Modification structurale et fonctionnelle myocardique dans l'HTA et essais de régression de la masse VG

Gilles Barone-Rochette
Clinique Universitaire de Cardiologie
INSERM U877
CHU Grenoble

Objectifs pédagogiques

- Physiopathologie
- Méthode de détection
- Un marqueur de risque et critère intermédiaire
- Une possible cible thérapeutique

Physiopathologie

Hypertrophie ventriculaire gauche (HVG)

Augmentation de la masse VG liée à des modifications de débit/postcharge

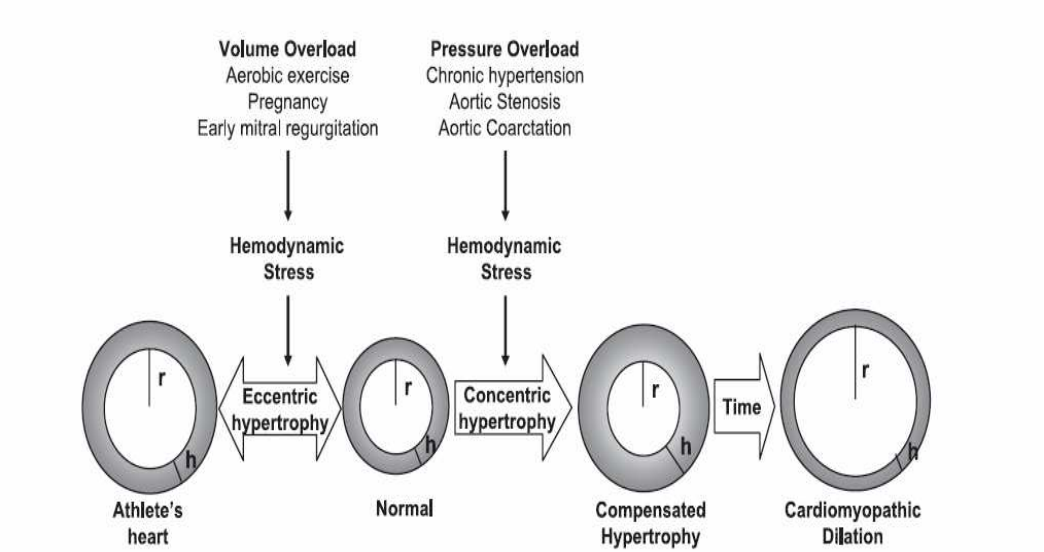
Physiologique :

- Croissance
- Sportif

Pathologique :

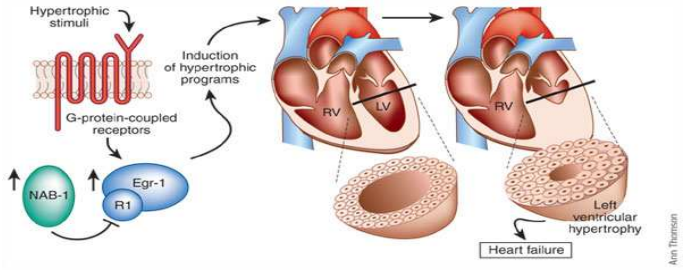
- HTA
- RA
- CMH (génétique)….

Hypertrophie ventriculaire gauche



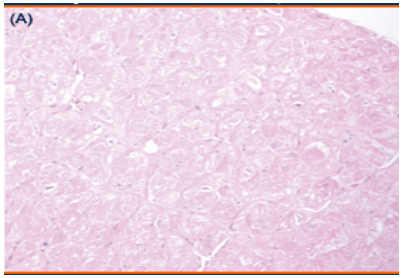
Physiopathologie

- Adaptation du VG à l ’augmentation de la post-charge
- Phénomène adaptatif complexe (Loi de Laplace → maintien constant du stress pariétal)

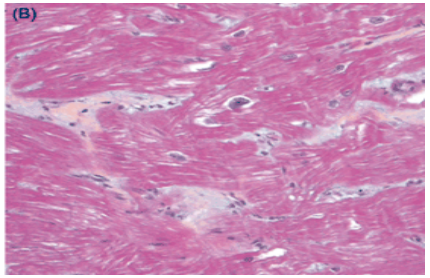


Physiopathologie de l'HVG

Cellular alterations
- Cardiomyocytes
  - Hypertrophy, atrophy, apoptosis, necrosis
- Non cardiomyocytes
  - Hyperplasia and apoptosis of fibroblasts
  - Hypertrophy and/or hyperplasia of vascular smooth muscle cells



Noncellular alterations
- Interstitial and perivascular fibrosis
- Microscopic scarring
- Medial thickening of coronary arterioles
- Diminished number of capillaries



La Fibrose est caractéristique du remodelage pathologique

Weber et al. NEJM 1999;341:753-5

Modification structurale et fonctionnelle → manifestations pathologiques

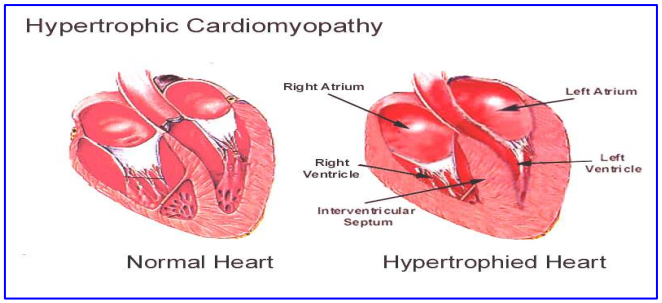
HTA

↓

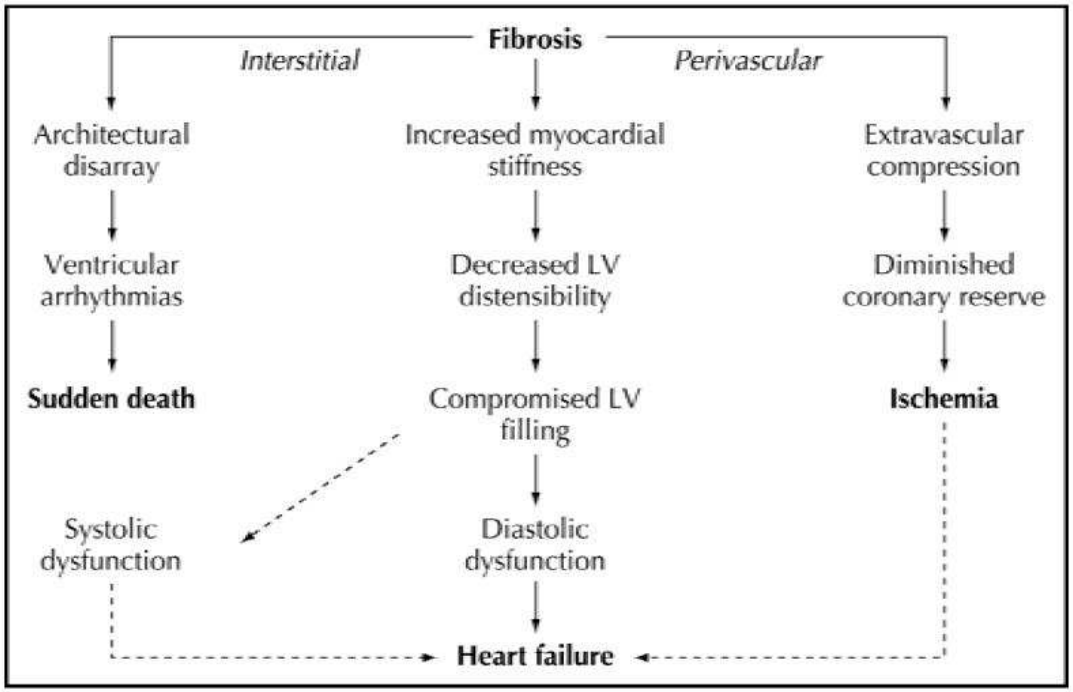
Augmentation post-charge

↙ ↓ ↘

HVG secondaire | Fibrose myocardique | Dilatation de l'OG avec FA



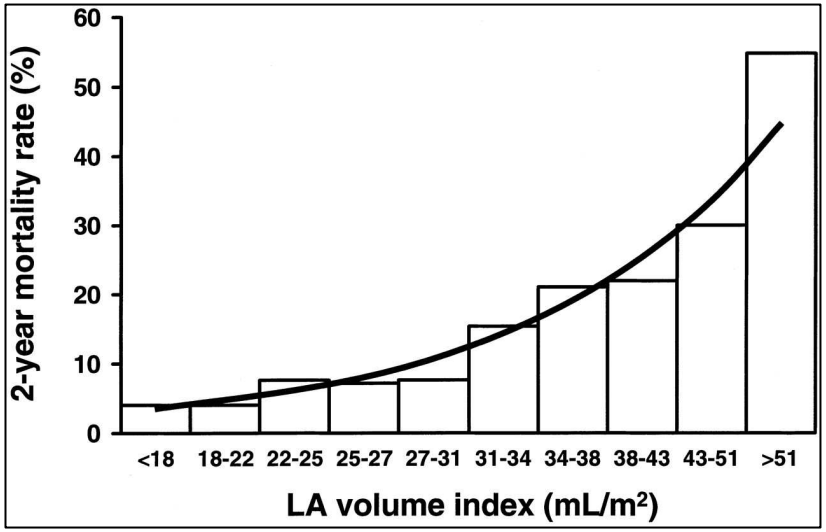
Fibrose et cardiopathie hypertensive



Remodelage de l ’OG

Importance du volume OG

- Prédicteur de la mortalité
- Association forte entre taille de l ’OG et risque de FA



Moller et al. Circulation 2003; 107: 2207.
Parkash et al. Am H J 2004; 148: 649.

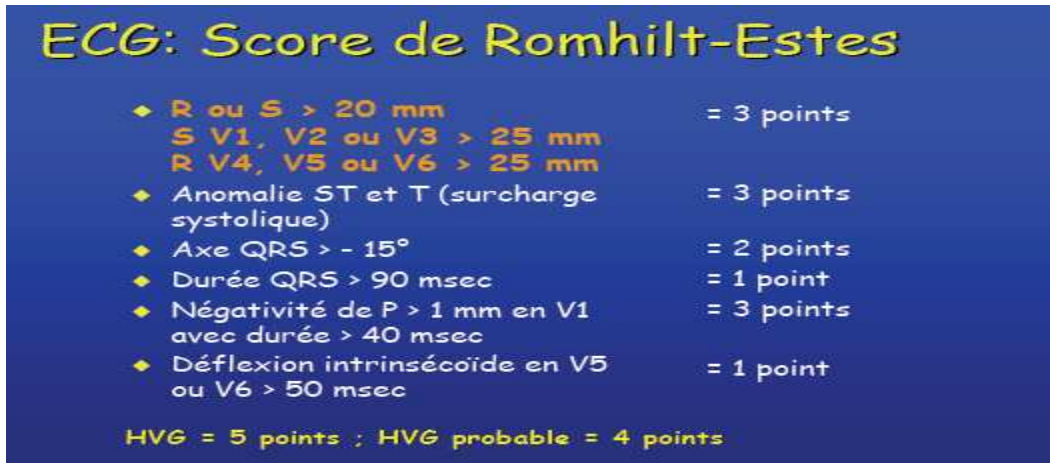
Détection de l’HVG

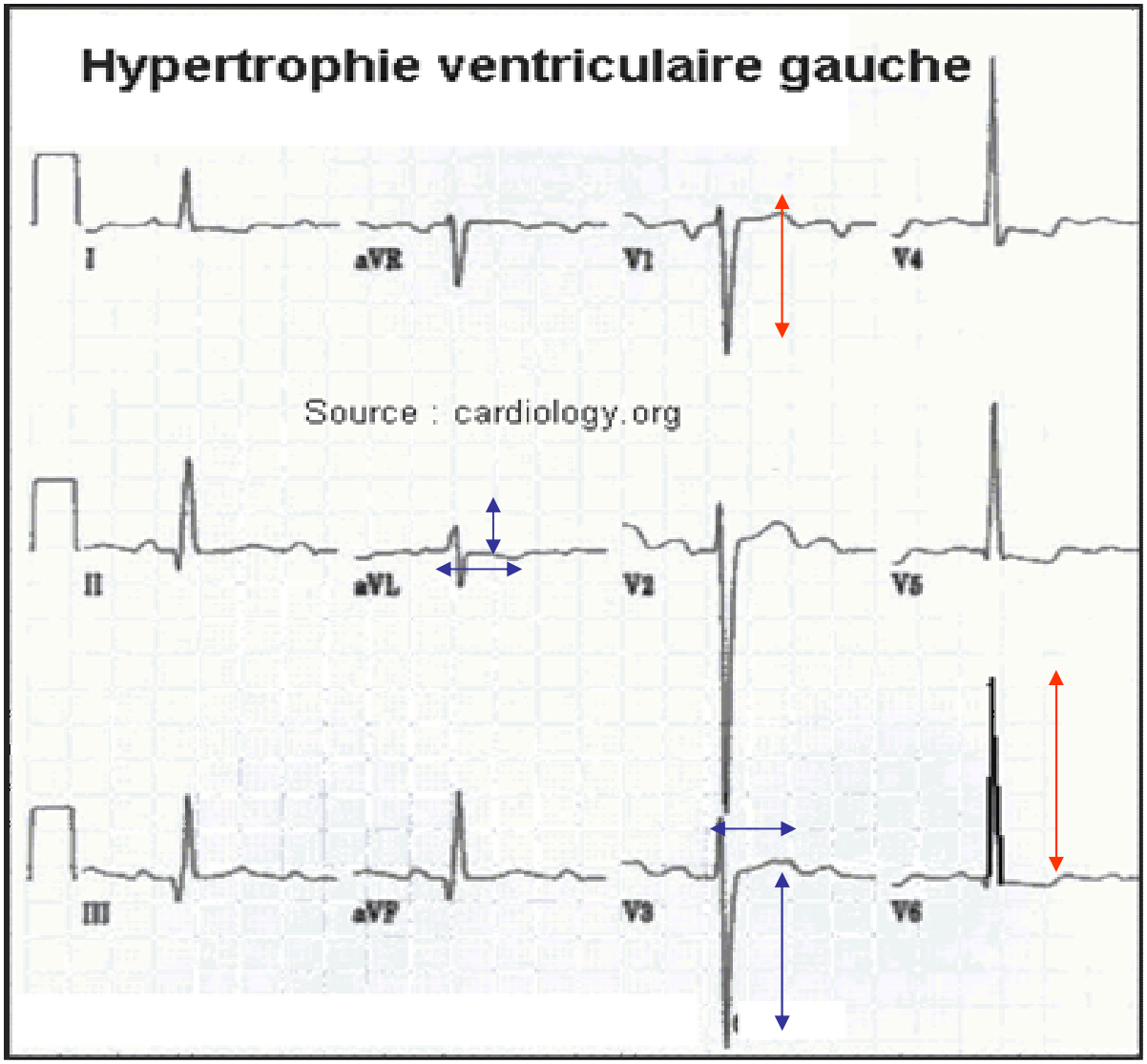
l ’ECG

- Sokolow-Lyon : SV1 + RV5 ou V6 ≥ 38 mm

- Cornell : SV3 + RVL > 28 mm (H) ou > 20 mm (F)

  Product > 2440 mm*ms



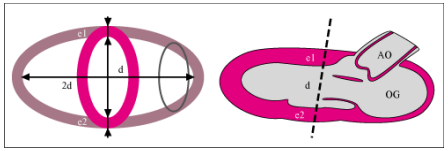

Hypertrophie ventriculaire gauche
I
aVR
V1
V4
Source : cardiology.org
II
aVL
V2
V5
III
aVF
V3
V6

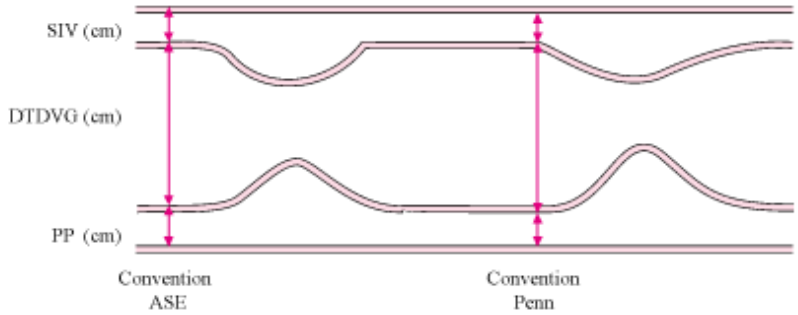
Sensitivity and specificity for selected ECG criteria of LVH

Criterion	Sensitivity (%)	Specificity (%)
- Sokolow Lyon Voltage	22	100
- Cornell Voltage Criteria	42	96
- Cornell Voltage Duration Criteria	51	95
- RaVL > 11 mm	11	100
- Romhilt-Estes > 4 points	54	85
- Romhilt-Estes > 5 points	33	94

Détection de l ’HVG: l ’echocardiographie

- Mesure de la masse VG (TM)





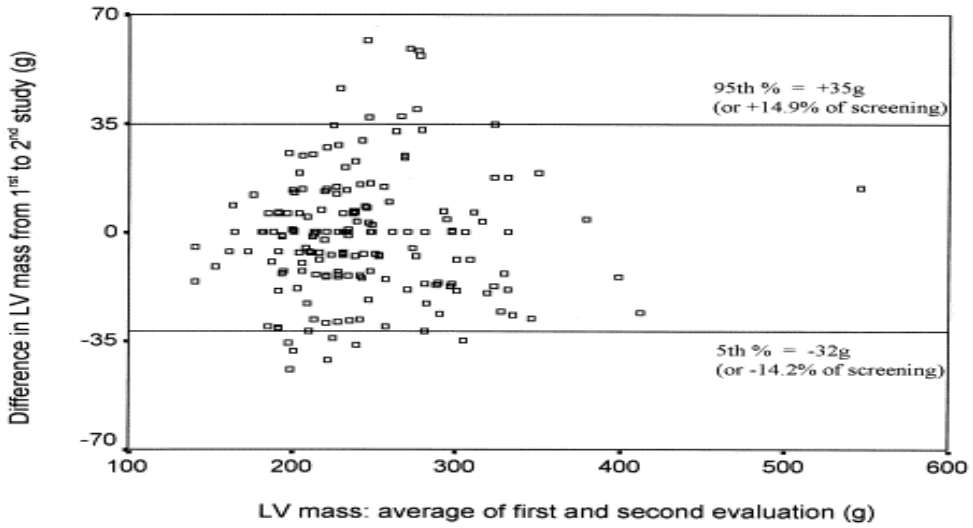
Détection de l ’HVG: l ’échocardiographie

- Mesure de la masse VG
- MVG (g): 0.8[1.04[(DTDVG+SIV+PP)^3-DTDVG^3]]+0.6 (ASE)
- MVG (g): 1.04 [(DTDVG+SIV+PP) ^{3}-DTDVG^3]-13.6 (Penn)

125 g/m² H ; 110 g/m² F (ESC-ESH 2007)

Détection de l 'HVG/écho

Reproductibilité médiocre !



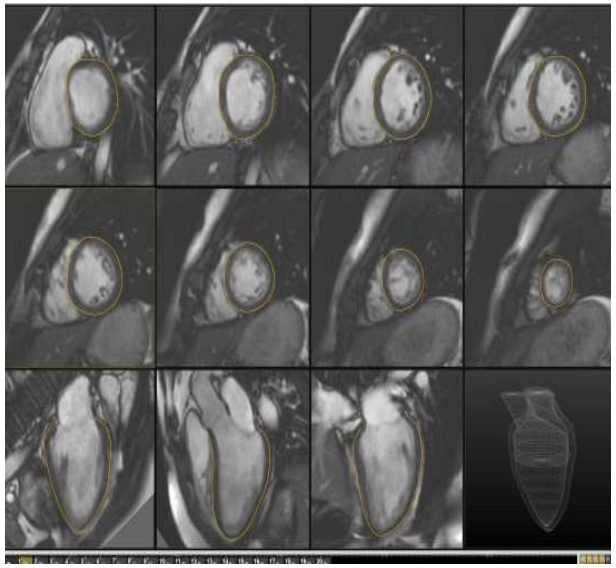
Palmieri V JACC 1999

Détection de l ’HVG: l’IRM

L ’IRM

Reproductibilité excellente

≈ 8 g entre deux examens



Recommandation SFC/SFR 2009

Effect of the Direct Renin Inhibitor Aliskiren, the Angiotensin Receptor Blocker Losartan, or Both on Left Ventricular Mass in Patients With Hypertension and Left Ventricular Hypertrophy

Scott D. Solomon, MD; Evan Appelbaum, MD; Warren J. Manning, MD; Anil Verma, MD; Tommy Berglund, MD; Valentina Lukashevich, MD; Cheraz Cherif Papst, MS; Beverly A. Smith, RN; Björn Dahlöf, MD, PhD; for the Aliskiren in Left Ventricular Hypertrophy (ALLAY) Trial Investigators

Background—Left ventricular (LV) hypertrophy, a marker of cardiac end-organ damage, is associated with an increased risk of cardiovascular morbidity and mortality. Inhibitors of the renin-angiotensin-aldosterone system may reduce LV mass to a greater extent than other antihypertensive agents. We compared the effect of aliskiren, the first orally active direct renin inhibitor, the angiotensin-receptor blocker losartan, and their combination on the reduction of LV mass in hypertensive patients.

Methods and Results—We randomized 465 patients with hypertension, increased ventricular wall thickness, and body mass index >25 kg/m^2 to receive aliskiren 300 mg, losartan 100 mg, or their combination daily for 9 months. Patients were treated to standard blood pressure targets with add-on therapy, excluding other inhibitors of the renin-angiotensin-aldosterone system and β-blockers. Patients underwent cardiovascular magnetic resonance imaging for assessment of LV mass at baseline and at study completion. The primary objective was to compare change in LV mass index from baseline to follow-up in the combination and losartan arms; the secondary objective was to determine whether aliskiren was noninferior to losartan in reducing LV mass index from baseline to follow-up. Systolic and diastolic blood pressures were reduced similarly in all treatment groups (6.5±14.9/3.8±10.1 mm Hg in the aliskiren group; 5.5±15.6/3.7±10.7 mm Hg in the losartan group; 6.6±16.6/4.6±10.5 mm Hg in the combination arm; $P<0.0001$ within groups, $P=0.81$ between groups). LV mass index was reduced significantly from baseline in all treatment groups (4.9-, 4.8-, and 5.8 g/m^2 reductions in the aliskiren, losartan, and combination arms, respectively; $P<0.0001$ for all treatment groups). The reduction in LV mass index in the combination group was not significantly different from that with losartan alone ($P=0.52$). Aliskiren was as effective as losartan in reducing LV mass index ($P<0.0001$ for noninferiority). Safety and tolerability were similar across all treatment groups.

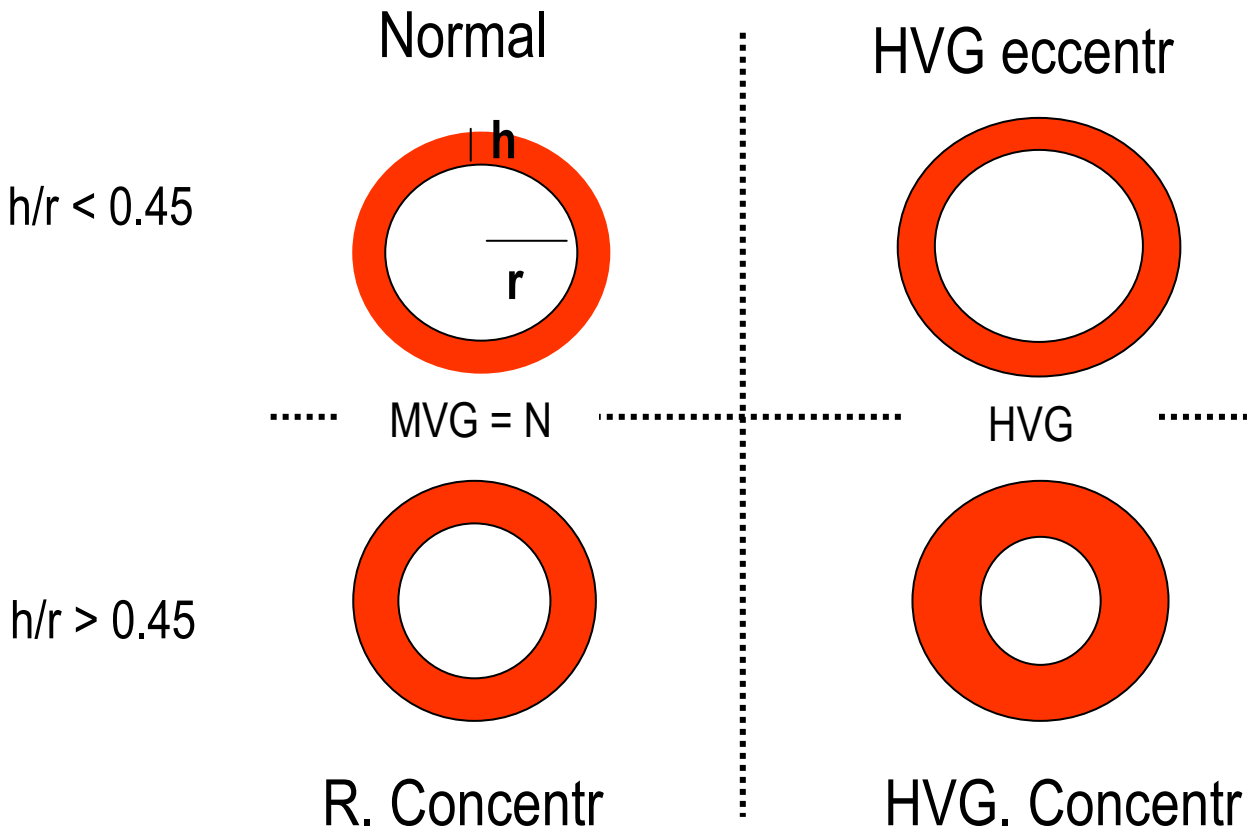
Conclusions—Aliskiren was as effective as losartan in promoting LV mass regression. Reduction in LV mass with the combination of aliskiren plus losartan was not significantly different from that with losartan monotherapy, independent of blood pressure lowering. These findings suggest that aliskiren was as effective as an angiotensin receptor blocker in attenuating this measure of myocardial end-organ damage in hypertensive patients with LV hypertrophy. (***Circulation.*** **2009;119:530-537.)**

Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol

Methods We did a double-masked, randomised, parallel-group trial in 9193 participants aged 55–80 years with essential hypertension (sitting blood pressure 160–200/95–115 mm Hg) and LVH ascertained by electrocardiography (ECG). We assigned participants once daily losartan-based or atenolol-based antihypertensive treatment for at least 4 years and until 1040 patients had a primary cardiovascular event (death, myocardial infarction, or stroke). We used Cox regression analysis to compare regimens.

Björn Dahlöf et al. Lancet 2002; 359: 995–1003

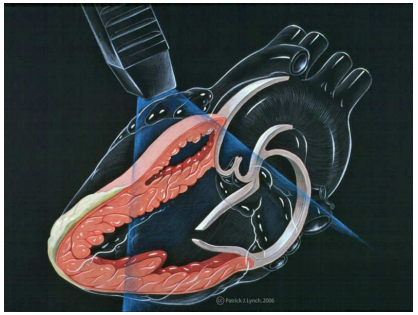
Autres apports de l'échocardiographie : Géométrie du VG



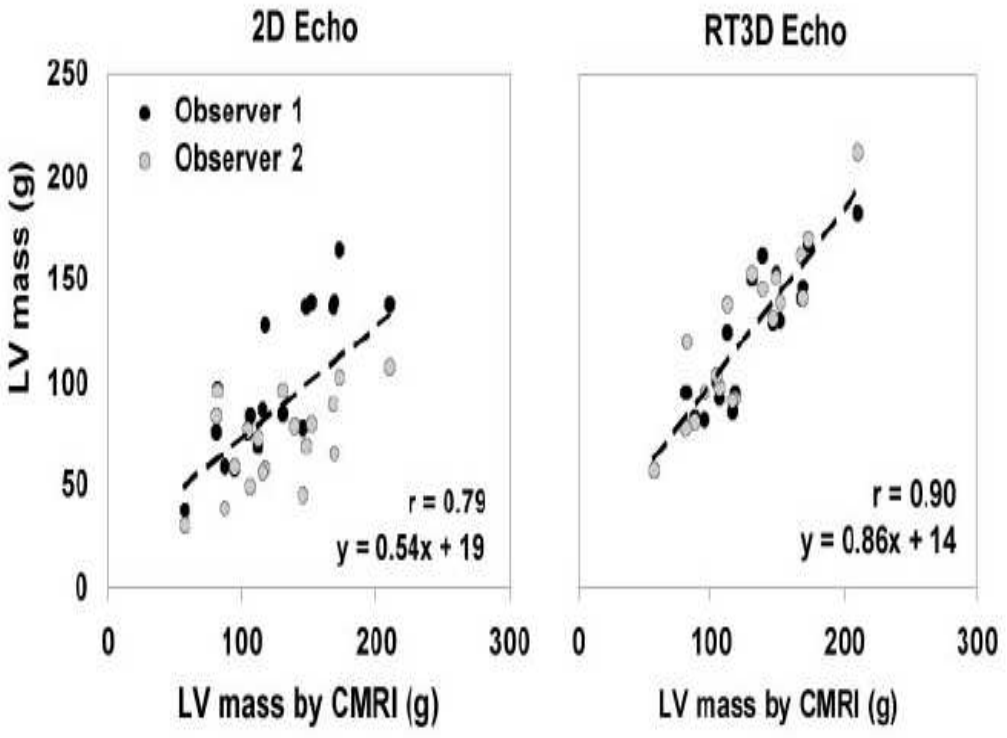
Autres apports de l'échocardiographie :

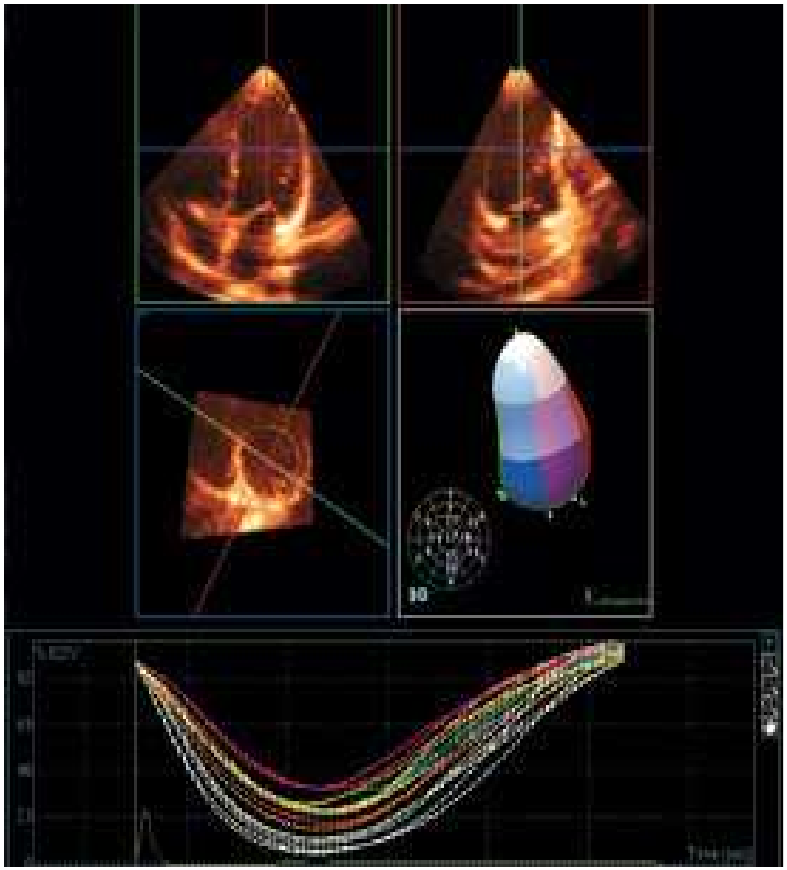
Diagnostic différentiel
Valvulopathies RAC
CMH (doppler tissulalire, strain…..)

Autres informations sur la structures et fonction cardiaque
Étude de la fonction systolique et diastolique
troubles de la cinétique segmentaire
HVG (concentrique, excentrique)
Cavités droites ou gauches dilatées
Valvulopathies - aorte initiale
Mesure des pressions pulmonaires
OG dilatée
Péricarde
AAA



Echo 3D

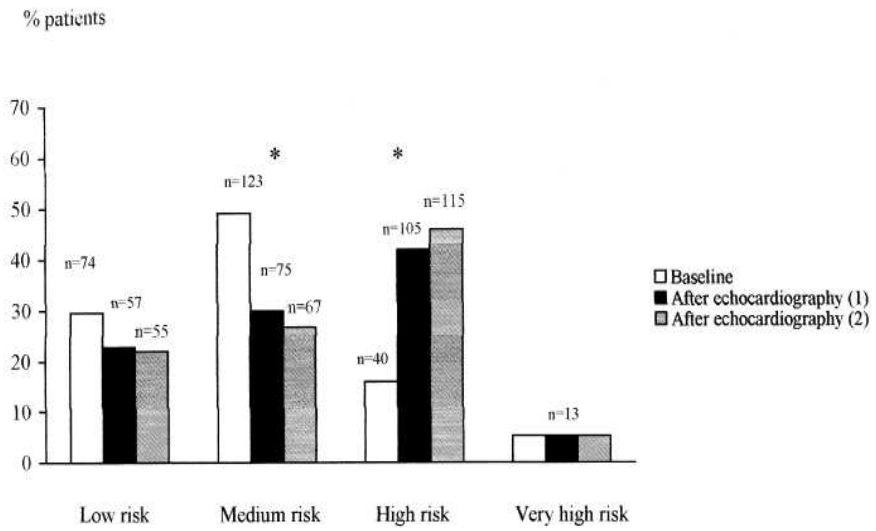




Mor-avi et al. Circulation 2004;110:1814-1818

Prévalence de l ’HVG : fonction du niveau de PA

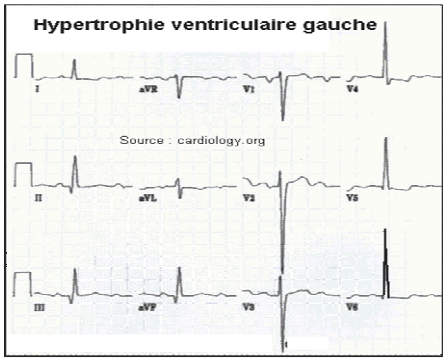
250 patients, cardiovascular risk stratification

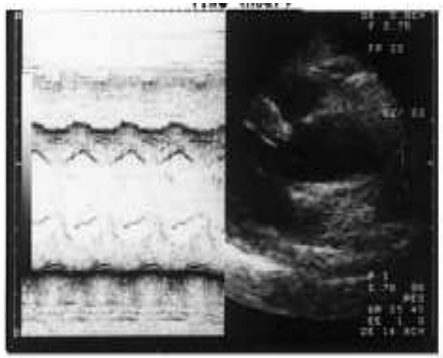


AJH 2003; 16:556–563

Prévalence de l ’HVG : Fonction de la méthode

430 hypertendus (H 54%), Suivi 3.2 ans, Critère combiné : MI, angina, stroke, etc.





Romhilt-Estes score ≥ 5 : 5.3%

LVMI > 125 g/m2 : 26.0%

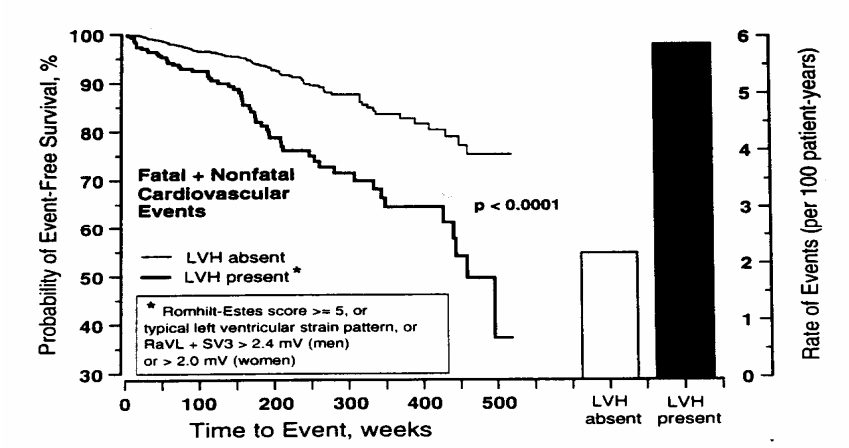
HVG ECG moins fréquente que HVG Echo

Verdecchia et al. Circulation 1998;97:48-54

Un marqueur de risque et critère intermédiaire

Rôle pronostique de l ’HVG

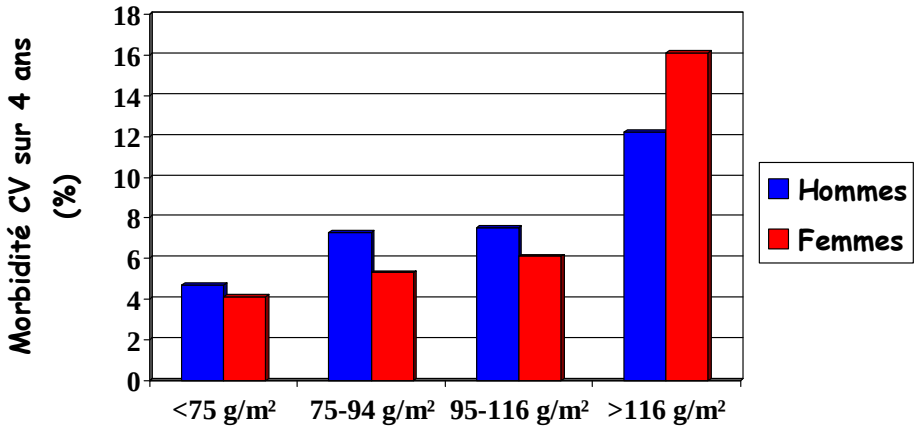
N = 1717 hypertendus, Suivi = 3,3 ans, Evnmts = Coronaires, AVC,AOMI, IC, IRC, OACR



Verdecchia et al. Circulation 1998;97:48-54

Rôle pronostique de l ’HVG

N = 3200 sujets
morbidité CV et mortalité



Levy et al. N Engl J Med. 1990;322:1561-6

Rôle pronostique de l ’HVG

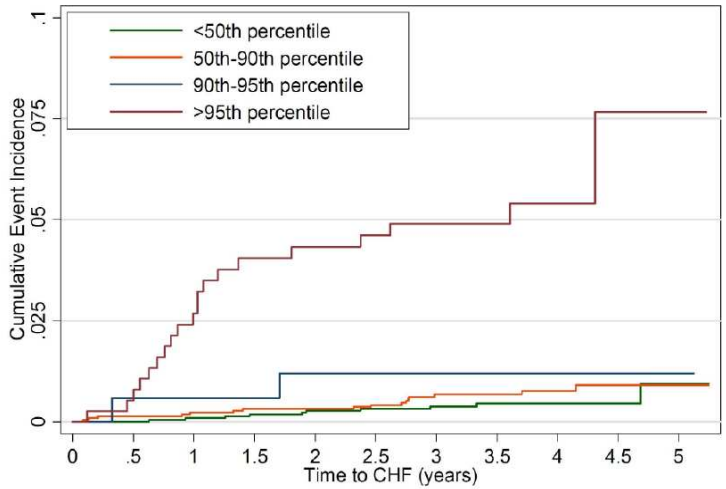
Evénements	Hommes	Femmes
Patho CV	1,49 (1,2-1,85)	1,57 (1,2-2,04)
DC CV	1,73 (1,19-2,52)	2,12 (1,28-3, 49)
DC toutes causes	1,49 (1,14-1,94)	2,01 (1,44-2,81)

Ajustement sur âge, BP, TTT, chol, tabac, diabète, BMI, HVG_{ECG}

Levy et al. N Engl J Med. 1990;322:1561-6

Rôle pronostique de l ’HVG

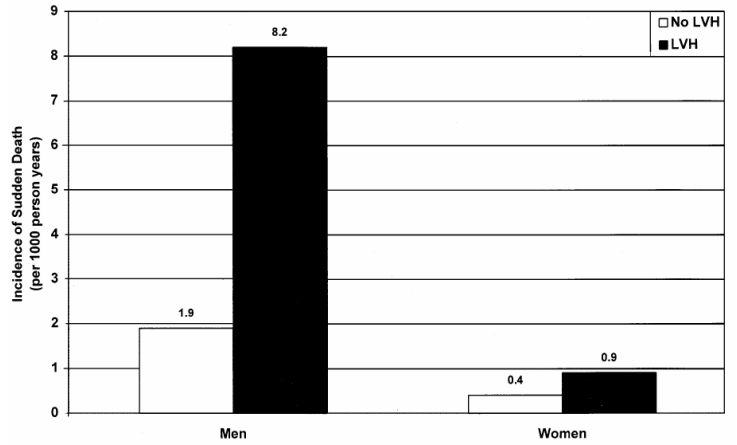
HVG et ICC, MESA Study, 5098 patients, HVG IRM, suivi de 4 ans



Bluemke et al. J Am Coll Cardiol. 2008 16;52(25):2148-55

Rôle pronostique de l ’HVG

HVG et mort subite, 3661 sujets, Framingham, 14 ans de suivi

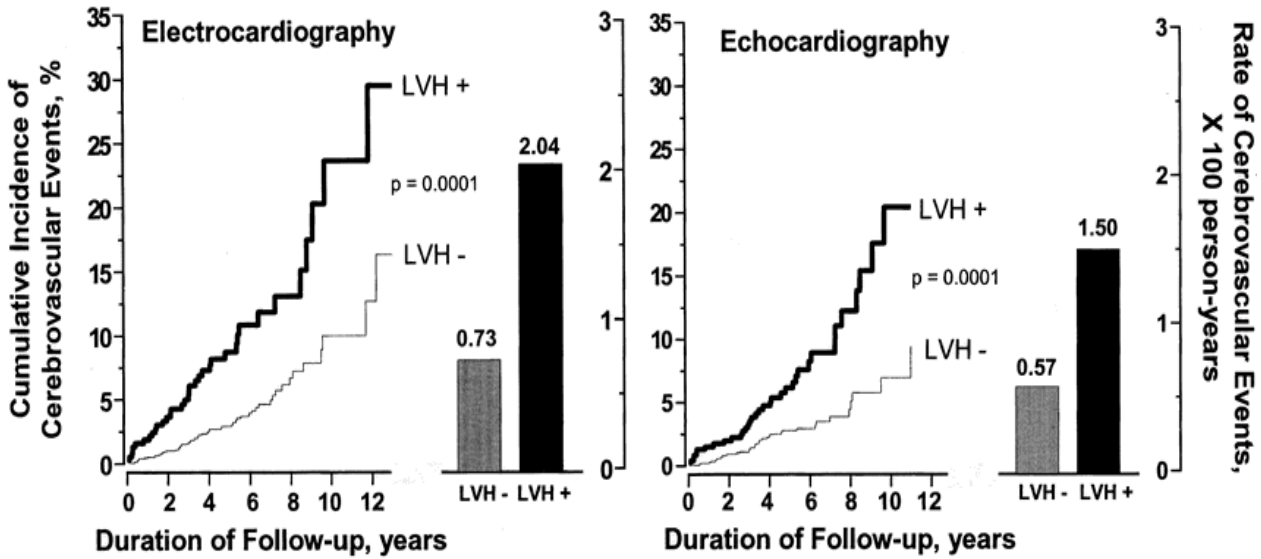


Increased LV mass and hypertrophy are associated with increased risk for sudden death after accounting for known risk factors

Haider et al. JACC 1998;32:1454-9

HVG et risque cérébral

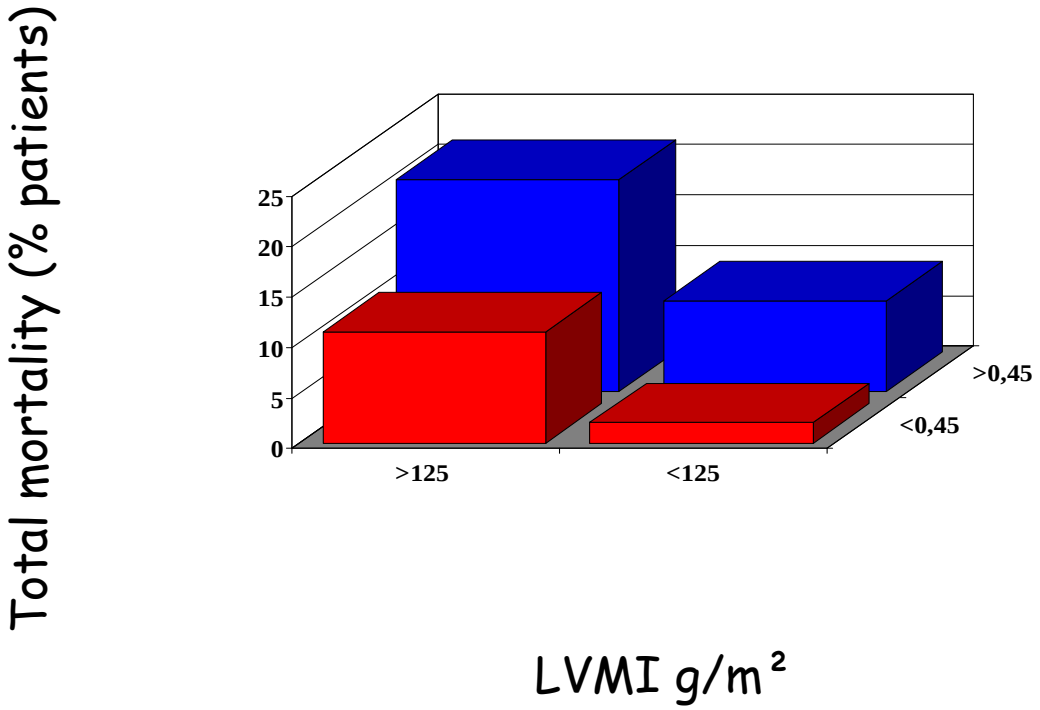
N= 2363 hypertendus Suivi = 5ans



Verdecchia et al Circulation 2001 23;104:2039-44

Formes d'HVG et risque

253 hypertendus, Follow-up : 10,2 ans

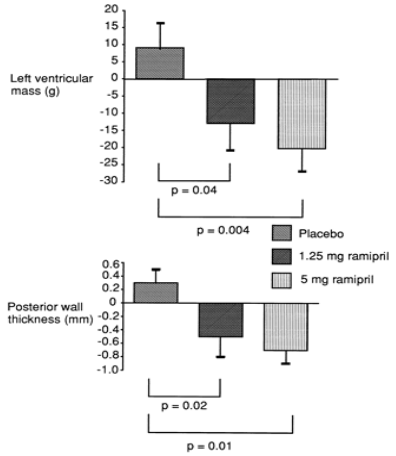


Koren et al. Ann Intern Med. 1991 1;114:345-52

Peut on agir ?

Régression de l ’HVG avec le traitement
HYCAR : effet du ramipril

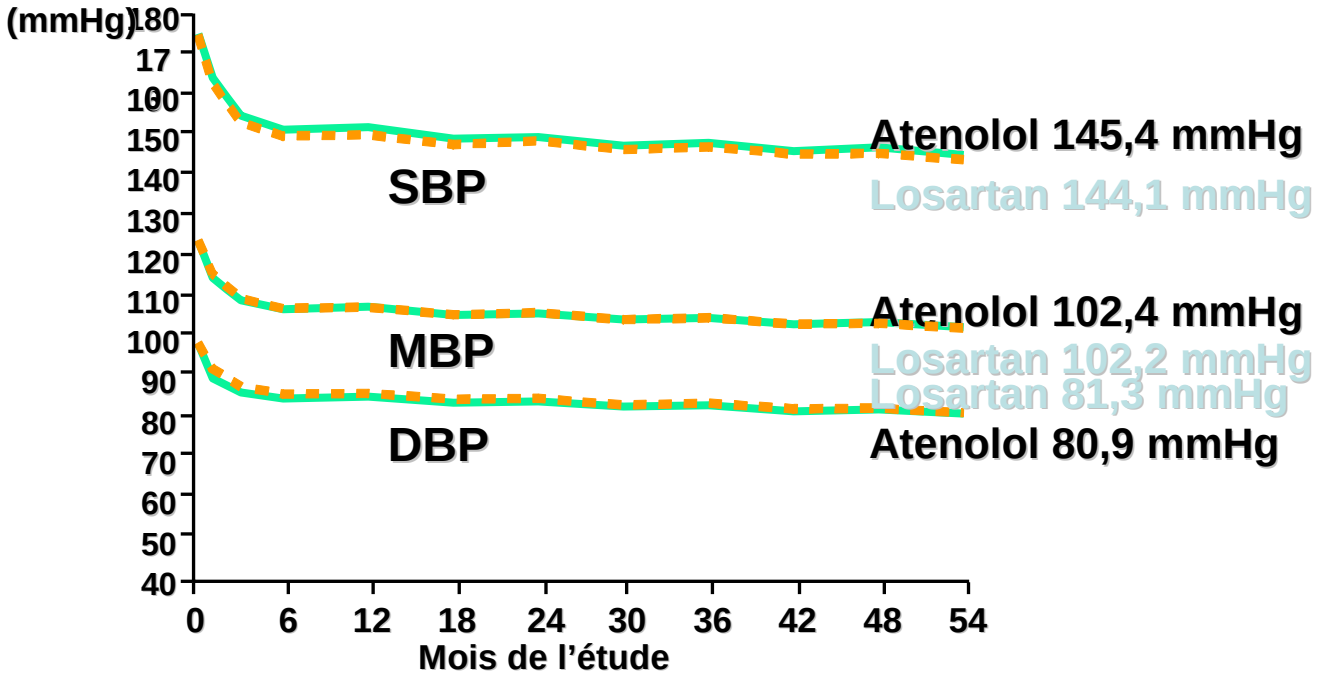
115 hypertendus
furosemide 20 mg/d - ramipril 1,25 ou 5 mg / placebo
Suivi 6 mois
Evolution



Lièvre M et al. Hypertension. 1995 ; 25:92-7

Régression de l ’HVG avec le traitement
LIFE : Losartan vs Atenolol

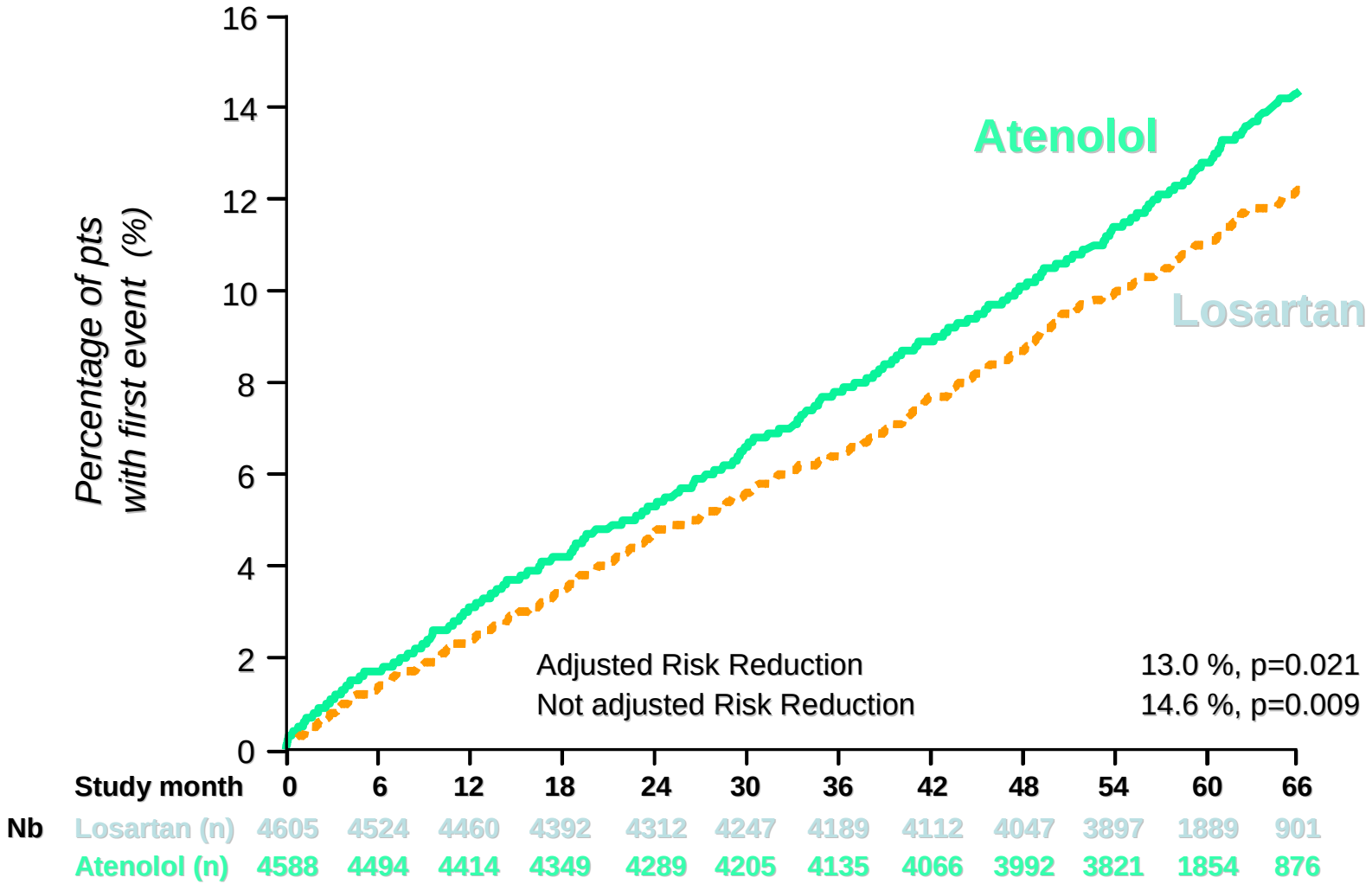
N= 9193 hypertendus, HVG +, Suivi moyen = 4,8 ans



Björn Dahlöf et al. Lancet 2002; 359: 995–1003

LIFE – Primary end point

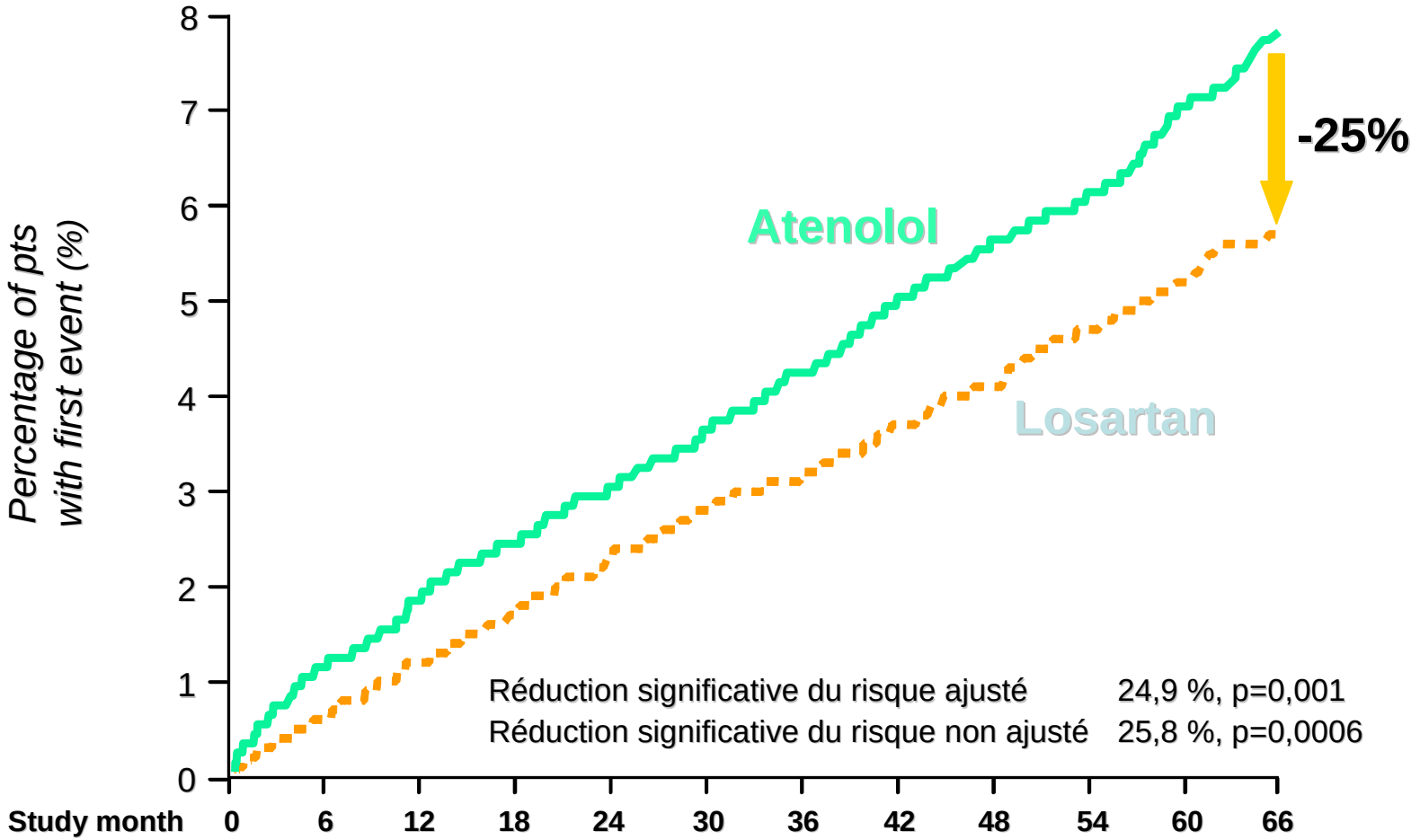
Combined endpoint: CV death, stroke and MI



Björn Dahlöf et al. Lancet 2002; 359: 995–1003

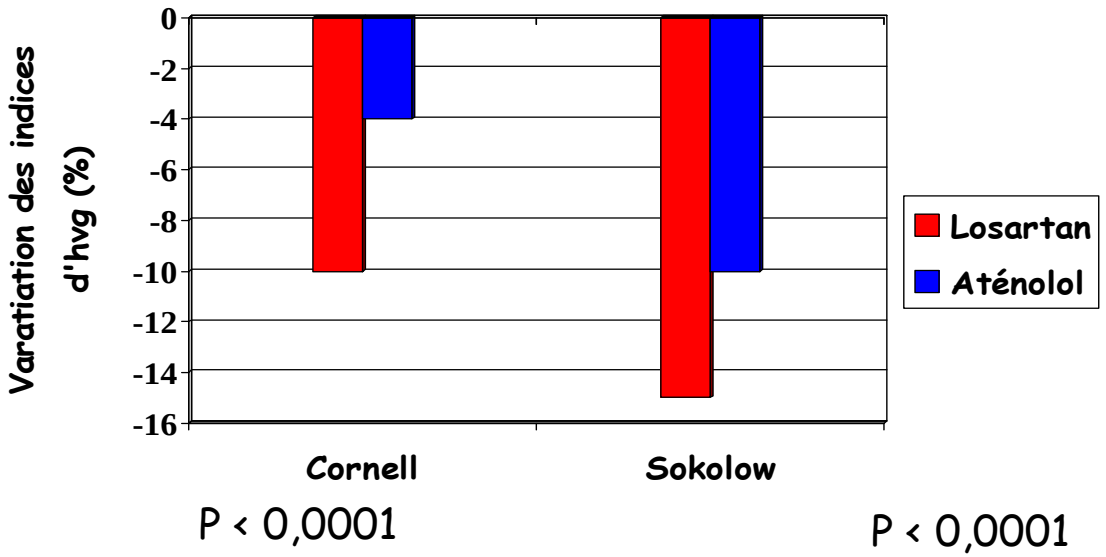
LIFE – Stroke

Fatal and non fatal stroke



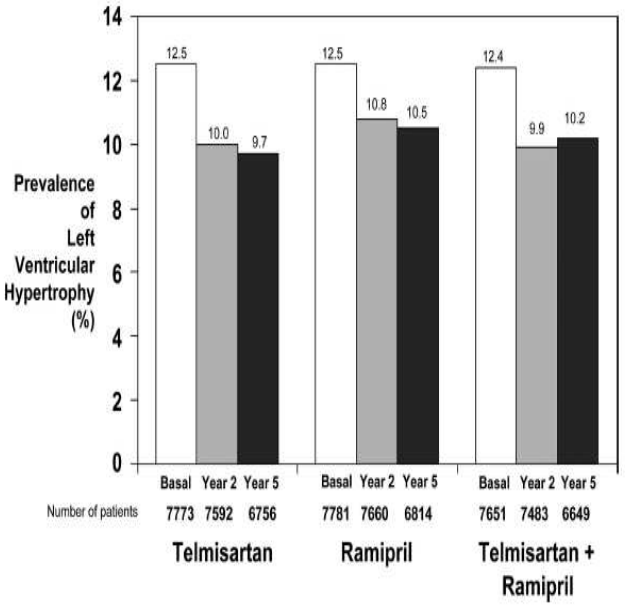
Björn Dahlöf et al. Lancet 2002; 359: 995–1003

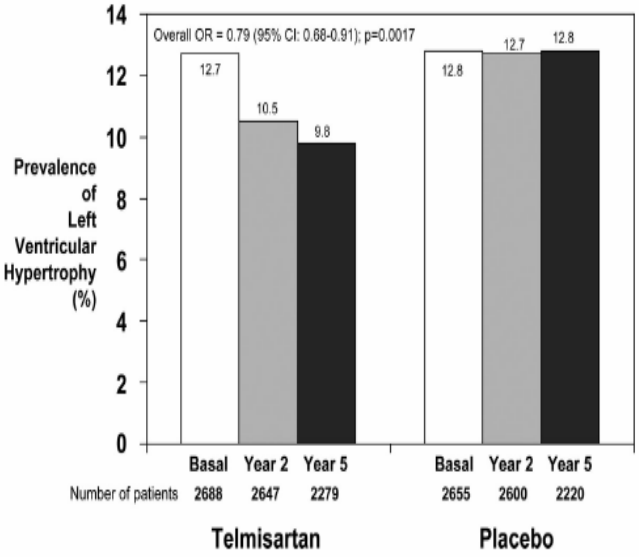
Régression de l ’HVG avec le traitement
LIFE : Losartan vs Atenolol



Björn Dahlöf et al. Lancet 2002; 359: 995–1003

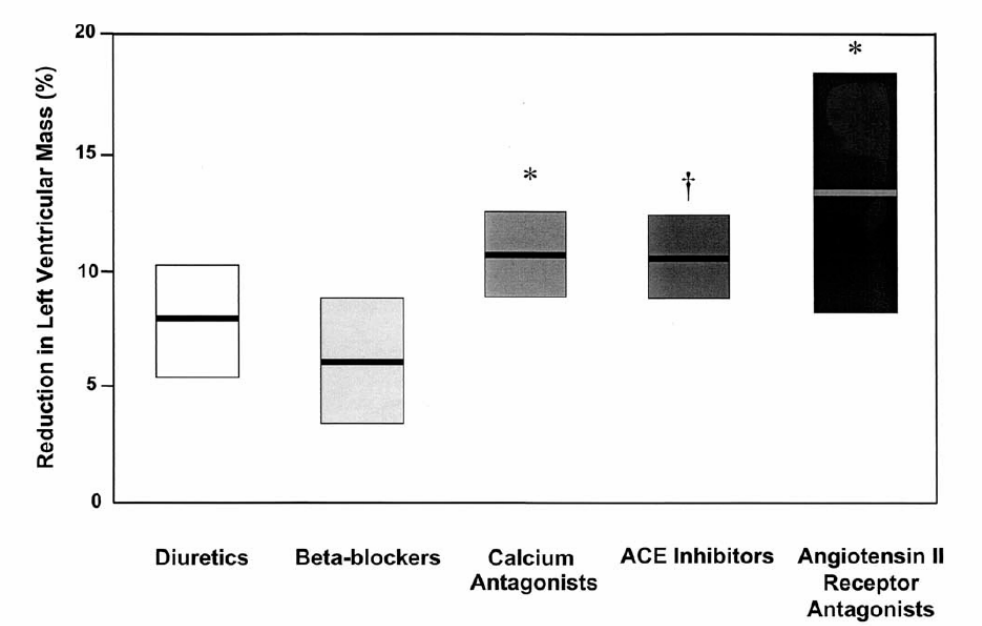
Régression de l ’HVG avec le traitement ONTARGET and TRANSCEND





Verdecchia et al. Circulation. 2009; 120:1380-1389

Effet des traitements sur l ’HVG



Klingbeil et al. Am J Med. 2003;115:41-6

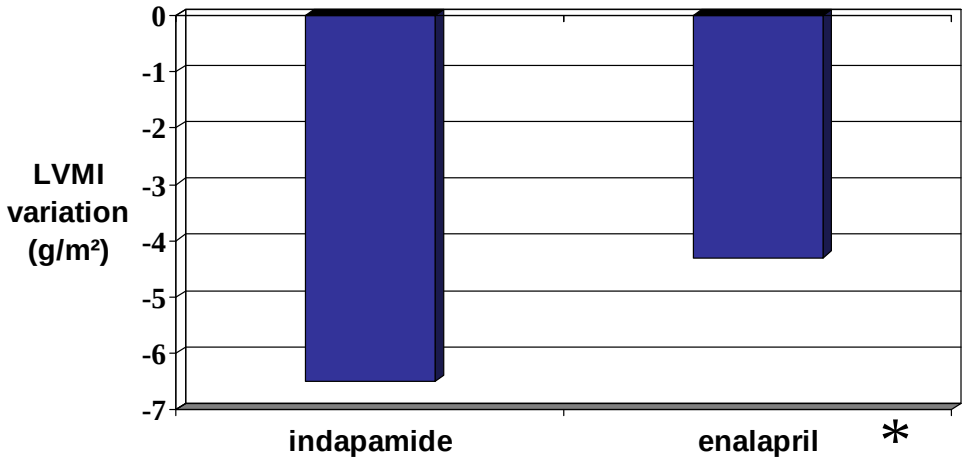
Régression de l ’HVG avec le traitement
Etude LIVE : indapamide vs enalapril

411 hypertendus avec HVG

indapamide 1,5 mg/j vs enalapril 20 mg/

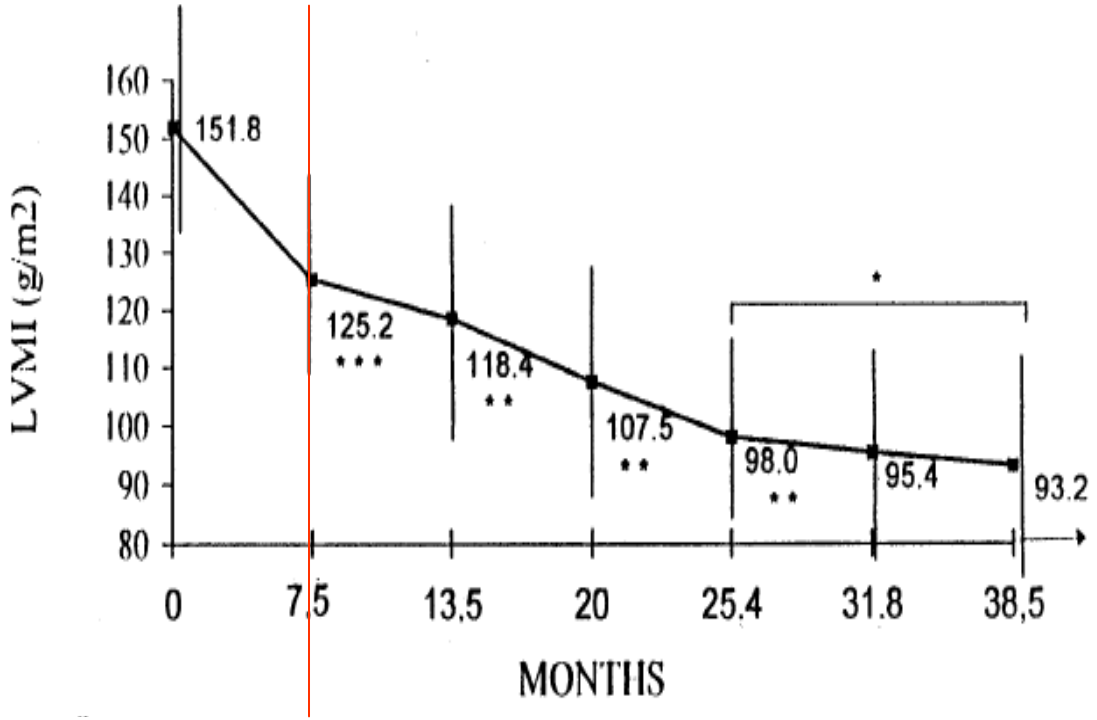
Suivi 48 sem avec évolution de la masse VG (écho)

Pas de différence de PA avec les deux TTT



Gosse P et al . J Hypertens. 2000 ;18:1465-75

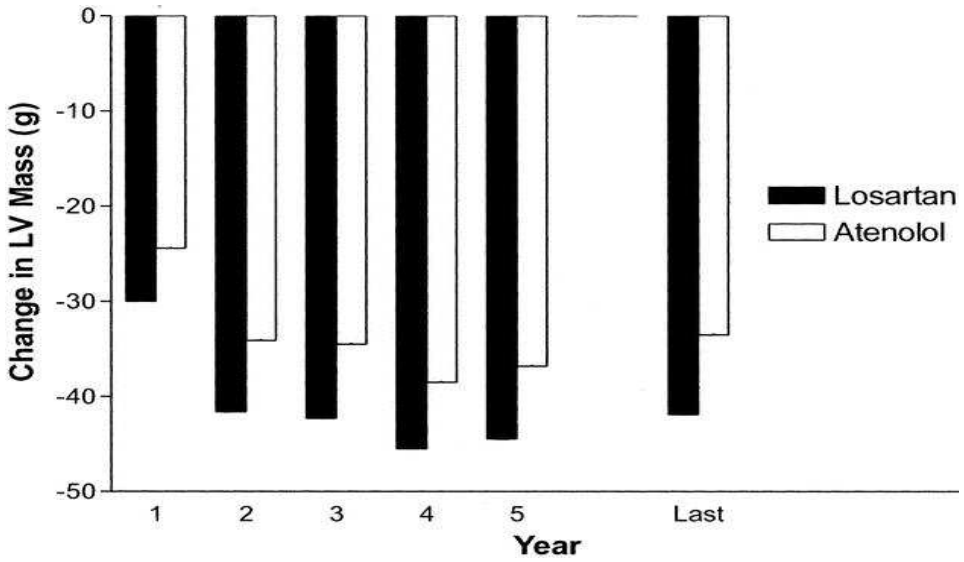
Régression de l'HVG : en combien de temps?



Franz et al. AJH 1999; 11: 631-9

La régression de l ’HVG : un bénéfice au delà de la PA ?

Régression de l ’HVG avec le traitement
LIFE : Losartan vs Atenolol



Losartan -21.7±21.8 vs Atenolol –17.7 ±19.6 g/m^2

Devereux RB et al. Circulation 2004 ;110 :1456-62

La régression de l ’HVG : un bénéfice au delà de la PA ?

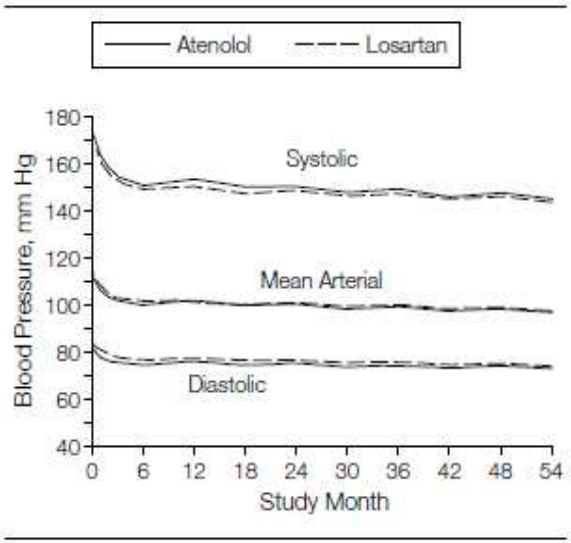
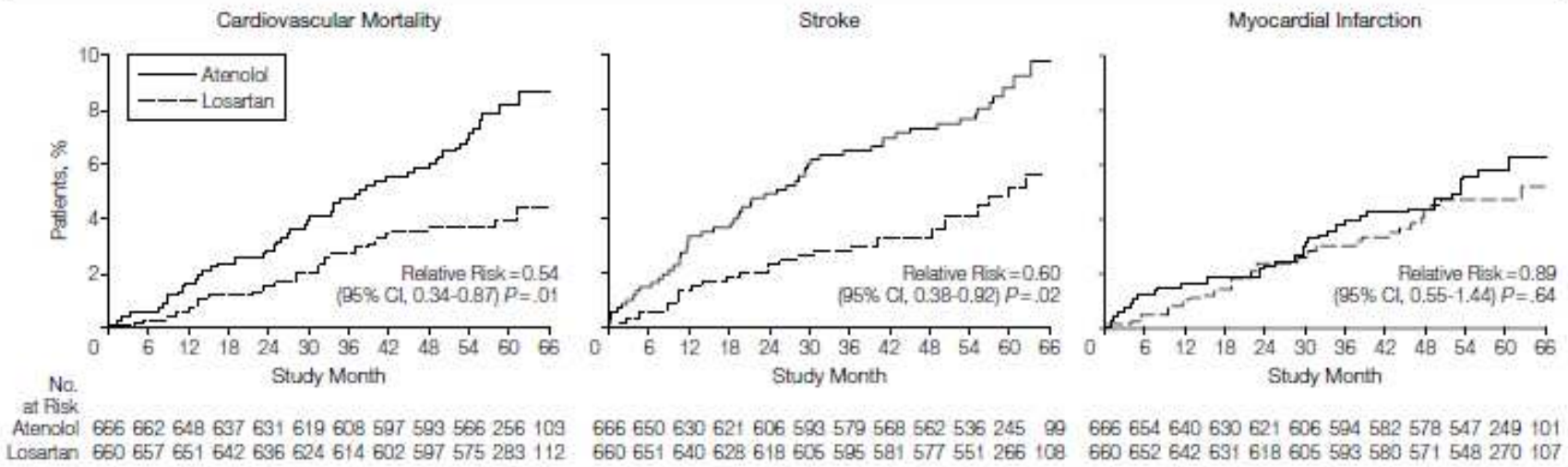


Figure 5. Kaplan-Meier Curves of Cardiovascular Mortality, Stroke, and Myocardial Infarction



CI Indicates confidence interval. Percentage of patients with first event are shown for stroke and myocardial infarction.

Kjeldsen et al. JAMA. 2002;288:1491-1498

La régression de l ’HVG : un bénéfice au delà de la PA ?

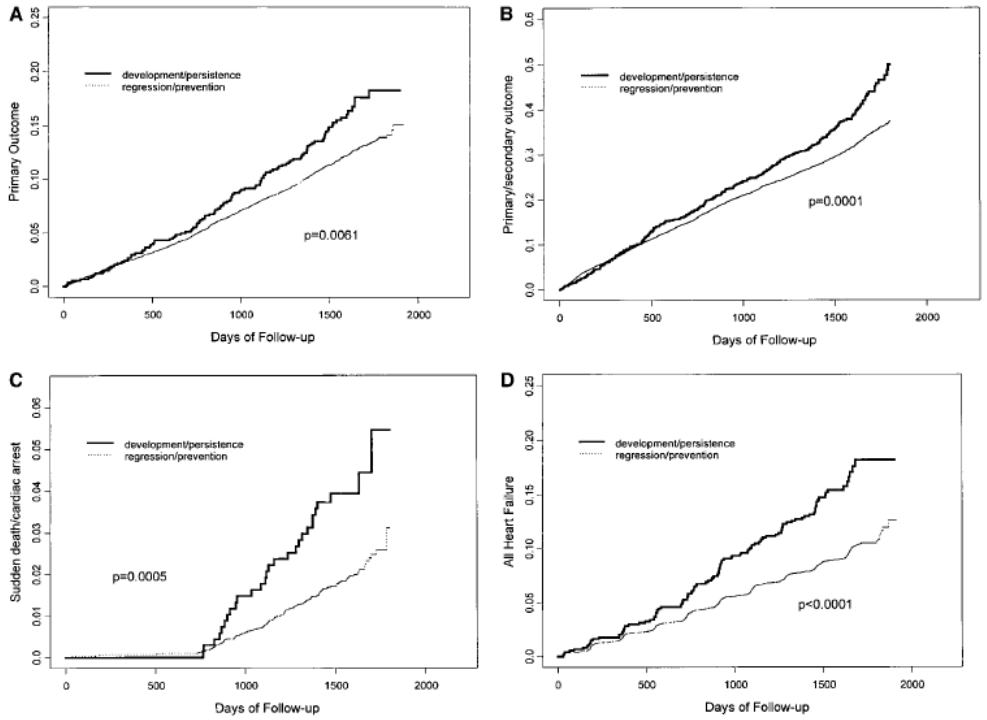
Reduction of Cardiovascular Risk by Regression of Electrocardiographic Markers of Left Ventricular Hypertrophy by the Angiotensin-Converting Enzyme Inhibitor Ramipril

James Mathew, MD, FCCP; Peter Sleight, MD, FRCP; Eva Lonn, MD, MSc; David Johnstone, MD; Janice Pogue, PhD; Qilong Yi, PhD; Jackie Bosch, MS; Bruce Sussex, MD, FRCPC; Jeffrey Probstfield, MD; Salim Yusuf, MBBS, DPhil, FRCP; for the Heart Outcomes Prevention Evaluation (HOPE) Investigators

Background—Electrocardiographic markers of left ventricular hypertrophy (LVH) predict poor prognosis. We determined whether the ACE inhibitor ramipril prevents the development and causes regression of ECG-LVH and whether these changes are associated with improved prognosis independent of blood pressure reduction.

Methods and Results—In the Heart Outcomes Prevention Evaluation (HOPE) study, patients at high risk were randomly assigned to ramipril or placebo and followed for 4.5years. ECGs were recorded at baseline and at study end. We compared prevention/regression and development/persistence of ECG-LVH in the two groups and related these changes to outcomes. At baseline, 676 patients had LVH (321 in the ramipril group and 355 in the placebo group) and 7605 patients did not have LVH (3814 in the ramipril group and 3791 in the placebo group). By study end, 336 patients in the ramipril group (8.1%) compared with 406 in the placebo group (9.8%) had development/persistence of LVH; in contrast, 3799 patients in the ramipril group (91.9%) compared with 3740 in the placebo group (90.2%) had regression/prevention of LVH ($P=0.007$). The effect of ramipril on LVH was independent of blood pressure changes. Patients who had regression/prevention of LVH had a lower risk of the predefined primary outcome (cardiovascular death, myocardial infarction, or stroke) compared with those who had development/persistence of LVH (12.3% versus 15.8%, $P=0.006$) and of congestive heart failure (9.3% versus 15.4%, $P<0.0001$).

Conclusions—The ACE inhibitor ramipril decreases the development and causes regression of ECG-LVH independent of blood pressure reduction, and these changes are associated with reduced risk of death, myocardial infarction, stroke, and congestive heart failure. (*Circulation*. 2001;104:1615-1621.)



James Mathew et al. Circulation. 2001;104:1615-1621

La régression de l ’HVG : un bénéfice au delà de la PA, par quel mécanisme ?

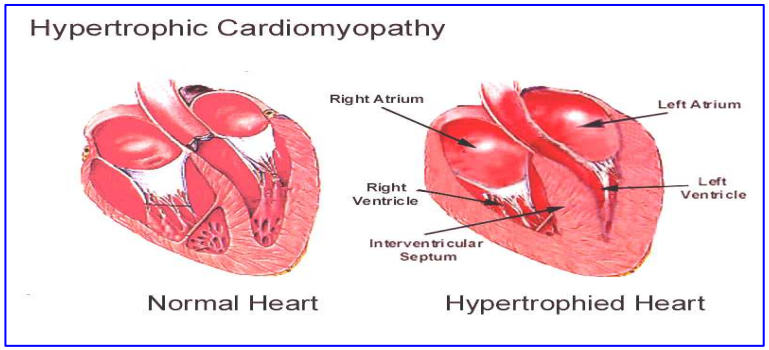
HTA

↓

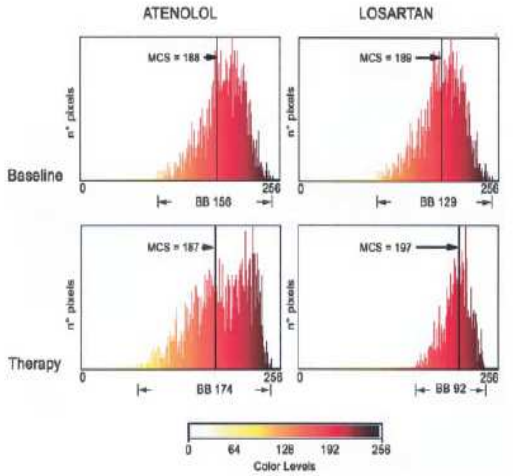
Augmentation post-charge

↙ ↓ ↘

HVG secondaire | Fibrose myocardique | Dilatation de l’OG avec FA



La régression de la fibrose



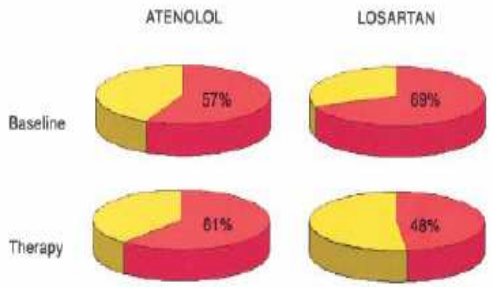
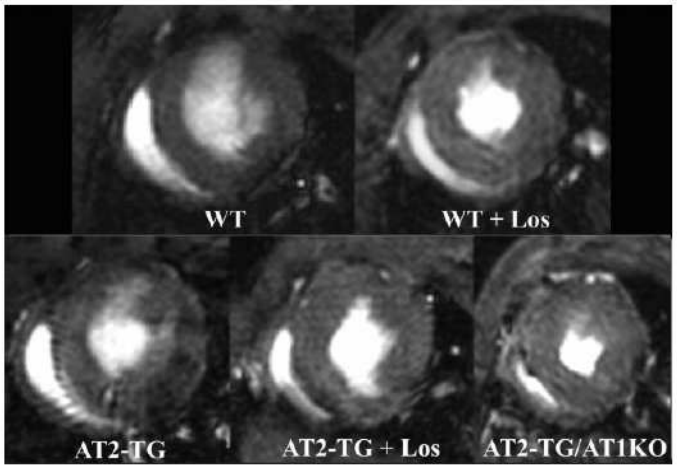


Figure 2. Prevalence of excessive fibrosis (defined as BB ≥100 color levels) in atenolol- and losartan-treated patients at baseline and after 36-week treatment. Note prevalence of excessive fibrosis was unchanged by atenolol and decreased by losartan.

Ciulla et al. Circulation. 2004;110:552-557

La régression de la fibrose

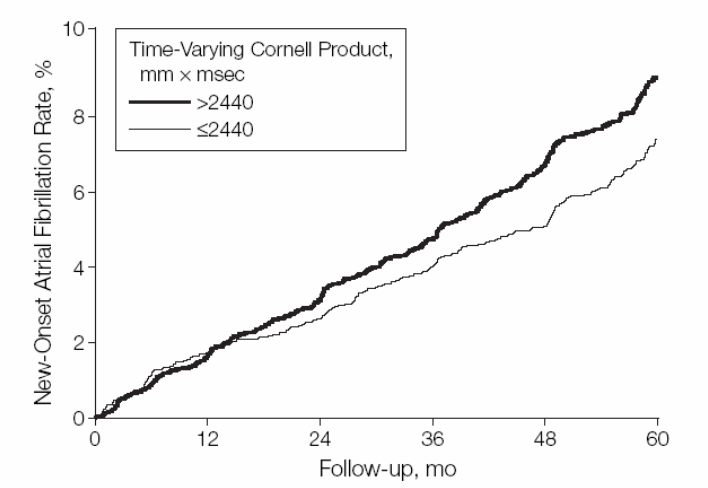


Veros et al. Am J Physiol Heart Circ Physiol. 2006;290:H1004-10

Régression HVG et prévention FA

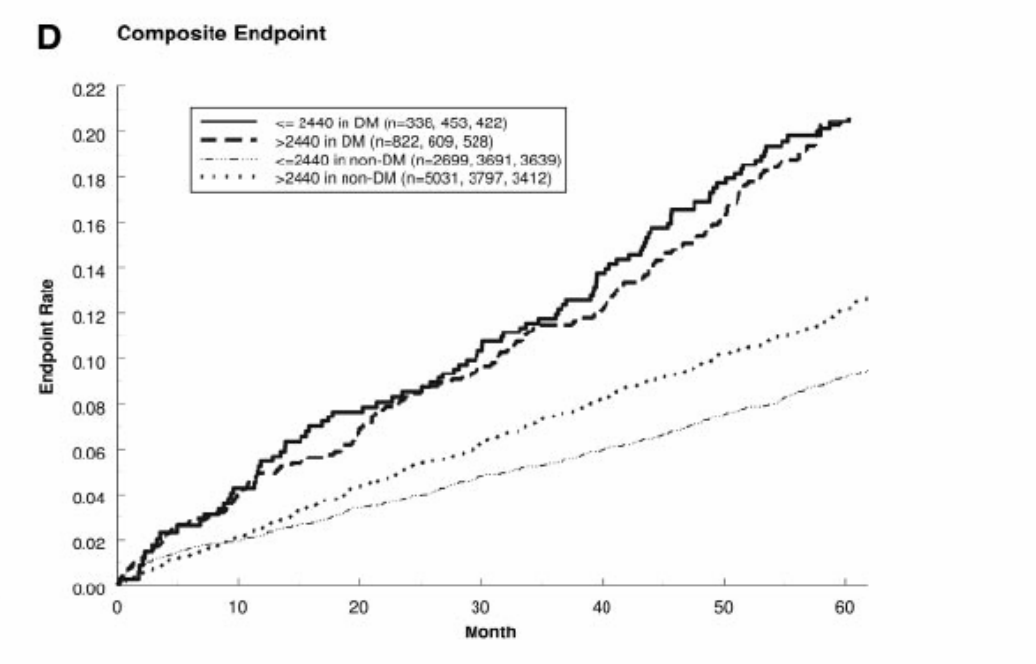
Encore LIFE…

17 % de réduction de risque
LVH-/LVH+ après ajustements
sur les covariables classiques



Okin PM et al. JAMA. 2006 ; 296 : 1242-8

Un bémol



OKin et al. Circulation. 2006 ;113:1588-96

Les recommandations

EUROPEAN SOCIETY OF CARDIOLOGY

ESH

Other risk factors, OD or disease		Blood pressure (mmHg) Normal SBP 120-129 or DBP 80-84	High normal SBP 130-139 or DBP 85-89	Grade 1 HT SBP 140-159 or DBP 90-99	Grade 2 HT SBP 160-179 or DBP 100-109	Grade 3 HT SBP ≥180 or DBP ≥110
No other risk factor	Risk level	Average risk	Average risk	Low added risk	Moderate added risk	High added risk
	Follow up visits /year	0	0	2	2	3.5
1-2 risk factors	Risk level	Low added risk	Low added risk	Moderate added risk	Moderate added risk	Very high added risk
	Follow up visits /year	3.5	3.5	2	2	3.5
3 or more risk factors, MS, OD or Diabetes	Risk level	Moderate added risk	High added risk	High added risk	High added risk	Very high added risk
	Follow up visits /year	3.5	3.5	3.5	3.5	3.5
Established CV or renal disease	Risk level	Very high added risk	Very high added risk	Very high added risk	Very high added risk	Very high added risk
	Follow up visits /year	3.5	3.5	3.5	3.5	3.5

Atteinte infra clinique des organes cibles

- HVG électrique (Sokolow-Lyon > 38 mm; Cornell >2400 mm*ms) ou
- HVG echo (MVG H $\geq$ 125 g/m²; F $\geq$ 110 g/m²)
- EIM carotide $\geq$ 12 m/s
- IPS < 0.9
- Discrète aug créatinine, FGE < 60 ml/min/1.73 m² ou Cl < 60 ml/min
- Micro Alb 30-300 mg/24 h ou Alb / creat >22 H et 31 F mg/g de creatinine

EUROPEAN SOCIETY OF CARDIOLOGY

HAUTE AUTORITÉ DE SANTÉ

Atteintes d'un organe cible : Hypertrophie ventriculaire gauche

Microalbuminurie : 30 à 300 mg/j ou 20 à 200 mg/l

Choix thérapeutique

Maladie coronaire	bêtabloquant Inhibiteur calcique
Insuffisance cardiaque systolique	Diurétique thiazidique/anse IEC ou ARA II (intolérance) bêtabloquants antialdostérone
HVG	ARA II diurétique thiazidique
AVC	diurétique thiazidique diurétique thiazidique + IEC

Conclusion HVG

- Faut il chercher une HVG chez l'hypertendu ?

  OUI

- Pourquoi ?

  Un marqueur de risque, un excellent critère intermédiaire
  une possible cible thérapeutique, un facteur de risque ?

- Comment ?

  ECG ou ETT

- Faut il la traiter *?*

  Oui avec ARA II ou inh calcique

Priorité à la baisse tensionnelle de nos patients

Merci pour votre attention …