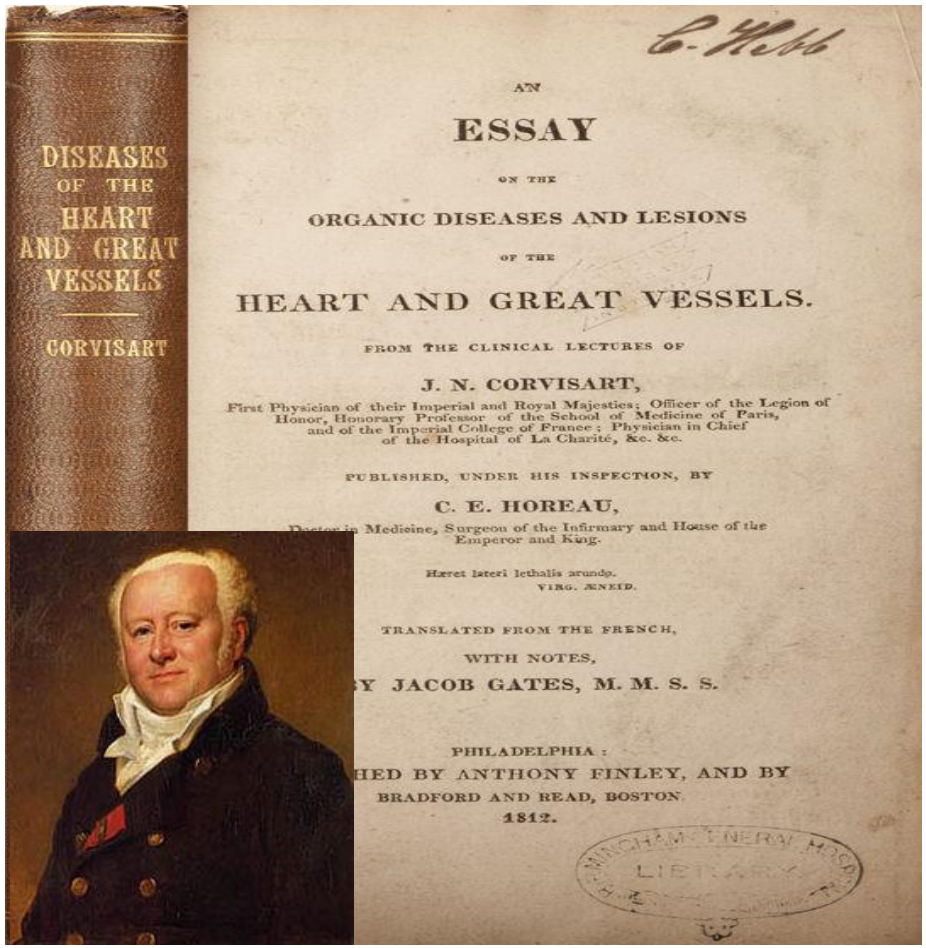
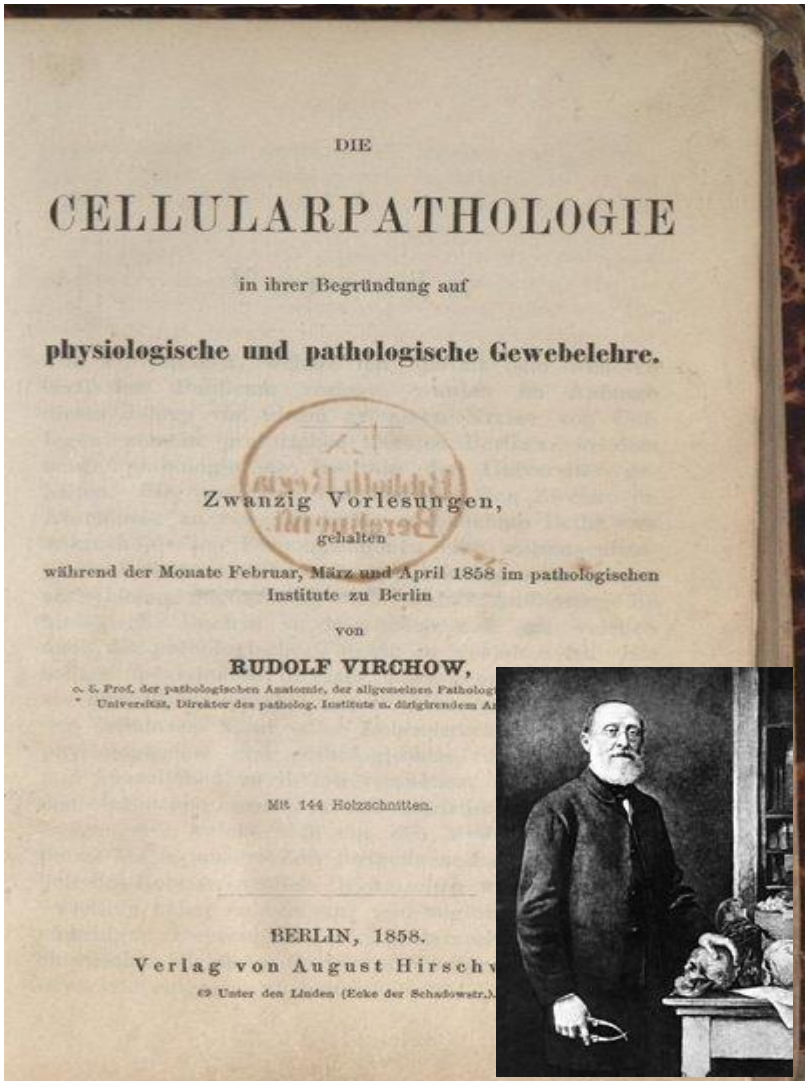
Συσχέτιση της λιπώδους καρδιάς με το λιπώδες ήπαρ

ΣΤΥΛΙΑΝΟΣ Μ. ΧΑΝΤΑΝΗΣ

Γ.Ν. Τζάνειο Πειραιά

ΛΙΠΩΔΗΣ ΚΑΡΔΙΑ





2003: Iacobellis et al. πρώτη ηχωκαρδιογραφική μέτρηση επικαρδιακού λίπους

ΕΠΙΚΑΡΔΙΑΚΟ ΛΙΠΟΣ

- Καρδιαγγειακός κίνδυνος σχετίζεται κυρίως με την τμηματική κατανομή του λιπώδους ιστού παρά με την ποσότητα του

  Rexrode KM et al, Int J Obes Relat Metab Disord 2001

- Γενικευμένη παχυσαρκία δεν σχετίζεται απαραίτητα με καρδιαγγειακή νόσο

  Wildman RP et al, Arch Intern Med 2008

- Σπλαχνικός λιπώδης ιστός μεγαλύτερη συμβολή στον καρδιαγγειακό κίνδυνο συγκριτικά με υποδόριο λιπώδη ιστό

  Fantuzzi G et al, Arterioscler Thromb Vasc Biol 2007

- “Φυσιολογικού βάρους παχύσαρκοι”

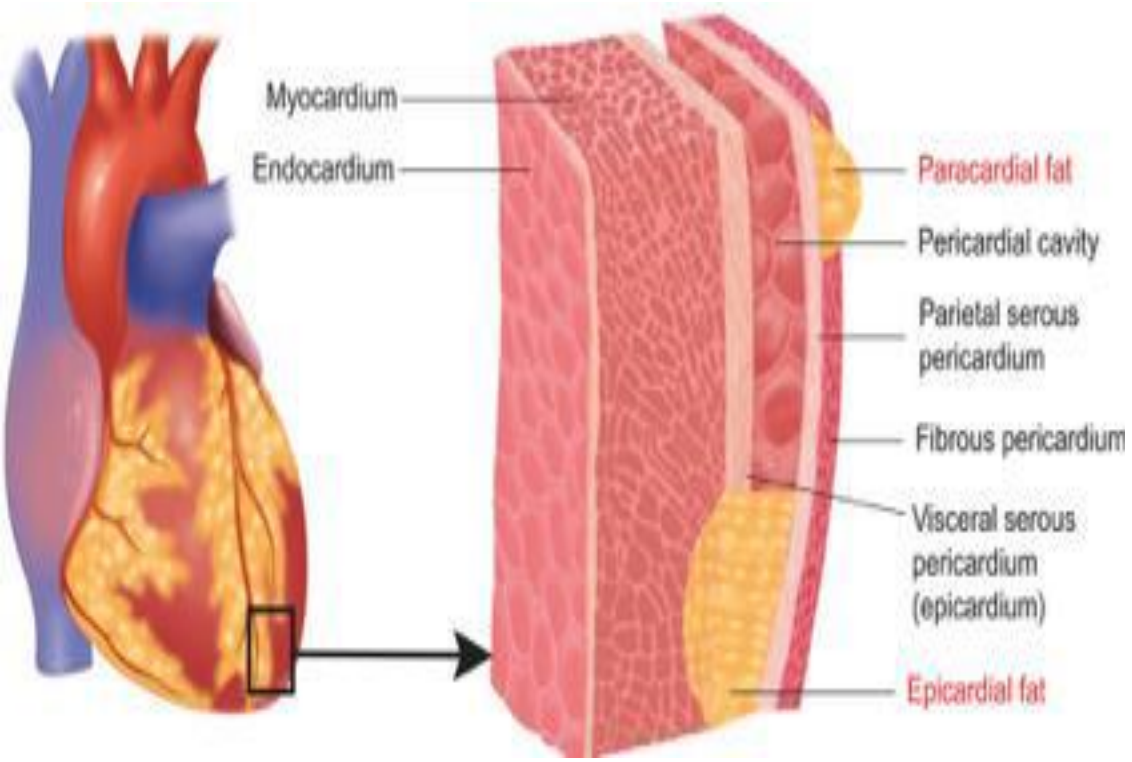
  Litwin SE et al, Circ Cardiovasc Imaging 2012

ΑΝΑΤΟΜΙΑ - ΟΡΙΣΜΟΙ

- Στη διεθνή βιβλιογραφία υπάρχει κάποια **σύγχυση ως προς την ονοματολογία** του καρδιακού λίπους

- **Ονοματολογία**

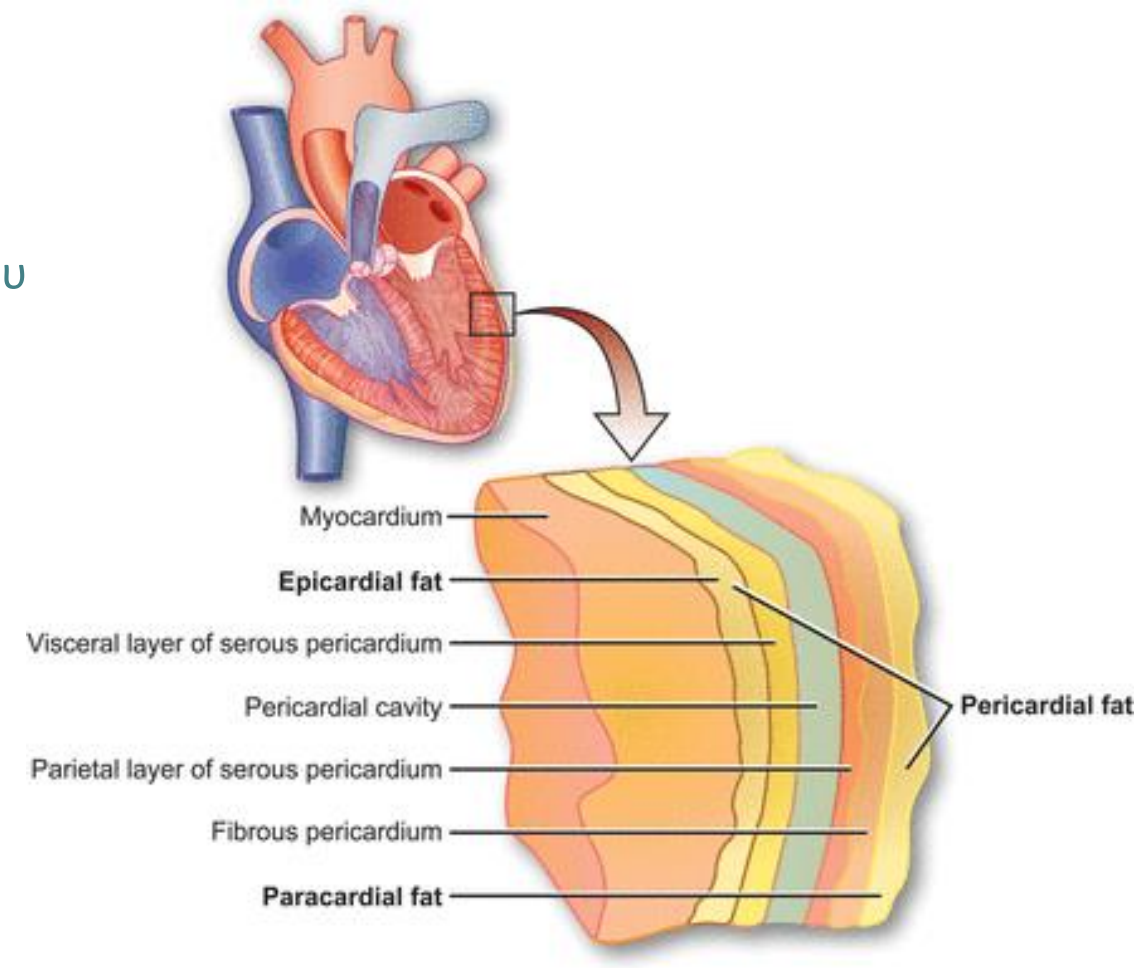
  - Μυοκαρδιακό
  - Επικαρδιακό
  - Παρακαρδιακό
  - Περικαρδιακό
  - Ενδοθωρακικό
  - Ενδιάμεσο



European Heart Journal doi:10.1093/eurheartj/ehw2013

ΑΝΑΤΟΜΙΑ - ΟΡΙΣΜΟΙ

- **Επικαρδιακό λίπος**
  - μεταξύ μυοκαρδίου και περισπλάχνιου πετάλου του περικαρδίου
- **Παρακαρδιακό λίπος**
  - εκτός του περίτονου πετάλου του περικαρδίου
- **Περικαρδιακό λίπος**
  - σύνολο λιπώδους ιστού



Bertaso AG, Arq Bras Cardiol 2013

ΣΤΟΙΧΕΙΑ ΦΥΣΙΟΛΟΓΙΑΣ…(1)

- Αληθής σπλαχνικός λιπώδης ιστός
- Κοινή εμβρυολογική προέλευση με κοιλιακό σπλαχνικό λίπος

Iacobellis G et al, J Clin Endocrinol Metab 2003

- Αντιπροσωπεύει το 20% καρδιακής μάζας (≈50g)

Corradi D et al, Cardiovasc Pathol 2004

ΣΤΟΙΧΕΙΑ ΦΥΣΙΟΛΟΓΙΑΣ…(2)

- Άμεση γειτνίαση με μυοκάρδιο/στεφανιαία αγγεία (απουσία χιτώνα)-κοινή μικροκυκλοφορία

Iacobellis G et al, Nat Clin Pract Cardiovasc Med 2005

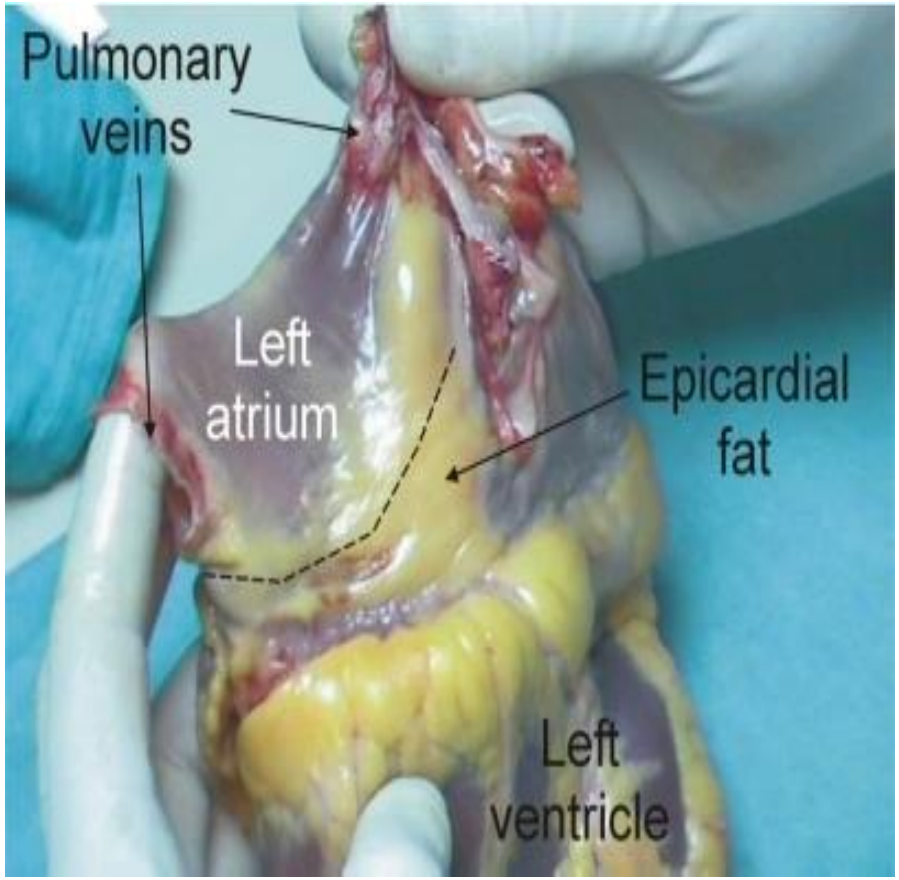
- Βιολογικά ενεργό όργανο – όχι απλά αποθήκη λίπους

- Αντικατοπτρίζει σπλαχνικό λίπος και όχι παχυσαρκία

Iacobellis G et al, J Am Soc Echocardiogr 2009

ΕΝΤΟΠΙΣΗ ΕΠΙΚΑΡΔΙΑΚΟΥ ΛΙΠΟΥΣ

- Κυρίως στεφανιαία αύλακα –επιμήκεις αύλακες
- Πλάγιο τοίχωμα δεξιάς κοιλίας
- Περικολπικα (ωτία)
- Πέριξ στεφανιαίων αγγείων
- Έκφυση μεγάλων αγγείων



Wu FZ et al, BMC Cardiovasc Disord 2014
Bertaso AG et al, Arq Bras Cardiol 2013
Iacobellis G et al, J Am Soc Echocardiogr 2009

ΡΟΛΟΣ ΕΠΙΚΑΡΔΙΑΚΟΥ ΛΙΠΟΥΣ

- Θερμορρύθμιση
- Ενεργειακή αποθήκη μυοκαρδίου
- Μηχανική προστασία στεφανιαίων αγγείων
- Αγγειοκινητικότητα στεφανιαίων αγγείων
- **Παρακρινική δράση έκκρισης κυττοκινών**

αντιφλεγμονώδη δράση

φλεγμονώδη δράση

Matloch et al Physiol. Res 2016

ΡΟΛΟΣ ΕΠΙΚΑΡΔΙΑΚΟΥ ΛΙΠΟΥΣ

- Άμεση επίδραση στο γειτονικό μυοκάρδιο - στεφανιαία αγγεια

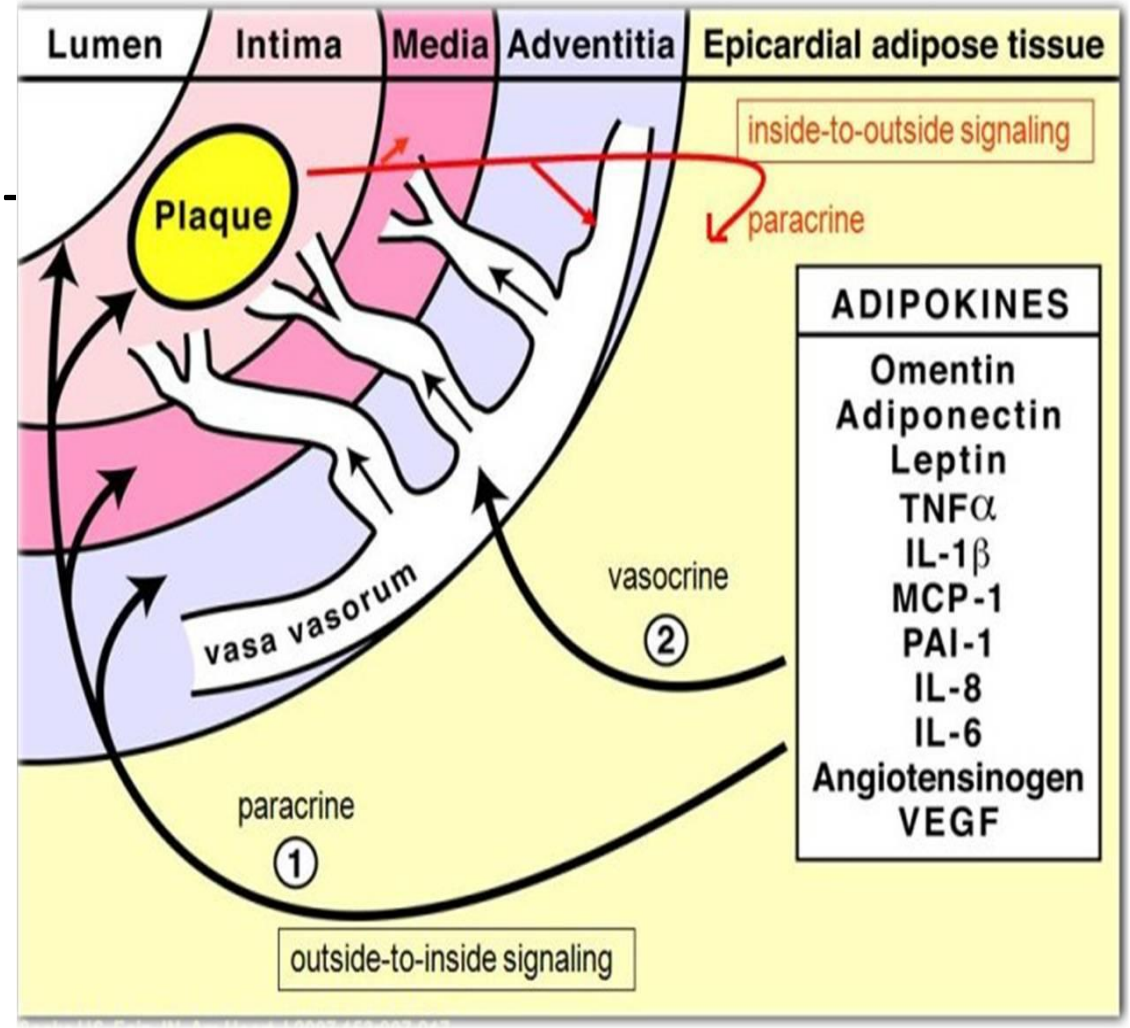


Image source : Sacks H.S, Fain J.N American heart journal 53 ; 907-917

ΕΠΙΚΑΡΔΙΑΚΟ ΛΙΠΟΣ - ΚΛΙΝΙΚΗ ΣΗΜΑΣΙΑ

- Μεταβολικό σύνδρομο

Iacobellis G et al, J Clin Endocrinol Metab 2003

- Αντίσταση στην ινσουλίνη

Iacobellis G et al, J Clin Endocrinol Metab 2005

- Στεφανιαία νόσο

Ahn SG, Heart 2008
Eroğlu S Nutr Metab Cardiovasc Dis 2009
Sade LE, Atherosclerosis 2009
Natale F, Eur J Echocardiogr2009

- Υπέρταση

Dicker D et al, J Clin Hypertens 2013

- Κολπική μαρμαρυγή

Al Chekakie et al. J Am Coll Cardiol 2010
C.X Wong et al. J Am Coll Cardiol 2011

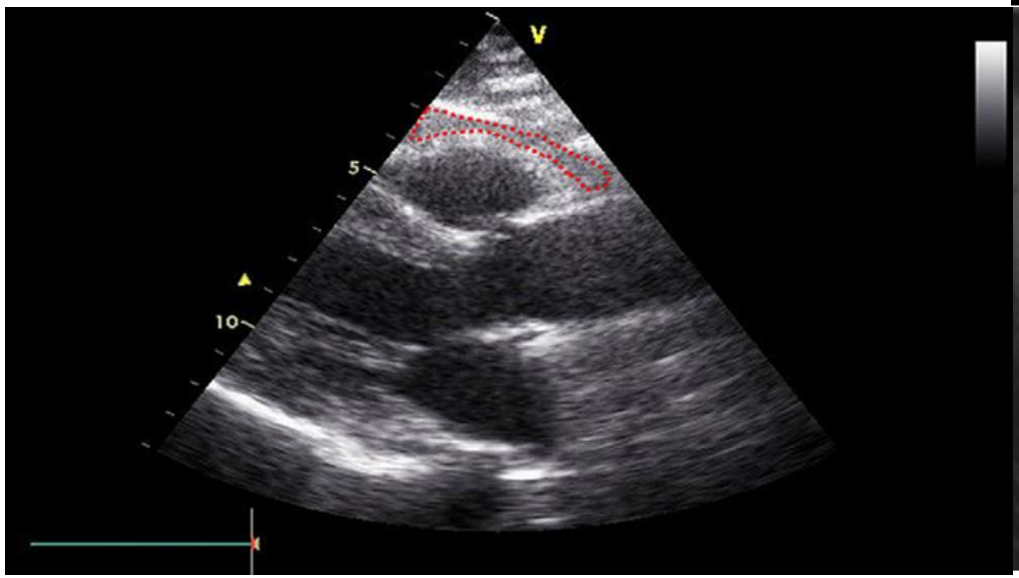
- Διαστολική δυσλειτουργία

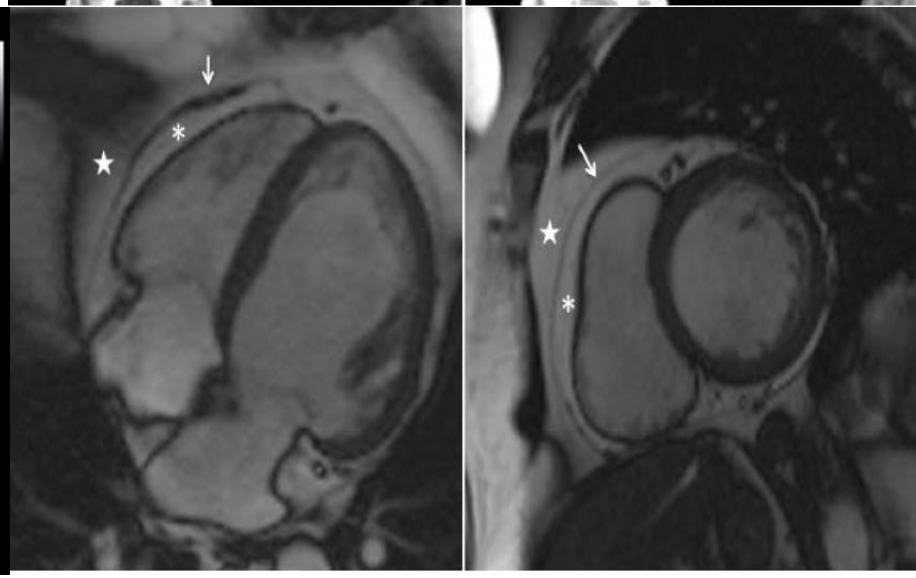
Iacobellis G et al, Int J Cardiol 2007

ΕΚΤΙΜΗΣΗ ΕΠΙΚΑΡΔΙΑΚΟΥ ΛΙΠΟΥΣ

- **Ογκομετρική ποσοτικοποίηση**
  πιο αξιόπιστος τρόπος (CMR, MDCT)

- **Προσδιορισμός του πάχους**
  πιο εύχρηστη και διαδεδομένη μέθοδος (2D-Echo)



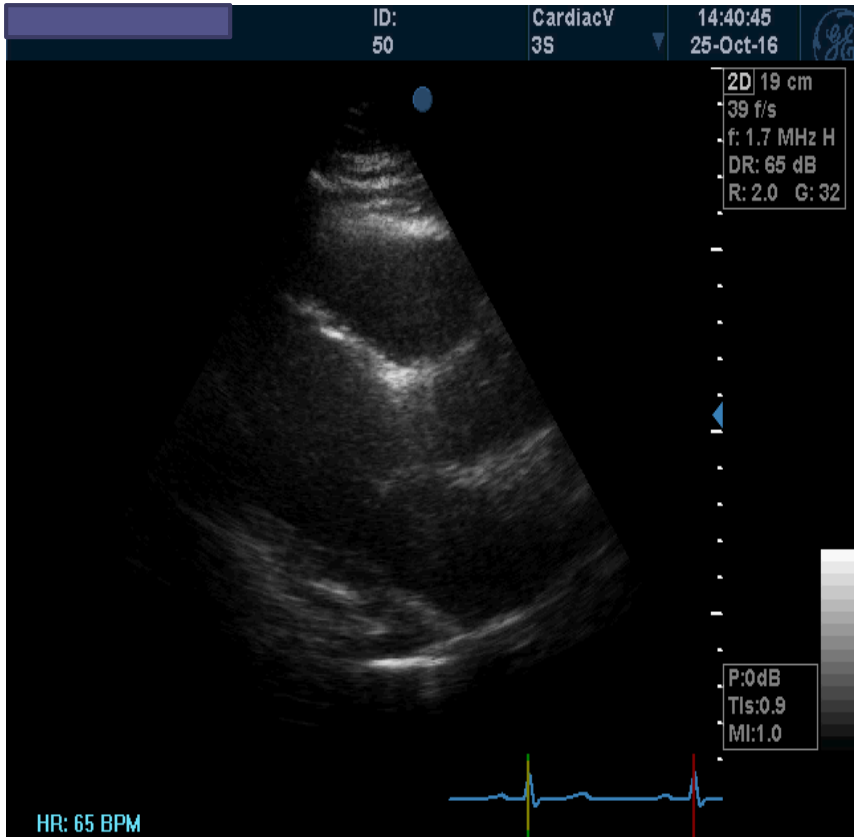


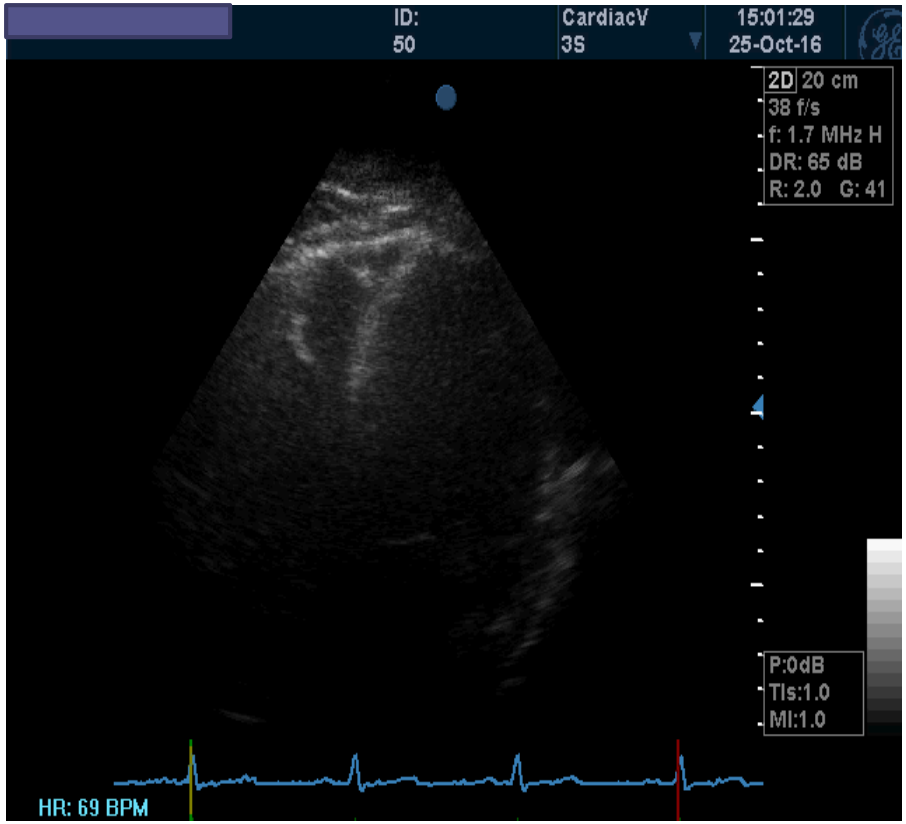
ΕΚΤΙΜΗΣΗ ΕΠΙΚΑΡΔΙΑΚΟΥ ΛΙΠΟΥΣ

Imaging modality	Spatial resolution	Variables that can be measured	Reproducibility	Cost	Limitations	Strengths
Echocardiography	+	Thickness	Good Reproducibility. Interobserver and intraobserver intraclass coefficient of correlation 0.90 and 0.98 respectively (30)	+	Variable imaging quality—particularly in obese subjects; unable to quantify total volume or area	Does not use ionizing radiation; low cost; non-invasive; readily available
Cardiac computer tomography	++	Thickness, volume, total area	Highly reproducible correlation coefficient r≥0.98 (31,32)	++	Radiation exposure	High spatial resolution; can simultaneously assess coronary artery disease
Cardiovascular magnetic resonance	+++ (gold standard)	Thickness, volume, total area	Highly reproducible; low intra and interobserver variability (33,34)	+++	Accessibility; high cost	High spatial resolution; does not use ionizing radiation

Talman et al, Cardiovasc Diagn Ther 2014

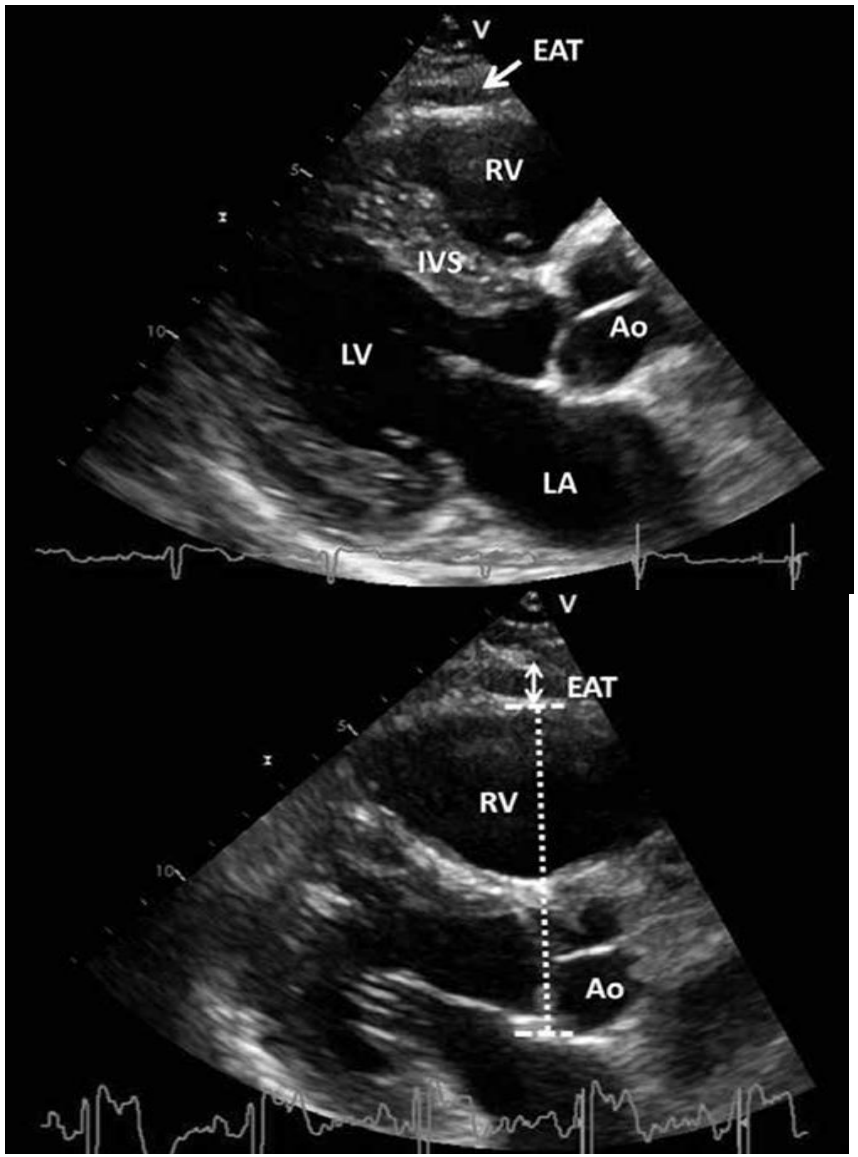
ECHO


ID:
50
CardiacV
3S
14:40:45
25-Oct-16
2D 19 cm
39 f/s
f: 1.7 MHz H
DR: 65 dB
R: 2.0 G: 32
P:0dB
TIs:0.9
MI:1.0
HR: 65 BPM


ID:
50
CardiacV
3S
15:01:29
25-Oct-16
2D 20 cm
38 f/s
f: 1.7 MHz H
DR: 65 dB
R: 2.0 G: 41
P:0dB
TIs:1.0
MI:1.0
HR: 69 BPM

ΜΕΤΡΗΣΗ ΤΟΥ ΕΠΙΚΑΡΔΙΑΚΟΥ ΛΙΠΟΥΣ

- Ελεύθερο τοίχωμα RV
- Χώρος ελεύθερος ήχων μεταξύ πετάλων περικαρδίου
- PLAX (κάθετα στον αορτικό δακτύλιο)
- PSAX (ύψος θηλοειδών μυών)
- Μ.Ο. τουλάχιστον 3 καρδιακών κύκλων από κάθε λήψη
- Μέσο πάχος PLAX/PSAX
- Τελοσυστολή ή τελοδιαστολή;;;;



Iacobellis G et al, Obes Res 2003
Iacobellis G et al, Obesity 2008
Natale F et al, Eur J Echocardiogr. 2009

ΜΕΤΡΗΣΗ ΤΟΥ ΕΠΙΚΑΡΔΙΑΚΟΥ ΛΙΠΟΥΣ

ΤΕΛΟΔΙΑΣΤΟΛΗ

- Σε συμφωνία με CT/MRI

Jeong JW, Circ J 2007

Ahn SG,Heart 2008

Jung-Won Hwang, J Cardiovasc Ultrasound 2008

- Συμπίεση επικαρδιακού λίπους από μυοκαρδιακή μάζα κατά τη τελοδιαστολή

- Δυσχερής διάκριση επικαρδιακού – παρακαρδιακού λίπους

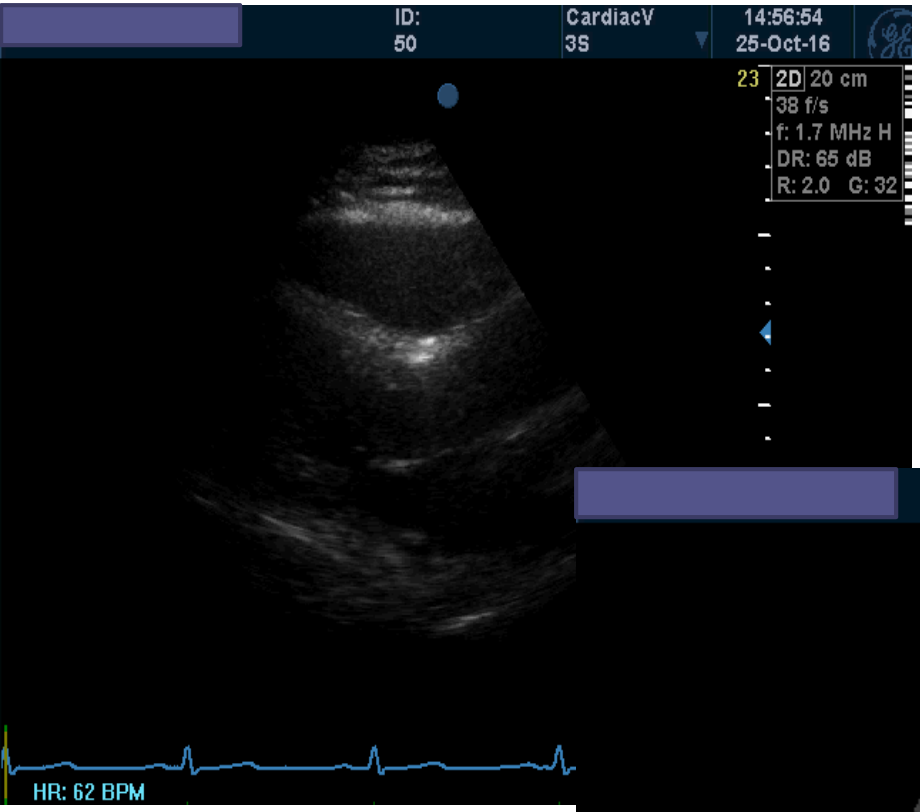
Iacobellis G,Obes Res 2003

Chaowalit N, Atherosclerosis 2006

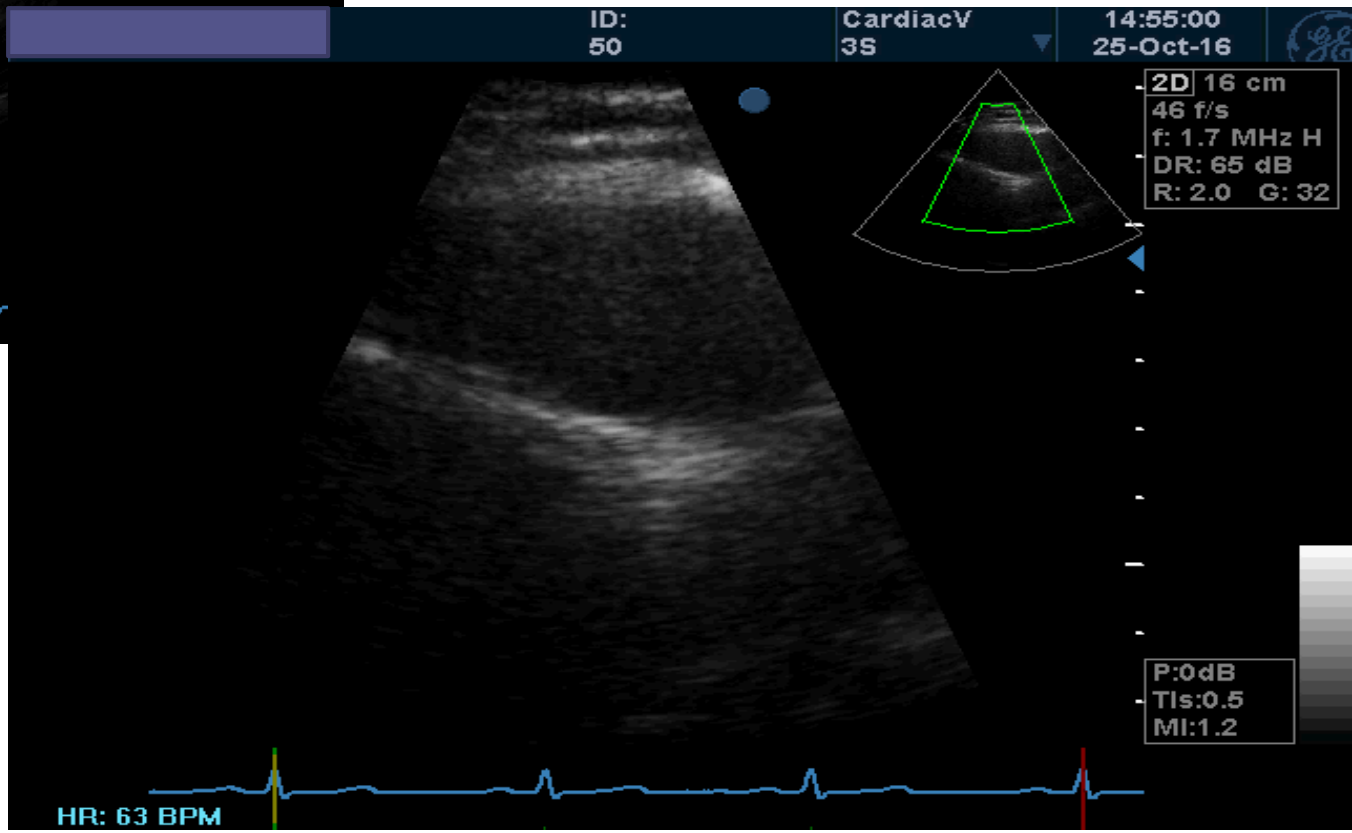
Willens, J Am Soc Echocardiogr2009

END SYSTOLIC FRAMES ARE NOW CONSIDERED IDEAL

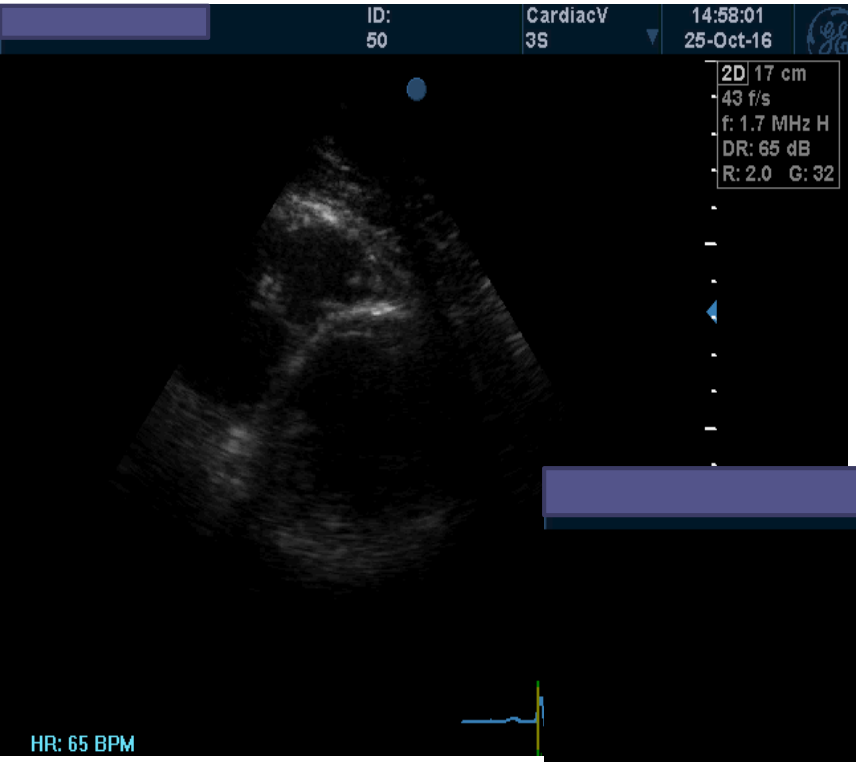
KAUSHIK, J AM COLL CARDIOL 2011

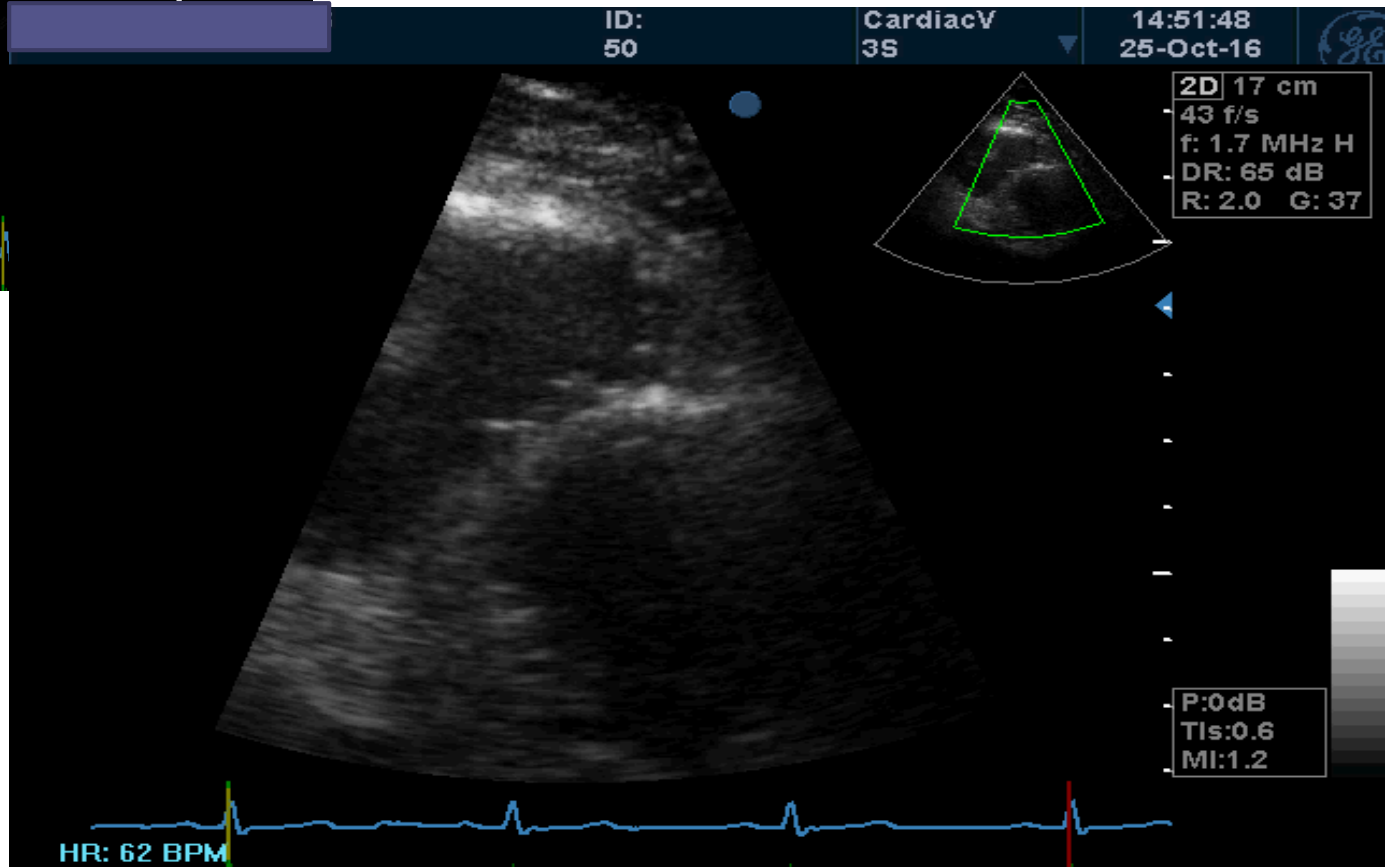

ID:
50
CardiacV
3S
14:56:54
25-Oct-16
23
2D 20 cm
38 f/s
f: 1.7 MHz H
DR: 65 dB
R: 2.0 G: 32
HR: 62 BPM

PLAX


ID:
50
CardiacV
3S
14:55:00
25-Oct-16
2D 16 cm
46 f/s
f: 1.7 MHz H
DR: 65 dB
R: 2.0 G: 32
P:0dB
TIs:0.5
MI:1.2
HR: 63 BPM

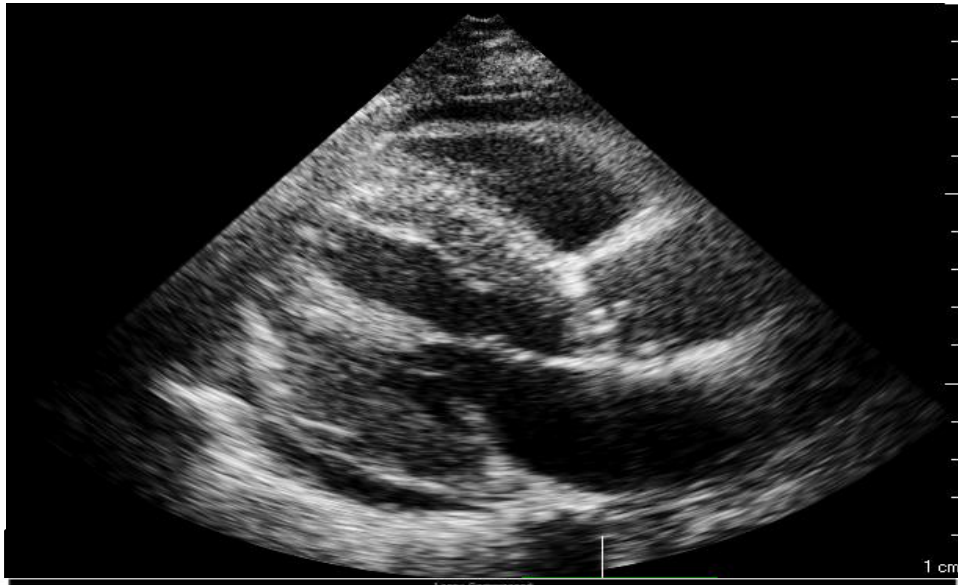
PSAX

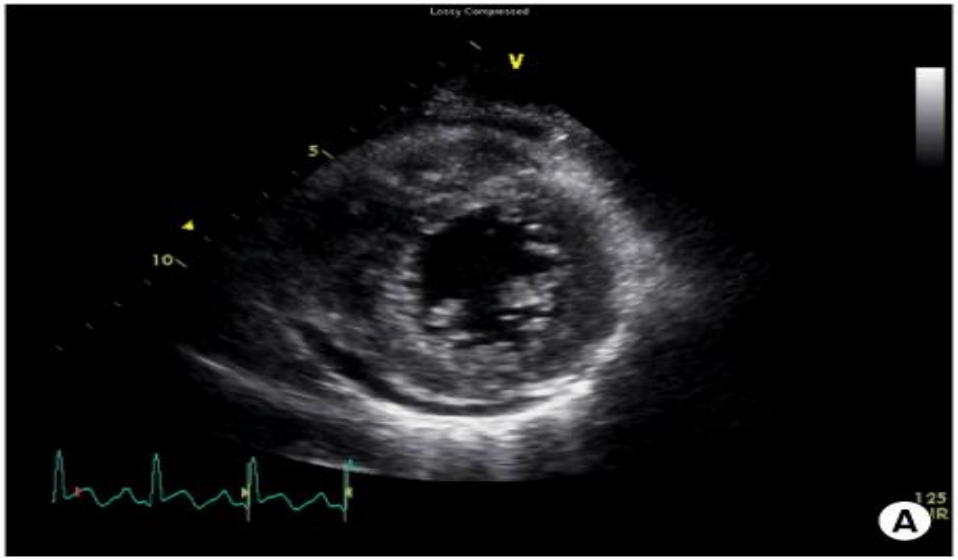

ID:
50
CardiacV
3S
14:58:01
25-Oct-16
2D 17 cm
43 f/s
f: 1.7 MHz H
DR: 65 dB
R: 2.0 G: 32
HR: 65 BPM

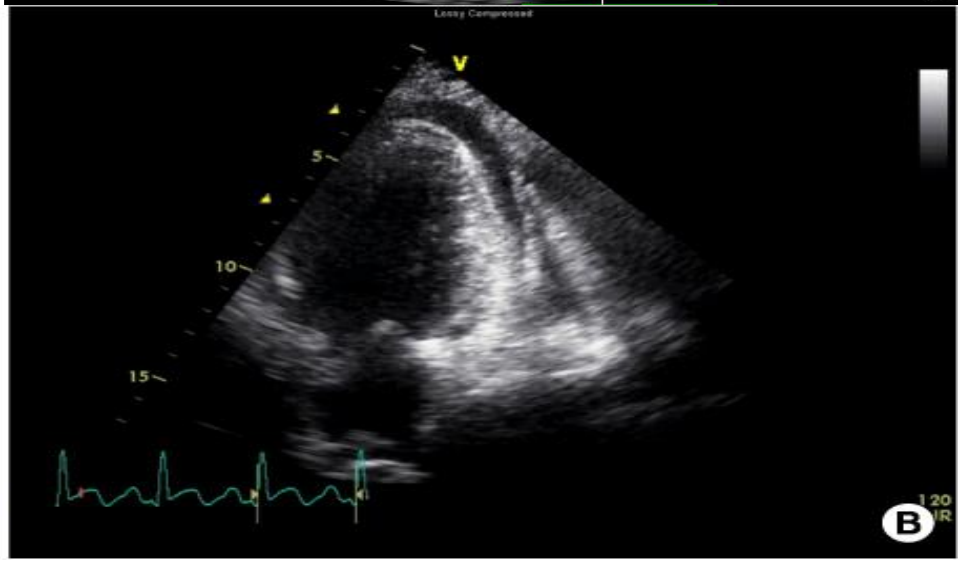

ID:
50
CardiacV
3S
14:51:48
25-Oct-16
2D 17 cm
43 f/s
f: 1.7 MHz H
DR: 65 dB
R: 2.0 G: 37
P:0dB
TIs:0.6
MI:1.2
HR: 62 BPM

ΕΠΙΚΑΡΔΙΑΚΟ ΛΙΠΟΣ vs ΠΕΡΙΚΑΡΔΙΑΚΟ ΥΓΡΟ

- Εντόπιση
- Περισσότερο υπόηχο το υγρό
- Κινητικότητα ελευθέρου τοιχώματος Δεξιάς κοιλίας







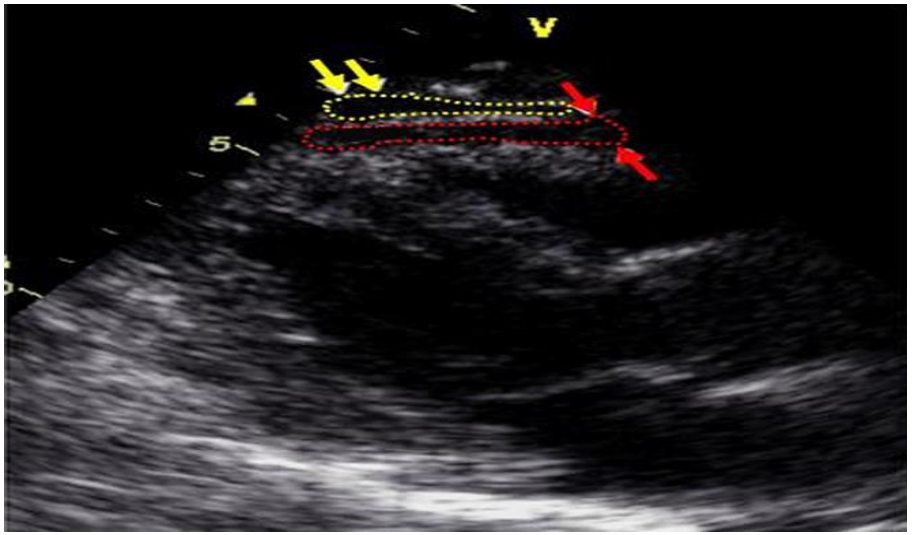
ΕΠΙΚΑΡΔΙΑΚΟ vs ΠΑΡΑΚΑΡΔΙΑΚΟ ΛΙΠΟΣ

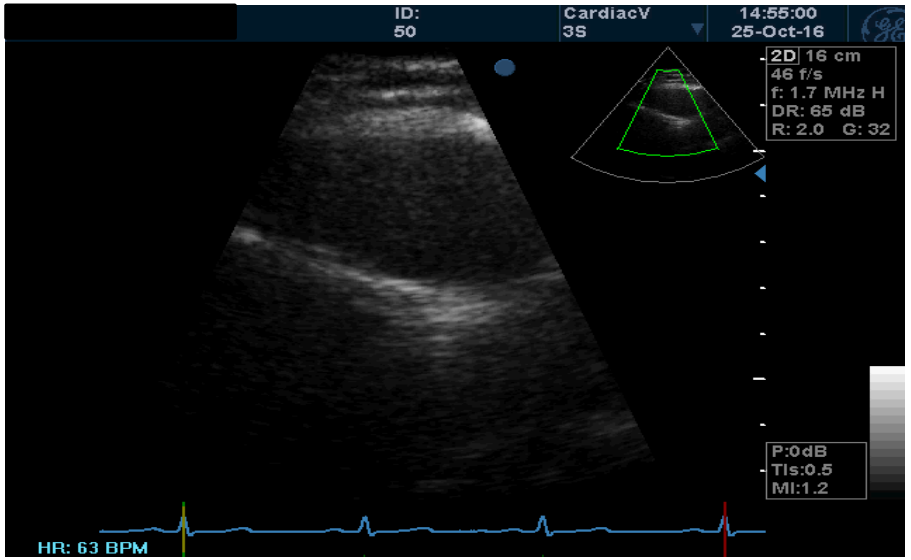
- Διαφορετική αιμάτωση
  - Επικαρδιακό λίπος από κλάδους στεφανιαίων αρτηριών
  - Παρακαρδιακό λίπος από κλάδους έσω μαστικής αρτηρίας

- Διαφορετική εμβρυολογική προέλευση
  - Επικαρδιακό λίπος από σπλαχνοπλευρικό μεσόδερμα
  - Παρακαρδιακό λίπος από θωρακικό μεσέγχυμα

  Marchington JM, Comp Biochem Physiol 1989

- ***Παρακαρδιακό λίπος δεν παραμορφώνεται με καρδιακούς κύκλους***





ΦΥΣΙΟΛΟΓΙΚΕΣ ΤΙΜΕΣ ΠΑΧΟΥΣ ΕΠΙΚΑΡΔΙΑΚΟΥ ΛΙΠΟΥΣ

- Ακόμα μη αυστηρά καθορισμένα όρια...
- Φύλο/ηλικία/φυλή (μικρότερο σε Αφρο-Αμερικανούς)

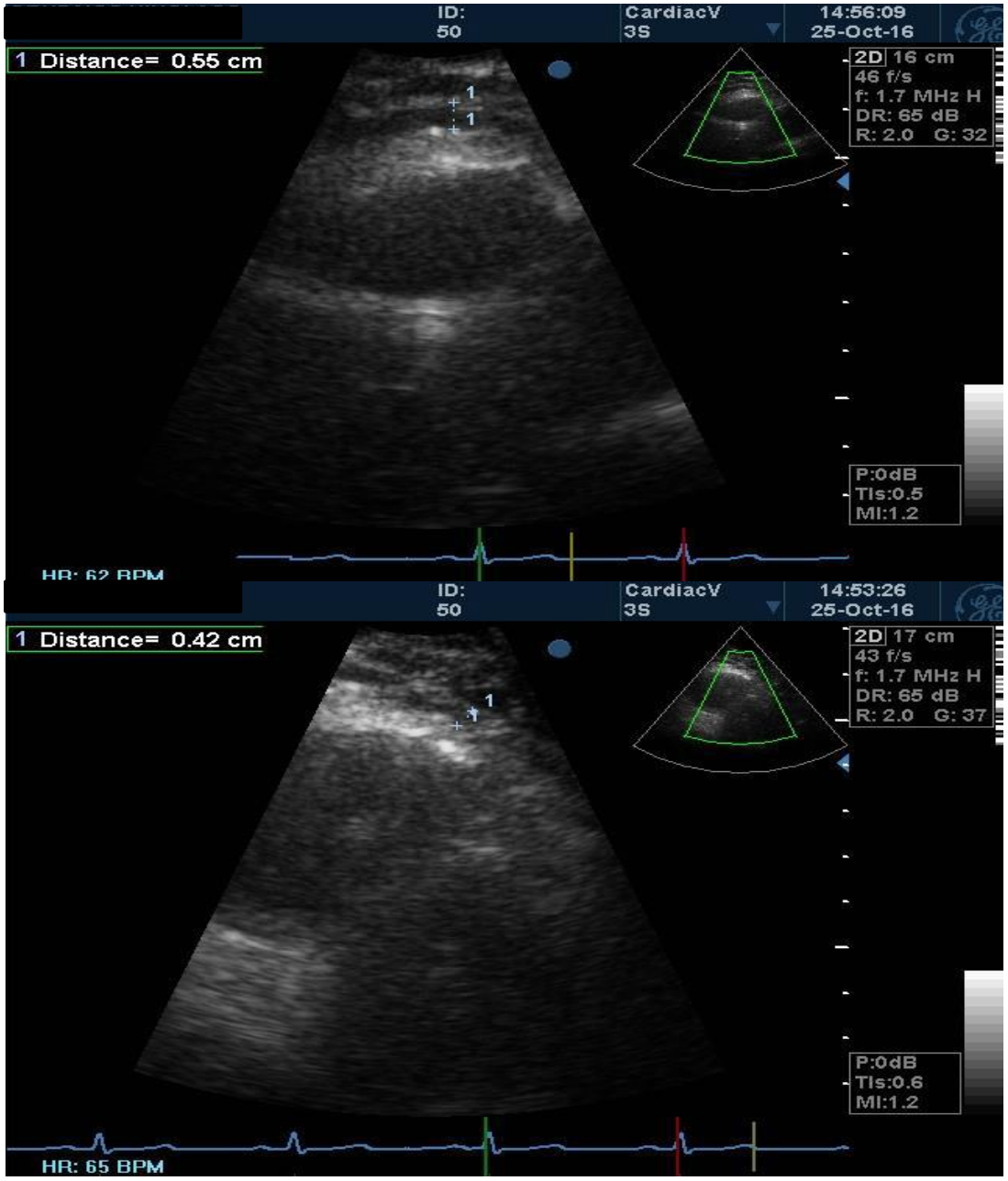
Willens HJ, Atherosclerosis. 2010

- Τελοδιαστολή ή Τελοσυστολή
- Διαφορετικά όρια για την πρόβλεψη διαφόρων καταστάσεων
- **Iacobellis et al: 7mm άνδρες, 6.5mm γυναίκες (τελοσυστολή)**
- **Bertaso et al: >5mm (τελοδιαστολή)**

ΑΝΔΡΑΣ
50 ΕΤΩΝ

Ht: 190 cm
W: 170 kg
BMI 47Kg/m²

EFT(PLAX):5,5mm
EFT(PSAX):4,2mm



ΣΥΣΧΕΤΙΣΗ ΜΕ ΜΕΤΑΒΟΛΙΚΟ ΣΥΝΔΡΟΜΟ

– Associations between Epicardial Fat (EF) and Metabolic Syndrome

Author	Patient source	Characteristics	N	MS Prevalence	EF measurement	Mean values of EF	Association or Mean
Iacobellis et al.[31], 2003	Referred to echocardiography	BMI between 22 and 47 kg/m^2	72	Not informed	EF in systole	M: 7.6 ± 3.6 mm F: 6.9 ± 3.7 mm	Men with MS: 9.9 ± 2.6 mm Without MS: 4.1 ± 1.7 mm Women with MS: 7.6 ± 3.0 mm Without MS: 3.1 ±1.9 mm (p < 0.01)
Ahn et al.[61], 2008	Referred to Cath	Suspected CAD	527	23%	EF Median in diastole (CO = 3.0 mm)	3,2 ± 2,5 mm	With MS: 3.5 mm Without MS: 1.6 mm r = 0.32; (p < 0.001)
Okyay et al.[62], 2008	Referred to echocardiography	Patients with MS and controls	246	Case:control 1:1	EF in diastole	Not informed	With MS: 5.1 ±1.7 mm Without MS: 3.4 ± 1.6 mm (p<0.001)
Iacobellis et al.[34], 2008	Referred to echocardiography	Mean BMI = 32 kg/m^2	246	58%	Median EF in systole	M: 7.0 mm F: 6.5 mm	With MS M: 9.5 mm F: 7.5 mm ROC Area = 0.79
Lai et al.[75], 2011	Referred for coronary artery disease screening	Asymptomatic	359	23%	EF thickness (CO = 8.0 mm)	7,6±1,4 mm	OR = 3.65 (95%CI: 2.62-5.09)* ROC Area = 0.80
Momesso et al.[76], 2011	Outpatients with Type 1 DM	Women with Type 1 DM (mean age 37 years)	45	45%	EF in diastole	Not informed	With MS: 6.1 ± 0.4 mm Without MS: 4.9 ± 0.3 mm (p = 0.006)
Pierdomenico et al.[77], 2011	Referred to echocardiography	Hypertensive Caucasians	174	12%	EF in diastole	Not informed	With MS 4.0 ± 0.8 mm Without MS 2.5 ± 0.9 mm (p < 0.01)*

Bertaso AG, ArqBras Cardiol 2013

ΣΥΣΧΕΤΙΣΗ ΜΕ ΣΤΕΦΑΝΙΑΙΑ ΝΟΣΟ

– Associations between Epicardial Fat (EF) and Coronary Artery Disease (CAD)

Author	Patients source	Characteristics	n	Exposure (CO – when reported)	Outcome (CO – when reported)	Association and/or Distribution
Chaowalit et al.[69], 2006	Referred to echocardiography and Cath	Not informed	139	CO 1 - EF: 0-1mm CO 2 - EF > 1mm	CAD (stenosis ≥50%)	EF Medians: 0-1mm:1.5 > 1mm:1
Jeong et al.[36], 2007	Referred to Cath	Patients with diagnosis of AMI or angina	203	EF ≥ 7.6mm in diastole	CAD (stenosis ≥ 50%)	OR: 10.53 (95%CI: 2.2 – 51.2)*
Ahn et al.[61], 2008	Referred to Cath	Suspected angina	527	EF ≥ 3mm in diastole	CAD (stenosis ≥50%)	OR: 3.36 (95%CI: 2.2 – 5.2)
Eroglu et al.[63], 2009	Referred to Cath	Suspected angina	150	EF thickness ≥ 5.3 mm in diastole	CAD (stenosis ≥20%)	OR: 4.57 (95%CI: 2.7 – 7.8)*
Yun et al.[7], 2009	Referred to Cath	Chest pain assessment	153	EF thickness ≥ 2.6 mm in diastole	CAD (stenosis ≥50%)	OR: 11.53 (95%CI: 3.61 - 36.8)*
Nelson et al., 2011[37]	Referred to cardiovascular risk assessment	Low pretest probability of CAD	356	EF thickness ≥ 5 mm in diastole	Coronary calcium score	r: 0.01 (p = 0.873)
Mustelier et al.[78], 2011	Referred to Cath	Suspected angina	250	EF thickness ≥ 5.2 mm in systole	CAD (stenosis ≥50%)	OR: 1.27 (95%CI: 1.1 - 1.5)*
Shemirani and Khoshav, 2012[79]	Referred to Cath	Unstable angina or stable angina	315	EF thickness	Presence of CAD vs. Absence of CAD	5.4 ± 1.9 mm vs. 4.4 ± 1.8 mm* (p = 0.001)

Bertaso AG, ArqBras Cardiol 2013

Clinical Investigation

Epicardial Adipose Tissue Thickness

Is an Independent Predictor of Critical and Complex Coronary Artery Disease by Gensini and SYNTAX Scores

Aycan Fahri Erkan, MD, PhD
Asli Tanindi, MD
Sinan Altan Kocaman, MD
Murat Ugurlu, MD
Hasan Fehmi Tore, MD

Epicardial adipose tissue thickness is associated with the severity and extent of atherosclerotic coronary artery disease. We prospectively investigated whether epicardial adipose tissue thickness is related to coronary artery disease extent and complexity as denoted by Gensini and SYNTAX scores, and whether the thickness predicts critical disease.

After performing coronary angiography in 183 patients who had angina or acute myocardial infarction, we divided them into 3 groups: normal coronary arteries, noncritical disease (≥1 coronary lesion with <70% stenosis), and critical disease (≥1 coronary lesion with ≥70% stenosis). We used transthoracic echocardiography to measure epicardial adipose tissue thickness, then calculated Gensini and SYNTAX scores by reviewing the angiograms.

Mean thicknesses were 4.3 ± 0.9, 5.2 ± 1.5, and 7.5 ± 1.9 mm in patients with normal coronary arteries, noncritical disease, and critical disease, respectively (P <0.001). At progressive thicknesses (<5, 5–7, and >7 mm), mean Gensini scores were 4.1 ± 5.5, 19.8 ± 15.6, and 64.9 ± 32.4, and mean SYNTAX scores were 4.7 ± 5.9, 16.6 ± 8.5, and 31.7 ± 8.7, respectively (both P <0.001). Thickness had strong and positive correlations with both scores (Gensini, r =0.82, P <0.001; and SYNTAX, r =0.825, P <0.001). The cutoff thickness value to predict critical disease was 5.75 mm (area under the curve, 0.875; 95% confidence interval, 0.825–0.926; P <0.001).

Epicardial adipose tissue thickness is independently related to coronary artery disease extent and complexity as denoted by Gensini and SYNTAX scores, and it predicts critical coronary artery disease. ***(Tex Heart Inst J 2016;43(1):29-37)***

- The cutoff thickness value to predict critical disease was **5.75 mm**
- **Parasternal long-axis view at end-systole**
- Epicardialadipose tissue thickness is independently related to coronary artery disease extent and complexity as denoted by Gensini and **Syntax** scores, and it predicts critical coronary artery disease

Heart Vessels (2016) 31:1758–1766
DOI 10.1007/s00380-016-0802-5

ORIGINAL ARTICLE

Measurement of epicardial fat thickness by transthoracic echocardiography for predicting high-risk coronary artery plaques

Motomi Tachibana[1] · Toru Miyoshi[1] · Kazuhiro Osawa[1] · Norihisa Toh[1] · Hiroki Oe[2] · Kazufumi Nakamura[1] · Takanori Naito[1] · Shuhei Sato[3] · Susumu Kanazawa[3] · Hiroshi Ito[1]

- Cutoff value of EAT thickness (**≥5.6 mm**)
- **Parasternal long-axis view at end-systole**
- This study demonstrates that thick EAT, as measured b echocardiography, is an independent factor associated with CAD and is informative for **predicting the presence of high-risk coronary plaques** in patients with suspected CAD

Europace (2017) **00**, 1–6
doi:10.1093/europace/euw398

CLINICAL RESEARCH

Is epicardial fat depot associated with atrial fibrillation? A systematic review and meta-analysis

Maddalena Gaeta[1†], Francesco Bandera[2†], Federico Tassinari[1], Capasso Lorenzo[1], Miriam Cargnelutti[1], Gabriele Pelissero[1], Alexis Elias Malavazos[3], Cristian Ricci[1,4*]

[1]Department of Public Health, Experimental and Forensic Medicine, Unit of Biostatistics and Clinical Epidemiology, Unit of Hygiene, University of Pavia, Via Strada Nuova 65, 27100 Pavia, Italy; [2]Department of Cardiology, IRCCS Policlinico San Donato, Piazza Edmondo Malan, 1, 20097 San Donato Milanese MI, Italy; [3]Diabetology and Metabolic Diseases Unit, IRCCS Policlinico San Donato, Piazza Edmondo Malan, 1, 20097 San Donato Milanese MI, Italy; and [4]Centre of Excellence for Nutrition (CEN), North-West University, Hoffman street 11, 2520 Potchefstroom, South Africa

Received 26 August 2016; editorial decision 9 November 2016; accepted 13 November 2016

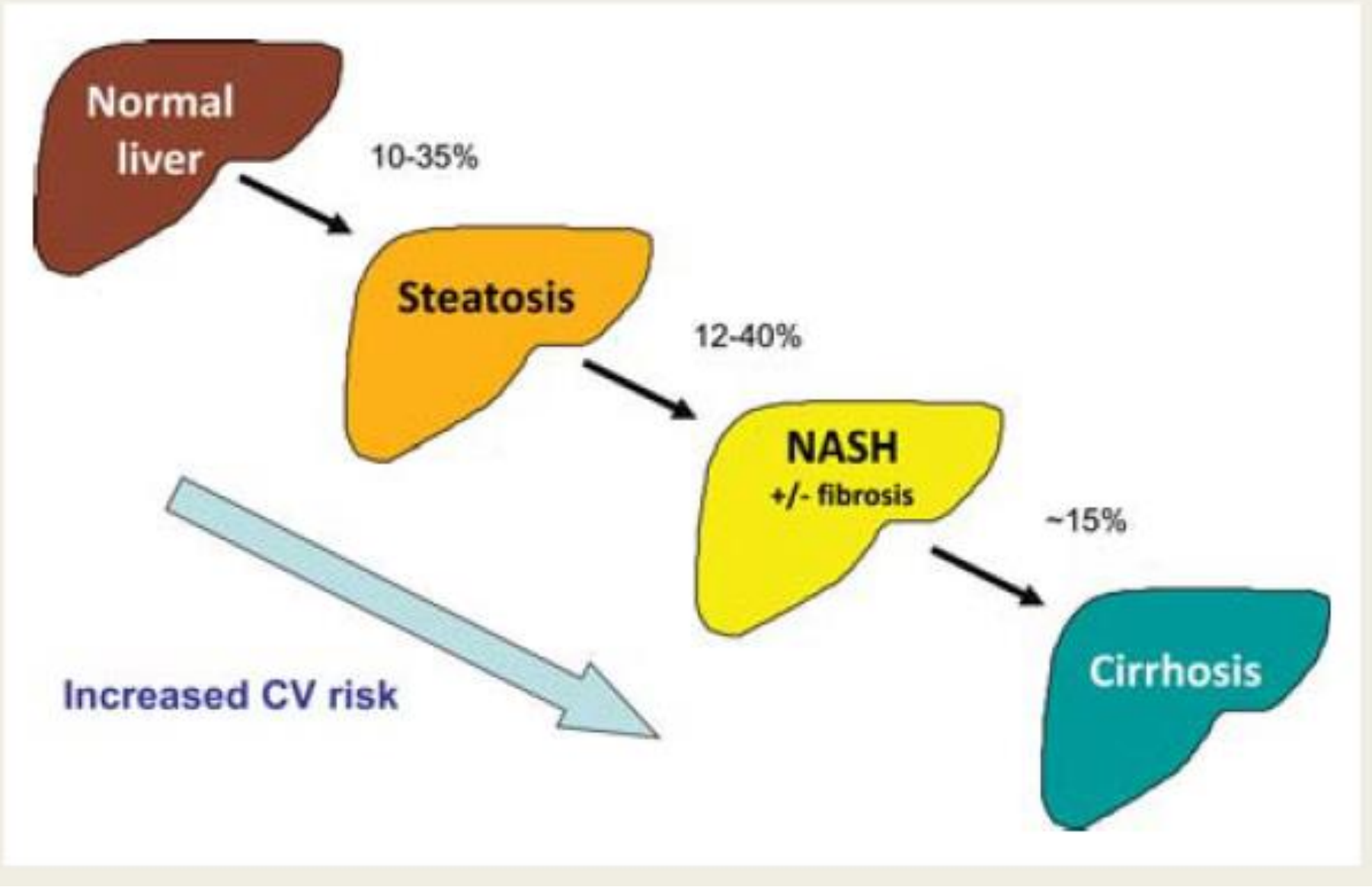
- **Association between the presence of AF and an increased EF amount**
- EF difference between healthy subjects and all AF subjects may range between 20–40 mL
- When looking at paroxysmal AF may range between 10–20 mL
- EF difference between healthy subjects and subjects having persistent AF is supposed to range between 25-70 mL

ΛΙΠΩΔΕΣ ΗΠΑΡ

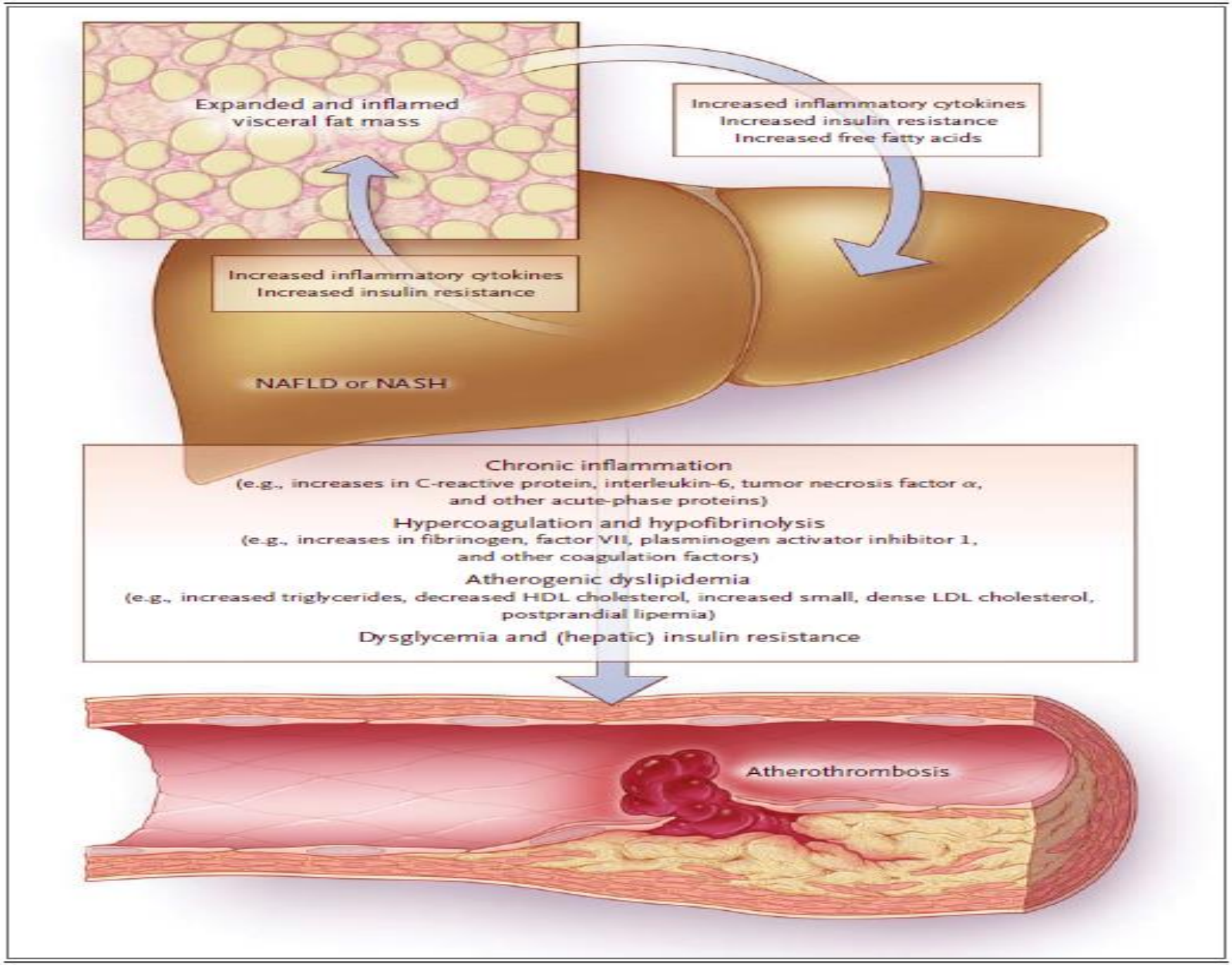
- Non-alcoholic fatty liver disease (NAFLD) is now the commonest cause of abnormal liver function tests in the UK (1/3 of the population)
- 30% of the general population have steatosis
- Obesity, insulin resistance, metabolic syndrome
- 95% of obese persons and 75% of diabetics
- Prevalence of NAFLD in non-obese patients ~ 7%
- 90 % simple steatosis (benign prognosis) → 10-30% non-alcoholic steatohepatitis (NASH) → 25-40% advanced fibrosis → 20-30% cirrhosis

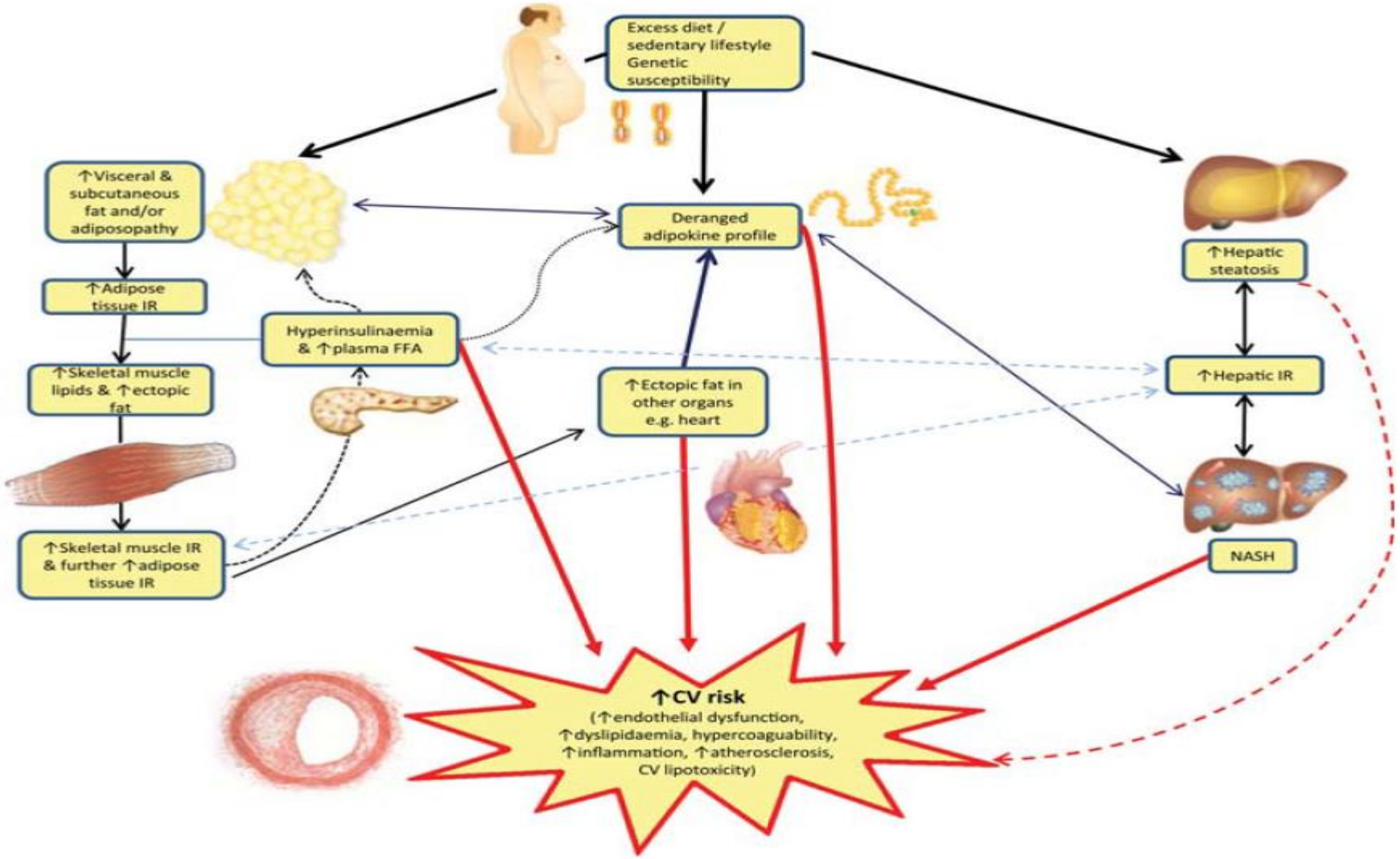
Dyson JK, et al. Frontline Gastroenterology 2013;0:1–8

V de Lédinghen et al. Journal of Gastroenterology and Hepatology 31 (2016) 848–855



L.S. Bhatia et al. European Heart Journal (2012) 33, 1190–1200


Expanded and inflamed visceral fat mass
Increased inflammatory cytokines
Increased insulin resistance
Increased free fatty acids
Increased inflammatory cytokines
Increased insulin resistance
NAFLD or NASH
Chronic inflammation
(e.g., increases in C-reactive protein, interleukin-6, tumor necrosis factor α, and other acute-phase proteins)
Hypercoagulation and hypofibrinolysis
(e.g., increases in fibrinogen, factor VII, plasminogen activator inhibitor 1, and other coagulation factors)
Atherogenic dyslipidemia
(e.g., increased triglycerides, decreased HDL cholesterol, increased small, dense LDL cholesterol, postprandial lipemia)
Dysglycemia and (hepatic) insulin resistance
Atherothrombosis



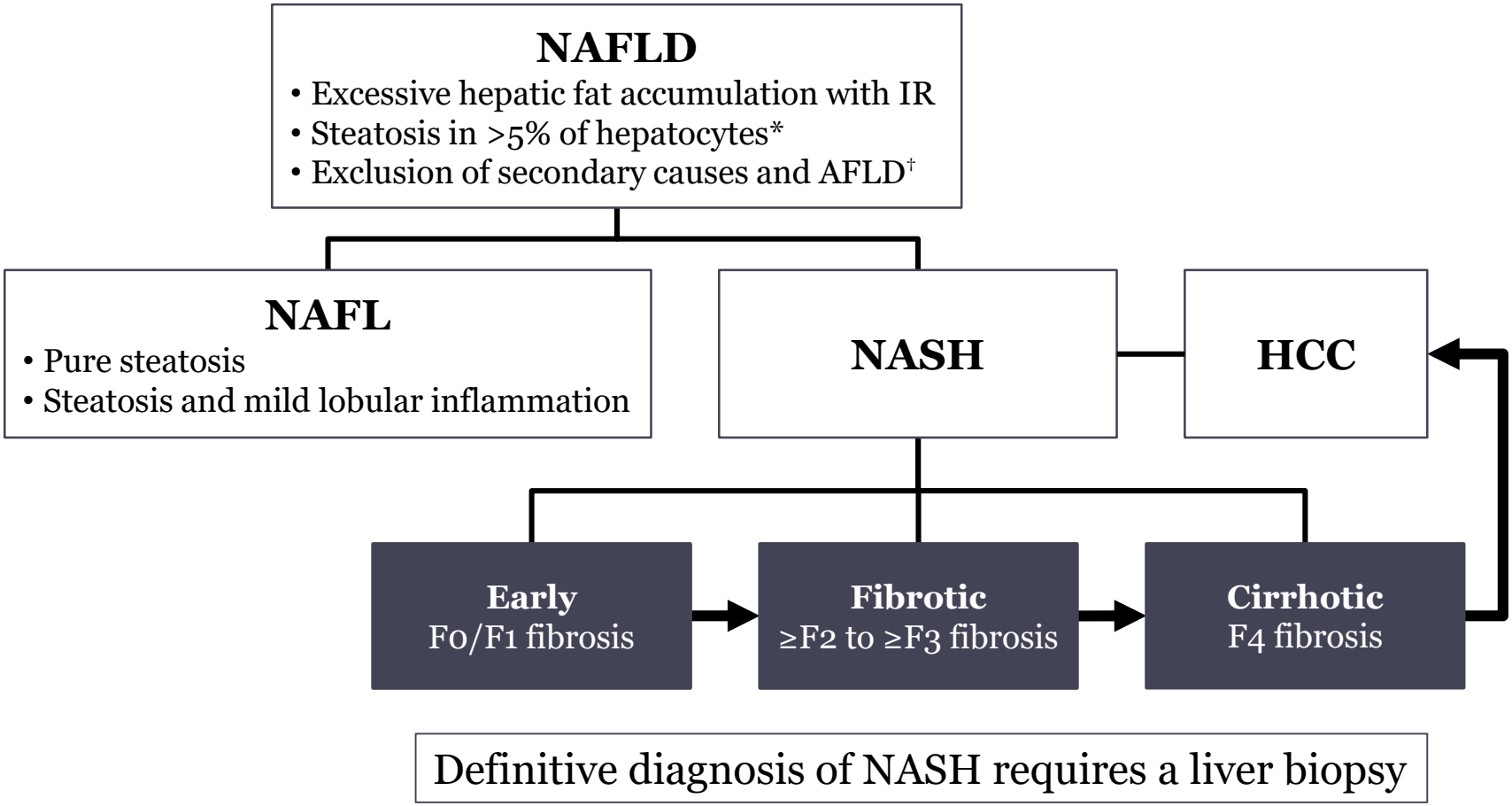
L.S. Bhatia et al. European Heart Journal (2012) 33, 1190–1200

Clinical Practice Guidelines

Non-alcoholic fatty liver disease

EASL™
The Home of Hepatology

Definitions of NAFLD, NAFL and NASH



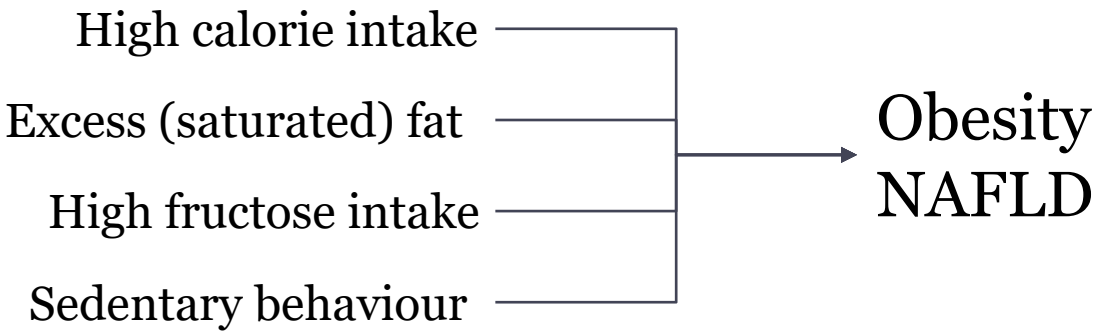
*According to histological analysis or proton density fat fraction or >5.6% by proton MRS or quantitative fat/water-selective MRI;

†Daily alcohol consumption of ≥30 g for men and ≥20 g for women

EASL–EASD–EASO CPG NAFLD. J Hepatol 2016;64:1388–402

Pathogenesis: **lifestyle** and genes

- A Western diet/lifestyle has been associated with weight gain and obesity, and NAFLD[1]

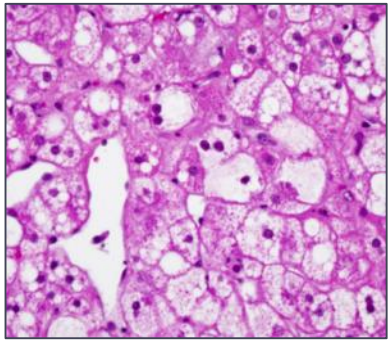


Recommendation	Grade of evidence	Grade of recommendation
Unhealthy lifestyles play a role in the development and progression of NAFLD. The assessment of dietary and physical activity habits is part of comprehensive NAFLD screening	A	1

1. Barrera F, George J. Clin Liver Dis 2014;18:91–112;
EASL–EASD–EASO CPG NAFLD. J Hepatol 2016;64:1388–402

Liver biopsy

- Liver biopsy is essential for the diagnosis of NASH
  - Clinical, biochemical or imaging measures cannot distinguish NASH from steatosis
- NAFL encompasses
  - Steatosis alone plus **ONE** of lobular or portal inflammation **OR** ballooning
- NASH requires
  - Steatosis **AND**
  - Lobular or portal inflammation **AND**
  - Ballooning
- NAS scoring indicates disease severity*



Recommendations	Grade of evidence	Grade of recommendation
NASH has to be diagnosed by a liver biopsy showing **steatosis, hepatocyte ballooning and lobular inflammation**	A	1

*Should not be used for initial diagnosis

EASL–EASD–EASO CPG NAFLD. J Hepatol 2016;64:1388–402

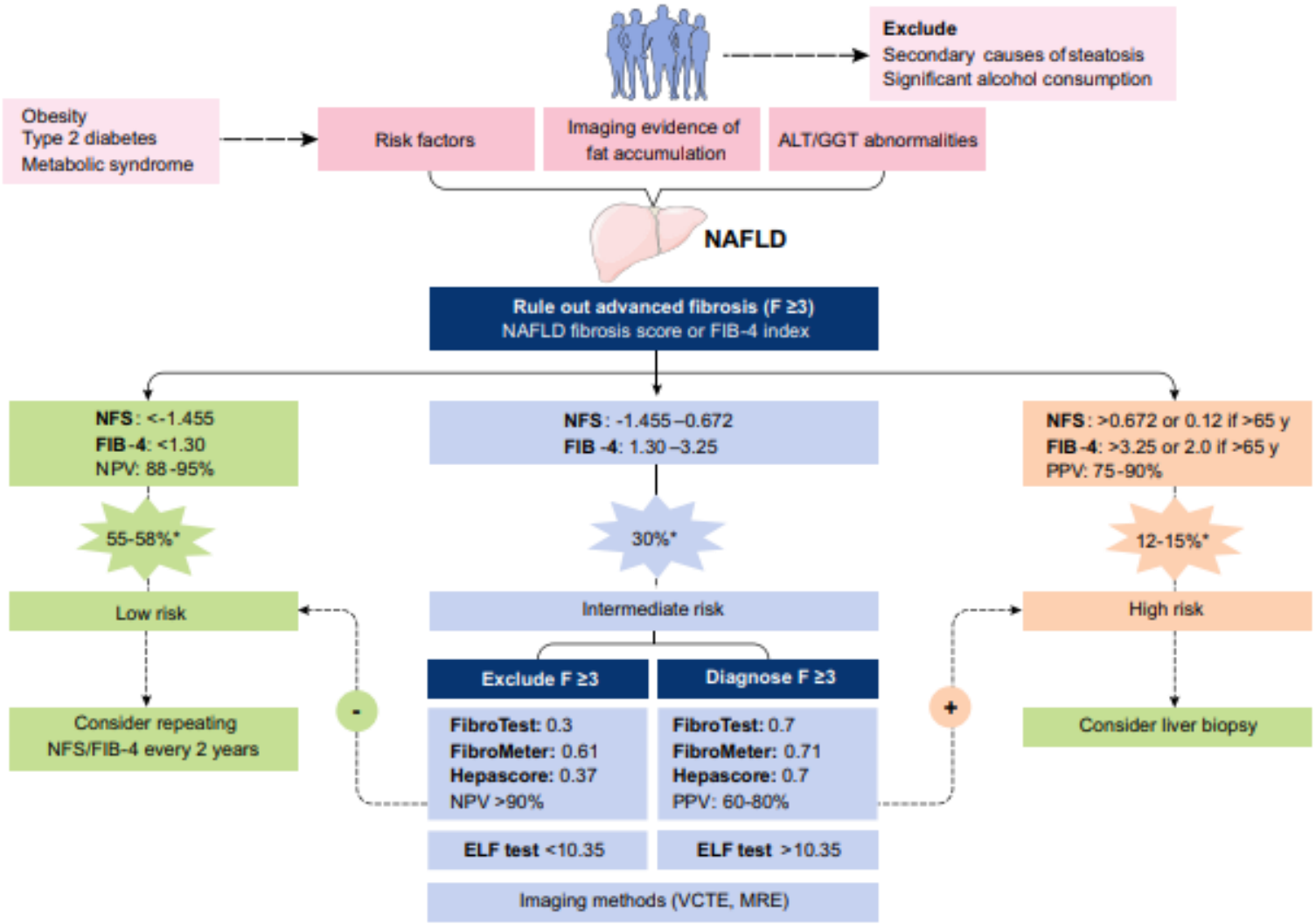
Role of non-invasive assessments

- Non-invasive markers should aim to:
  - Identify the risk of NAFLD among individuals with increased metabolic risk in primary care
  - Identify those with a worse prognosis in secondary and tertiary care
    - E.g. severe NASH
  - Monitor disease progression
  - Predict response to therapeutic interventions

Achieving these aims could reduce the need for liver biopsy

EASL–EASD–EASO CPG NAFLD. J Hepatol 2016;64:1388–402

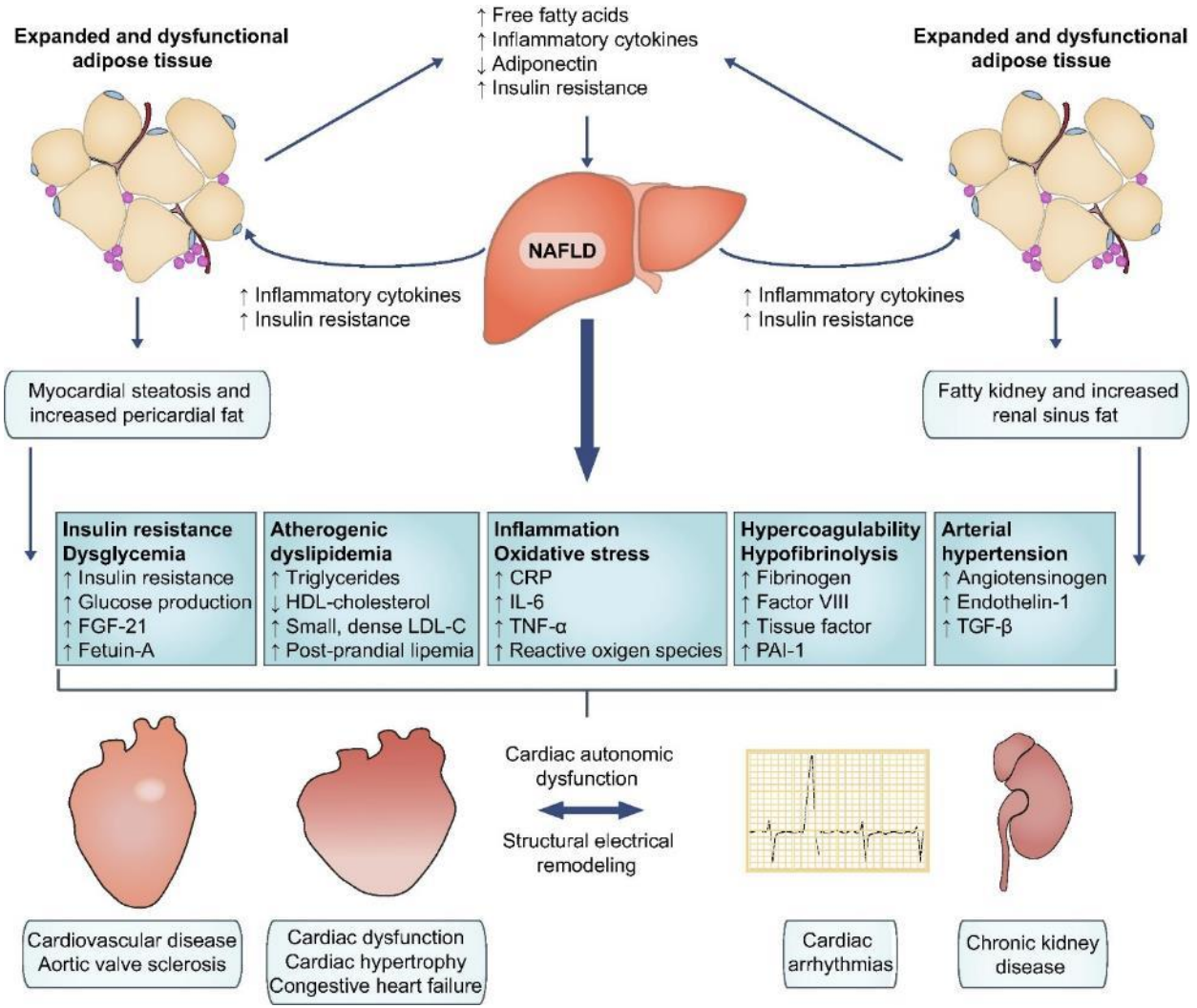
Potential algorithm for non-invasive assessment: prediction rules and blood-based biomarkers



*Estimated prevalence for low-, intermediate- and high-risk groups

Vilar-Gomez E, Chalasani N. J Hepatol 2018;68:305–15

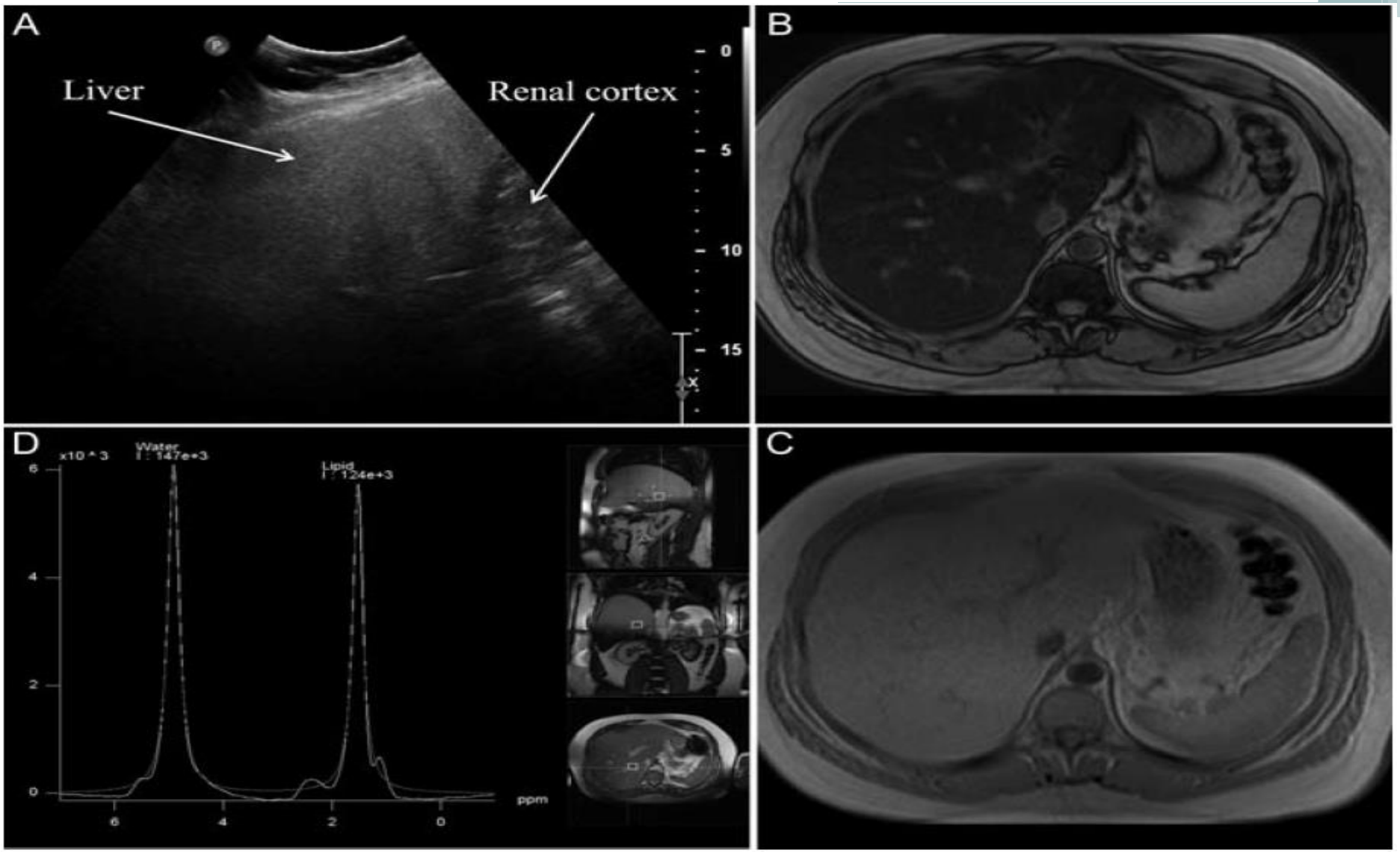
Putative connection between NAFLD, CVD and CKD



Byrne CD, Targher G. J Hepatol 2015;62:S47–64

ΑΠΕΙΚΟΝΙΣΗ ΣΤΕΑΤΩΣΗΣ

- Echo: first-line investigation (very effective where >33% of hepatocytes are steatotic)
- **The finding of a normal liver on echo does not rule out mild fatty infiltration of the liver**
- CT or MRI (not routinely used in the assessment of steatosis)
- MRI and proton magnetic resonance spectroscopy (MRI/1H-MRS) are the most accurate non-invasive measures of steatosis



L.S. Bhatia et al. European Heart Journal (2012) 33, 1190–1200

ΑΠΕΙΚΟΝΙΣΗ ΣΤΕΑΤΩΣΗΣ

Ultrasound Grading

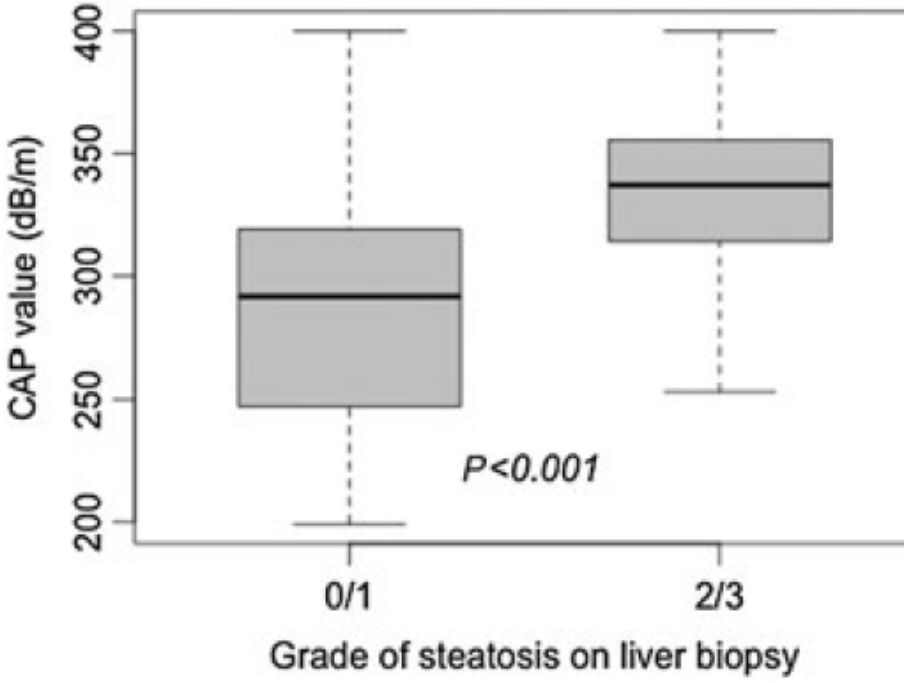
- **grade I**: diffusely increased hepatic echogenicity but periportal and diaphragmatic echogenicity is still appreciable
- **grade II**: diffusely increased hepatic echogenicity obscuring periportal echogenicity but diaphragmatic echogenicity is still appreciable
- **grade III**: diffusely increased hepatic echogenicity obscuring periportal as well as diaphragmatic echogenicity

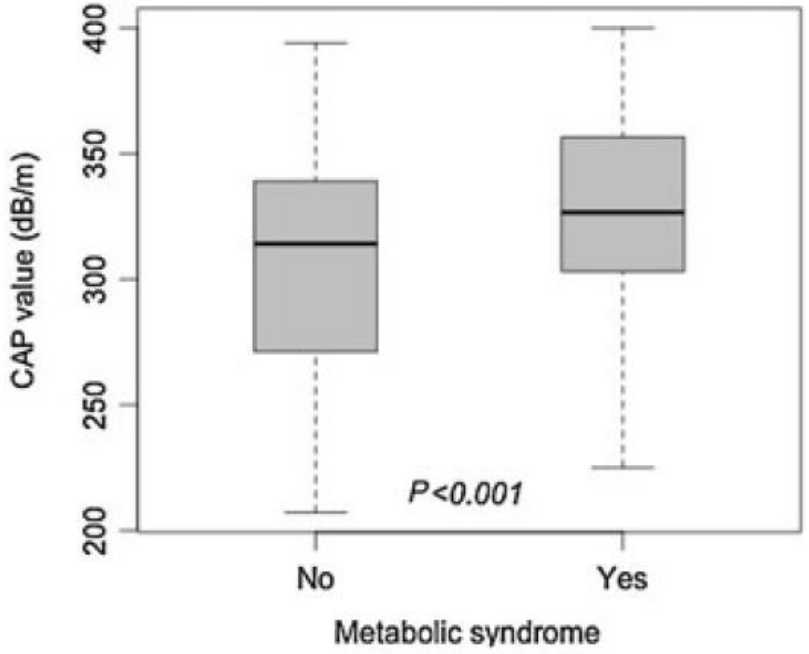
ΑΠΕΙΚΟΝΙΣΗ ΣΤΕΑΤΩΣΗΣ

Controlled Attenuation Parameter (CAP)

- Ultrasound-based technique to measure steatosis simultaneously with assessment of liver stiffness using transient elastography

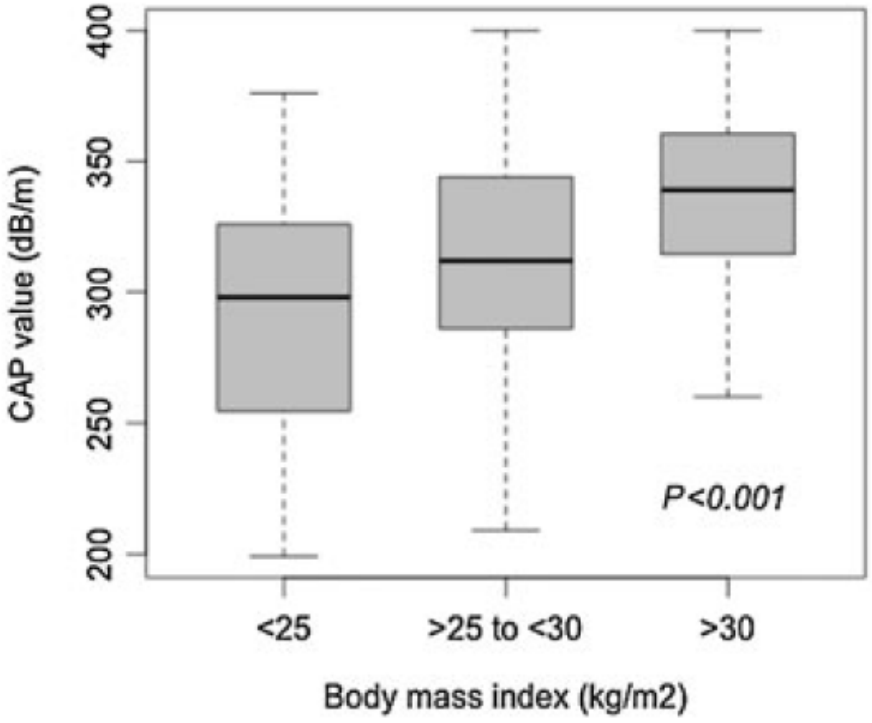
V de Lédinghen et al. Journal of Gastroenterology and Hepatology 31 (2016) 848–855 851





ΑΠΕΙΚΟΝΙΣΗ ΣΤΕΑΤΩΣΗΣ

Controlled Attenuation Parameter (CAP)



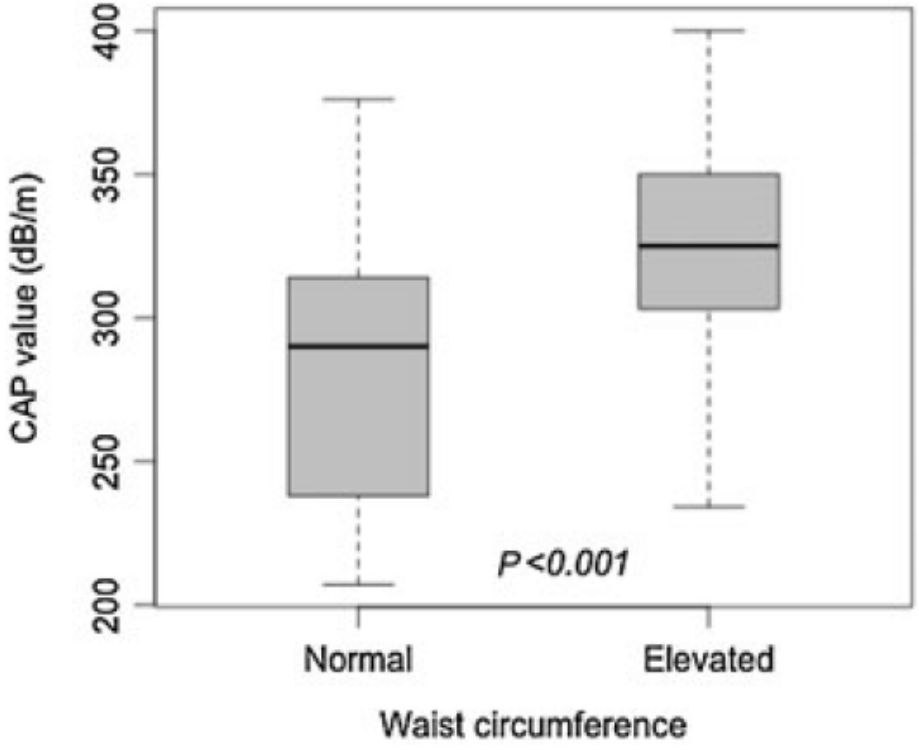


Table 4 Simple non-invasive tests for fibrosis

Score	Indices	Calculation	Interpretation
BARD score	BMI AST/ALT ratio T2DM	Weighted sum: 1. BMI ≥28=1 point 2. AAR ≥0.8=2 points 3. T2DM=1 point	Validated in 827 patients with biopsy proven NAFLD fibrosis[47] Score ≥2: Se 0.91, Sp 0.66, NPV 0.96 AUROC 0.81 for stage 3–4 fibrosis
NAFLD fibrosis score	Age Hyperglycaemia BMI Platelet count Albumin AST/ALT ratio	−1.675+0.037×age (years)+0.094×BMI (kg/m^2) +1.13×IFG or diabetes (yes=1, no=0) +0.99×AST/ALT ratio—0.013×platelet (×109/L) —0.66×albumin (g/dL)	Validated in 733 patients with NAFLD[48] AUROC 0.88 for stage 3–4 fibrosis
FIB-4 score	Age AST ALT	Age×AST (IU/L)/platelet count (×109/L)×$\sqrt{}$ALT (IU/L)	Validated in 541 patients with biopsy-proven NAFLD AUROC 0.80 for stage 3–4 fibrosis[49]

AAR, AST/ALT ratio; AUROC, area under receiver operating characteristic; BMI, body mass index; IFG, impaired fasting glucose; NAFLD, non-alcoholic fatty liver disease; NPV, negative predictive value; Se, sensitivity; Sp, specificity; T2DM, type 2 diabetes mellitus.

NAFLD liver fat score = -2.89 + 1.18 * metabolic syndrome (*yes* = 1/ *no* = 0) + 0.45 * type 2 diabetes (*yes* = 2 / *no* = 0) + 0.15 * fS-insulin (*mU/L*) + 0.04 * fS-AST (*U/L*) – 0.94 * AST/ALT

Figure 1. The NAFLD liver fat score.

Liver fat (%) = 10^(-0.805 + 0.282 * metabolic syndrome (*yes* = 1 / *no* = 0) + 0.708 * type 2 diabetes (*yes* = 2 / *no* = 0) + 0.525 * *LOG* (fs-insulin *[mU/L]*) + 0.521 * *LOG* (fs-AST *[U/L]*) – 0.454 * *LOG* (AST/ALT))

Figure 2. The NAFLD liver fat equation.

Table 1 Risk factors for NAFLD

Age[2]	Higher risk with increasing age
Metabolic syndrome (table 2)	70–90% of patients have NAFLD Metabolic syndrome is an independent predictor of fibrosis
Gender[2]	Commoner in men Women are at higher risk of advanced fibrosis[67]
Certain ethnic groups[2]	High risk in Hispanics Lower risk in blacks
Dietary factors	High cholesterol and saturated fats[68] High fructose intake[69] Low carbohydrates[70] Caffeine may be protective[71]
Obstructive sleep apnoea[72]	Increased risk of hepatic fibrosis[73]
Genetic factors	Patatin-like phospholipase domain-containing 3 (PNPLA3) gene[74 75]

NAFLD, non-alcoholic fatty liver disease.

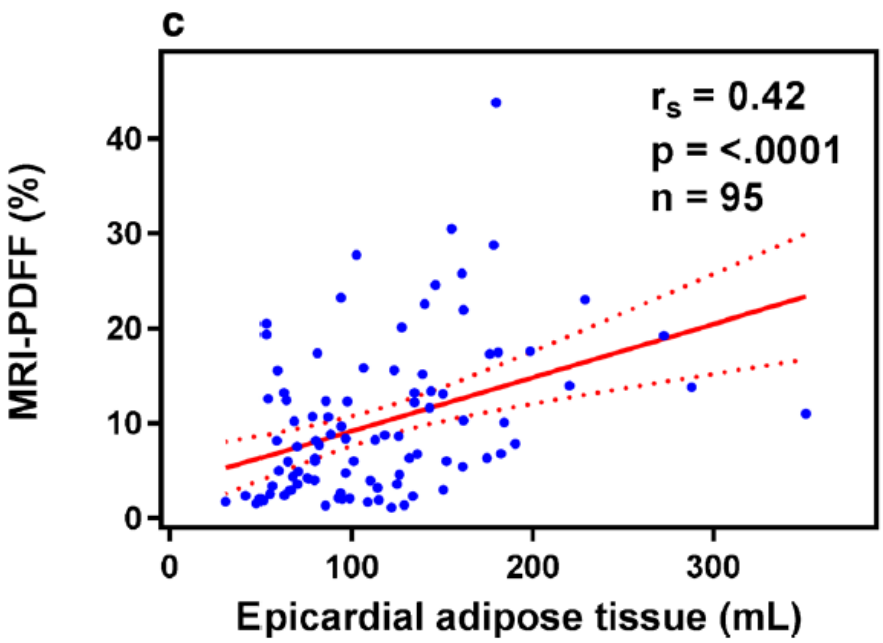
Table 3 NAFLD activity score (NAS)[34]

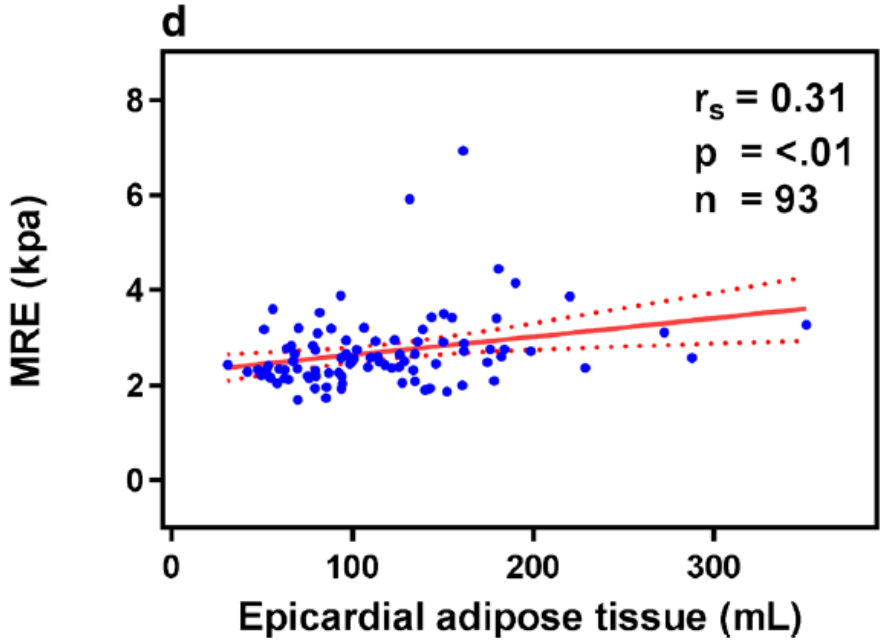
Histological feature	Score	Category definition
Steatosis	0	<5%
	1	5–33%
	2	34–66%
	3	>66%
Plus		
Hepatocyte ballooning	0	None
	1	Few
	2	Many
Plus		
Inflammation	0	None
	1	1–2 foci per ×20 field
	2	2–4 foci per ×20 field
	3	>4 foci per ×20 field
NAS total 0–8		
Fibrosis	0	No fibrosis
	1a	Zone 3 mild perisinusoidal fibrosis
	1b	Zone 3 moderate perisinusoidal fibrosis
	1c	Periportal/portal fibrosis only
	2	Zone 3+periportal/portal fibrosis
	3	Bridging fibrosis
	4	Cirrhosis
Fibrosis score 0–4		

A score of ≥5 with steatosis and hepatocyte ballooning is generally considered diagnostic of non-alcoholic steatohepatitis (NASH), but patients can still have NASH with lower NAS scores if steatosis and hepatocyte ballooning are present.
NAFLD, non-alcoholic fatty liver disease.

Increased severity of liver fat content and liver fibrosis in non-alcoholic fatty liver disease correlate with epicardial fat volume in type 2 diabetes: A prospective study

Sharon S. Brouha[1] · Phirum Nguyen[2,3] · Ricki Bettencourt[2,3,4] · Claude B. Sirlin[3] · Rohit Loomba[2,3,4]





European Society of Radiology 2017

Ectopic Fat Depots and Left Ventricular Function in Nondiabetic Men With Nonalcoholic Fatty Liver Disease

Marit Granér, MD, PhD; Kristofer Nyman, MD; Reijo Siren, MD; Markku O. Pentikäinen, MD, PhD; Jesper Lundbom, PhD; Antti Hakkarainen, BSc; Kirsi Lauerma, MD, PhD; Nina Lundbom, MD, PhD; Markku S. Nieminen, MD, PhD; Marja-Riitta Taskinen, MD, PhD

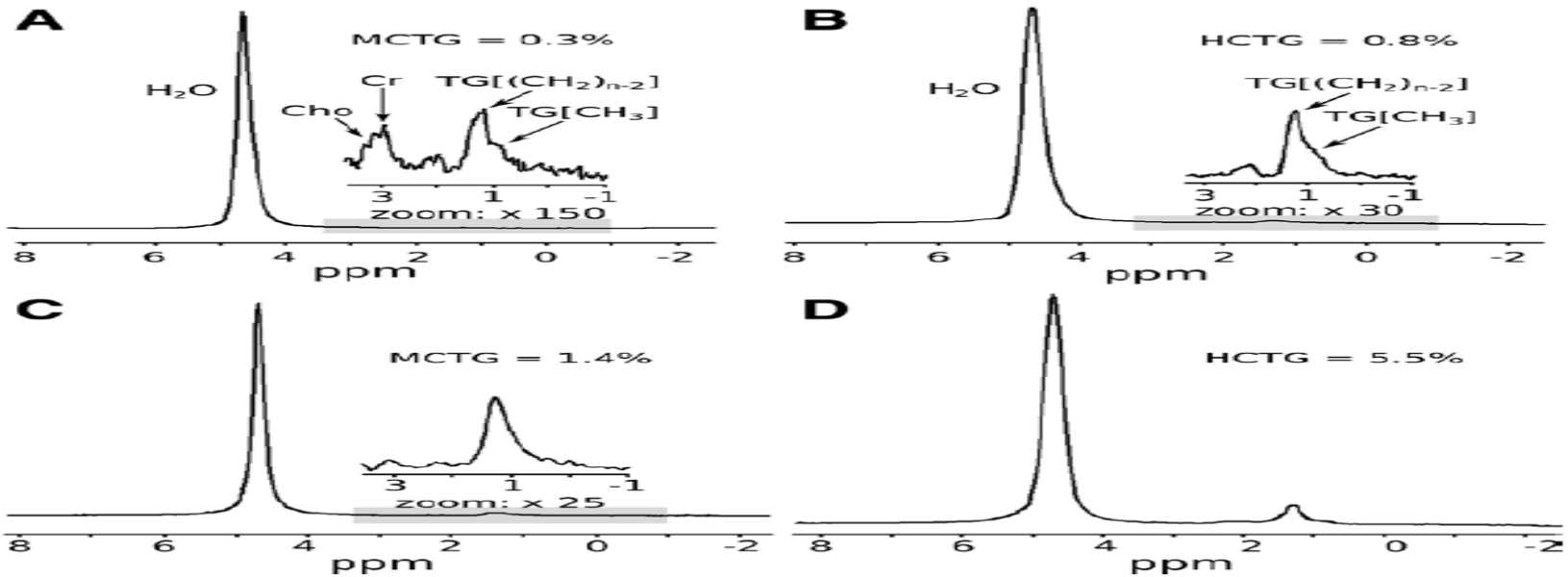
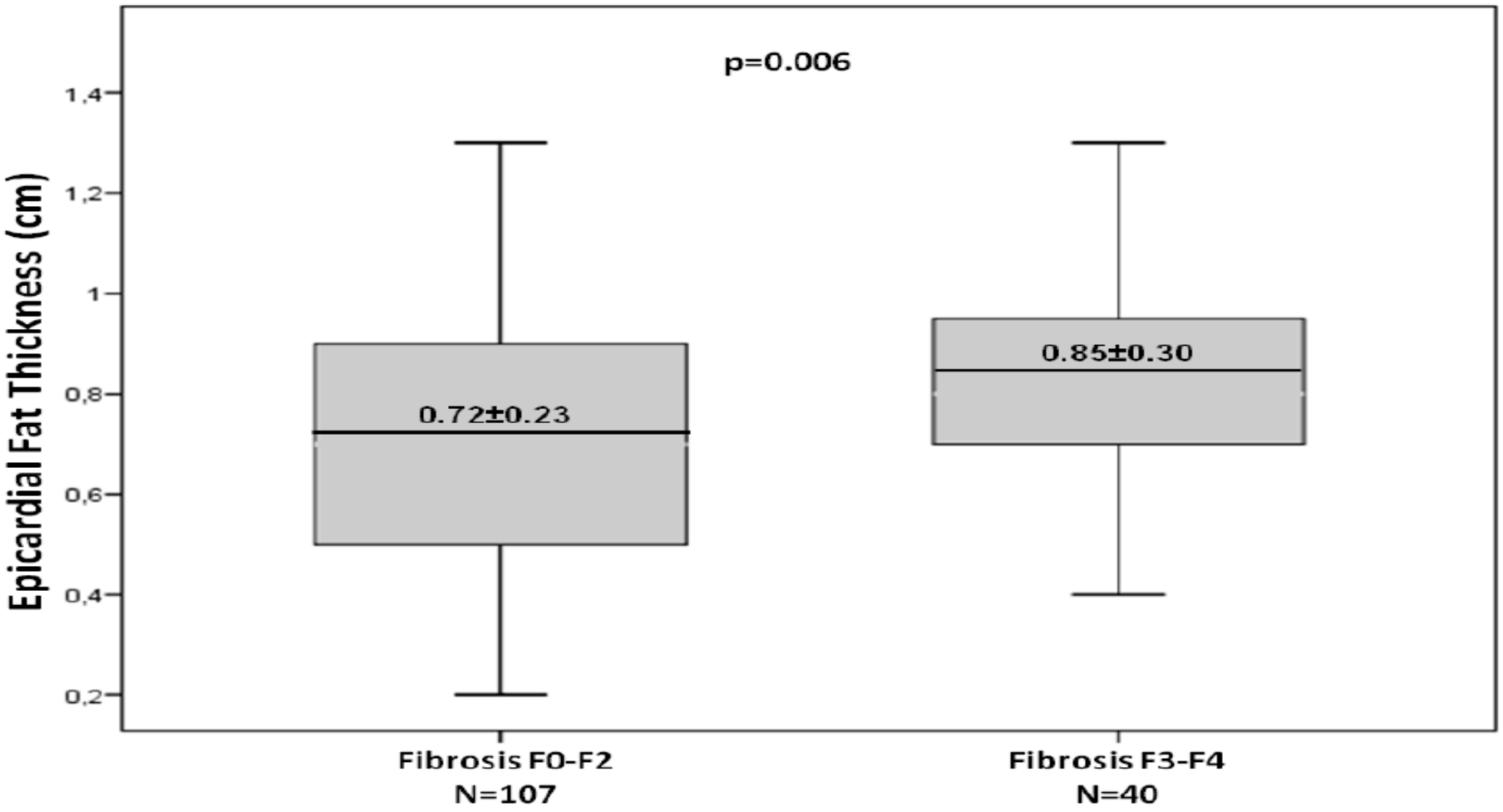


Figure 1. Cardiac and hepatic spectra from 2 subjects: one with low (**A**) myocardial and (**B**) hepatocellular triglyceride (HCTG) contents, and the other with high (**C**) myocardial (MCTG) and (**D**) HCTG contents. Shaded areas have been zoomed above by factors 150, 30, and 25 for spectra **A**, **B**, and **C**, respectively.

Granér et al. Circ Cardiovasc Imaging. 2015;8:e001979

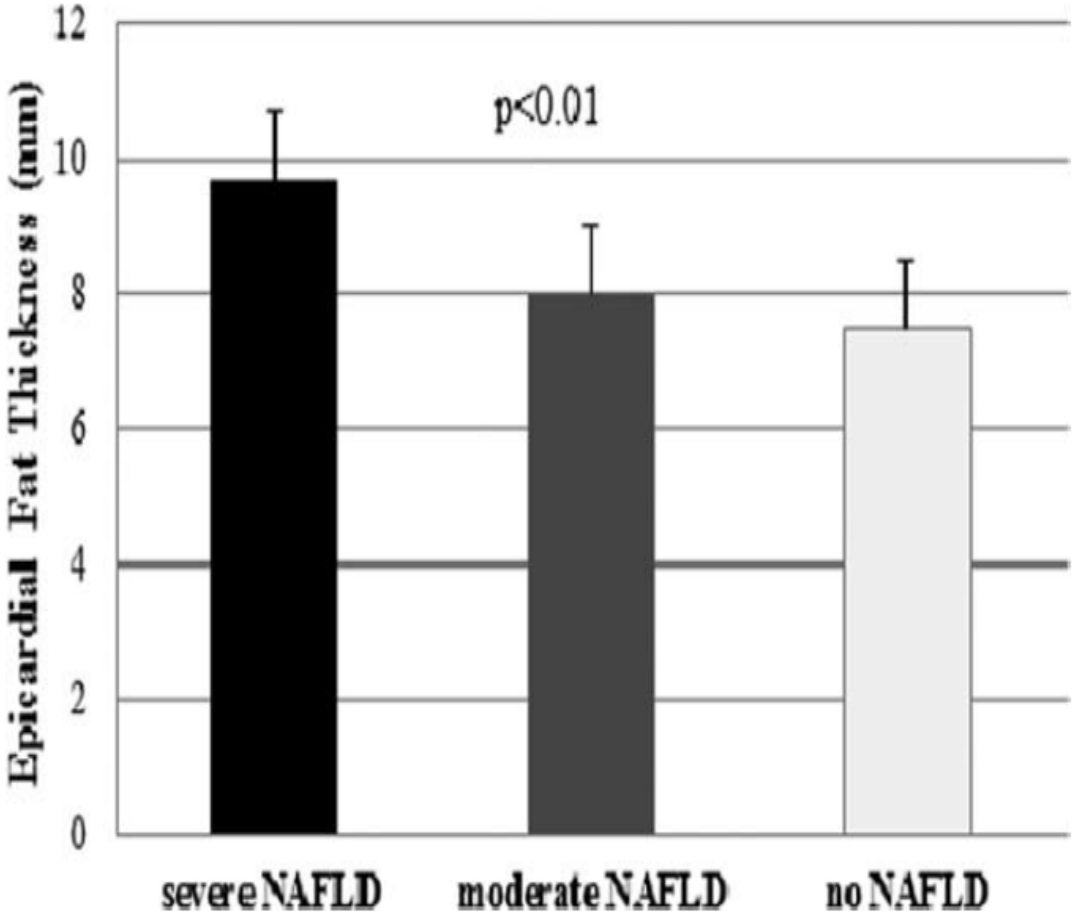


Epicardial fat thickness is an independent indicator of the severity of liver fibrosis

Salvatore Petta et al. Journal of Hepatology (2014)

Epicardial Fat Thickness and Nonalcoholic Fatty Liver Disease in Obese Subjects

Gianluca Iacobellis[1], Giorgio Barbarini[2], Claudio Letizia[3] and Giuseppe Barbaro[4]



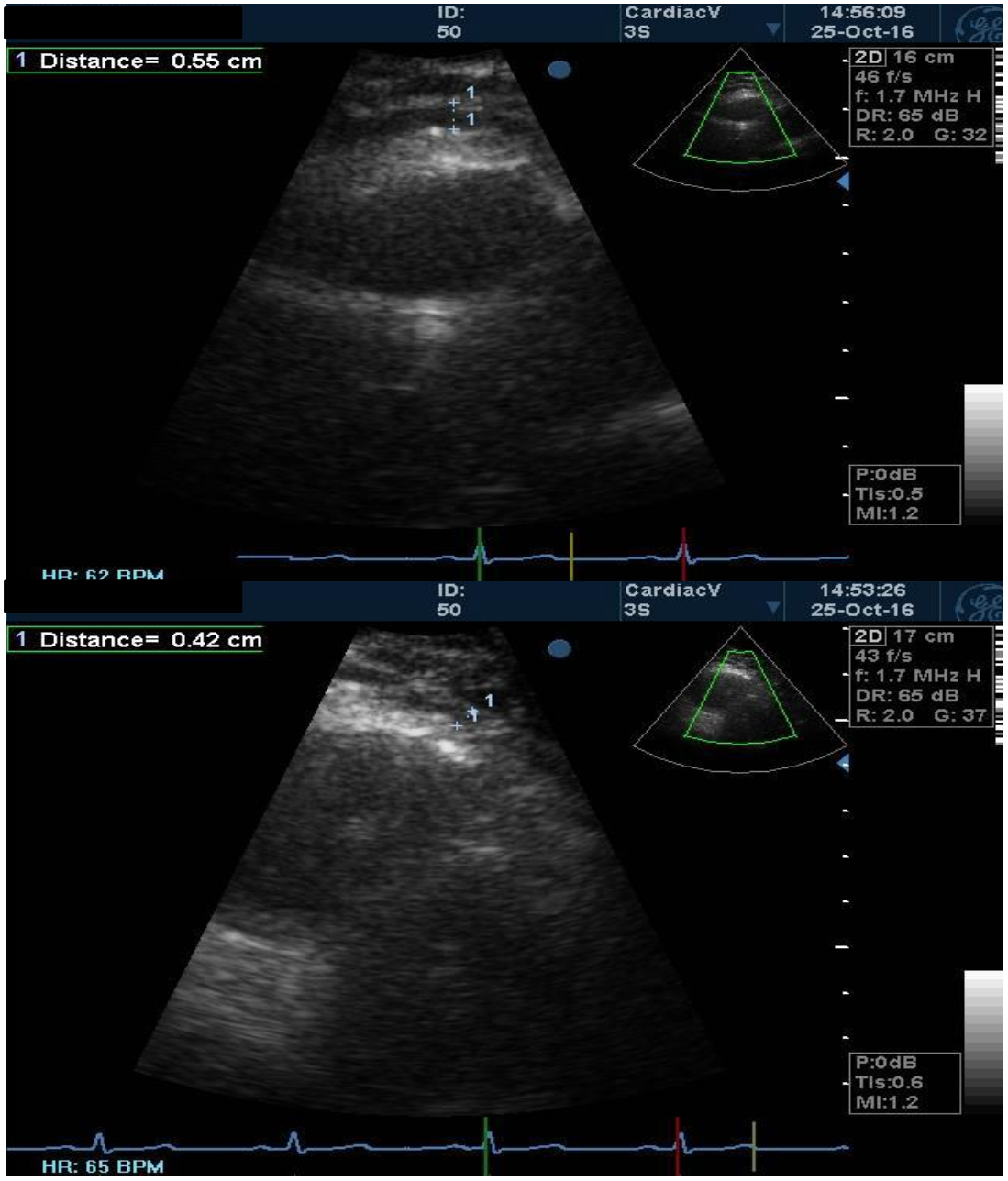
- Epicardial fat is a good predictor of liver steatosis in obese subjects
- Echocardiographic epicardial fat predicts ultrasound-measured fatty liver better than BMI or waist circumferences does
- Patients with severe fatty liver infiltration presented with the highest amount of cardiac fat accumulation

Obesity (2014) 22, 332–336

ΑΝΔΡΑΣ
50 ΕΤΩΝ

Ht: 190 cm
W: 170 kg
BMI 47Kg/m²

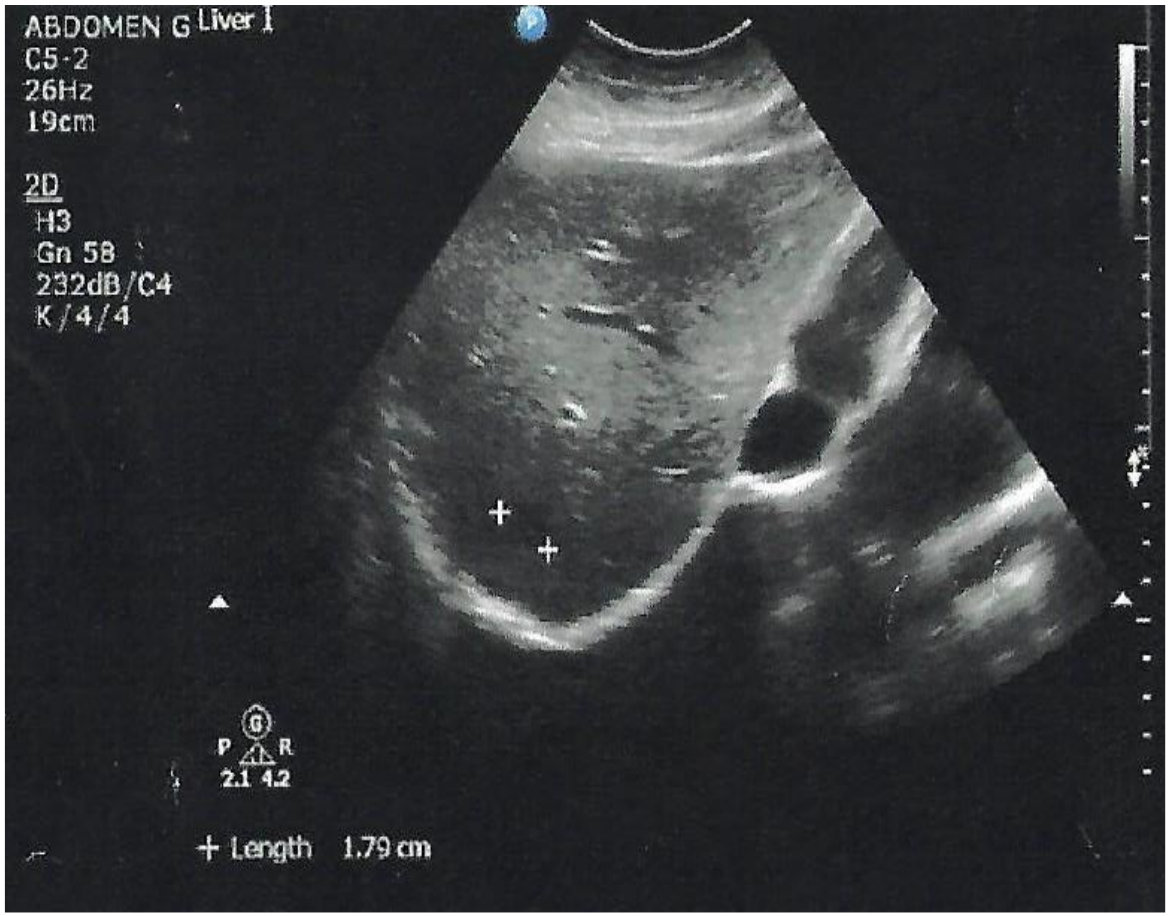
EFT(PLAX):5,5mm
EFT(PSAX):4,2mm



ΑΝΔΡΑΣ
50 ΕΤΩΝ

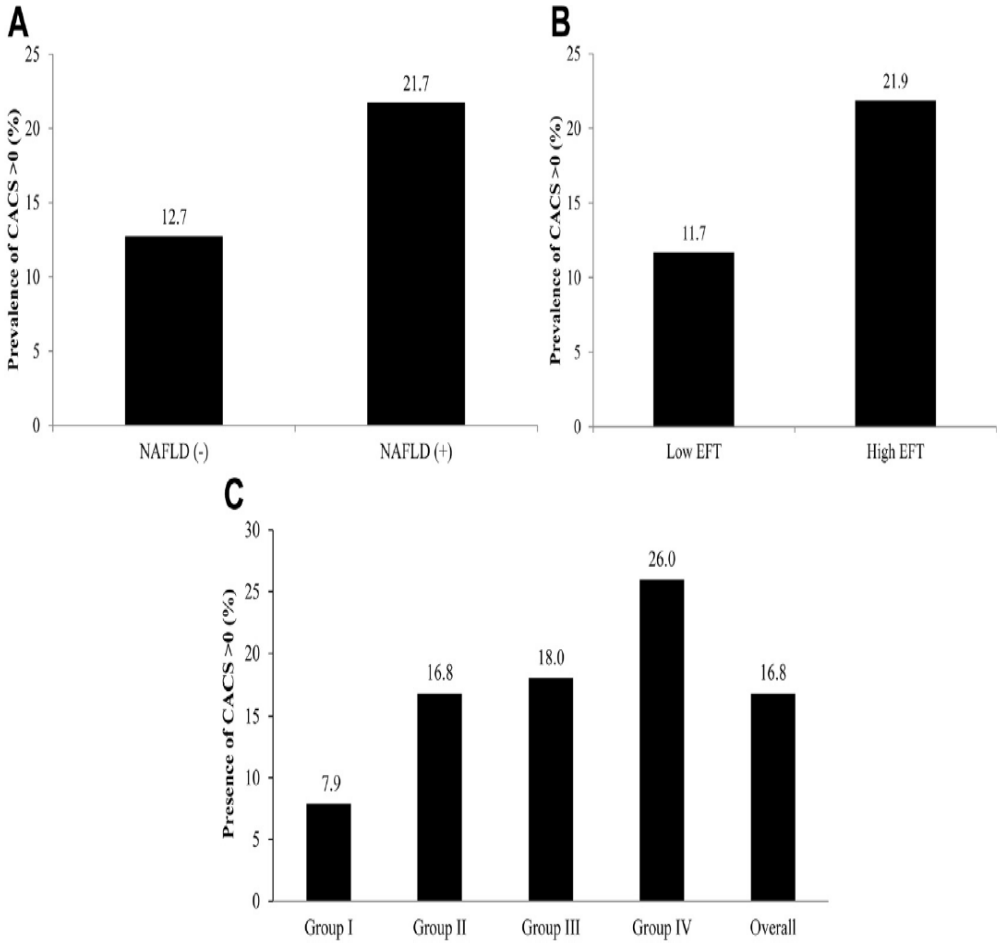
Ht: 190 cm
W: 170 kg
BMI 47Kg/m²

EFT(PLAX):5,5mm
EFT(PSAX):4,2mm



Relationship of epicardial fat thickness and nonalcoholic fatty liver disease to coronary artery calcification: From the CAESAR study

Byung Jin Kim, MD, PhD*,[1], Eun Sun Cheong, MD[1], Jung Gyu Kang, MD, Bum Soo Kim, MD, PhD, Jin Ho Kang, MD, PhD

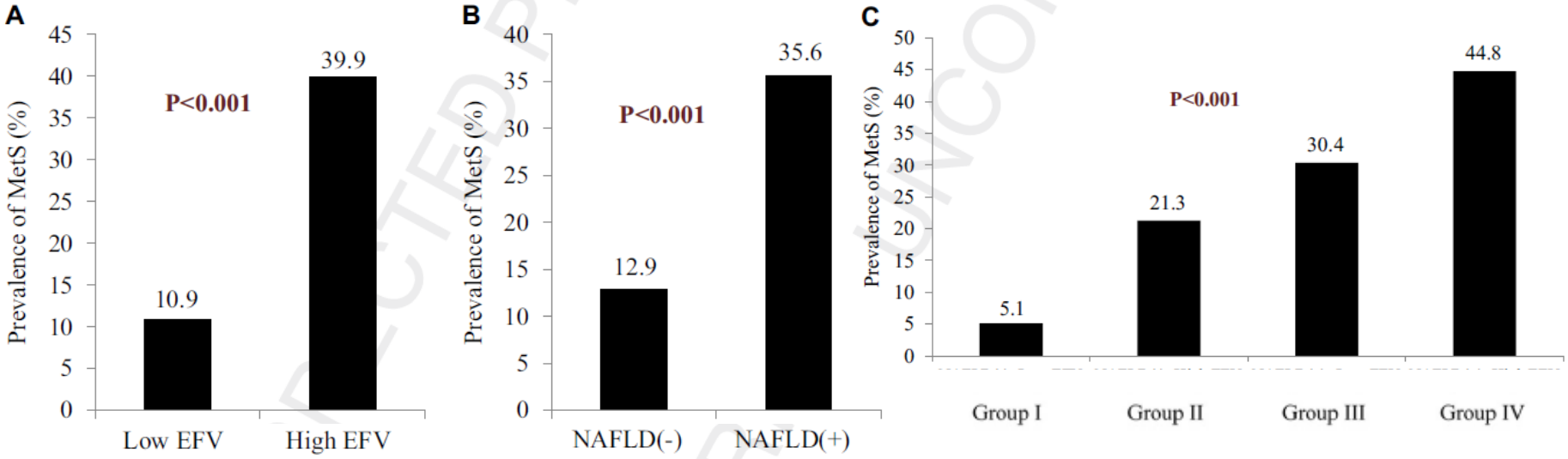


- Increased EFT and presence of NAFLD are associated with coronary artery calcification
- Increased EFT is more strongly related to CAC than NAFLD
- NAFLD has greater cardiometabolic risk than EFT

Journal of Clinical Lipidology (2016)

Association of epicardial fat volume and nonalcoholic fatty liver disease with metabolic syndrome: From the CAESAR study

Byung Jin Kim, MD, PhD*, Hak Soo Kim, MD, Jung Gyu Kang, MD, Bum Soo Kim, MD, PhD, Jin Ho Kang, MD, PhD



- Increased EFV and NAFLD are associated with the presence of MetS
- EFV was more influenced by MetS

Journal of Clinical Lipidology (2016)

ΘΕΡΑΠΕΙΑ

Μείωση πάχους επικαρδιακού λίπους:

1. Απώλεια βάρους

   Iacobellis G, Obesity 2008

2. Άσκηση

   Kim MK, Med Sci Sports Exerc 2010

3. Atorvastatin

   Park JH, J Cardiovasc Ultrasound 2010

4. Ezetimibe

   Takase H, Euro J Clin Invest 2012

5. Ipragliflozin

   T. Fukuda et al. Diabetes Ther (2017) 8:851–861

Treatment: pharmacotherapy

- Treatment should be indicated in:
  - Progressive NASH
  - Early-stage NASH with risk of fibrosis progression*
  - Active NASH with high necroinflammatory activity
- Treatment should reduce NASH-related mortality and progression to cirrhosis or HCC
  - Resolution of NASH-defining lesions accepted as surrogate endpoint
- Safety and tolerability are prerequisites
  - Extensive comorbidities associated with significant polypharmacy and increased likelihood of DDIs

Recommendations	Grade of evidence	Grade of recommendation
Pharmacotherapy should be reserved for patients with NASH, particularly for those with significant fibrosis (stage F2 and higher). Patients with less severe disease, but at high risk of disease progression could also be candidates for treatment	B	1

*Age > 50 years, diabetes, MetS, increased ALT

EASL–EASD–EASO CPG NAFLD. J Hepatol 2016;64:1388–402

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No drugs are approved for NASH
No specific therapy can be recommended
Any drug treatment is off label

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*Age > 50 years, diabetes, MetS, increased ALT
EASL–EASD–EASO CPG NAFLD. J Hepatol 2016;64:1388–402

Treatment: pharmacotherapy

- Lipid-lowering agents
  - Statins have not been adequately tested in NASH

Recommendations	Grade of evidence	Grade of recommendation
Statins may be confidently used to reduce LDL cholesterol and prevent cardiovascular risk, with no benefits or harm to liver disease. Similarly, n-3 polyunsaturated fatty acids reduce both plasma and liver lipids, but there are no data to support their use specifically for NASH	B	1

EASL–EASD–EASO CPG NAFLD. J Hepatol 2016;64:1388–402

Table 3: Studies of therapeutic measures to decrease the epicardial fat volume.

Author (reference)	Methodology	Conclusions
Park et al. [157]	Retrospective study in 145 patients who underwent PCI and coronary angiography scheduled for 6 to 8 months later; they underwent two-dimensional TTE in two stages; 82 patients received atorvastatin (20 mg) and 63 patients received simvastatin/ezetimibe (10/10 mg)	The use of statins, particularly atorvastatin, is associated with a reduction in the volume of EAT in patients with CAD; EAT change was 0.47 ± 0.65 mm in the atorvastatin group versus 0.12 ± 0.52 mm in the simvastatin/ezetimibe group; $p = 0.001$; multivariate analysis: atorvastatin group: OR: 0.509; 95% CI: 0.162–0.855; $p = 0.005$
Sacks et al. [158]	Study in 55 patients (12 controls) with CAD, MS, or DM who underwent open heart surgery for fat sample acquisition; genetic analysis was performed by RT-PCR; 7 diabetic patients received pioglitazone 25 mg for 24 months (average)	The use of pioglitazone in patients with coronary artery disease and type 2 DM was associated with a decrease in the genetic expression of proinflammatory and anti-inflammatory cytokines in EAT
Lima-Martínez et al. [159]	Intervention pilot study for 24 weeks in 26 type 2 diabetic patients with HbA1c $\geq 7\%$ on metformin monotherapy; those who met the inclusion criteria received metformin 1000 mg/10 mg sitagliptin and underwent two-dimensional TTE	The addition of sitagliptin to metformin therapy produces a rapid decline in the volume of EAT, thus serving as a noninvasive method (measured by ultrasound) of change in visceral fat during pharmacological interventions (before: 9.98 ± 2.63; after: 8.10 ± 2.11 mm; $p = 0.001$)
Elisha et al. [160]	Randomized pilot study intervention for 6 months in 56 patients (36 treated with insulin detemir and 20 with insulin glargine) who underwent two-dimensional TTE	The use of insulin detemir yielded a reduction in the volume of EAT and less fat gain in comparison with the use of insulin glargine (detemir, -1.7 ± 0.52 mm, versus glargine, -1.1 ± 1.6 mm; $p < 0.05$)
Kim et al. [161]	Study in 24 obese patients who underwent a 12-week supervised exercise training program (60–70% of the maximal heart rate, 60 min/day, 3 days/wk) besides two-dimensionally guided M-mode TTE	The aerobic training significantly reduced the thickness of the EAT, which was also associated with a decrease in visceral adipose tissue (8.11 ± 1.64 versus 7.39 ± 1.54 mm before and after exercise training, resp.; $p < 0.001$)

Juan Salazar et al, Cardiology Research and Practice 2016

ΘΕΡΑΠΕΙΑ

Treatment	Summary of benefit in NAFLD	Associated CV benefit/risk	Comments
Lifestyle Intervention (e.g. weight loss, increased physical exercise)	↓ liver enzymes, ↓hepatic fat (MRS & US), ↑insulin sensitivity, improved or unchanged NAFLD histological staging	Improved LV function and cardiac geometry. Improved VO2 max. ↓ Blood pressure.	NAFLD improvement only with >5-7% weight loss. Regular exercise showed improvements in NAFLD independent of body weight or visceral fat changes. Rapid weight loss can lead to ↑hepatic fat.
Thiazolidinediones (e.g. rosiglitazone, pioglitazone)	↓ liver enzymes, ↓ hepatic fat (MRS), ↑insulin sensitivity, improved or unchanged NAFLD histological staging	↑ risk of non-fatal MI (rosiglitazone only) and CHF. Pioglitazone: ↓ risk of major adverse CV events (excluding CHF) in diabetics.	Causes significant weight gain and oedema.
Metformin	↓ liver enzymes, unchanged or ↓ hepatic fat (US), ↑ insulin sensitivity, no change in histological staging (overall)	↓ risk of MI and overall mortality in overweight diabetics.	Gastrointestinal symptoms common. Risk of lactic acidosis (rare).
Statins	↓ liver enzymes, unchanged or ↓ hepatic fat (US), no change in histological staging.	↓↓ risk of adverse CV events and death in primary and secondary prevention, regardless of lipid levels.	Generally well-tolerated with large evidence base for CV benefit. Safe in NAFLD – no need for liver enzyme monitoring.
Fibrates	↓ liver enzymes, no histological improvement observed.	↓ TG, ↑ HDL & ↓ small, dense LDL, but overall no CV mortality benefit across all groups. ↓ in CV events only seen in atherogenic dyslipidaemic patients.	Useful only in certain population groups (e.g. ↑↑TG).
N-3 polyunsaturated fatty acids (PUFAs)	↓ liver enzymes, ↓ hepatic fat (MRS & US), ↑insulin sensitivity or unchanged	↓ mortality & SCD post-MI, ↓ mortality & HF hospitalisations in CHF, possible ↓ in AF burden. ↓ TG. Carotid plaque stabilisation. May ↑ LDL. May ↑ ventricular arrhythmias in angina patients.	Generally well-tolerated, but dose important (only high dose effective for NAFLD).
Angiotensin-II antagonists	↓ liver enzymes, ↑ insulin sensitivity, improved NAFLD histological staging (telmisartan only)	↓ Blood pressure. May improve impaired glucose tolerance.	Limited studies.
Antioxidants (Vitamin E)	liver enzymes unchanged, insulin sensitivity unchanged, improved or unchanged NAFLD histology	Overall no conclusive benefit.	Dose and duration likely to be important.
Weight-loss drugs (e.g. orlistat, rimonabant (now withdrawn))	↓ liver enzymes, ↓ hepatic fat (CT & US), ↑insulin sensitivity	Similar to associated weight loss benefits.	Limited studies.
Bariatric Surgery	↓ liver enzymes, ↑ insulin sensitivity, improved NAFLD histological staging but liver fibrosis may worsen slightly	Similar to associated weight loss benefits.	Long-term benefit appears to be dependent on improvement in insulin sensitivity, rather than weight loss.

Summary of NAFLD outcomes in different treatment/intervention trials in NAFLD and associated cardiovascular benefits/risks of intervention

L.S. Bhatia et al. European Heart Journal (2012) 33, 1190–1200

ΣΥΜΠΕΡΑΣΜΑ

- Εχει αποδειχθει η συσχετιση μεταξυ επικαρδιακου λιπους και λιπωδους ηπατος καθως και η συμβολη τους στην προοδο της καρδιαγγειακης νοσου
- Η θεραπεια παραμενει διαιτα και απωλεια βαρους
- Οι ηχογραφικες τεχνικες μπορουν να τις αναγνωρισουν και να τις εκτιμησουν στην καθ'ημερα κλινικη πρακτικη.
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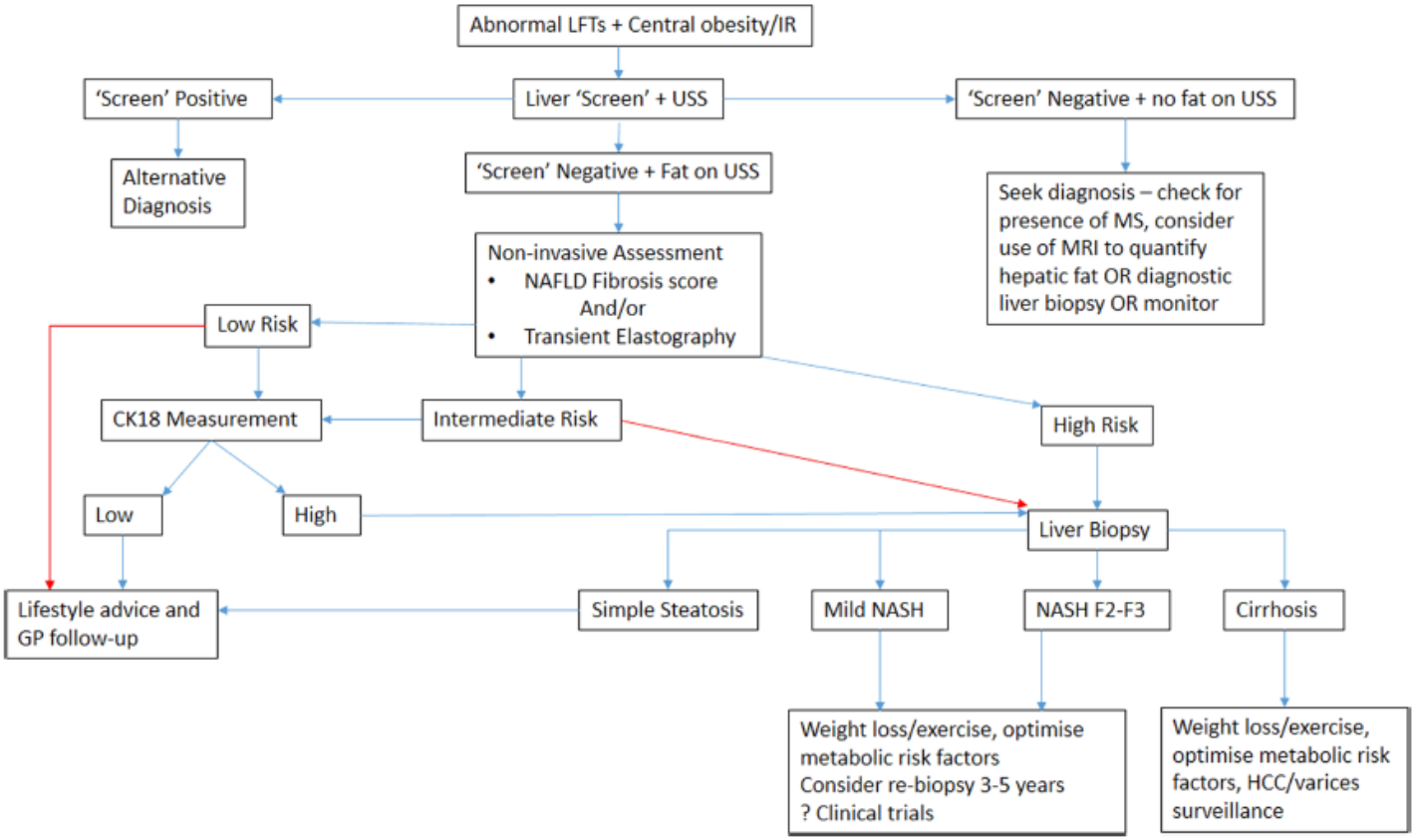

Figure 1 Example of algorithm for clinical assessment of patients at risk of non-alcoholic fatty liver disease.[36 37 44] . CK-18 levels are not routinely available in many centres, so patients at intermediate and high risk have to be managed according to the high-risk arm of the algorithm (red arrows). 'Screen'- blood tests to rule out common causes of liver disease; USS, ultrasound; MS, metabolic syndrome; IR, insulin resistance; HCC, hepatocellular carcinoma.

Dyson JK, et al. Frontline Gastroenterology 2013;0:1–8