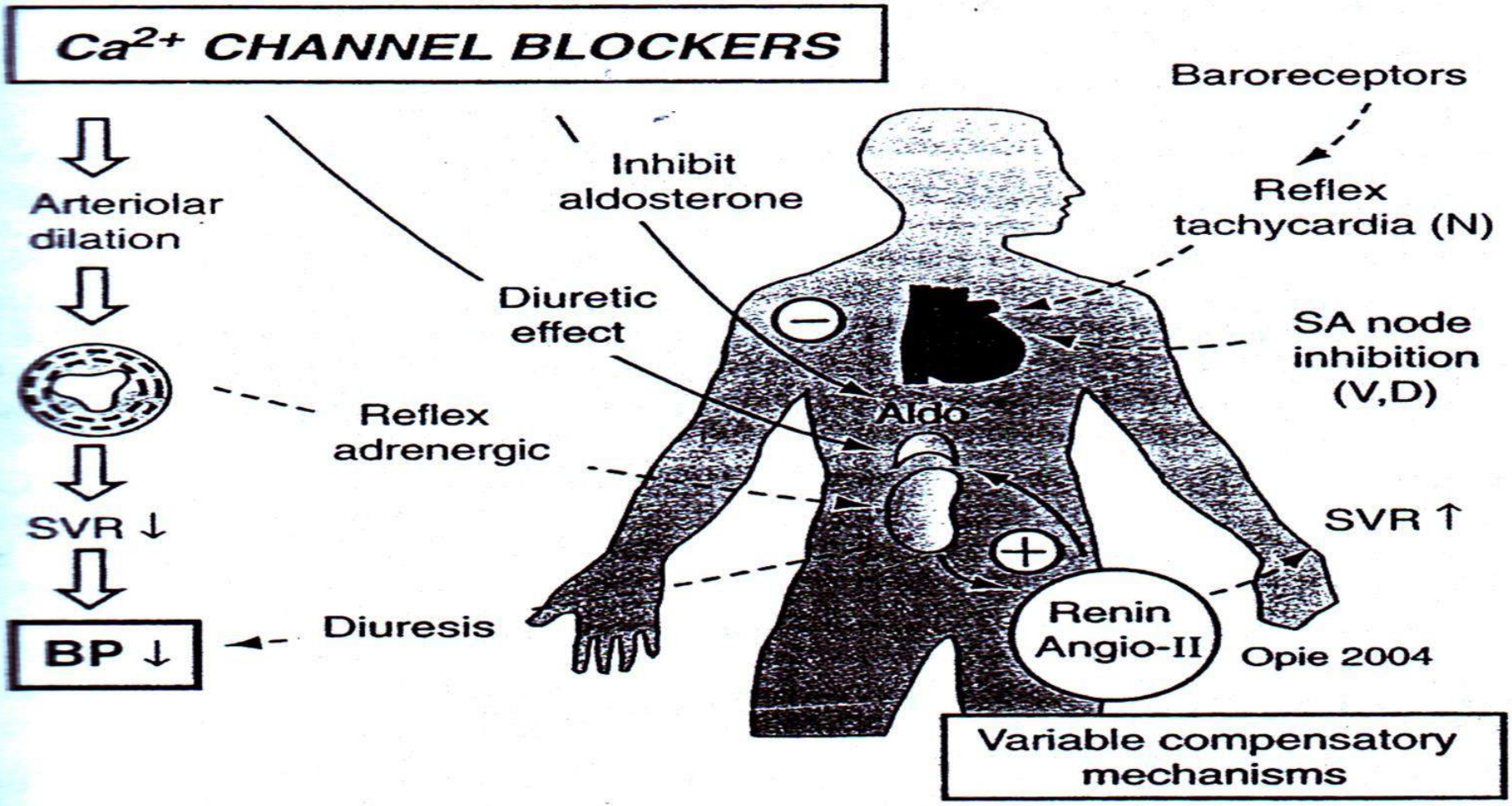


Figure 7-8 Calcium channel blockers (*CCBs* = calcium antagonists) act largely by peripheral arterial dilation, with a lesser diuretic effect. They also evoke counterregulatory mechanisms, dependent on stimulation of renin and formation of angiotensin, as well as on reflex release of norepinephrine. Such acute adrenergic stimulation with short-acting nifedipine *(N)* may precipitate myocardial ischemia in the presence of coronary disease (see Fig. 3-6). Currently only long-acting CCBs are used in the treatment of hypertension. The inhibition of aldosterone release obviates overall fluid retention. *D* = diltiazem; *SVR* = systemic vascular resistance; *V* = verapamil. (*Figure © LH Opie, 2005.*)

Golongan dihidropiridin

- Selektivitas vaskular tinggi, efek thdp jantung minimal → relatif aman dalam kombinasi dg beta blocker
- Absorpsi oral cepat → TD ↓ dg cepat (kecuali amlodipin)
- Bioavailabilitas oral rendah & bervariasi (menatb lintas I tinggi)
- T1/2 relatif pendek → pemberian 2-3 kali sehari
- Aman untuk pasien gangguan fungsi ginjal

Indikasi

- AH tahap I
- Krisis Ht : nifedidpin sublingual
- Gol benzotiazepin (diltiazem) :
  - Efek terhadap jantung >> DHP
  - Untuk angina & antiaritmia

Angiotensin II Reseptor Blocker (ARB): losartan, valsartan , irbesartan, eposartan

Reseptor Angiotensin 2 tdd :

- Reseptor AT1 : pada ginjal, jantung, sel otot pemb darah, otak kelenjar adrenal
- Reseptor AT2 : pada uterus , kel adrenal & jaringan fetus

ANGIOTENSION-II RECEPTOR SUBTYPES

Opie 2004

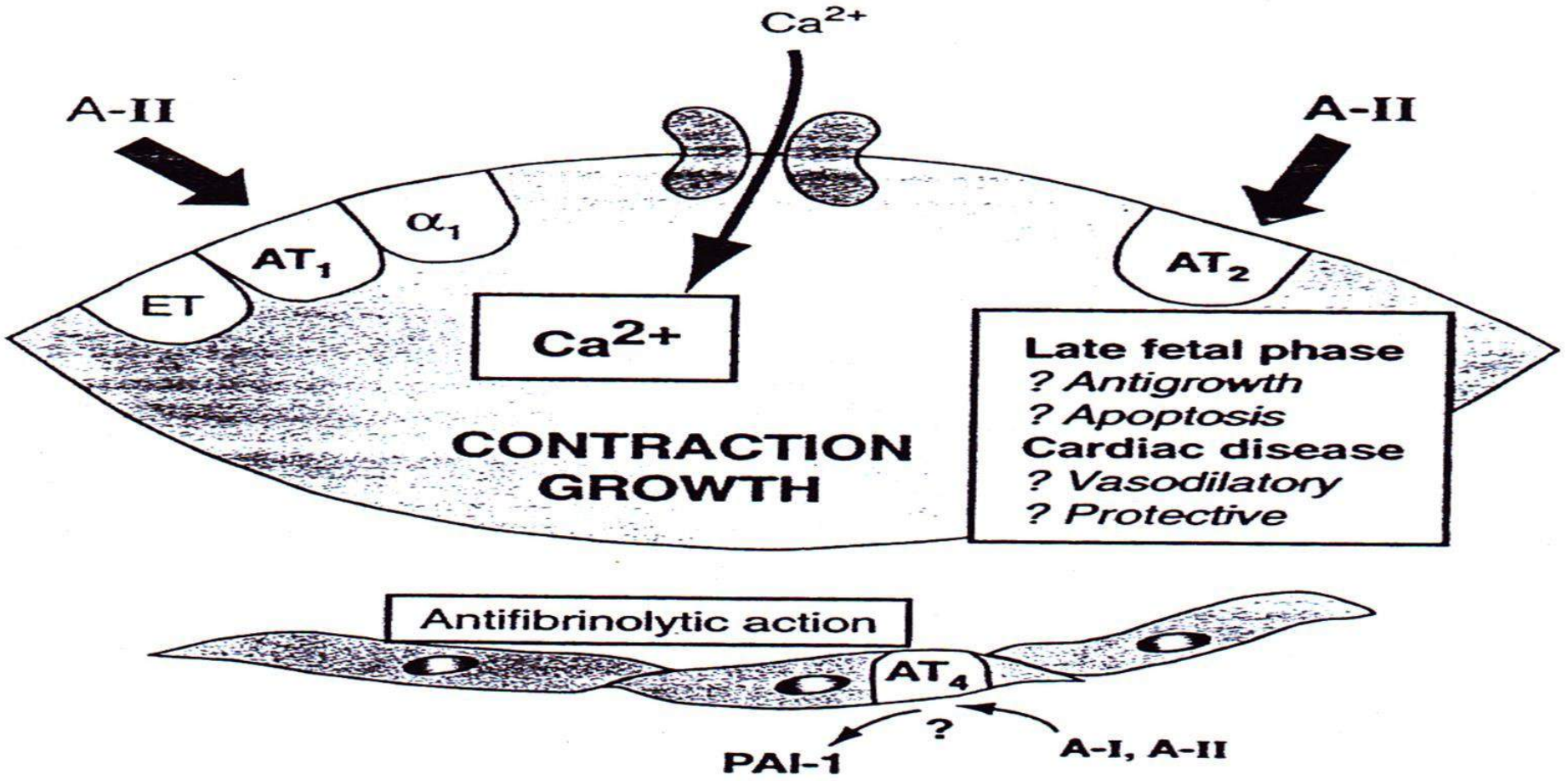


Figure 5-3 Proposed roles of angiotensin II receptor subtypes, which are called AT-1, AT-2 and (putative) AT-4 subtypes. Most of the physiological effects in adult vascular smooth muscle cells are conveyed by the AT-1 receptor subtype. The AT-2 receptor is of substantial importance in late fetal vascular growth, exerting an antigrowth effect. Hypothetically, these receptors may also play a beneficial role in various myocardial pathophysiological conditions (see text). AT-4 receptors are postulated to have an antifibrinolytic effect. (*Figure © LH Opie, 2005.*)

ACE, A-II EFFECTS and ARBs

Opie 2004

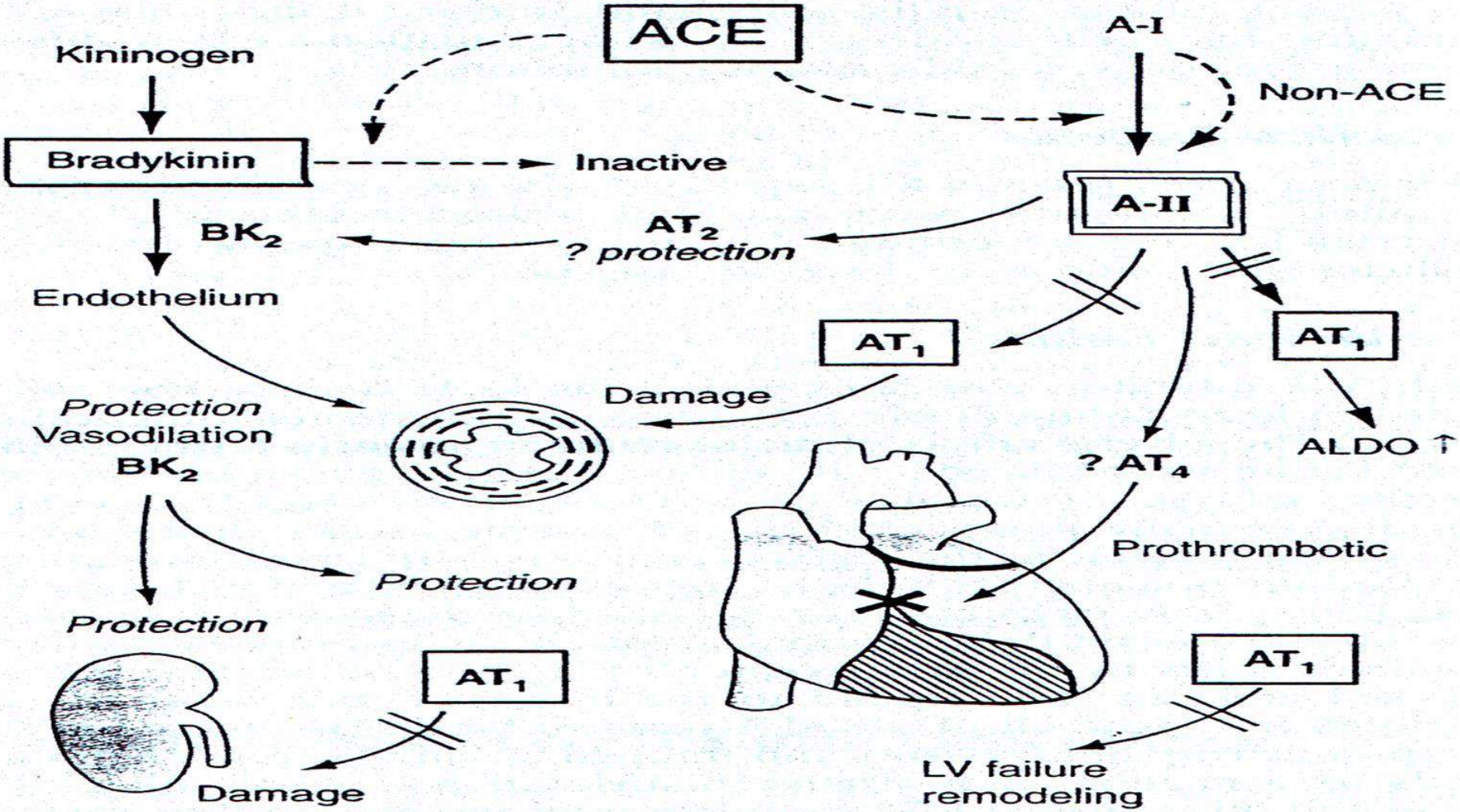


Figure 5-11 Mechanisms whereby angiotensin-II (*A-II*) exerts adverse effects on cardiovascular system. Most of the damaging effects are via the AT-1 receptor, with possible protection via the unopposed AT-2 receptor (see Fig. 5-3) that may unexpectedly lead to relatively small amounts of bradykinin formation. The putative AT-4 receptor may mediate prothrombotic effects. Bradykinin (*BK*), formed especially during inhibition of ACE (angiotensin-converting enzyme), mediates protection by activation of the BK-2 receptor.

Compound and Indications	Pharmacokinetics	Doses (FDA-Approved)	Side Effects and Contraindications
Losartan potassium (Cozaar) Hypertension	Converted in liver to active metabolite with $t_{1/2}$ 6–9 h; dominant fecal excretion; minimal food effect	25–100 mg total in one or two doses; usual start with 50 mg, half if volume depletion or liver disease	S/E in hypertension = placebo; C/I = pregnancy, bilateral renal artery stenosis; Care: liver disease
Candesartan cilexetil (Atacand) Hypertension	Converted to active candesartan by ester hydrolysis during GI absorption, then excreted unchanged in bile and feces; $t_{1/2}$ 9 h; no food effect	8–32 mg total in one or two doses; usual start with 16 mg; less if volume depletion	As above
Irbesartan (Avapro) Hypertension Diabetic type 2 nephropathy	No metabolite. Rapid oral absorption, high bioavailability; $t_{1/2}$ 11–15 h; 80% excreted unchanged in bile and feces. High tissue distribution.	150 mg once daily; half if volume depletion; up to 300 mg daily; no changes for moderate hepatic or severe renal disease	As above
Valsartan (Diovan) Hypertension; HF, ACEi-intolerant	Rapid absorption. Food effect (AUC↓40%, C_{max}↓50%). No metabolite, $t_{1/2}$ 6 h, 83% biliary and fecal excretion. Low tissue distribution.	80 mg up to max 320 mg once daily; less in severe hepatic or renal failure (*caution*: volume depletion)	As above but in VALUE similar withdrawal rate to amlodipine Care: severe renal disease
Telmisartan (Micardis) Hypertension	No active metabolite, $t_{1/2}$ 24 h, food effect (6–20%), almost all excreted unchanged (bile, feces). Nonlinear kinetics, ↑ AUC and C_{max} with higher dose	40–80 mg daily, can't go below 40 mg for volume depletion or liver failure	As above

ACEi = angiotensin-conv[illegible]; LVH = left ventricular hypertrophy.