How to manage hypertension with the target organ damage

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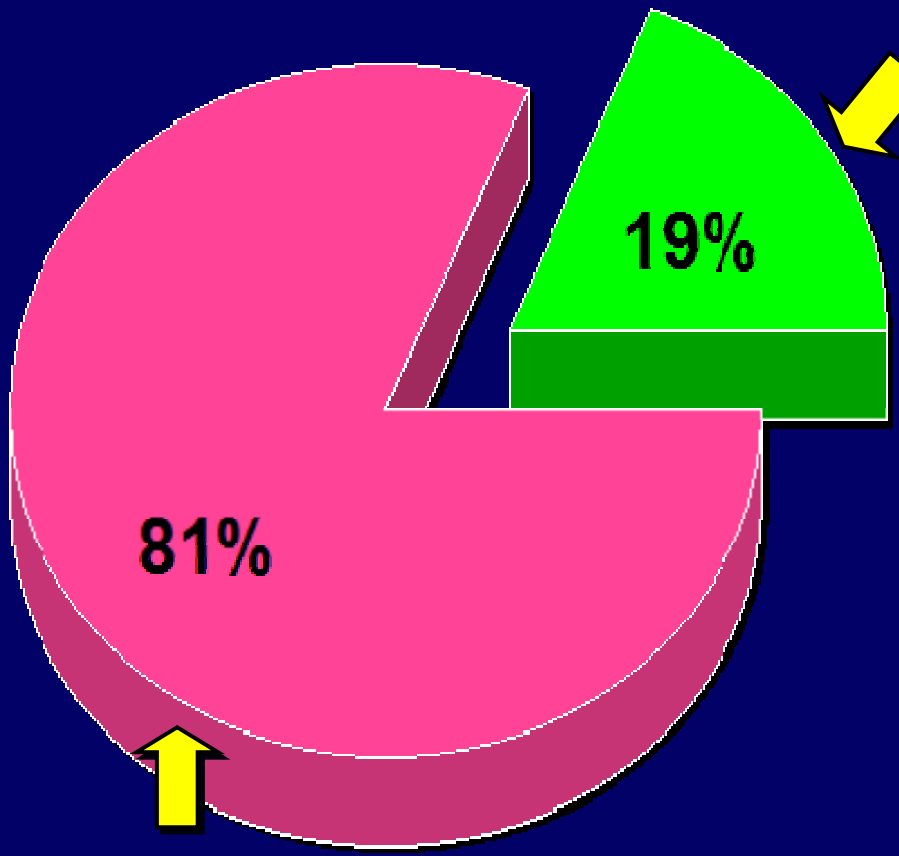
김 동 수

Most Hypertensive Patients Have Complex Hypertension



COMPLEX HYPERTENSION

- HTN ≥ 1 additional CV risk factor
- CAD, LVH
- Diabetes, Metabolic syndrome
- Renal Disease
- High-risk population

Framingham Offspring Study (men aged 18-74)

Target Organ Damage (TOD)

- 심장: 심비대, 심전도에서 허혈이나 좌심실비대소견,
  협심증, 심근경색증, 관동맥 재관류 병력, 심부전
- 망막병증: 망막 삼출 및 출혈, 유두부종
- 만성 신장질환
  - **SCr. ; M>1.5 mg/dL, F>1.4mg/dL**
  - **proteinuria; >300mg/day**
  - *** microalbumiuria(20-300mg/day)**
- 뇌: 뇌졸중, 뇌출혈, 일시적 뇌허혈발작**(TIA)**
- 말초동맥질환

Factors Influencing Prognosis

심혈관 질환의 위험 인자들

- 수축기와 확장기 혈압의 정도 (1-3도)
- 남자 > 55세
- 여자 > 65세
- 흡연
- 총콜레스테롤 >240 mg/dl 혹은 LDL-c >160 mg/dl
- HDL-c M<40, F<45 mg/dl
- 조기 심혈관 질환의 가족력 (50세 전)
- 비만, 운동부족

표적 장기 손상

- 좌심실 비대 (심전도, 심초음파)
- 미세단백뇨 (20-300mg/day)
- 방사선 혹은 초음파 등으로 확인 된 동맥경화반 (대동맥, 경동맥, 관상동맥, 좌골동맥, 대퇴동맥)
- 고혈압성 망막증 (3 혹은 4도)

동반된 임상 상태

- 당뇨병
- 뇌혈관질환
  - 허혈성 뇌졸중
  - 뇌출혈
  - 일과성 허혈 발작
- 심장질환
  - 심근경색증
  - 협심증
  - 관동맥 재건술
  - 울혈성 심부전
- 신장 질환
  - 혈장 크레아틴
    - F>1.4 mg/dl
    - M>1.5 mg/dl
  - 알부민뇨 >300mg/day
- 말초 혈관 질환

2003 WHO/ISH Guidelines
J Hypertens 2003;21:1983-92.

Stratification of risk to quantify prognosis

Other risk factors and disease history	Blood pressure(mmHg)		
	Grade 1 (SBP 140-159 or DBP 90-99)	Grade 2 (SBP 160-179 or DBP 100-109)	Grade3 (SBP ≥180 or DBP ≥110)
I No other risk factors	Low risk	Medium risk	High risk
II 1-2 risk factors	Medium risk	Medium risk	High risk
III 3 or more risk factors , or TOD, or ACC	High risk	High risk	High risk

ACC, associated clinical conditions; TOD, target organ damage; SBP, systolic blood pressure; DBP, diastolic blood pressure

2003 WHO/ISH Guidelines

J Hypertens 2003;21:1983-92.

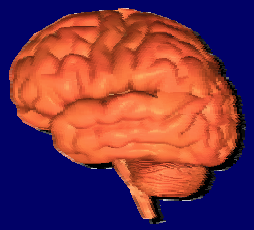
언제 약물치료를 시작하는가?

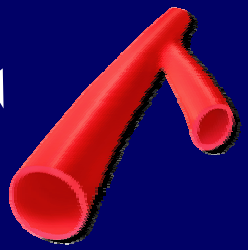
Systolic BP	lifestyle modification	no DM or TOD	DM or TOD
120-139	yes		consider specific drug therapy
140-159	yes	initial monotherapy	initial monotherapy or 2 drug combination
>160	yes	initial monotherapy or 2 drug combination	2 drug combination

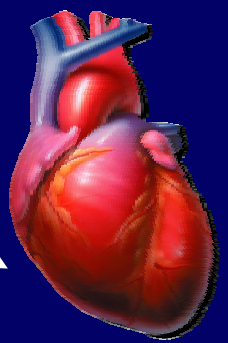
TOD(target organ damage); angina, myocardial infarction, LVH, heart failure, stroke, transient ischemic attack, chronic renal disease, peripheral arterial disease

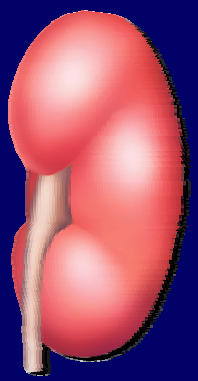
Goals for blood pressure, stratified by risk

HYPERTENSION POPULATION (MMHG)	BLOOD PRESSURE GOAL
No diabetes or target-organ damage	<140/90
Diabetes, with or without target-organ damage	<130/80
Diabetic nephropathy >1g/day	125/75









고혈압

동맥경화
혈관내피세포장애
혈전생성

뇌졸중

협심증
심근경색증
말초동맥질환

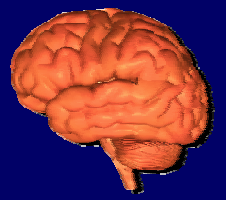
좌심실비대
섬유화

심부전
부정맥

DEATH

신실질 경화
GFR 감소
단백뇨

신부전

고혈압 →  → 뇌혈관질환

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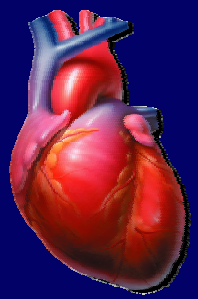
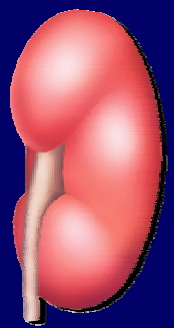
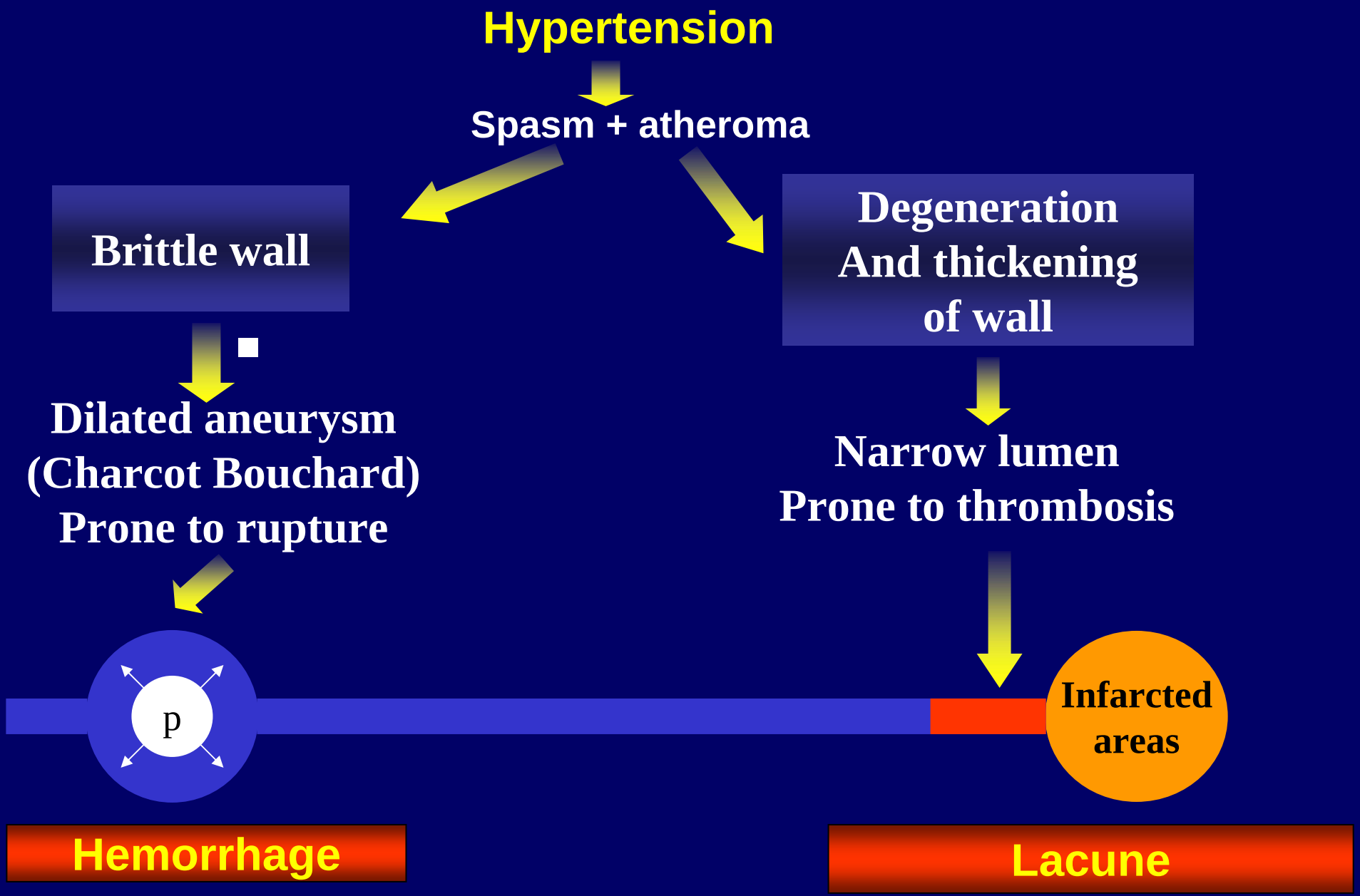




신부전

Ischemic stroke(80%)
Cerebral hemorrhage(10~15%)
Subarachnoid hemorrhage(5%)



A summary of the effects of hypertension on the cerebrovascular tree

Stroke Prevention Interventions

- Blood pressure lowering
- Antiplatelet therapy
- Anticoagulant therapy for patients with atrial fibrillation
- Statin therapy
- Carotid revascularization for patients with severe symptomatic stenosis

Blood Pressure and Stroke Prevention

Blood pressure lowering and primary stroke prevention

- **BP lowering in various high-risk groups reduces the risk of stroke by approximately one-third.**
- **BP lowering not only benefits hypertensive patients, but also high-risk patients with normal BP.**
- **Trials have shown that drugs from five major classes (diuretics, beta-blockers, ACE inhibitors, CCB, ARBs) are effective in lowering BP and the risk of stroke.**
- **Diuretics have been found to be at least as effective as other drugs in preventing stroke.**

ISH: statements on blood pressure and stroke. J Hypertens 2003;21:649-50.

Blood Pressure and Stroke Prevention

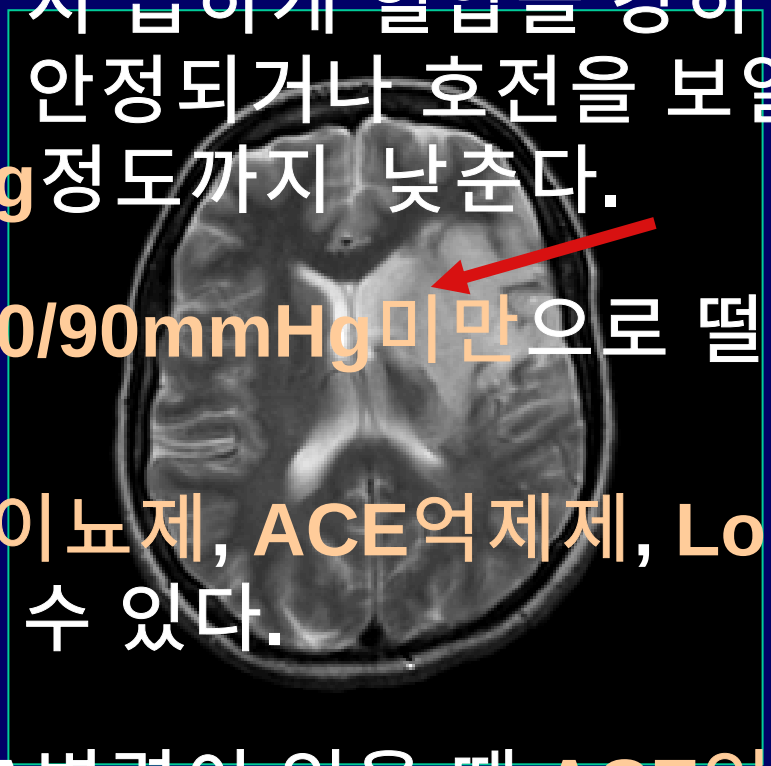
Blood pressure lowering and secondary stroke prevention

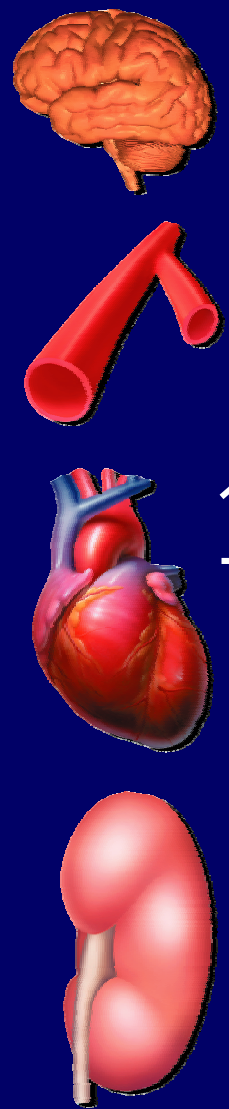
- BP lowering in patients with previous cerebrovascular disease, using a diuretic and ACE inhibitor, reduces the risk of subsequent stroke by approximately 30%.
- Treatment effects appear to be similar in men and women, subjects above and below the age of 65 years, and normotensive patients as well as those elevated BP.
- Available evidence is still limited and further data are needed about the relative effectiveness of different drug classes for various types of stroke.

ISH: statements on blood pressure and stroke. J Hypertens 2003;21:649-50.

Summary: Hypertension and Stroke

- 급성으로 발병 시 급하게 혈압을 강하 시키기 보다는 환자의 상태가 안정되거나 호전을 보일 때 까지는 **160/100mmHg**정도까지 낮춘다.
- 강압목표는 **140/90mmHg미만**으로 떨어뜨린다.
- 초기약제로서 이뇨제, **ACE**억제제, **Long-acting DHP CCB**을 사용할 수 있다.
- 뇌졸중이나 **TIA**병력이 있을 때 **ACE**억제제와 이뇨제 병합요법이 뇌졸중의 이차예방효과가 좋다.





고혈압

뇌졸증

협심증, 심근경색증

좌심실비대

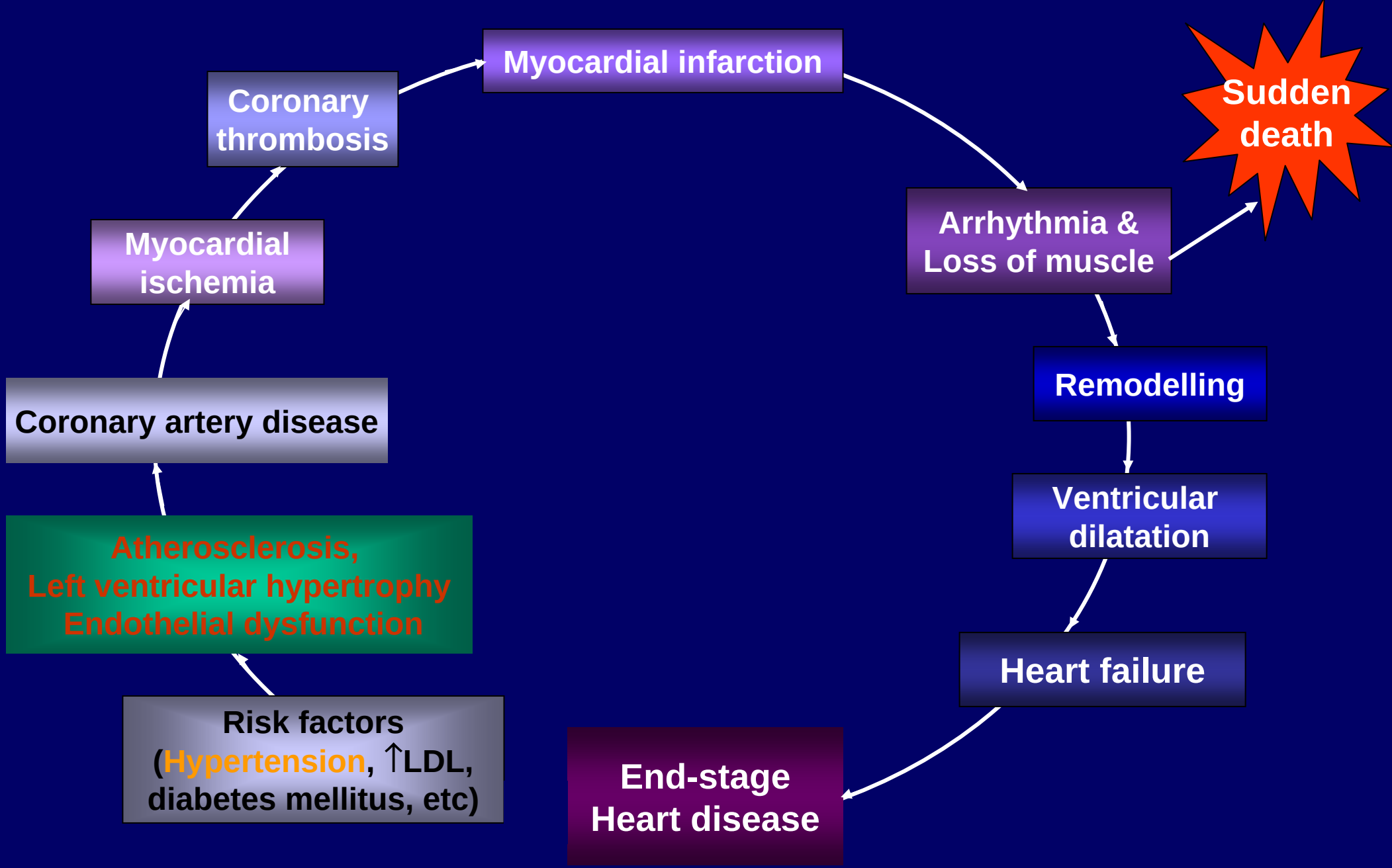
대동맥, 말초혈관질환

심부전

부정맥

신부전

당뇨병



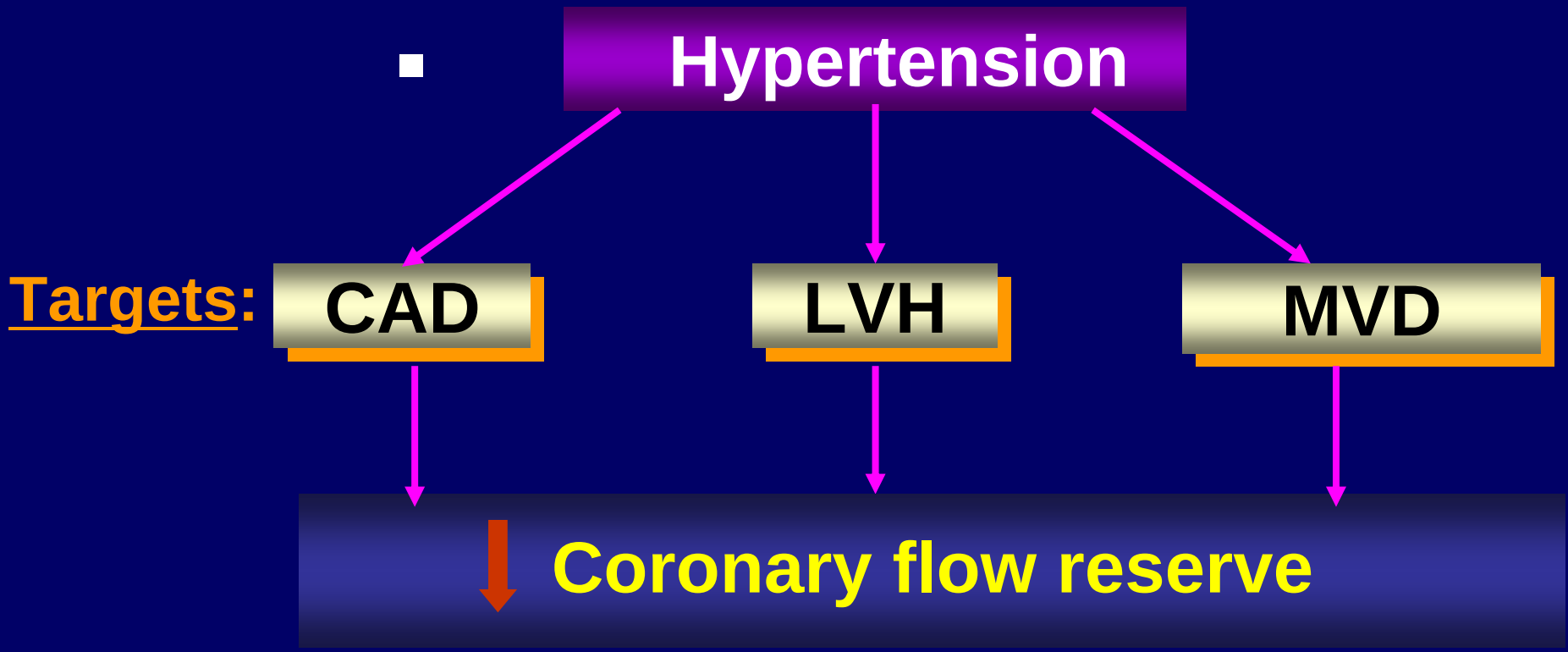
The cardiovascular continuum

관동맥질환을 동반한 고혈압의 치료

- **Angina pectoris**
  - **CCB: long-acting DHP계**
    (rapid-onset short-acting제제는 피한다)
  - **β-Blockers: coronary spasm시 주의해서 사용**
  - **Combination therapy with DHP계CCB & β-Blockers**

- **Myocardial infarction**
  - **β-Blockers(non-ISA), ACE Inhibitors(low EF)**
  - **Diltiazem, Verapamil: β-Blockers are ineffective or contraindicated, NQMI, after MI with normal EF**

The multiple pathways of myocardial ischemia in hypertensive patients



MVD; microvascular disease

고혈압과 관동맥질환

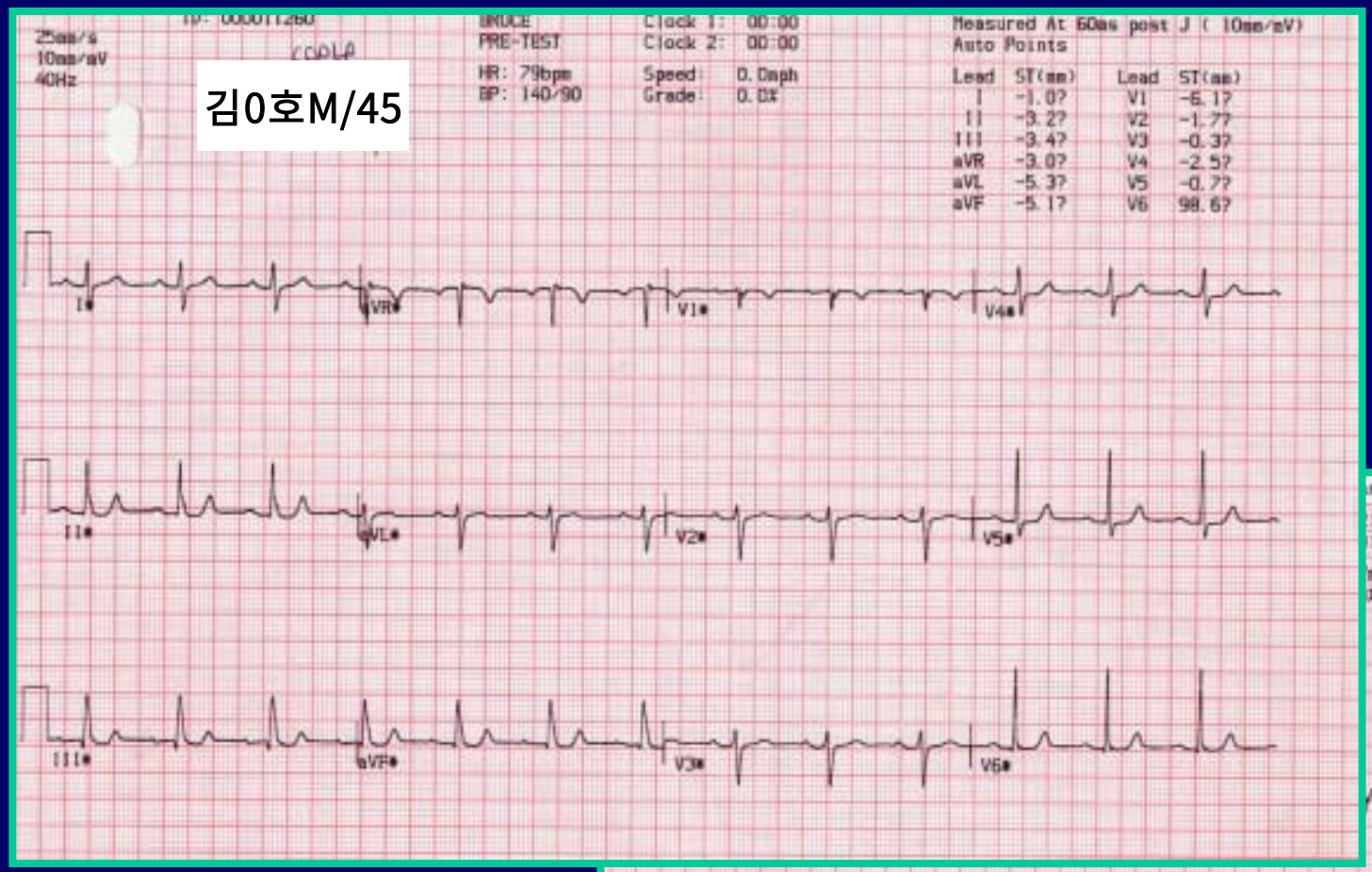
Case. 김 0 호 M/45

2년 전부터 시작한 흉부불쾌감이 최근 심해지면서 내원. 증상은 지하철 계단을 오를 때 발생하고 안정하면 1~2분 내에 소실되었다.

혈압 180/100mmHg. 흡연력(+). 다른 소견은 없었다.

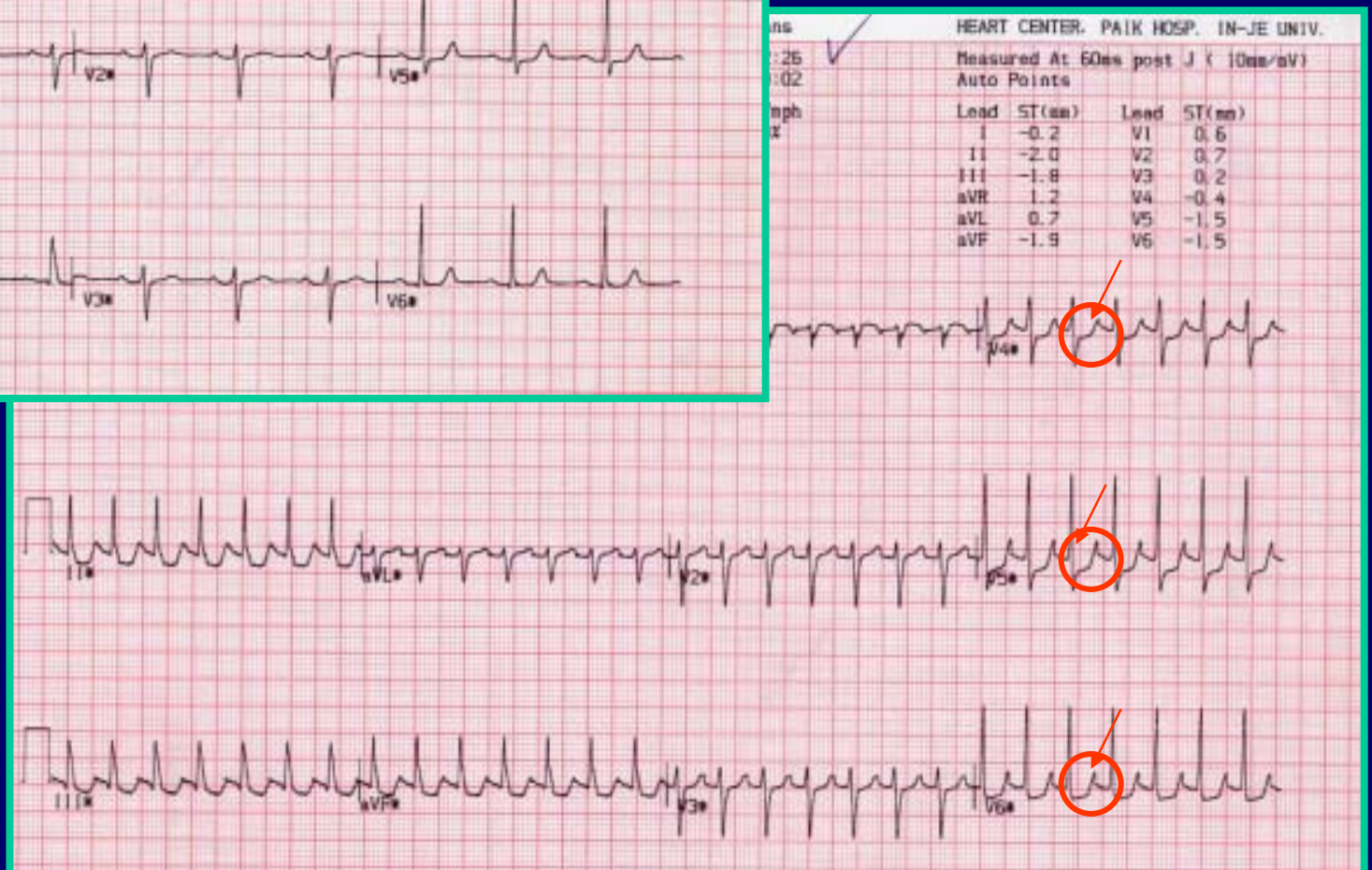
- 심전도: WNL, NSR
- 운동부하검사

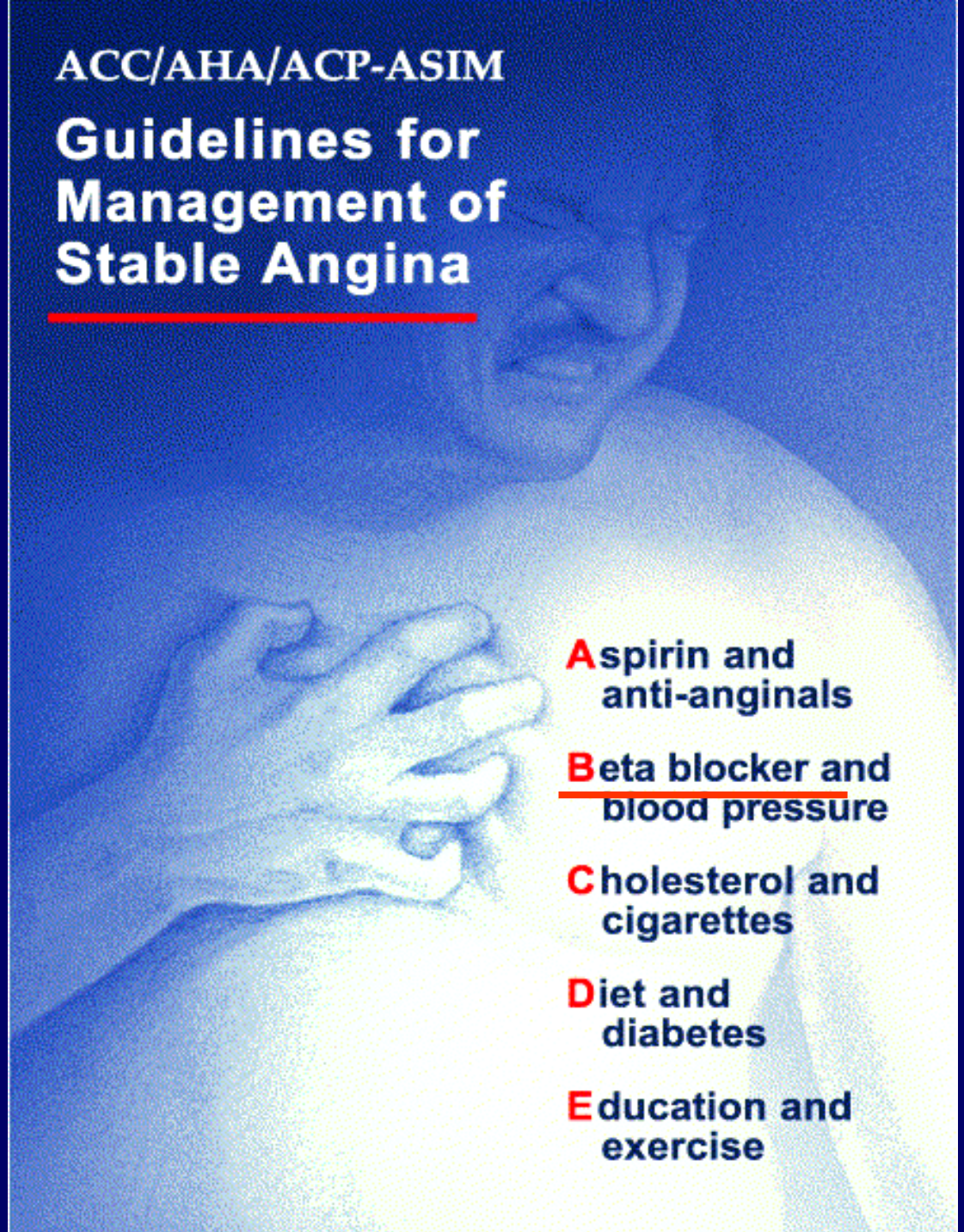
Treadmill test



resting

Exercise 7 Met's





JACC 1999;33:2092

환자에게 우선적으로 사용 될 약제는?

베타차단제

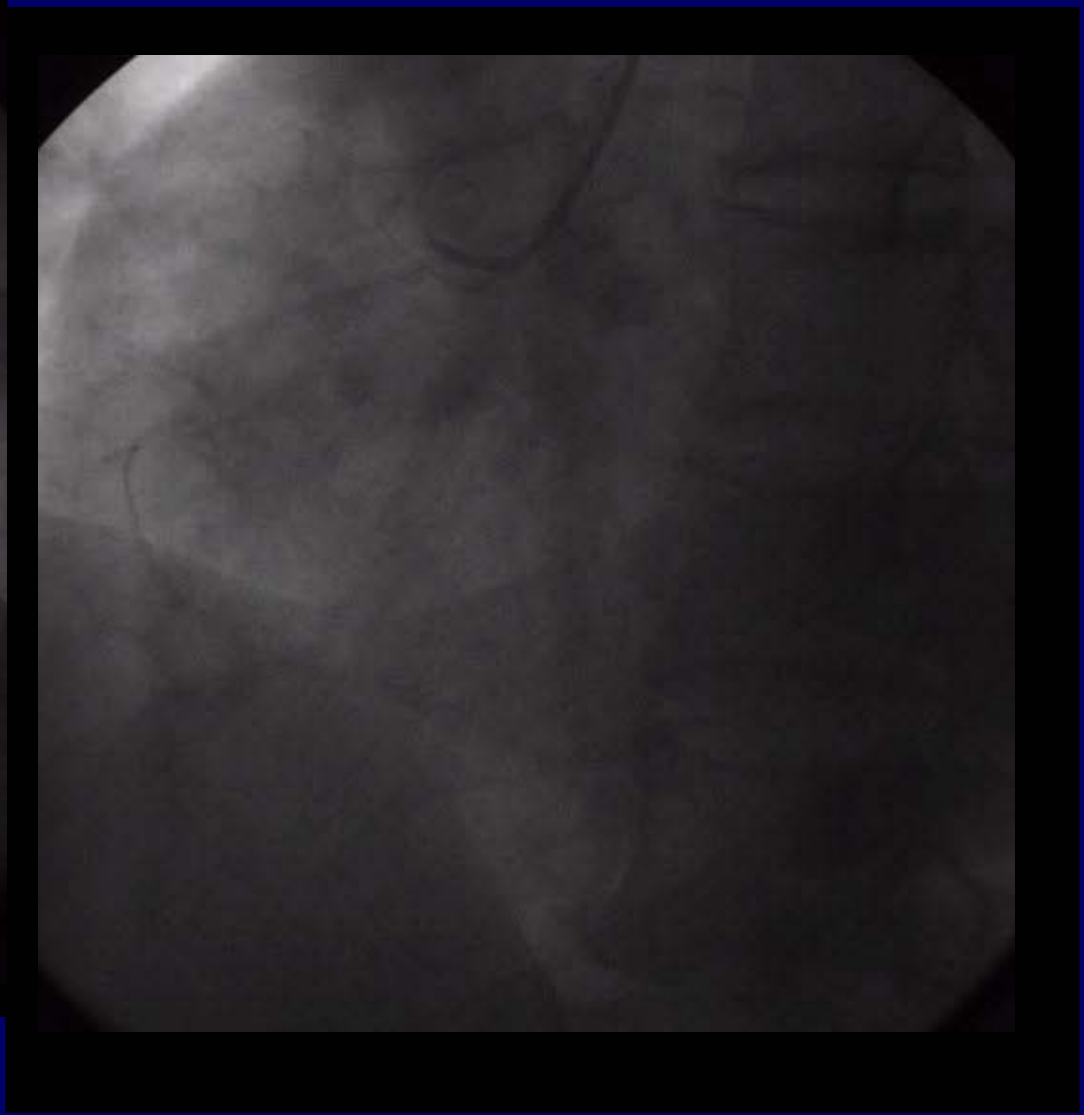
혈압이 150/90mmHg로 잘 조절되지 않는다면 추가 할 수 있는 적당한 혈압강하제는?.

서방형 DHP계 칼슘길항제 또는 이뇨제

베타차단제와 DHP-CCB병용투여로 혈압은 120/80mmHg로 조절되었으나, 간헐적인 운동시 흉통이 있어 CAG를 시행하였다.

LCA

RCA



CAG에서 협착은 없고 관동맥혈류가 느린 소견

↓

Endothelial dysfunction에 의한 Coronary Flow Reserve 감소

↓

Microvascular disease

↓

Treatment:

Coronary vascular resistance↓

ACE inhibitors, DHP-CCB

관동맥혈관의 기능이상의 개선

- **ACE inhibitors:**

  ↑ Bradykinin, ↓ AII→ EDRF/NO, Prostacyclin, t-PA

  - antiproliferative and antimigratory effects on SMC

  - improve and/ or restore endothelial function

  - improve antiplatelet effects

- **CCB**
- **Beta-blockers ***
- **Diuretics ***

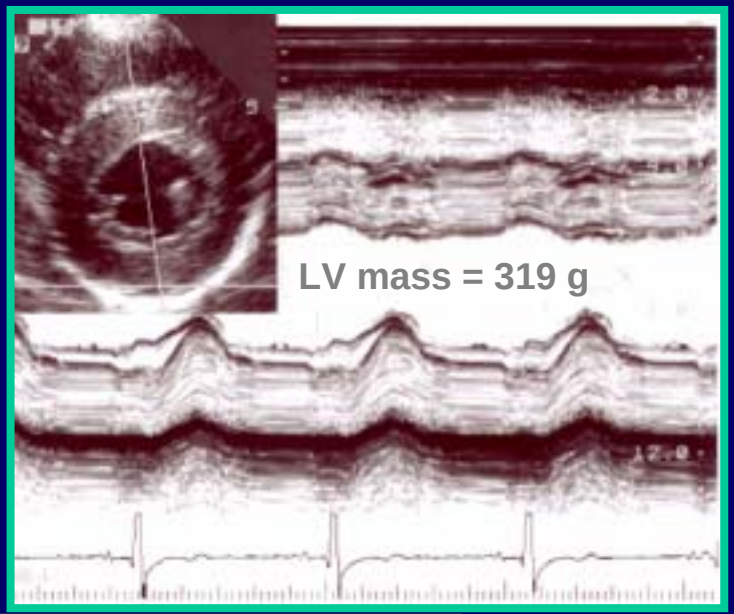
*** Minimal evidence of effects on endothelial function**

LVH in a patient with severe hypertension

Negative P wave component in $V_1 \geq 1$ mm x 1 mm

$S_{V1} + R_{V5} = 54$ mm

LV mass "cube" (g) = 1.04 x [(IVS + LVID + PW)^3 - (LVID)^3]



$R_I + S_{III}$ = 28 mm

R wave in V_5 = 30 mm

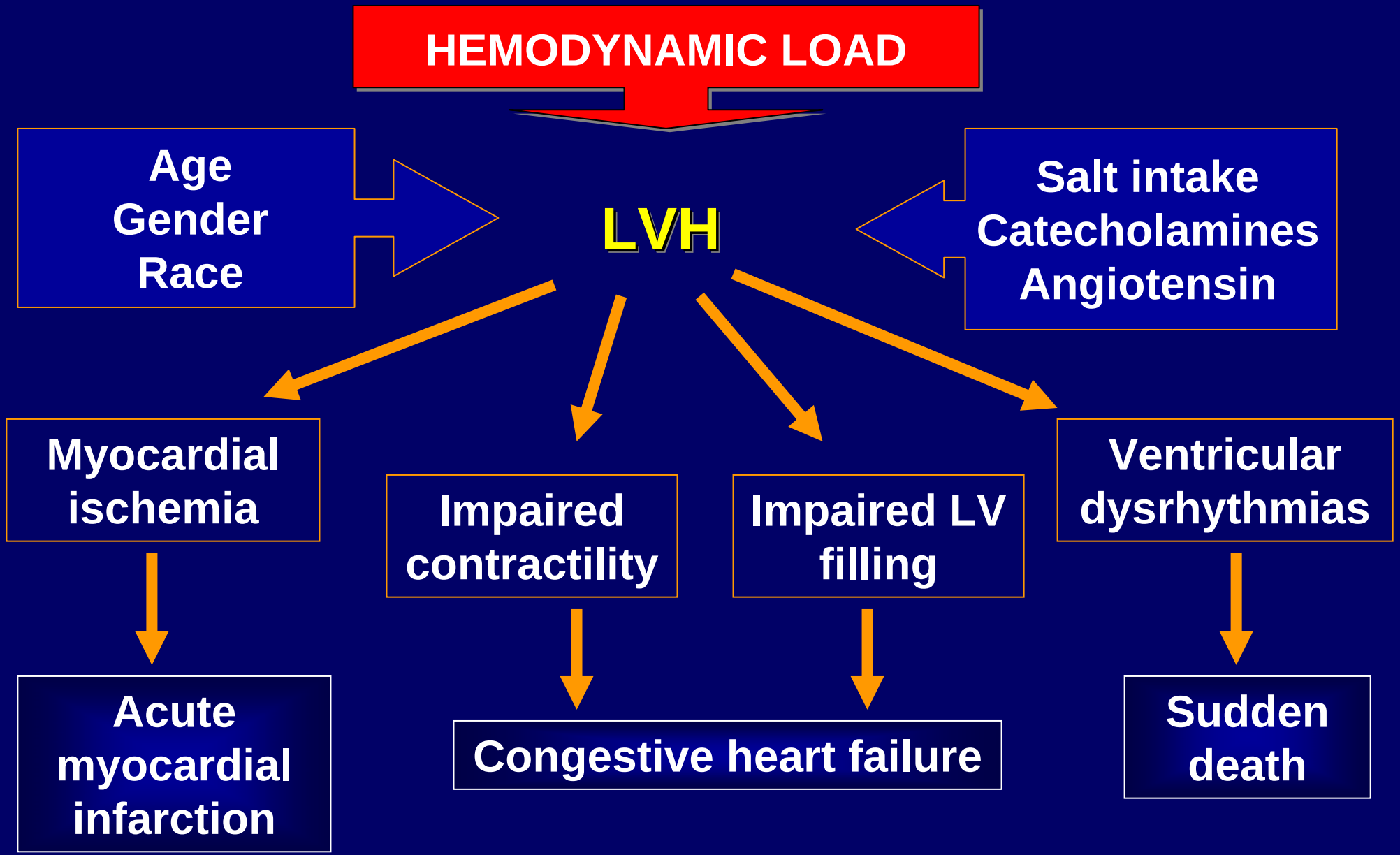
RaVL + S_{V3} = 40 mm

Typical strain

ECG criteria fulfilled:

1. Lewis
2. Gubner-Ungerleider
3. Sokolow-Lyon
4. Romhilt-Estes
5. Framingham
6. Minnesota 3.1
7. Cornell
8. Perugia

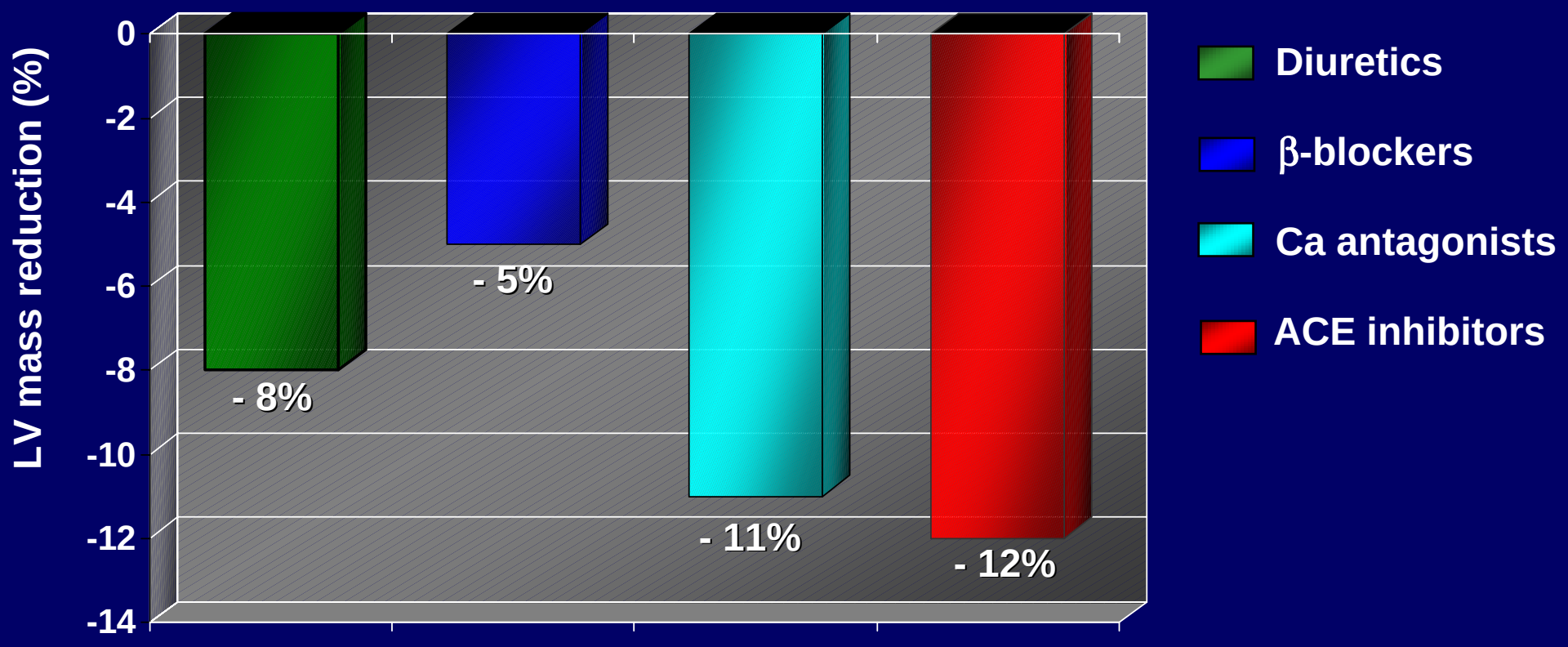
LVH: determinants and consequences



Left Ventricular Hypertrophy: Should It Be Reduced?

- **Effects of reducing LVH**
  - Improvement in coronary reserve
  - Improved diastolic dysfunction
  - Preservation of systolic function
  - Reduced ventricular arrhythmias

Meta-analysis of randomized, controlled trials of LVH regression in essential hypertension



N = 50 Studies

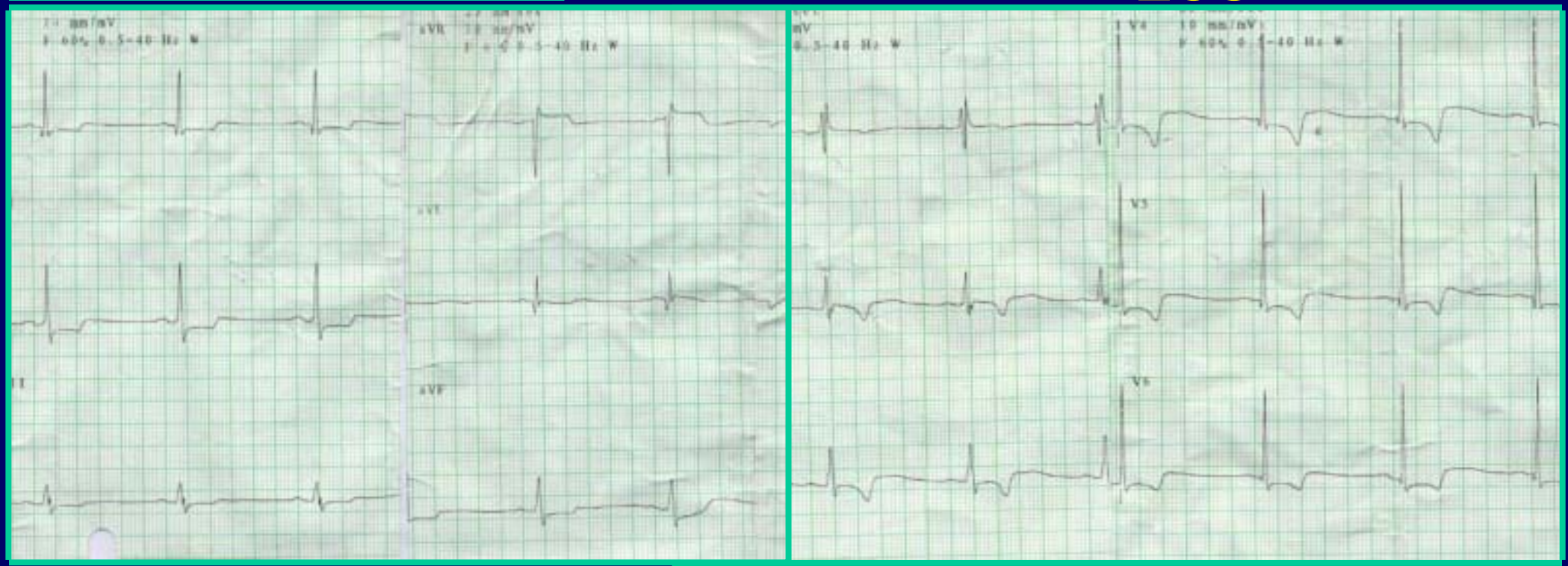
고혈압과 LVH

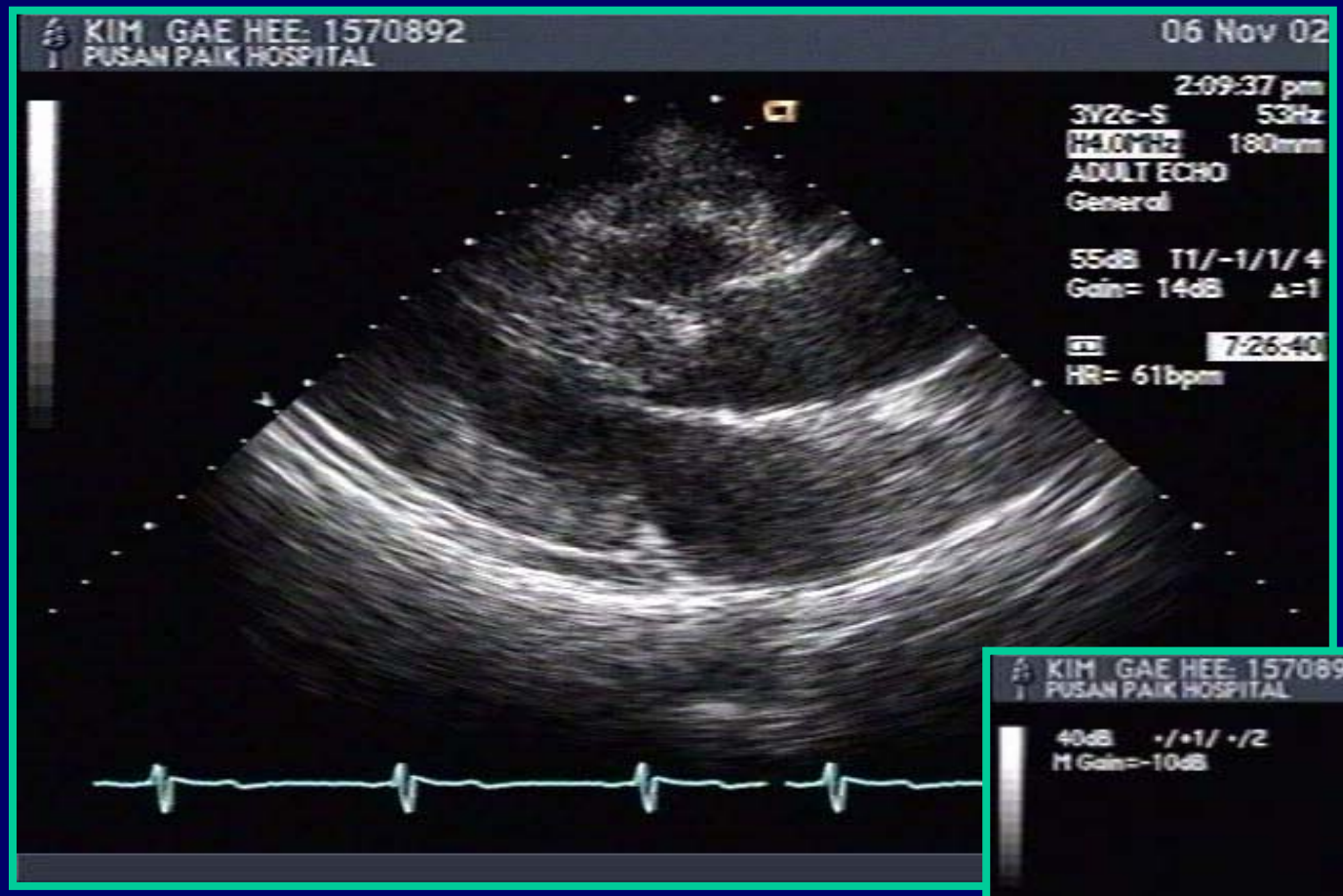
Case: 53세 여자

- C.C; chest pain, BP: 170/95mmHg
- Lab: TC/TG/HDL-C(262/200/34mg/dL)

Chest PA

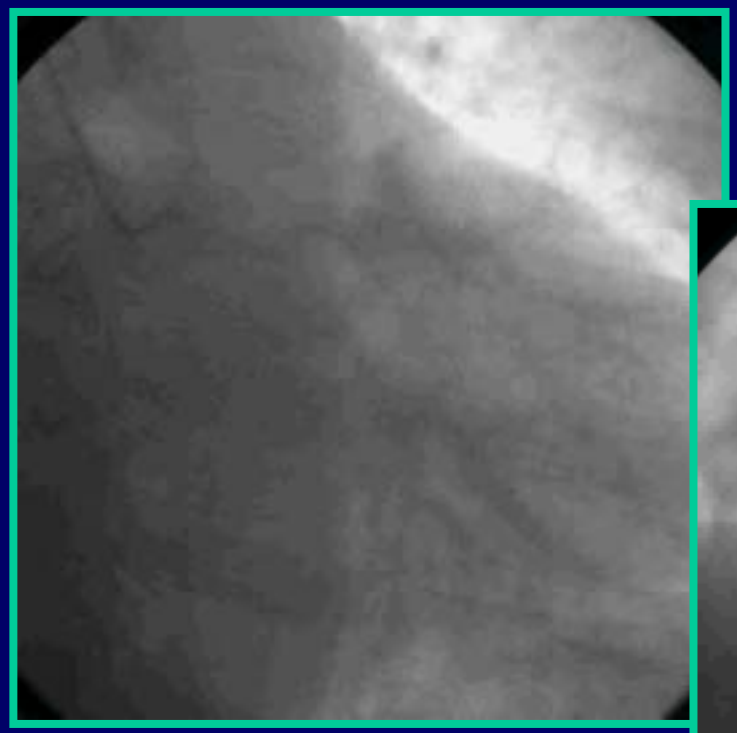
ECG



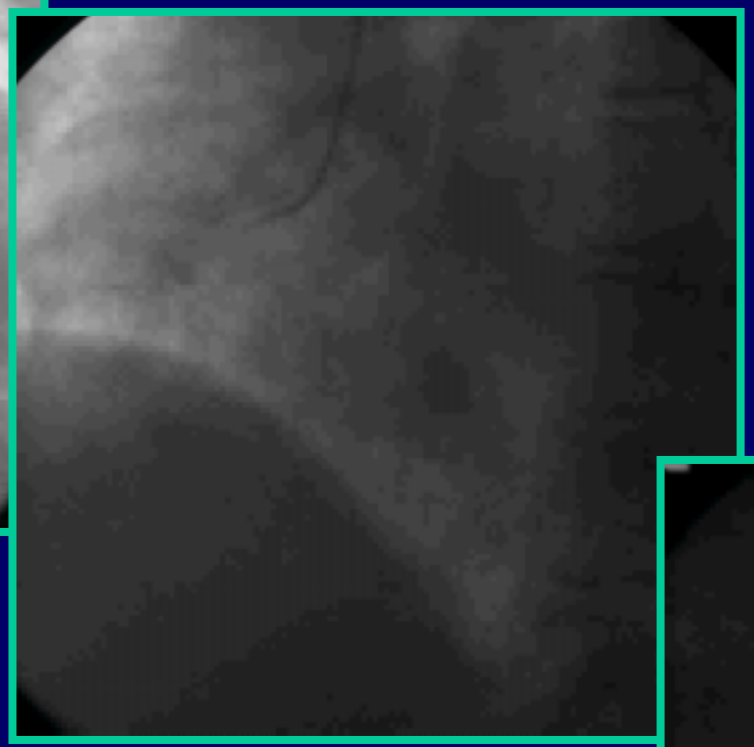


Cardiac Echo.

CAG

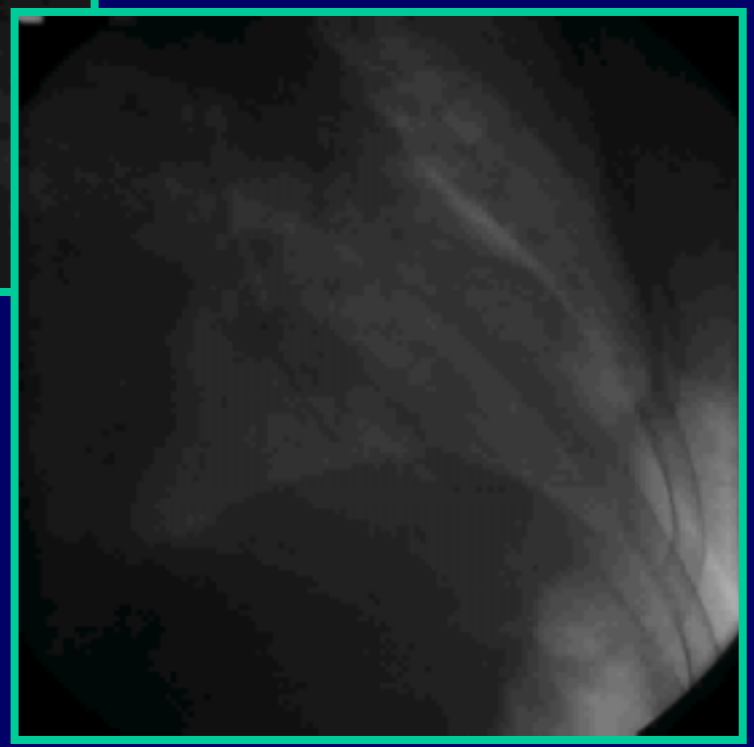


LCA



RCA

LVG



1. 가장 효과적인 강압제는? : **ACE inhibitors**

2. 강압목표는? : **<130/80mmHg**

3. **Enalapril 10mg/D, HCTZ 12.5mg/D, Amlodipine 5mg/D, ASA 100mg/D, atorvastatin 10mg/D** 2주일 투여로 혈압은 **125-130/75-85 mmHg**로 유지 되었으나, 잦은 기침이 발생되었다. 다음 단계의 조치는?

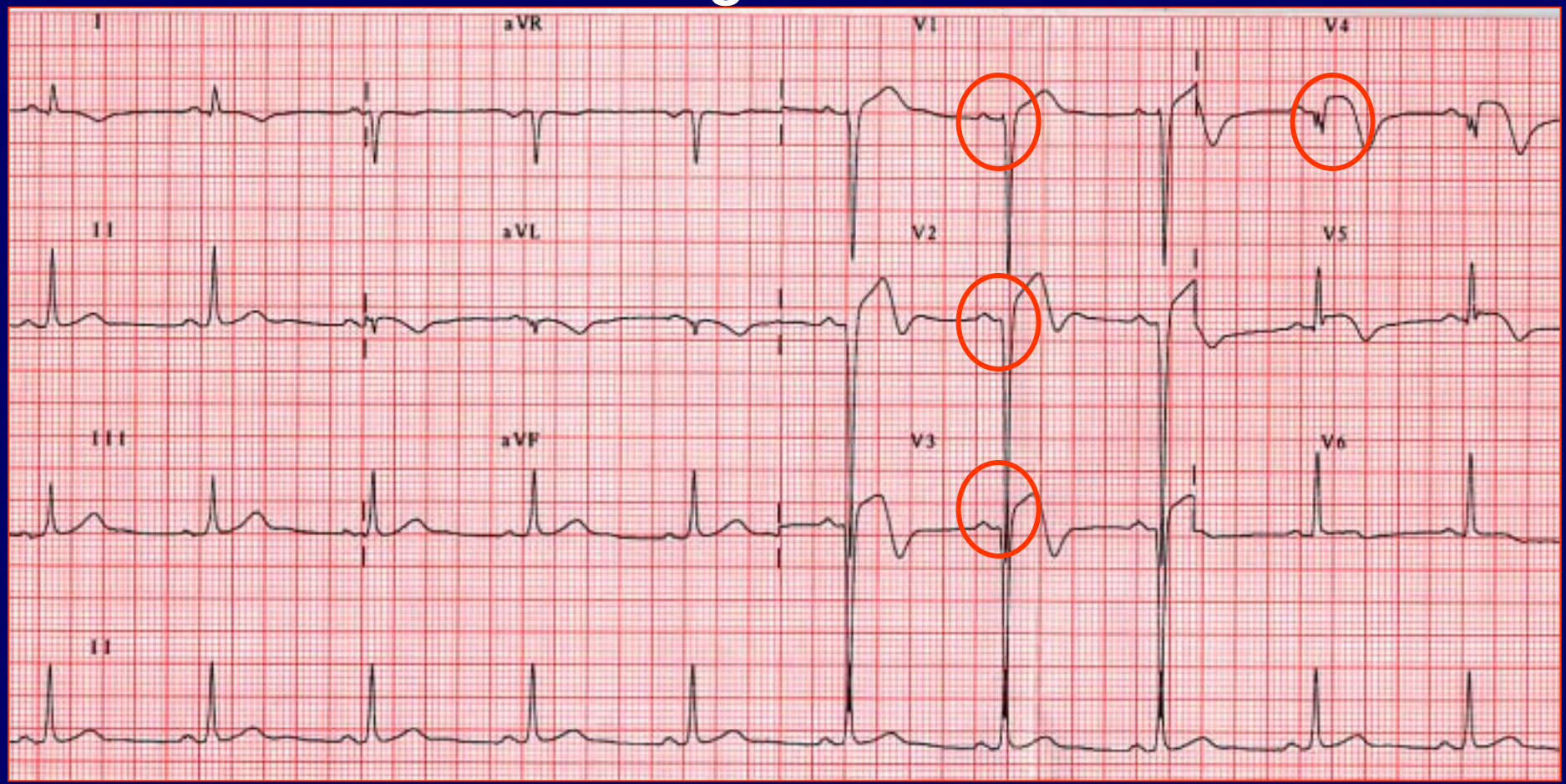
: **ACE inhibitors→ARB**로 대체

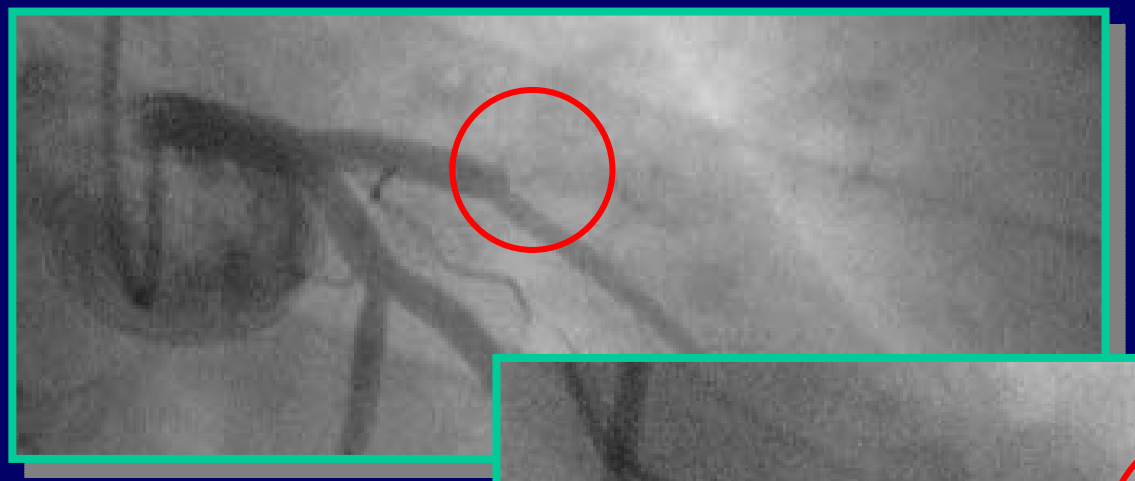
4. 기침 없이 혈압이 **120/80mmHg**로 유지 되었다. 다음 단계로 고려해야 할 것은?

: **ARB**와 이뇨제를 **fixed dose combination**으로 바꾼다.

Case. 61세 남자

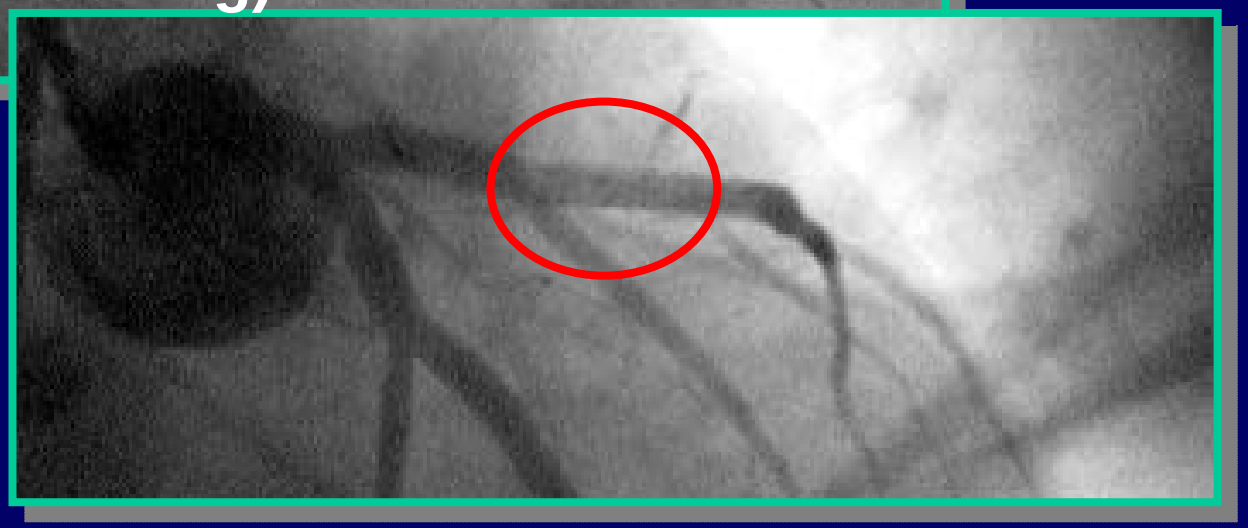
2시간 전부터 시작된 터질듯한 심한 흉통으로 응급실로 내원. **BP 150 / 100 mmHg**





Initial

PCI (ballooning)



Final after Stenting

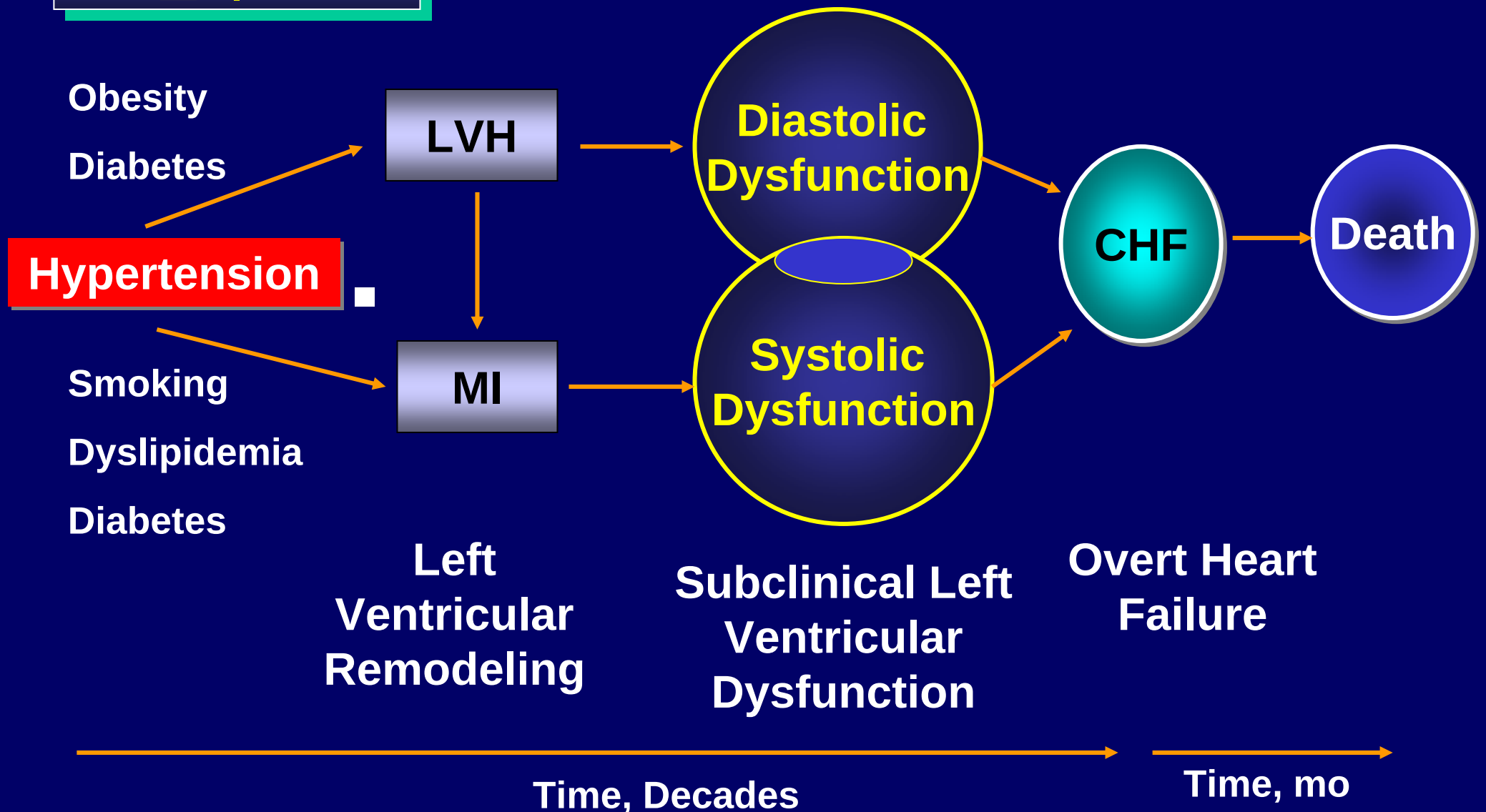
심근경색증을 동반한 고혈압의 치료방침은?

베타차단제(non-ISA), ACE 억제제(low EF)

베타차단제의 효과가 없거나 금기인 경우, 혹은 **NQMI**, 정상 **EF**을 보이는 경우에 사용될 수 있는 약제는?

Verapamil, Diltiazem

심부전



Progression from hypertension to congestive heart failure.

만성 수축기 심부전의 치료 및 적절한 강압제

	For symptoms	For survival/morbidity *Mandatory therapy*	For symptoms if intolerance to ACE inhibitor or beta-blockade
NYHA I	Reduce/stop diuretic	Continue ACE inhibitor if asymptomatic. Add beta-blocker if post MI	
NYHA II	+/– diuretic depending on fluid retention	**ACE inhibitor as first-line treatment** Add beta-blocker if still symptomatic	ARB if ACE inhibitor intolerant or ACE inhibitor + ARB if beta-blocker intolerant
NYHA III	+ diuretics + digitalis if still symptomatic + nitrates/hydralazine if tolerated	ACE inhibitor and beta-blockade add spironolactone,	ARB if ACE inhibitor intolerant or ACE inhibitor + ARB if beta-blocker intolerant
NYHA IV	Diuretics + digitalis + nitrates/hydralazine if tolerated + temporary inotropic support	ACE inhibitor beta-blockade spironolactone	ARB if ACE inhibitor intolerant or ACE inhibitor + ARB if beta-blocker intolerant

Treatment of diastolic heart failure

- **Class I**
  1. Diuretics
  2. Rate control in patients with atrial fibrillation
  3. Treatment of hypertension
- **Class IIa**

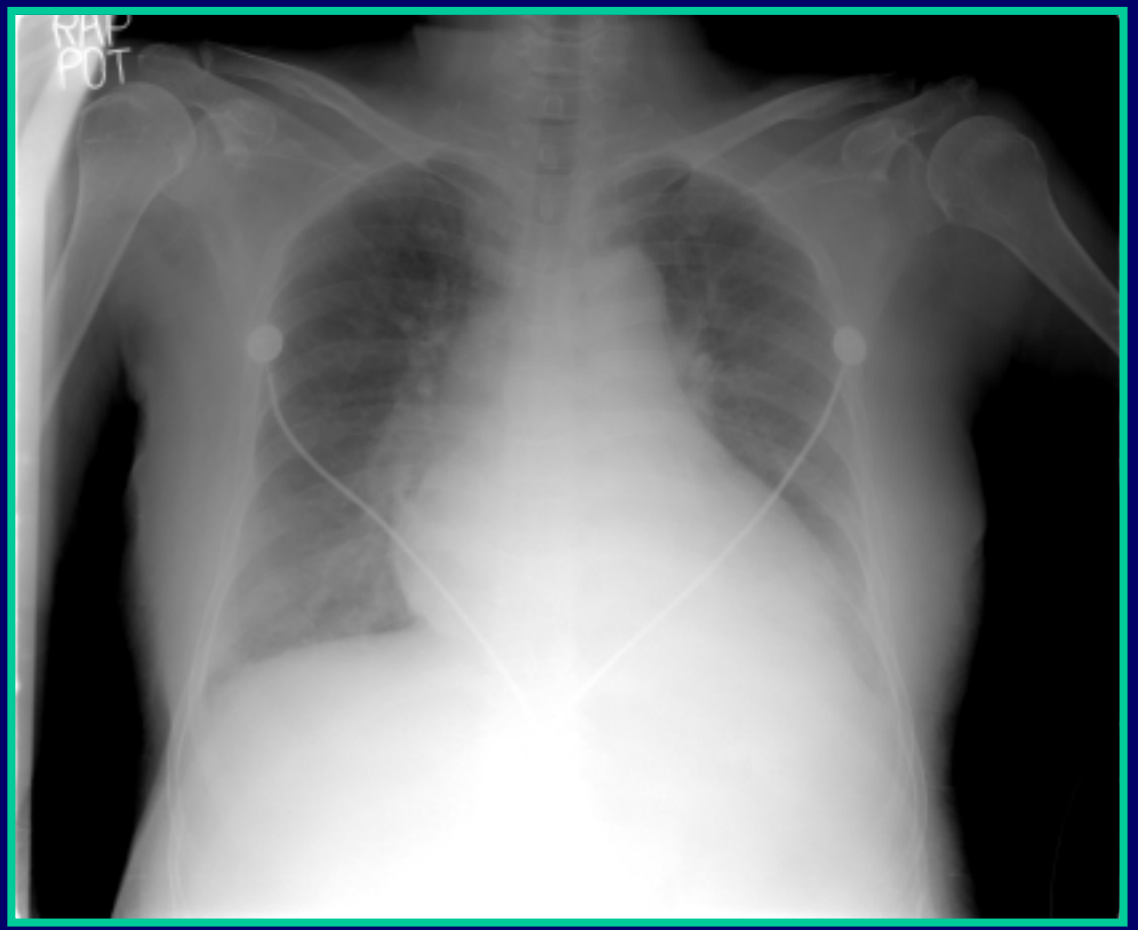
  Coronary revascularization in patients with CAD
- **Class IIb**
  1. Restoration of sinus rhythm in patients with atrial fibrillation
  2. Beta-adrenergic blockers, ACE inhibitors, ARB or CCB in patients with controlled hypertension
  3. Digitalis

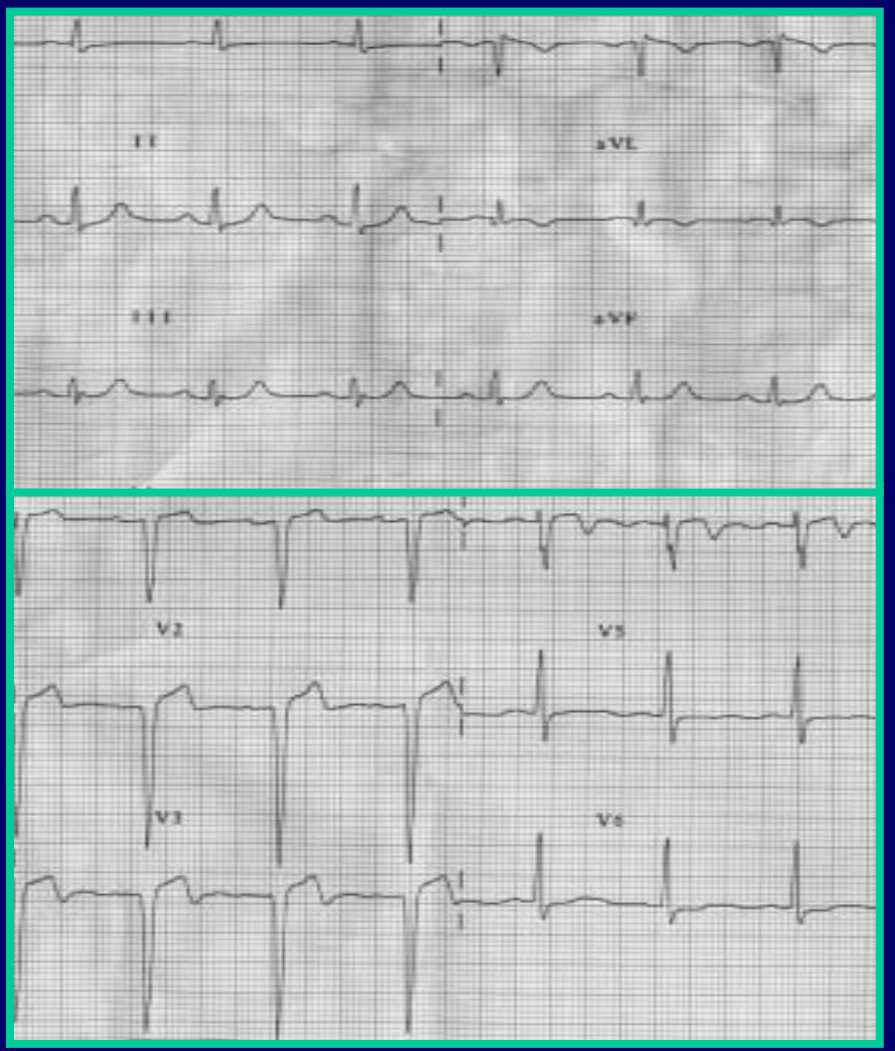
Hunt SA et al. ACC/AHA guideline for the evaluation and management of chronic heart failure in the adult.2001

Case. 60세 남자

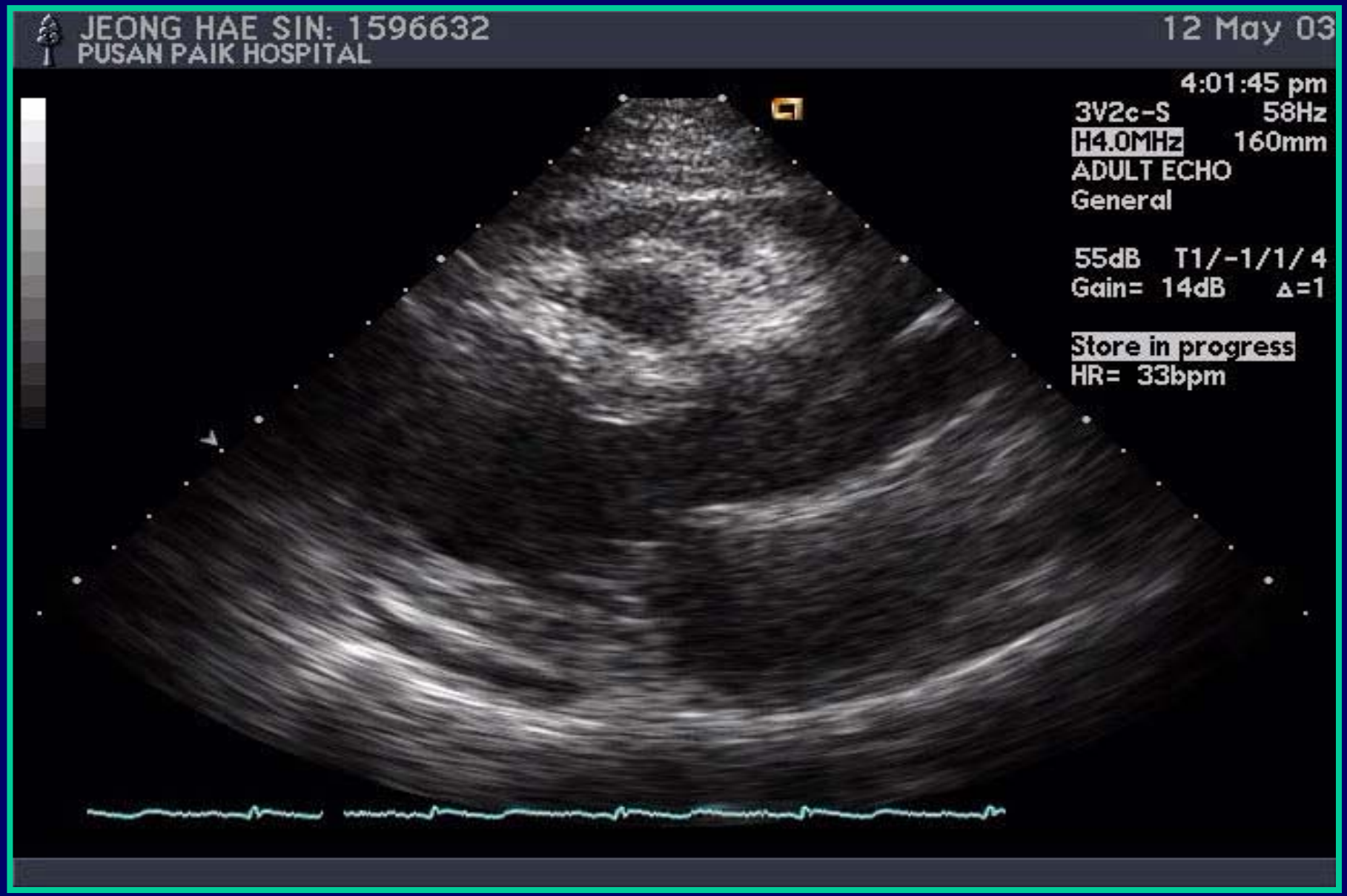
당뇨병과 고혈압이 있었던 환자가 흉통과 호흡곤란을 주소로 내원. 2년 전 전벽심근경색증으로 입원치료→그 후 F/U안됨.

혈압:165/100mmHg

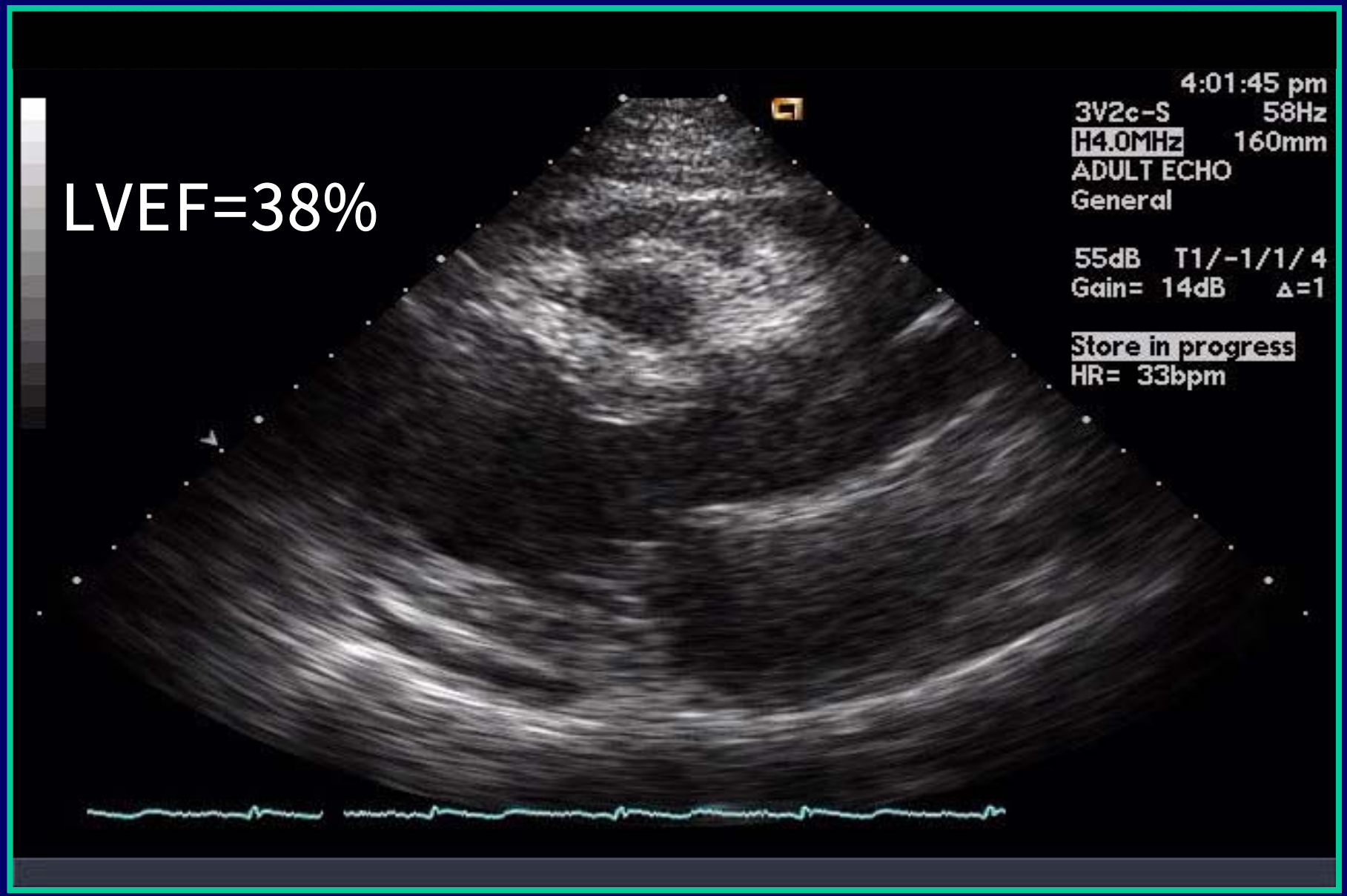




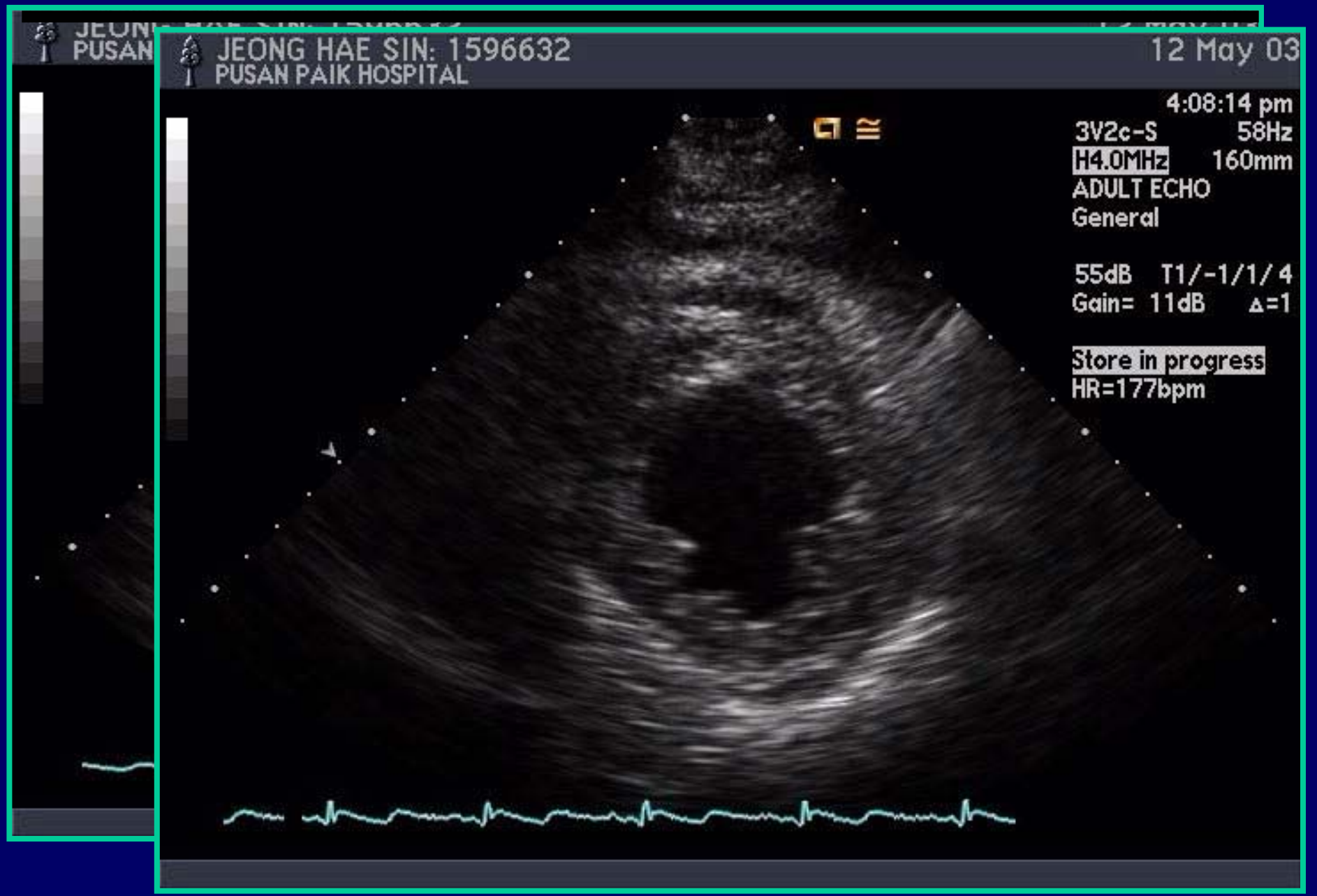
Cardiac Echo.



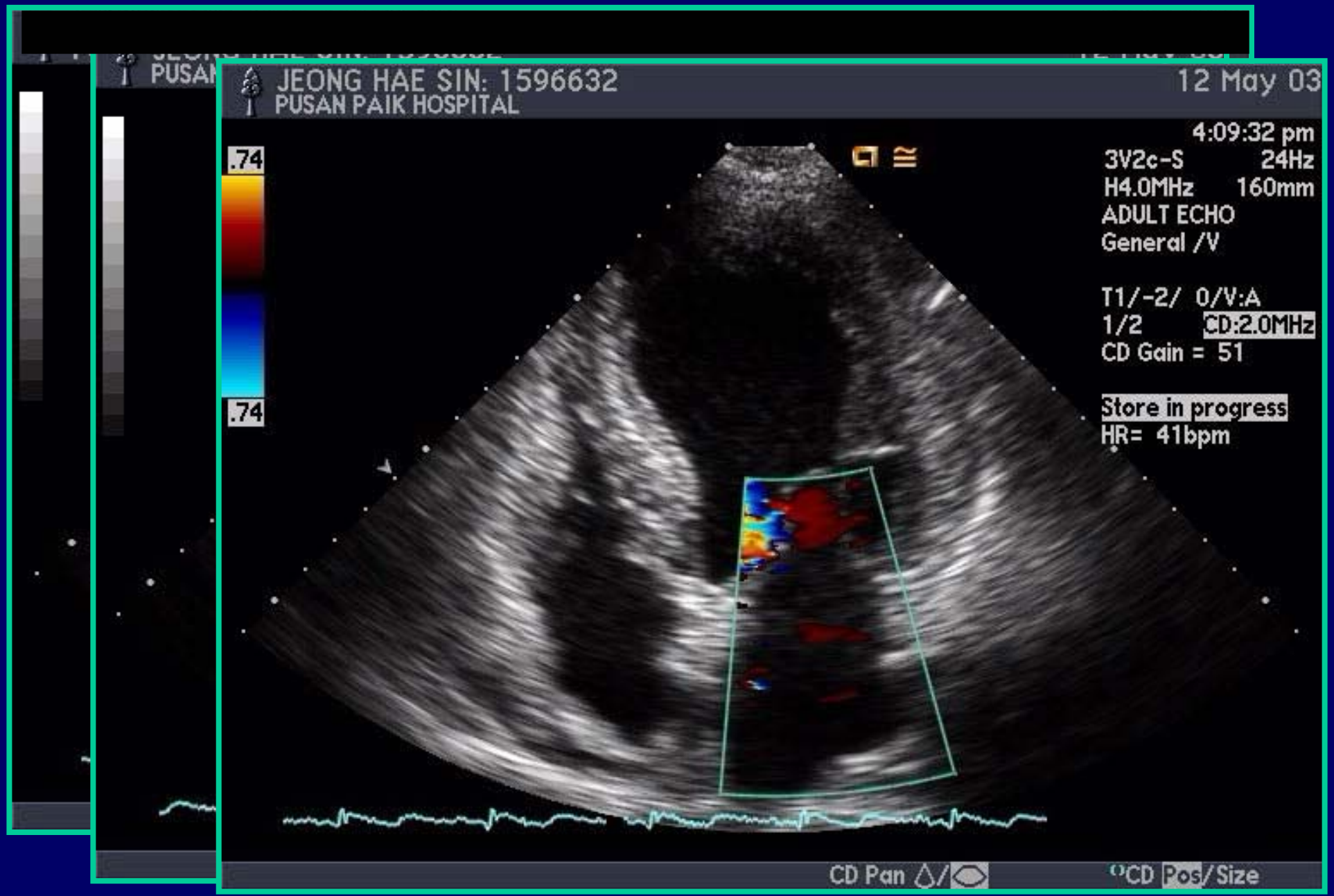
Cardiac Echo.



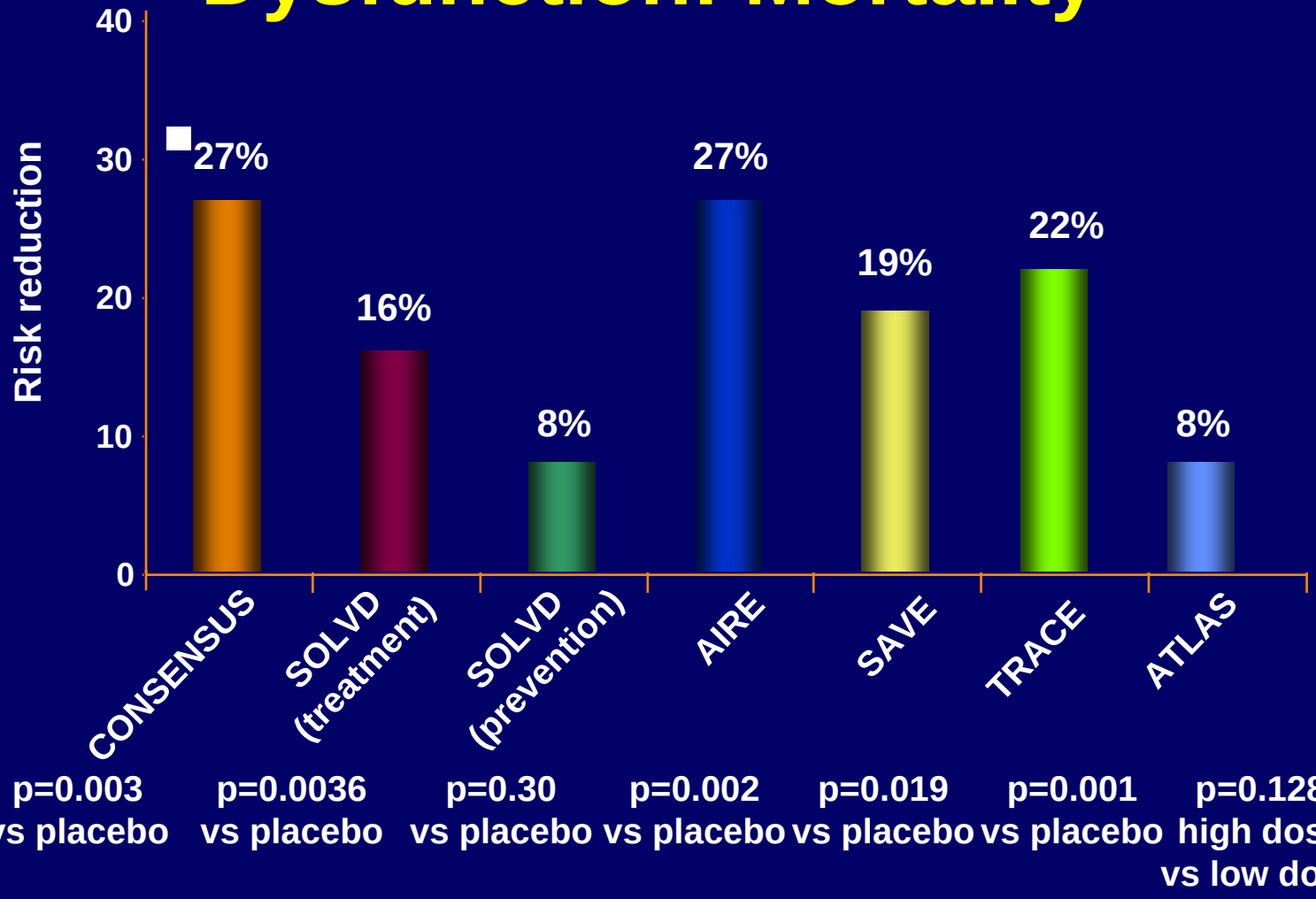
Cardiac Echo.



Cardiac Echo.

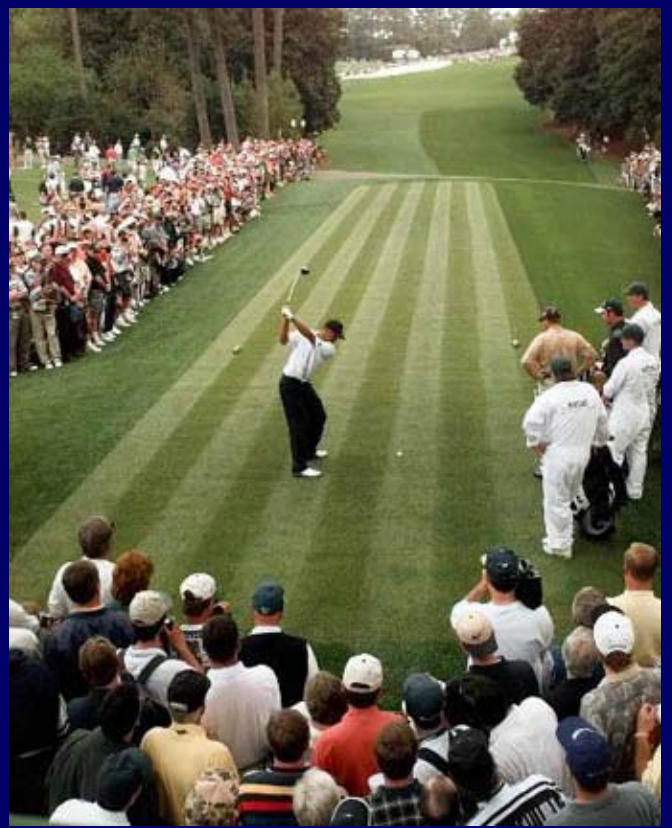


Primary Outcomes of ACE Inhibitors in Heart Failure and/or LV Dysfunction: Mortality



Titration regimen for β-blockers

Bisoprolol	1.25 mg qd	2.5 mg qd	5 mg qd	10 mg qd
Metoprolol	12.5mg bid	25mg bid	50 mg bid	100 mg bid
Carvedilol	3.125 mg bid	6.25 mg bid	12.5 mg bid	25 mg bid



Increments every 2–4 weeks or more

Klein L, et al. Am J Cardiol 2003;91(suppl):18F-40F

Lasix 와 digoxin으로 증상조절 중인 허혈성 심부전(ischemic heart failure)환자에서 사용될 수 있는 약제는?

- **ACE억제제, 베타차단제**

호흡곤란의 증상이 계속적으로 있을 때 추가 투여할 약제로서 추천될 수 있는 약제는?

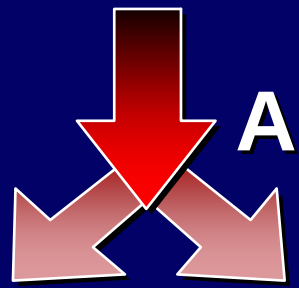
Aldosterone 길항제

Aldosterone antagonists

Mechanism of Action

Spironolactone

Competitive antagonist of the aldosterone receptor (myocardium, arterial walls, kidney)



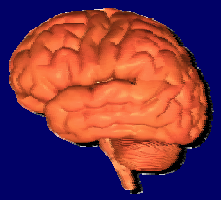
ALDOSTERONE

- Retention Na^+ → **Edema**
- Retention H_2O
- Excretion K^+ → **Arrhythmias**
- Excretion Mg^{2+}

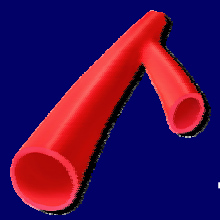
- Collagen deposition → **Fibrosis**
  - myocardium
  - vessels

Sympathetic activation, Parasympathetic inhibition, Baroreceptor dysfunction

고혈압

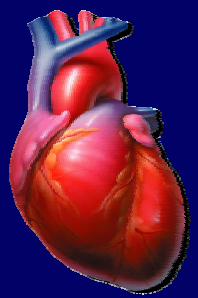


뇌혈관질환

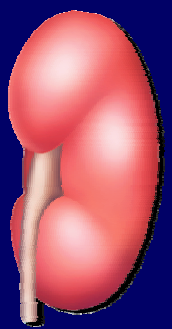


협심증, 심근경색증

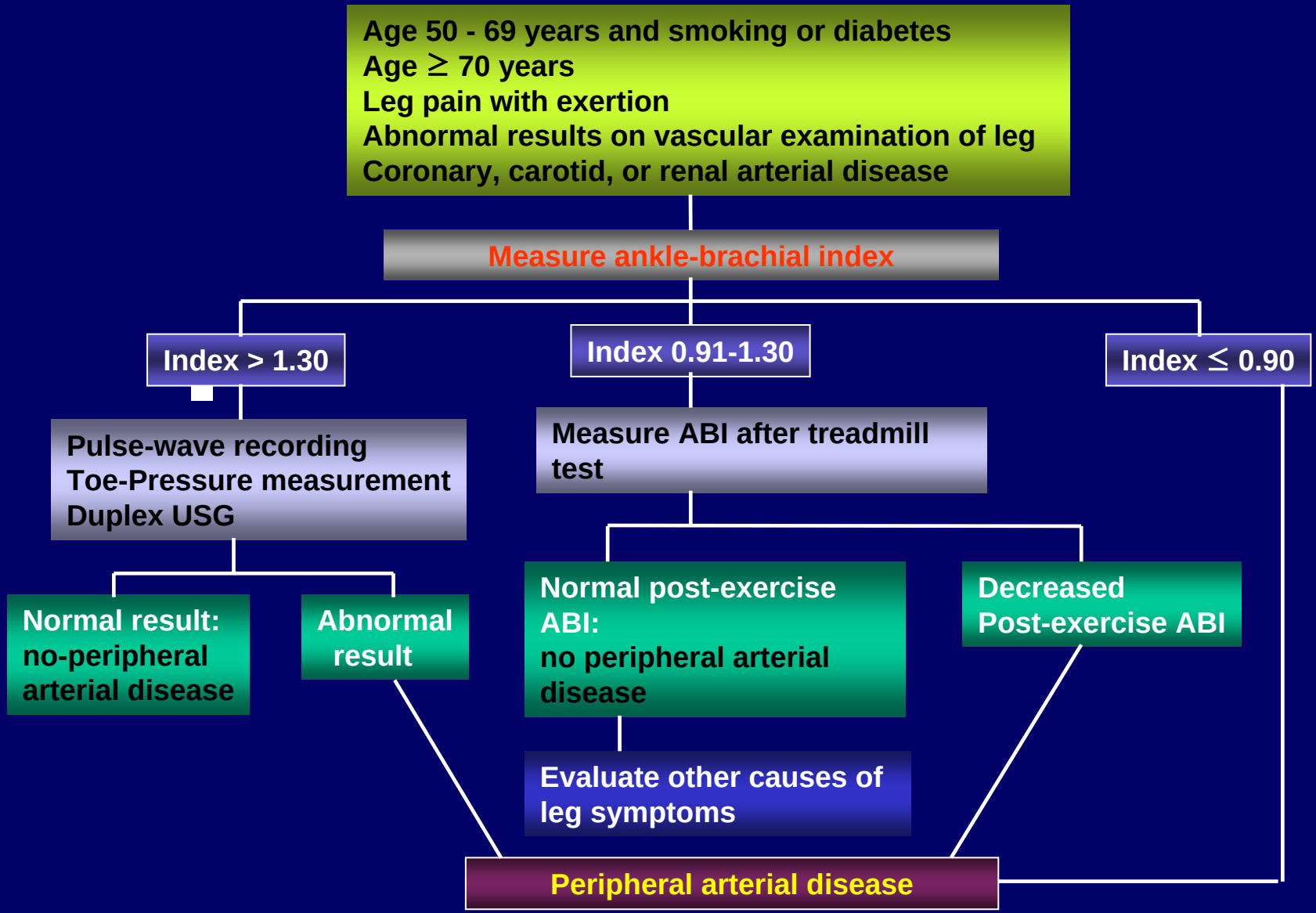
대동맥, 말초혈관질환



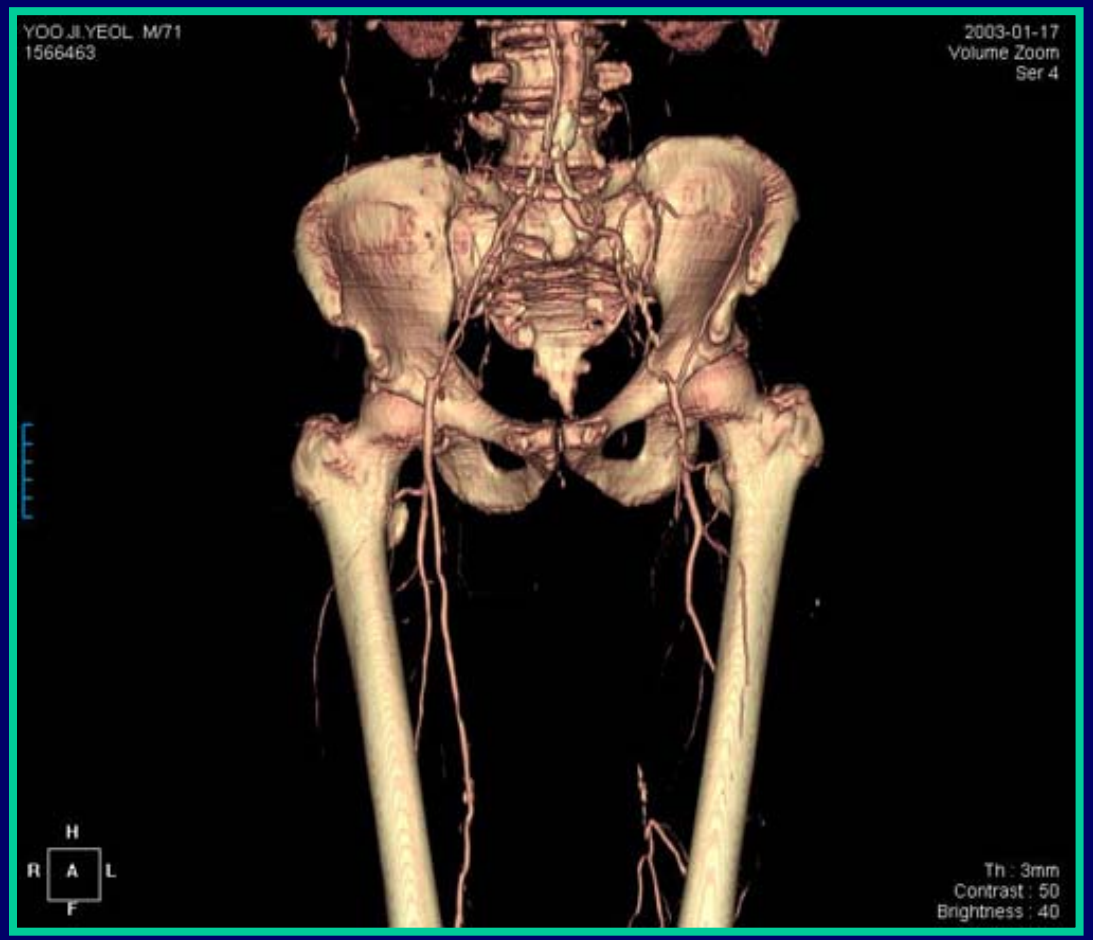
Abdominal Aortic Aneurysm
Aortic Dissection
Peripheral Vascular Disease



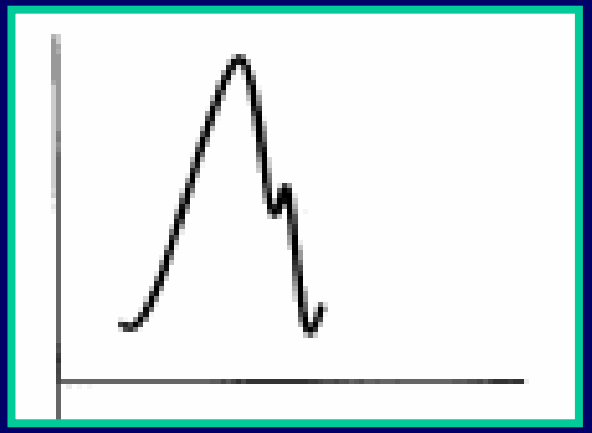
신부전



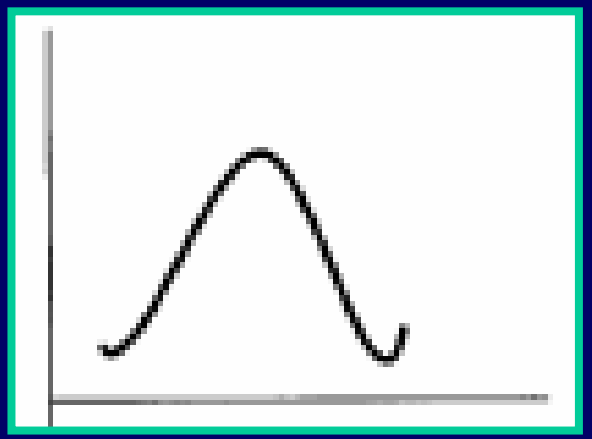
Evaluation of patients in Whom peripheral arterial disease is suspected



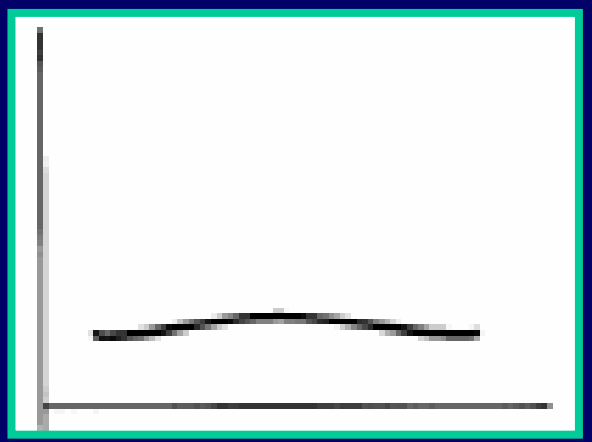
Pulse volume recording wave morphology in plethysmography



정상



경한 말초
동맥 질환



진행된 말초
동맥 질환

말초혈관질환을 동반한 고혈압 치료

- **Symptomatic PVD: intermittent claudication**
- **Measurement of ABI(≤0.9), Duplex USG, Plethysmography**
- **Encouraged to stop smoking and increase level of physical exercise**
- **BP↓: drugs with vasodilating capacity**

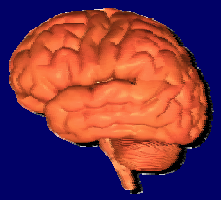
CCB(DHP), ACE Inhibitors, α-Blockers

**** β-Blockers;unsuitable***

대동맥박리를 동반한 고혈압의 치료

- 내과적 치료 적응증:
  - 후유증 없는 만성 **proximal dissection**
  - 안정되고 **aortic arch**에 국한 된 대동맥박리
  - **distal dissection**
- 치료목표:
  - 혈압조절; **SBP 100~120mmHg**
  - 대동맥 벽에 미치는 **stress** 감소; **HR 60~80/min**

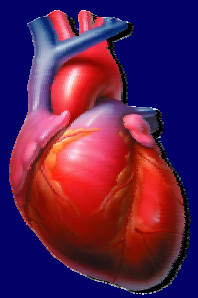
IV sodium nitroprusside, labetalol



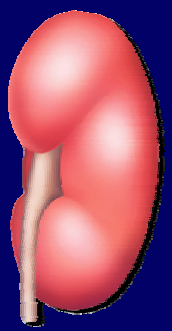
뇌혈관질환

협심증, 심근경색증

대동맥, 말초혈관질환



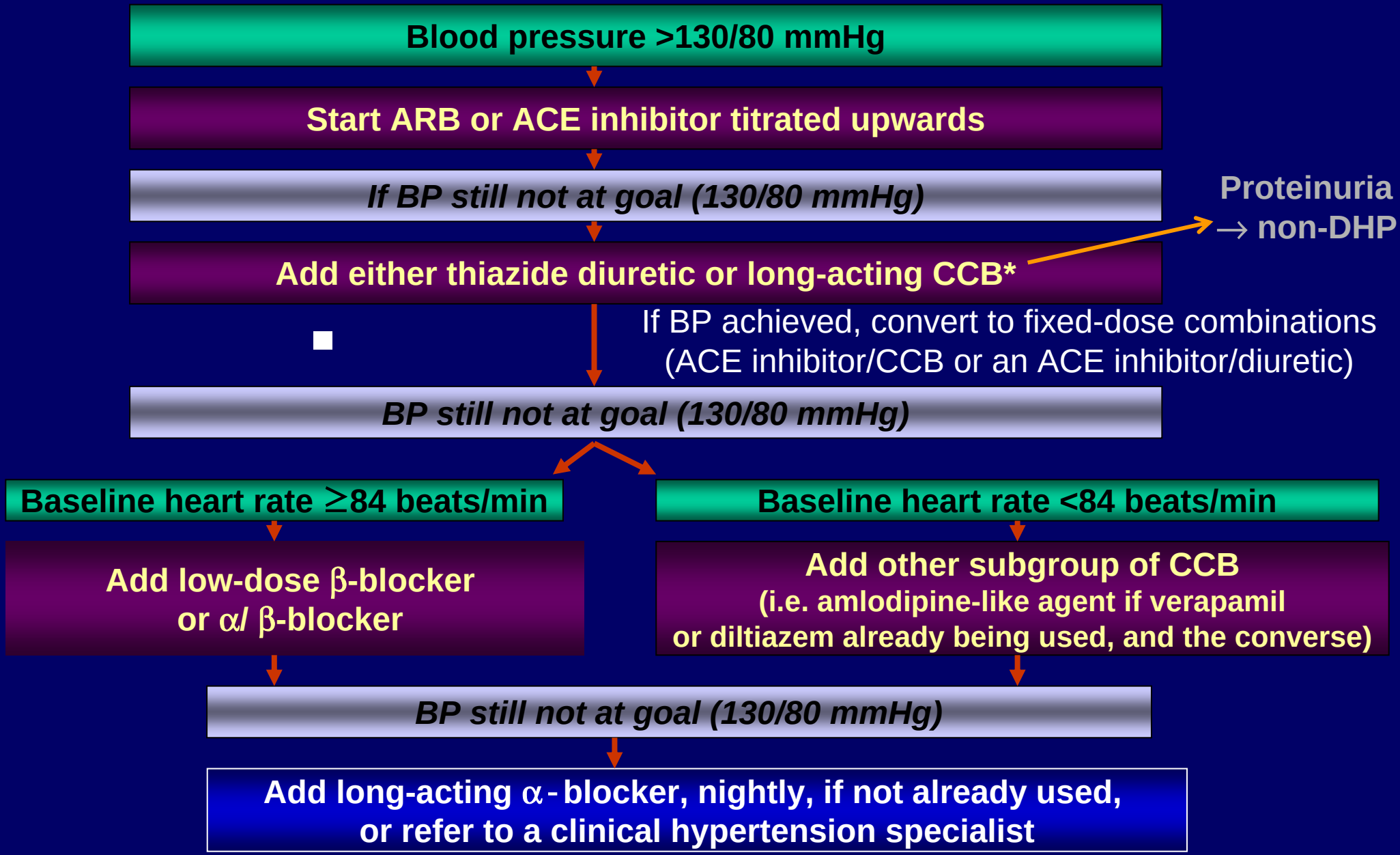
LVH, 심부전

고혈압 →  → 신부전

만성신장질환을 동반한 고혈압

- 만성신장질환:
  - GFR < 60mL/mim per 1.73m^2(F;Cr ≥1.3mg/dL, M;Cr ≥1.5mg/dL)
  - 단백뇨>300mg/d
- 치료목표:
  - <130/80mmHg
  - <125/75mmHg(단백뇨>1.0g/d)
  - 3가지 이상 약제의 병합사용
- 필수처방약제: ACE 억제제/ARBs, non-DHP CCB
  - Cr ≥3.0mg/dL시 일시적인 혈중 Cr 과 K 상승으로 추적검사필요
  - Cr이 초기보다 35%이상 상승해도 hyperkalemia 없으면 계속 투여
  - Cr ≥2.5-3.0mg/dL시 loop diuretics 용량 증가로 병합사용

ACE 억제제/ARBs를 기본으로 CCB, 베타차단제, 이뇨제 등을 병용 투여하고, 불충분할 시에는 minoxidil을 첨가하는 것이 바람직하다.



National Kidney Foundation suggested approach for achieving BP goals in patients with diabetes, renal insufficiency, or both.

Am J Kidney Dis 2000,36:646

표적장기손상에 따른 추천 고혈압약물

강제 적응	이뇨제	BB	ACEI	ARB	CCB	Aldo-Ant
심부전	O	O	O	O		O
심근경색 후		O	O			O
관동맥 질환		O	O		O(non DHP)	
단백뇨			O	O		
만성 신질환	O(loop계)		O	O		
뇌졸중	O		O			
경동맥 죽상경화					O(DHP)	
말초동맥질환			O	O	O(DHP)	

BB: beta-blocker, ACEI:ACE inhibitor, ARB: angiotensin receptor blocker, CCB: calcium channel blocker, Aldo-Ant: aldosterone antagonist