# PARMA DIABETE 2017 – XI EDIZIONE

# NON-ALCOHOLIC FATTY LIVER DISEASE (NAFLD) E COMPLICANZE CARDIOVASCOLARI NEL DIABETE

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Diapositiva preparata da ALESSANDRO MONTAVANI e ceduta alla Società Italiana di Diabetologia.
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# DISCLOSURE

- **Il dr. Alessandro Mantovani dichiara di <u>NON</u> aver ricevuto negli ultimi due anni compensi o finanziamenti da Aziende Farmaceutiche e/o Diagnostiche.**

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# DEFINITION OF NAFLD

- NAFLD is characterized by an **excessive liver fat accumulation**, often associated with insulin resistance, and histologically defined by the presence of macrovesicular steatosis in more than 5% of hepatocytes in individuals who consume little or no alcohol.

- NAFLD is subdivided into two major subtypes: ***nonalcoholic fatty liver*** (**NAFL**, also termed *'simple steatosis'*) and ***nonalcoholic steatohepatitis*** (***NASH***), the progressive form of NAFLD that can lead to cirrhosis, hepatocellular carcinoma (HCC) and liver-related mortality.

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# DIAGNOSIS OF NAFLD

**NAFLD diagnosis is based mainly on the following three criteria:**

1. **hepatic steatosis on imaging methods (mostly ultrasound) or histology**
2. **no excessive alcohol consumption (a threshold of 30 g/day for men and 20 g/day for women is conventionally adopted)**
3. **no other competing causes for hepatic steatosis (*e.g.*, virus, drugs, iron overload, autoimmunity)**

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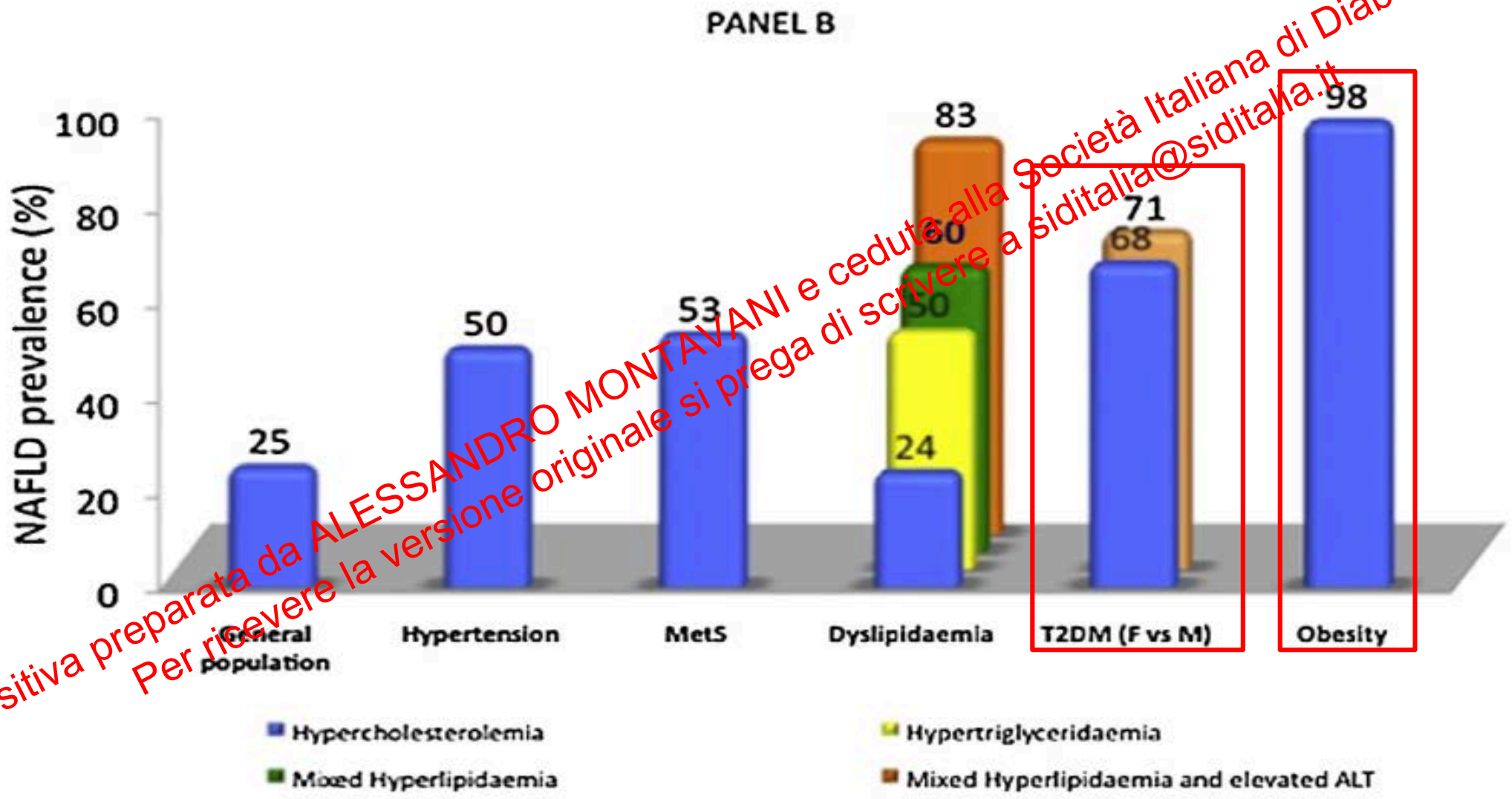
# PREVALENCE OF NAFLD IN VARIOUS HIGH-RISK PATIENT GROUPS COMPARED TO THE GENERAL ADULT POPULATION

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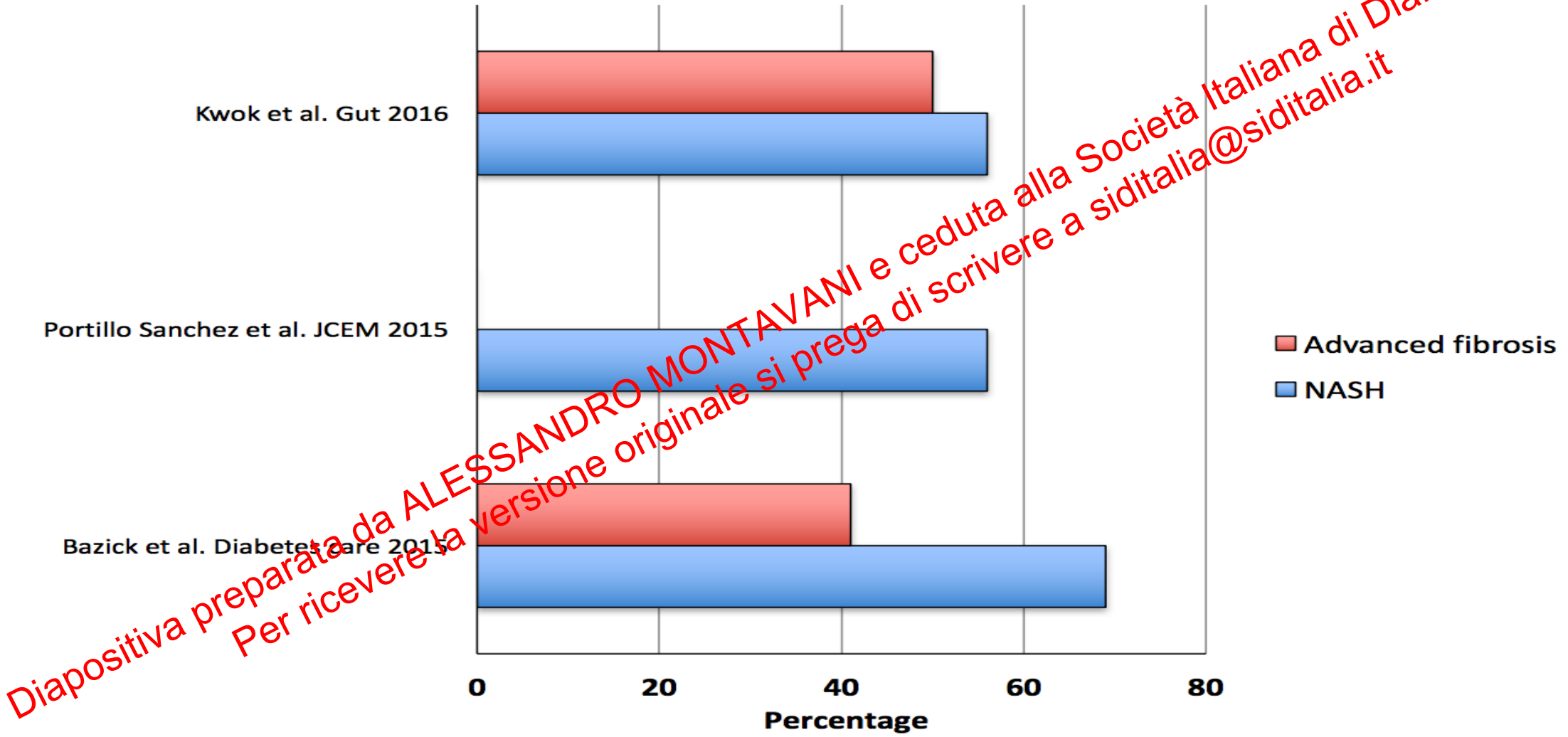
Lonardo A, Targher G et al. Dig Liver Dis 2015;47:997-1006

# PREVALENCE OF NASH OR ADVANCED FIBROSIS ON HISTOLOGY IN PATIENTS WITH TYPE 2 DIABETES (IRRESPECTIVE OF SERUM AMINOTRANSFERASE LEVELS)

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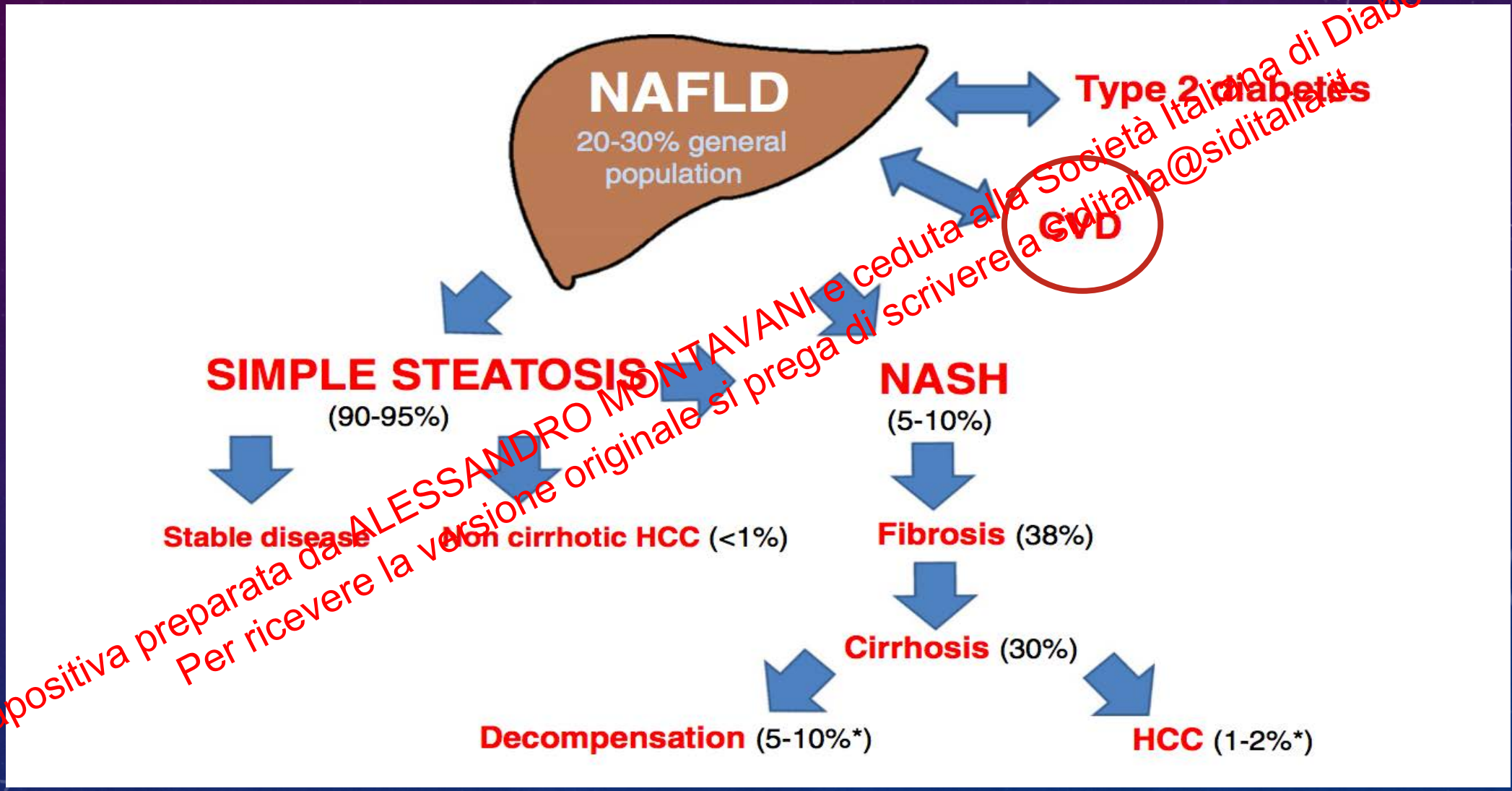
Lonardo A, Nascimbeni F, Mantovani A, Targher G. J Hepatol 2017, *in press*

# SCHEMATIC NATURAL HISTORY OF NAFLD

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Buzzetti E *et al.* Metabolism 2016;65:1038–48

# CAUSES OF DEATH IN PATIENTS WITH NAFLD

**Longitudinal study: *n* = 229 Sweden patients with biopsy-proven NAFLD and elevated serum liver enzymes (49% with NASH); mean follow-up 26.4 years**

**Table 3. Causes of Death in NAFLD Patients [n (%)]**

| Cause of Death | Number of Patients (n = 96) |
|---|---|
| Cardiovascular disease | 41 (43%) |
| Non-gastrointestinal malignancy | 18 (19%) |
| Hepatocellular carcinoma | 5 (5%) |
| Infection | 5 (5%) |
| Gastrointestinal malignancy | 4 (4%) |
| Cirrhosis | 4 (4%) |
| Endocrine | 3 (3%)* |
| Respiratory | 3 (3%) |
| Other | 7 (7%) |
| Missing | 6 (6%) |

*All three patients died from complications related to type 2 diabetes.

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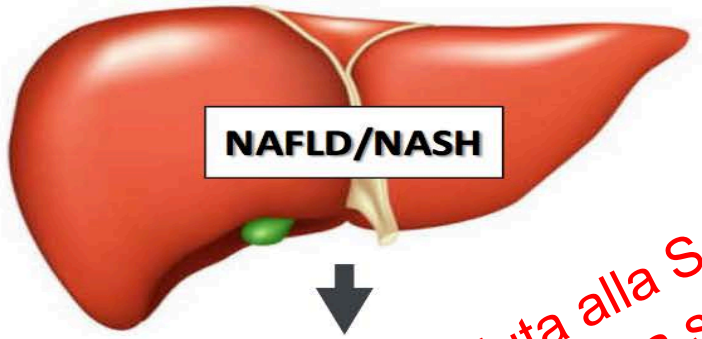
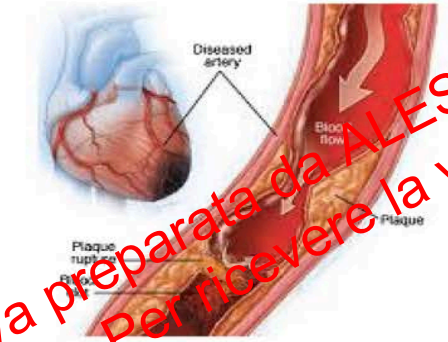
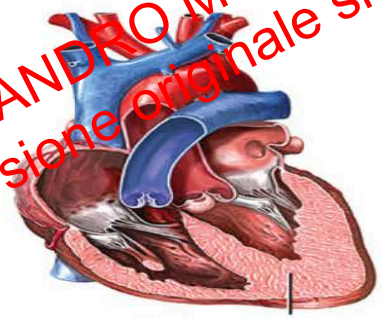
Ekstedt *et al*. Hepatology 2015;61:1547-54

# CARDIAC COMPLICATIONS ASSOCIATED WITH NAFLD

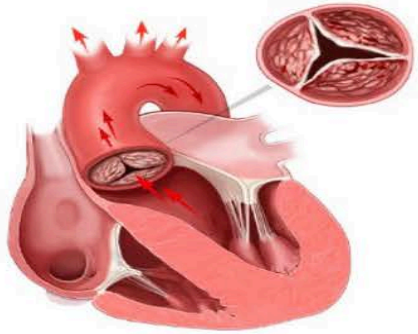


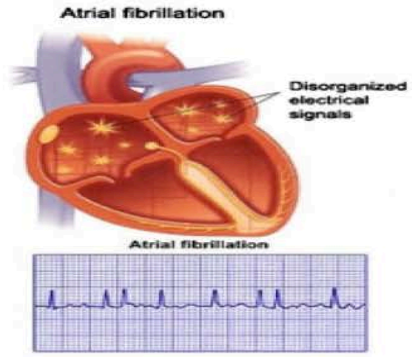

## NAFLD-related cardiac complications



Enlargement of heart muscle






| | | | |
|---|---|---|---|
| | Cardiac Dysfunction<br>Cardiac Hypertrophy | Aortic-Valve Sclerosis | Atrial Fibrillation |
| Coronary Heart Disease | Heart Failure | Mitral Annulus Calcification | QTc Prolongation |

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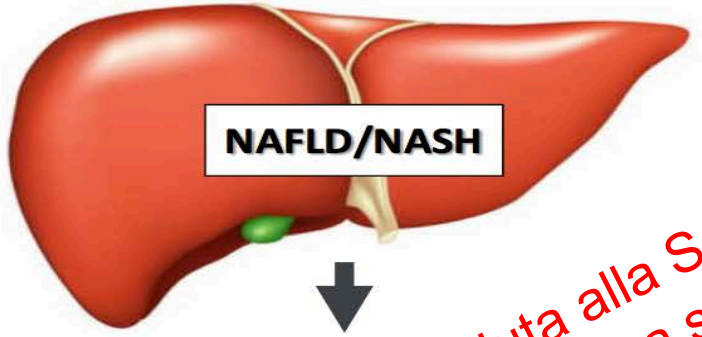
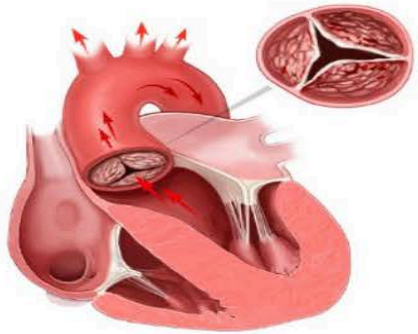
Mantovani A *et al.* Dig Dis Sci 2016;61:1246-67

# NAFLD AND HEART VALVE CALCIFICATION (HVC)




**NAFLD-related cardiac complications**



- Aortic-Valve Sclerosis
- Mitral Annulus Calcification

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Mantovani A *et al.* Dig Dis Sci 2016;61:1246-67

# Heart valve calcification in patients with type 2 diabetes and nonalcoholic fatty liver disease

Cross-sectional study: n= 247 T2DM outpatients (mean age 68 yrs; 71% with NAFLD on US) without previous history of heart failure, valvular heart diseases or hepatic diseases

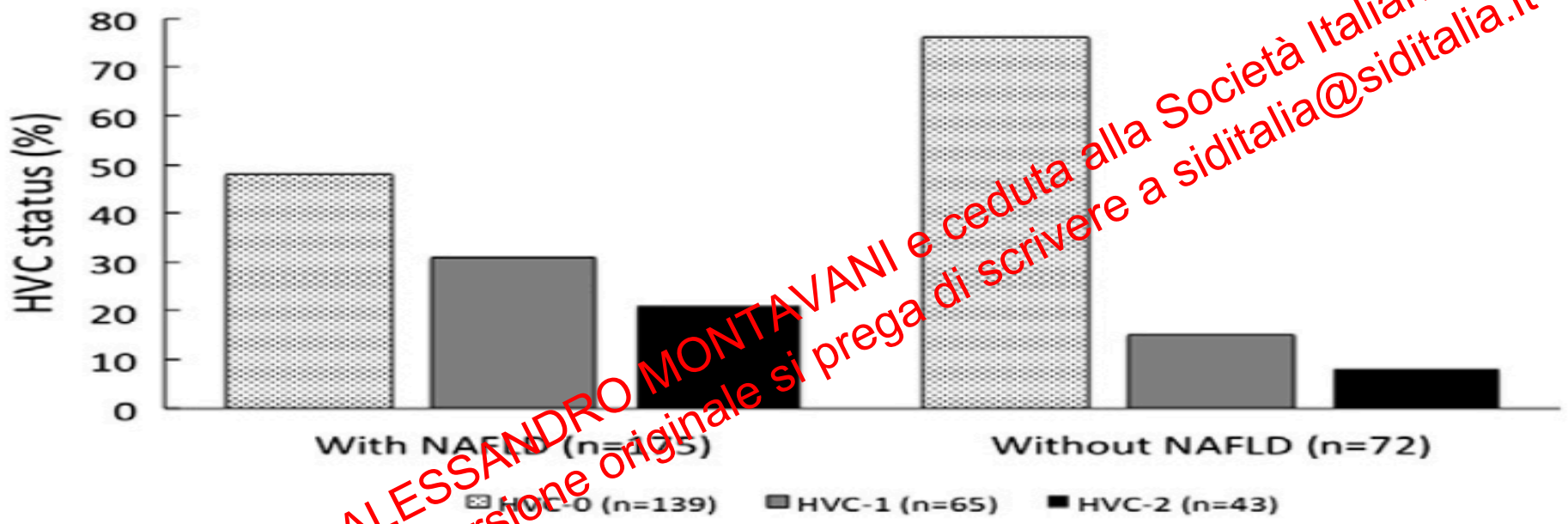


**Fig. 1 – Prevalence of HVC score in patients with type 2 diabetes stratified by NAFLD status. P-value <0.001 for the difference by the $\chi^2$ test.**

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**N.B.:** 139 (56.3%) patients had no heart valve calcification (HVC-0), 65 (26.3%) patients had one valve affected (HVC-1) and 43 (17.4%) patients had both valves affected (HVC-2).

Mantovani A *et al.* Metabolism 2015;64:879-84

# Heart valve calcification in patients with type 2 diabetes and nonalcoholic fatty liver disease

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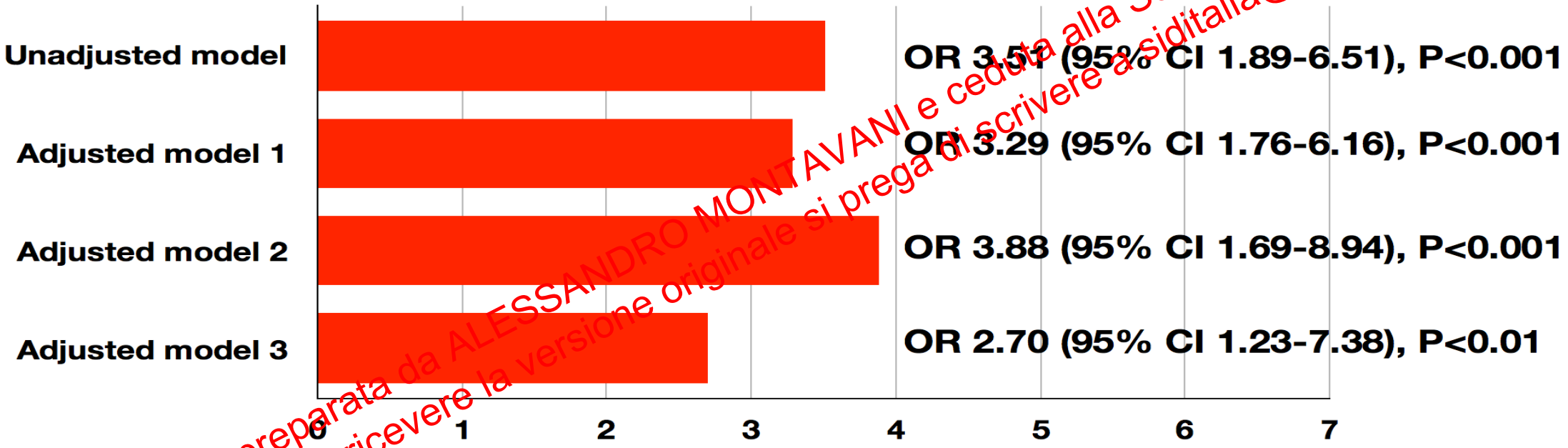
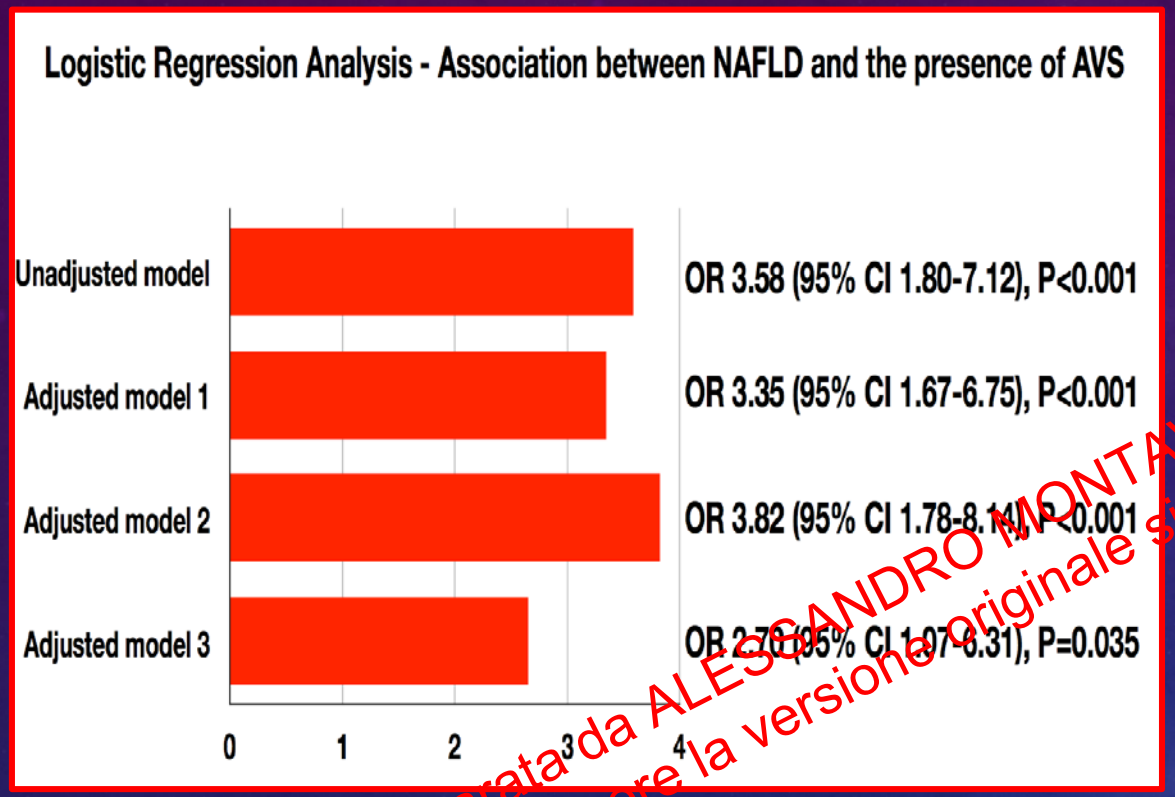
## Logistic Regression Analysis - Association between NAFLD and the presence of AVS, MAC or both

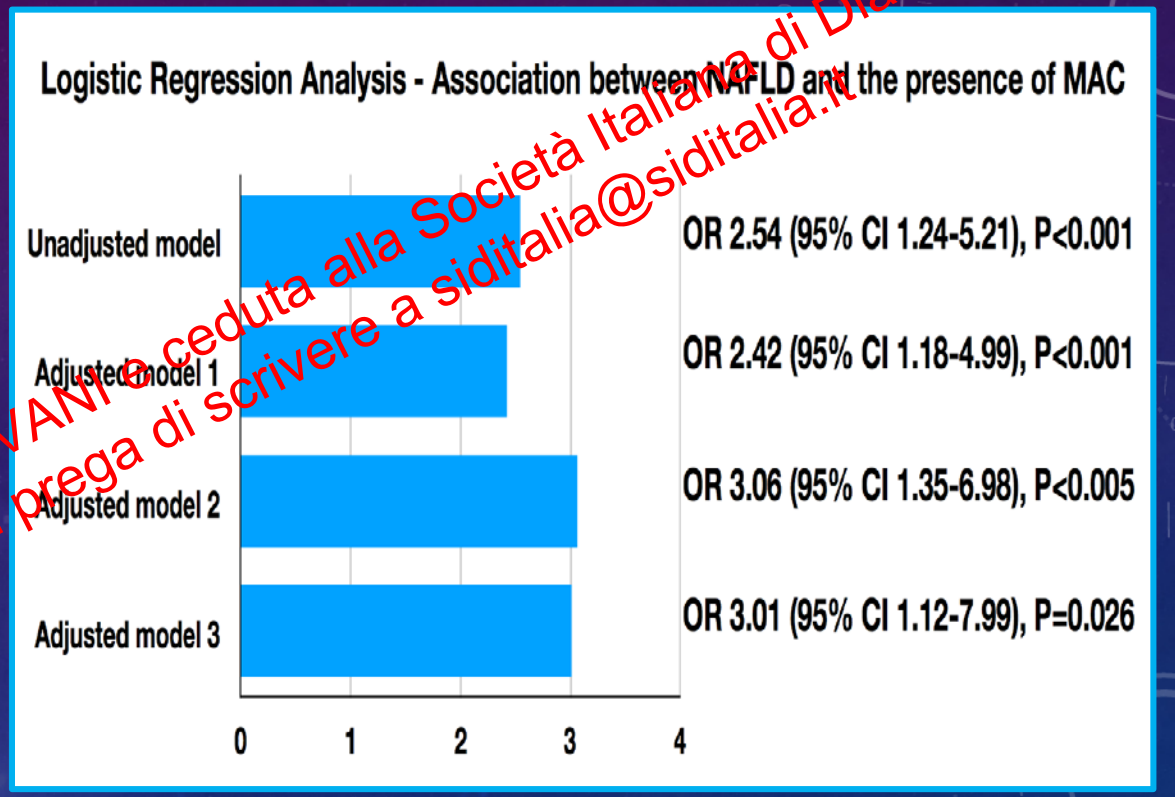



Model 1: age and sex; model 2: age, sex, waist circumference, smoking history, HbA1c, LDL-cholesterol, eGFR, diastolic blood pressure, use of any hypoglycemic, lipid-lowering and anti-hypertensive drugs; model 3: adjustment for the same variables included in model 2 plus E/e' ratio.

Mantovani A *et al.* Metabolism 2015;64:879-84

# Heart valve calcification in patients with type 2 diabetes and nonalcoholic fatty liver disease

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**Model 1:** age and sex; **Model 2:** age, sex, waist circumference, smoking, HbA1c, LDL-cholesterol, eGFR, diastolic blood pressure, use of hypoglycemic, lipid-lowering and anti-hypertensive drugs; **Model 3:** adjustment for the same variables included in model 2 ***plus*** E/e' ratio.

Mantovani A *et al.* Metabolism 2015;64:879-884

# Hepatic Steatosis Is Associated With Aortic Valve Sclerosis in the General Population

## The Study of Health in Pomerania (SHIP)

**Community-based study: n=2,022 middle-aged German individuals (39.7% with NAFLD on US)**

**Table 2. Prevalence OR for Aortic Valve Sclerosis in Participants Stratified by Presence vs Absence of Hepatic Steatosis (Defined Based on Ultrasound)**

| Hepatic Steatosis | Age-Sex–Adjusted OR (95% CI) | Model 2–Adjusted OR (95% CI) | Model 3–Adjusted OR (95% CI) | Model 4–Adjusted OR (95% CI) |
|---|---|---|---|---|
| No hepatic steatosis (reference) (n=1335) | 1.0 | 1.0 | 1.0 | 1.0 |
| Hepatic steatosis (n=877) | 1.48 (1.19–1.79) | 1.29 (1.04–1.60) | 1.33 (1.06–1.66) | 1.32 (1.04–1.66) |
| *P* value* | <0.001 | 0.022 | 0.014 | 0.021 |

Model 2: age, sex, waist-to-height ratio, smoking, alcohol consumption, and physical activity. Model 3: model 2+systolic blood pressure, antihypertensive medication, total/HDL cholesterol ratio, antilipemic medication, glycosylated hemoglobin, antidiabetic medication, antiplatelet medication, and estimated glomerular filtration rate. Model 4: model 3+high-sensitive C-reactive protein, serum ferritin levels, and white blood cells. CI indicates confidence interval; HDL, high-density lipoprotein; and OR: odds ratio.

*P value for comparison with the reference group no hepatic steatosis.

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Markus M *et al.* Arterioscler Thromb Vasc Biol 2013;33:1690-95

# KEY MESSAGE - 1

- Cross-sectional studies suggested that imaging-diagnosed NAFLD is independently associated with the presence of cardiac calcification (*i.e.*, AVS and MAC) in both the aortic and mitral valves in patients with and without type 2 diabetes.

- Although future prospective studies are needed, these findings suggest that valvular calcification of the aortic and mitral valves might represent a further link underpinning the increased risk of incident CVD observed in patients with NAFLD.

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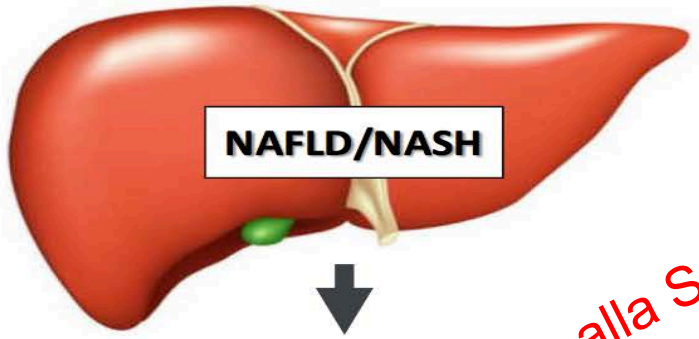
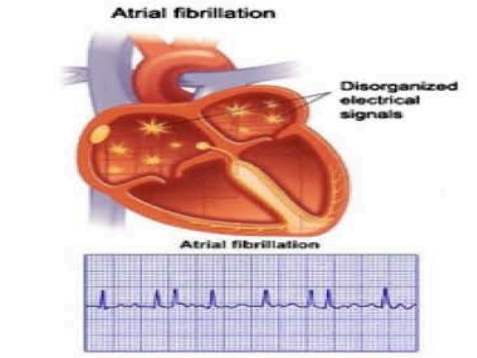
# NAFLD AND CARDIAC ARRHYTHMIAS




## NAFLD-related cardiac complications




- Atrial Fibrillation
- QTc Prolongation

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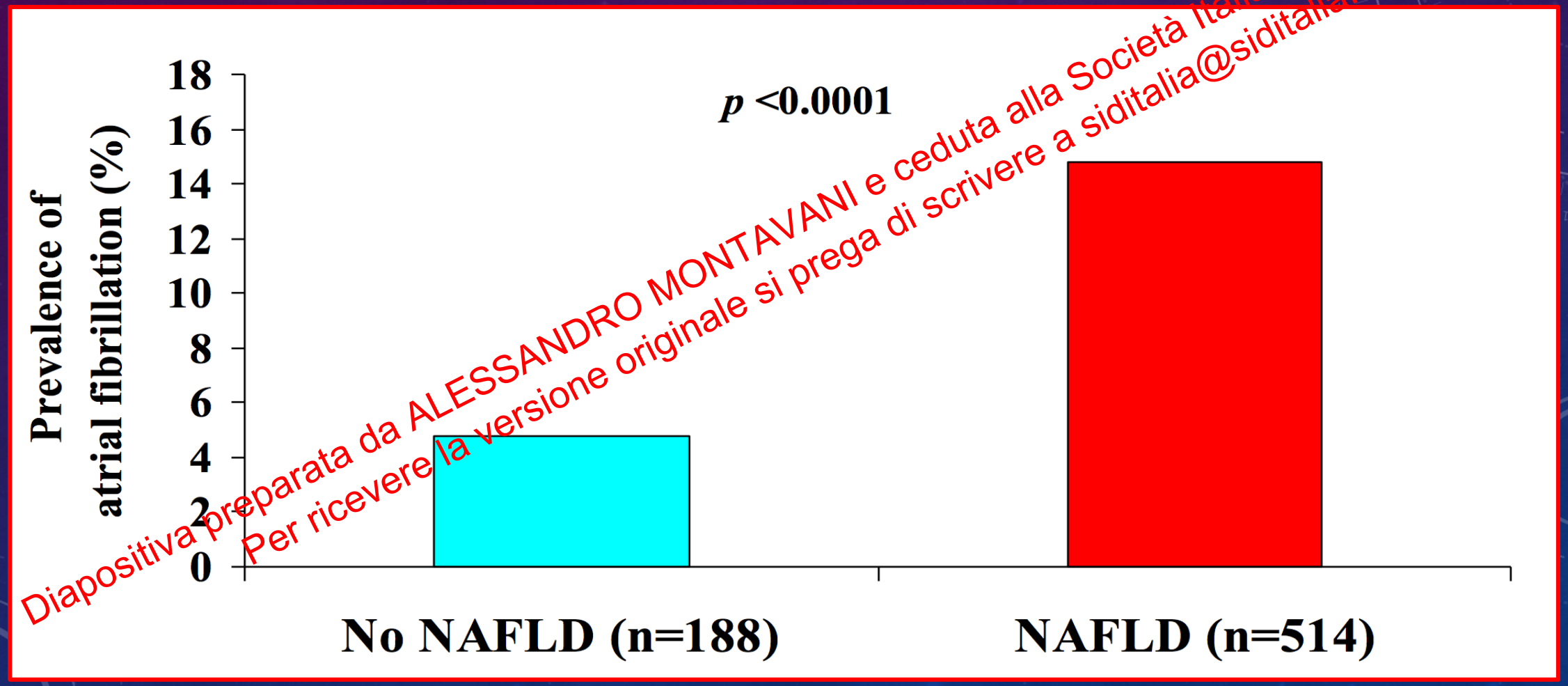
Mantovani A *et al.* Dig Dis Sci 2016;61:1246-67

# Non-alcoholic fatty liver disease is associated with an increased prevalence of atrial fibrillation in patients with type 2 diabetes

Cross-sectional study: n= 702 hospitalized patients T2DM (mean age 67 yrs; 73.2% with NAFLD on US) without malignances, ESRD, hepatic diseases and excessive alcohol consumption

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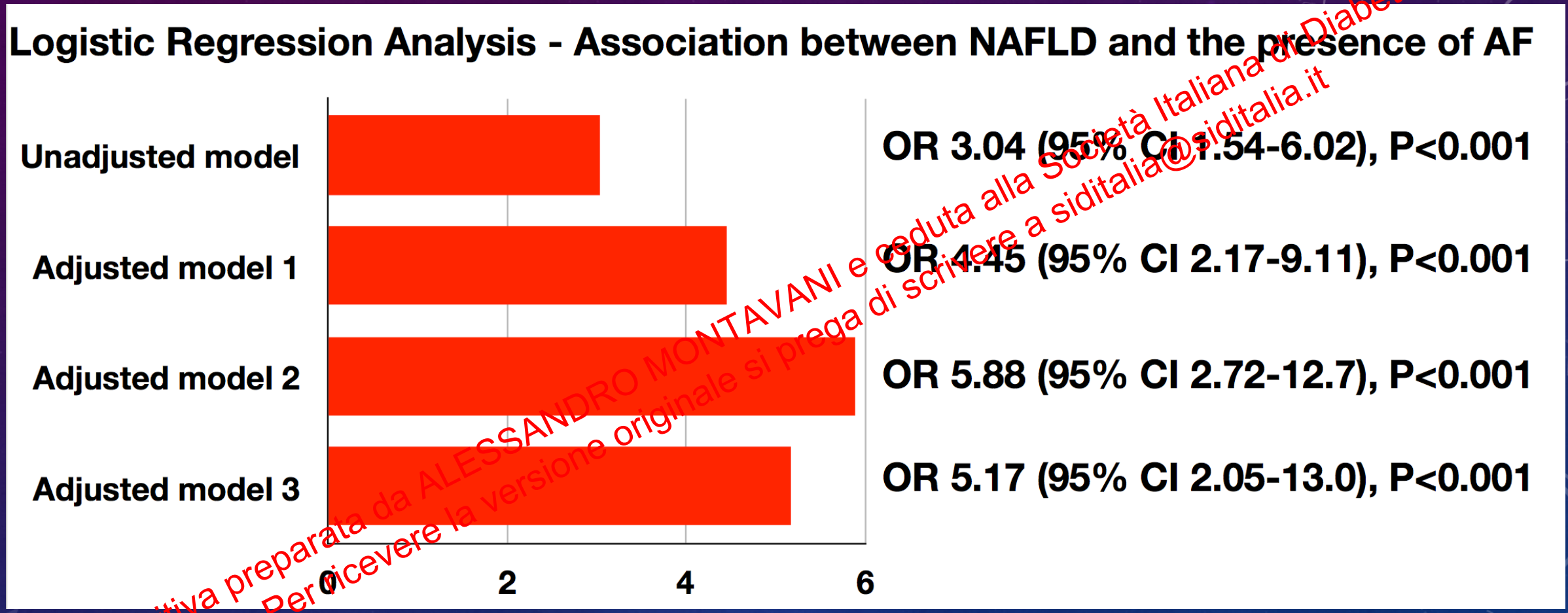
Targher G, Mantovani A e*t al.* Clinical Science 2013;125:301–309

# Non-alcoholic fatty liver disease is associated with an increased prevalence of atrial fibrillation in patients with type 2 diabetes

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**Model 1**: age and sex; **Model 2**: age, sex, systolic BP, HbA1c, eGFR, total cholesterol, electrocardiographic LVH, COPD, prior history of HF, VHD or hyperthyroidism; **Model 3**: model 2 ***plus*** serum GGT concentration and use of anti-hypertensive drugs, insulin, digoxin, nitroderivates and anticoagulants.

Targher G, Mantovani A *et al.* Clinical Science 2013;125:301–309

# Non-Alcoholic Fatty Liver Disease Is Associated with an Increased Incidence of Atrial Fibrillation in Patients with Type 2 Diabetes

**Longitudinal study: n= 400 outpatients with T2DM (mean age 66 yrs; 70% with NAFLD on US) without AF, moderate-to-severe VHD, and liver diseases at baseline; duration of follow-up 10 years.**

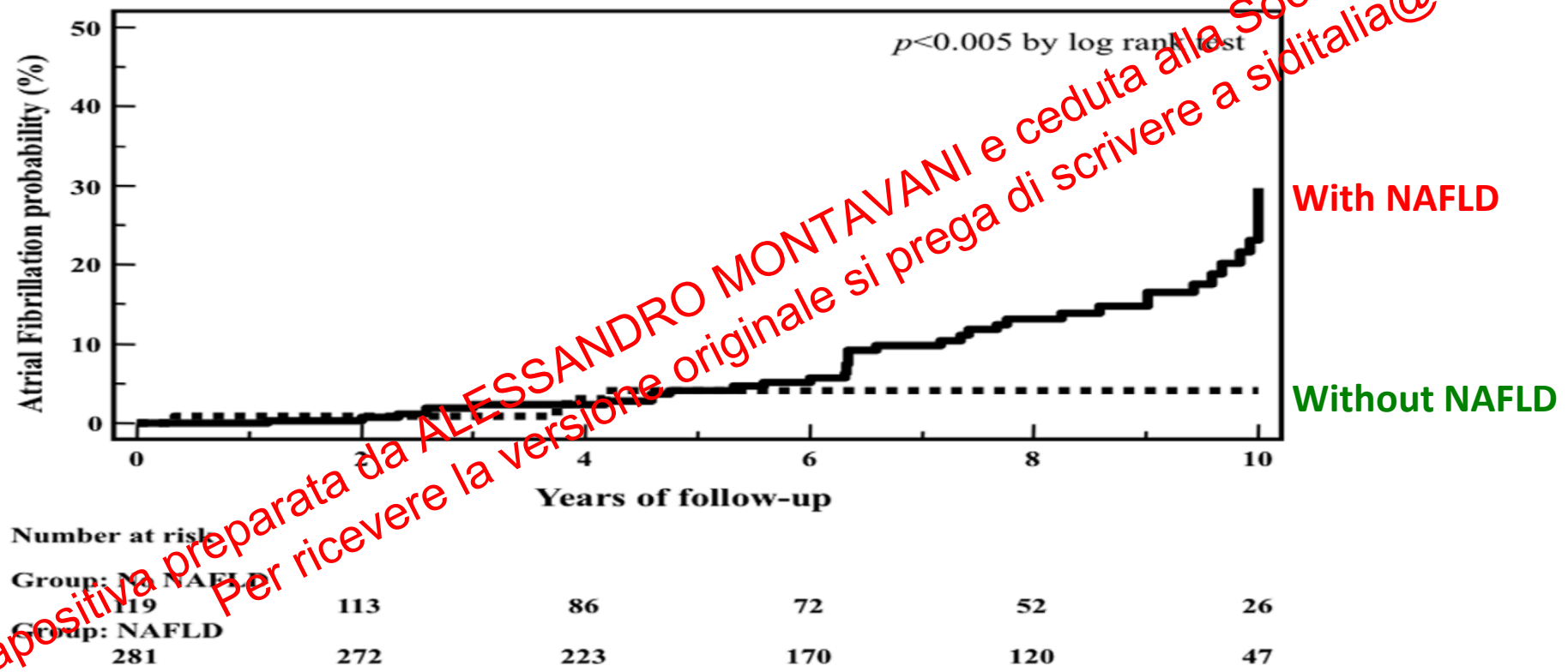


**Figure 3. Incidence curves for atrial fibrillation during follow-up, in patients with (solid line) and without (dotted line) NAFLD at baseline.**
doi:10.1371/journal.pone.0057183.g003

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Targher G *et al.* PLoS ONE 2013;8:e57183

# Non-Alcoholic Fatty Liver Disease Is Associated with an Increased Incidence of Atrial Fibrillation in Patients with Type 2 Diabetes

**Table 3.** Logistic regression models for NAFLD as a predictor for development of AF in patients with type 2 diabetes.

| Logistic Regression Models | Odds Ratios (95% CI) | *p* value |
|---|---|---|
| **NAFLD (yes *vs.* no)** | | |
| unadjusted model | 4.49 (1.6–12.9) | <0.005 |
| adjusted model 1 | 5.40 (1.8–15.9) | <0.005 |
| adjusted model 2 | 6.38 (1.7–24.2) | =0.005 |
| adjusted model 3 | 4.96 (1.4–17.0) | =0.01 |
| **Other independent predictors of incident AF in regression model 2** | | |
| Age (years) | 1.06 (1.01–1.12) | <0.01 |
| Electrocardiographic PR interval (msec) | 1.05 (1.03–1.06) | <0.001 |
| Electrocardiographic LVH (yes *vs.* no) | 4.29 (1.8–10.4) | <0.001 |

Sample size, $n=400$. Data are expressed as odds ratios ±95% confidence intervals as assessed by univariable (unadjusted) or multivariable logistic regression analyses. Other covariates included in multivariable logistic regression models were as follows: **model 1**: age and sex; **model 2:** age, sex, hypertension (blood pressure ≥140/90 mmHg or treatment), electrocardiographic PR interval and LVH; **model 3:** adjustment for variables included in the 10-year Framingham Heart Study-derived AF risk score (i.e. age, sex, BMI, systolic BP, hypertension treatment, electrocardiographic PR interval and history of heart failure).

doi:10.1371/journal.pone.0057183.t003

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Targher G *et al.* PLoS ONE 2013;8:e57183

RESEARCH ARTICLE

# Non-Alcoholic Fatty Liver Disease as a Predictor of Atrial Fibrillation in Middle-Aged Population (OPERA Study)

**Aki J. Käräjämäki, Olli-Pekka Pätsi, Markku Savolainen, Y. Antero Kesäniemi, Heikki Huikuri, Olavi Ukkola***

Research Unit of Internal Medicine, Medical Research Center Oulu, Oulu University Hospital, and University of Oulu, Oulu, Finland

**Longitudinal study: N= 958 subjects from the OPERA cohort (26% with NAFLD on US); mean follow-up 16.3 years.**

**Table 3. Association between NAFLD (n = 958) and risk of AF during follow-up.**

| | Cox regression model | | | |
|---|---|---|---|---|
| **Predictor** | **Unadjusted model** | **Adjusted model 1** | **Adjusted model 2** | **Adjusted model 3** |
| Fatty liver (yes vs. no) | **1.96 (1.29–2.97)** | **1.79 (1.18–2.71)** | **1.73 (1.09–2.73)** | **1.88 (1.03–3.45)** |
| Age (years) | | **1.09 (1.05–1.13)** | **1.09 (1.05–1.13)** | **1.06 (1.01–1.11)** |
| Sex (male vs female) | | **1.63 (1.07–2.49)** | **1.63 (1.07–2.49)** | 0.78 (0.32–1.90) |
| Study group (hypertensive vs. control) | | | 1.12 (0.73–1.71) | 0.70 (0.40–1.23) |
| Diabetes status (yes vs no) | | | 1.00 (0.53–1.91) | 1.01 (0.48–2.13) |
| BMI (kg/m$^2$) | | | | 0.91 (0.80–1.03) |
| Waist (cm) | | | | 1.03 (0.98–1.08) |
| Alcohol consumption (grams/week) | | | | 1.00 (0.99–1.00) |
| Smoking (pack years) | | | | 1.00 (0.98–1.02) |
| Serum ALT (U/l) | | | | 1.00 (0.99–1.01) |
| Systolic Blood Pressure (mmHg) | | | | 1.01 (1.00–1.02) |
| Quick Index | | | | 0.93 (0.06–14.90) |
| CAD, (yes vs no) | | | | 1.70 (0.86–3.39) |
| ANP (pmol/l) | | | | **1.002 (1.000–1.003)** |
| LVMI (g/m$^2$) | | | | **1.01 (1.00–1.02)** |
| Left atrial diameter (mm) | | | | 1.03 (0.97–1.09) |
| hs-CRP (mg/l) | | | | 1.00 (1.00–1.00) |

Values are expressed as ORs (95% CIs) as assessed by multivariate Cox regression analyses. Independent predictors of AF are highlighted in bold type. BMI, body mass index; ALT, alanine transferase; CAD, coronary artery disease; ANP, atrial natriuretic peptide; LVMI, left ventricular mass index; hs-CRP, high-sensitive C-reactive protein.

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Käräjämäki AJ *et al.* PLoS ONE 2015;10:e0142937

# Association of nonalcoholic fatty liver disease with QTc interval in patients with type 2 diabetes

**Cross-sectional study: n= 400 randomly selected T2DM outpatients (mean age 63 yrs; 70% with NAFLD on US) without pre-existing AF, moderate-to-severe VHD, hepatic diseases, and excessive alcohol consumption**

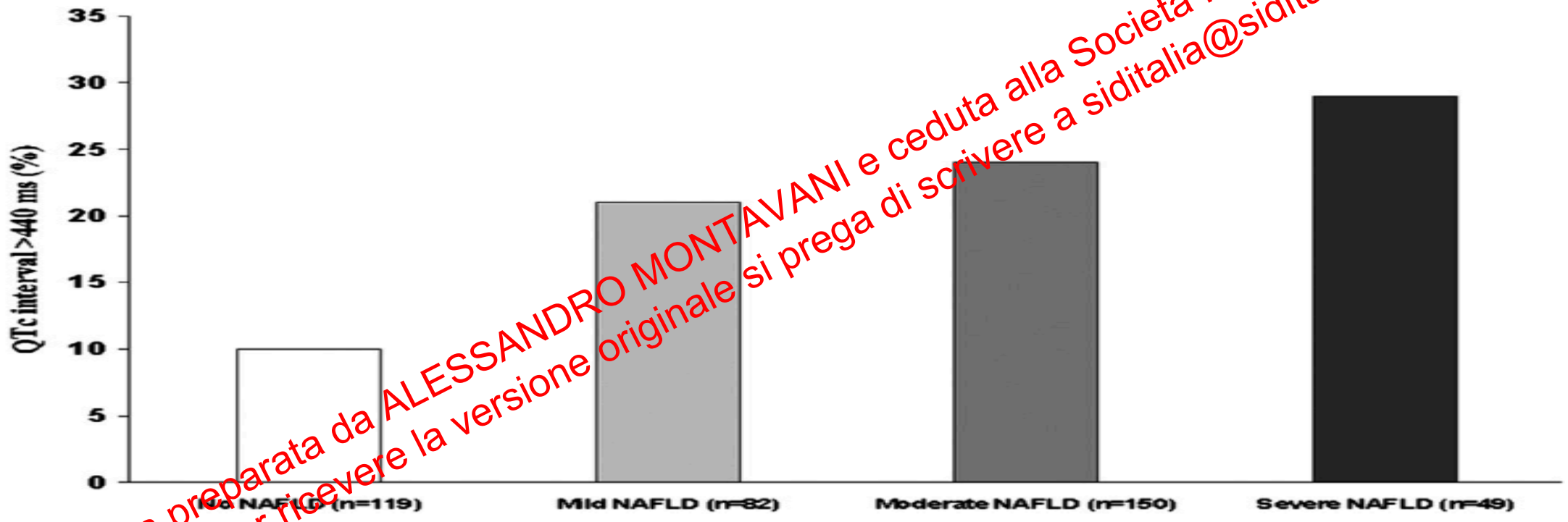


**Figure 2** Proportion of QTc interval duration >440 ms (as measured by the Bazett's formula) among patients with type 2 diabetes stratified by the ultrasonographic severity of NAFLD. $p < 0.005$ for trend by the chi-squared test.

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Targher G *et al.* NMCD 2014;24:663-69

# Association of nonalcoholic fatty liver disease with QTc interval in patients with type 2 diabetes

**Table 2** Logistic regression models for NAFLD as a predictor for increased QTc interval duration in patients with type 2 diabetes.

| Logistic regression models | OR (95% CI) | *p* Value |
|---|---|---|
| **NAFLD (yes *vs.* no)** | | |
| Unadjusted model | 2.16 (1.4—3.4) | <0.001 |
| Adjusted model 1 | 2.28 (1.5—3.6) | <0.001 |
| Adjusted model 2 | 2.20 (1.4—3.5) | <0.001 |
| Adjusted model 3 | 2.26 (1.4—3.7) | <0.001 |
| **Other independent predictors of increased QTc interval in model 3** | | |
| Sex (female) | 1.88 (1.2—2.9) | <0.01 |
| Hypertension (yes *vs.* no) | 2.01 (1.2—3.3) | <0.01 |
| Peripheral artery disease (yes *vs.* no) | 1.76 (1.1—3.0) | <0.05 |
| Lower-limb sensory neuropathy (yes *vs.* no) | 1.90 (1.1—3.5) | <0.05 |

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**Model 1** adjusted for age and sex; **model 2**: adjusted for age, sex, diabetes duration, hypertension, PAD and lower-limb sensory neuropathy; **model 3**: adjustment for the same variables included in model 2 ***plus*** BMI, alcohol consumption, smoking, HbA1c, LVH, CHD and CKD.

Targher G *et al.* NMCD 2014;24:663-69

# Nonalcoholic Fatty Liver Disease Is Associated With QT Prolongation in the General Population

Chi-Sheng Hung, MD;* Ping-Huei Tseng, MD, PhD;* Chia-Hung Tu, MD, MSc; Chien-Chuan Chen, MD; Wei-Chih Liao, MD, PhD; Yi-Chia Lee, MD, PhD; Han-Mo Chiu, MD, PhD; Hung-Ju Lin, MD; Yi-Lwun Ho, MD, PhD; Wei-Shiung Yang, MD, PhD; Ming-Shiang Wu, MD, PhD;† Ming-Fong Chen, MD, PhD†

**Cross-sectional study: n= 31,116 consecutive participants (41% with NAFLD on US)**

**Table 3.** Multivariable Logistic Regression: Severity of NAFLD to Predict QTc Prolongation (QTc ≥440 ms) Among All Participants

| | | Mild | | Moderate | | Severe | |
|---|---|---|---|---|---|---|---|
| | | Women | Men | Women | Men | Women | Men |
| NAFLD Severity | n (Women/Men) | OR (95% CI) | OR (95% CI) | OR (95% CI) | OR (95% CI) | OR (95% CI) | OR (95% CI) |
| Unadjusted | 15 107/16 026 | 1.42 (1.32 to 1.53)§ | 1.23 (1.14 to 1.34)§ | 2.61 (2.26 to 3.00)§ | 1.83 (1.65 to 2.03)§ | 3.45 (2.57 to 4.62)§ | 2.73 (2.28 to 3.26)§ |
| Model 1 | 15 107/16 026 | 1.33 (1.22 to 1.44)§ | 1.16 (1.06 to 1.26)§ | 2.22 (1.92 to 2.57)§ | 1.62 (1.45 to 1.80)§ | 2.72 (2.02 to 3.67)§ | 2.28 (1.892.74)§ |
| Model 2 | | | | | | | |
| All participants, by Bazett's criteria | 15 107/16 026 | 1.11 (1.01 to 1.21)† | 1.11 (1.01 to 1.21)† | 1.61 (1.36 to 1.90)§ | 1.39 (1.22 to 1.59)§ | 1.31 (1.16 to 2.24)‡ | 1.87 (1.51 to 2.31)§ |
| All participants, by Hodges' criteria | 15 107/16 026 | 1.04 (0.93 to 1.15) | 0.97 (0.86 to 1.09) | 1.36 (1.14 to 1.62)‡ | 1.20 (1.02 to 1.41)† | 1.37 (0.99 to 1.89)‡ | 1.56 (1.21 to 1.99)§ |

Model 1: adjusted for age, sex. Model 2: adjusted for age, sex, diabetes, hypertension, cholesterol, HDL, triglycerides, aspartate aminotransferase, body mass index, left ventricular hypertrophy, a history of coronary artery disease, hypokalemia, estimated glomerular filtration rate, high-sensitivity C-reactive protein, smoking, and metabolic syndrome (the fully adjusted model). HDL indicates high-density lipoprotein; NAFLD, nonalcoholic fatty liver disease; OR, odds ratio; QTc, corrected QT.

*In the subgroup analyses, all variables in model 2 other than the variable for stratification were included; all of the subgroup analyses were analyzed by Bazett's criteria, †$P<0.05$, ‡$P<0.01$, §$P<0.001$.

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Hung CS et *al.* J Am Heart Assoc 2015;4:e001820

# Nonalcoholic Fatty Liver Disease Is Associated With Ventricular Arrhythmias in Patients With Type 2 Diabetes Referred for Clinically Indicated 24-h Holter Monitoring

**Cross-sectional study: n= 330 consecutive T2DM outpatients (mean age 70 yrs; 72% with NAFLD on US) without AF, ESRD, or known liver diseases who had undergone 24-h Holter monitoring for clinical reasons**

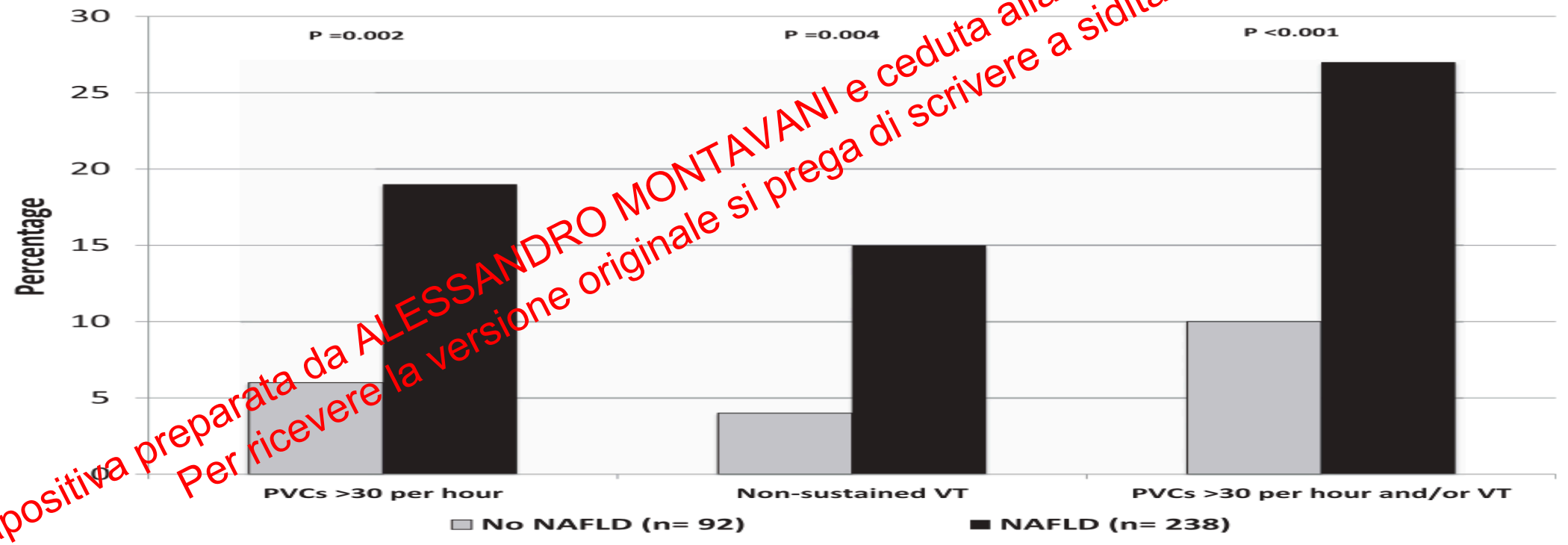


**Figure 2**—Prevalence of >30 PVCs/h, nonsustained VT, or both diagnosed on 24-h ambulatory Holter monitoring in patients with type 2 diabetes stratified by NAFLD status.

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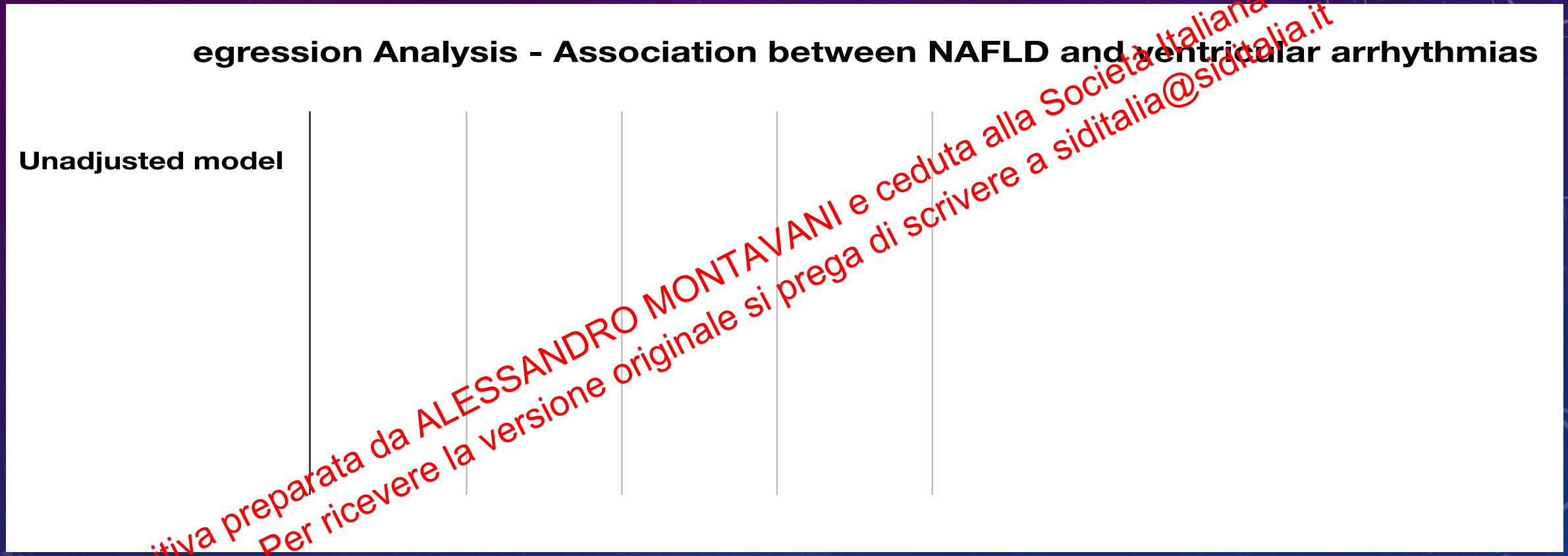
Mantovani A *et al.* Diabetes Care 2016;39:1416-23

# Nonalcoholic Fatty Liver Disease Is Associated With Ventricular Arrhythmias in Patients With Type 2 Diabetes Referred for Clinically Indicated 24-h Holter Monitoring

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Model 1, adjusted for age, sex; model 2, adjusted for age, sex, BMI, hypertension, smoking history, CKD, COPD, IHD, VHD, anti-arrhythmic drug use, or serum GGT; model 3, adjustment for the same variables included in model 2 *plus* LV ejection fraction.

Mantovani A *et al.* Diabetes Care 2016;39:1416-23

RESEARCH ARTICLE

# Nonalcoholic fatty liver disease is associated with an increased risk of heart block in hospitalized patients with type 2 diabetes mellitus

**Cross-sectional study: n= 751 hospitalized patients with T2DM (mean age 66±9 yrs; 70% with NAFLD on US) without excessive alcohol, known chronic liver disease, pre-existing AF, PM/ICD, VHD, malignancies, ESRD, COPD, electrolyte disturbances, thyroid dysfunction and use of any anti-arrhythmic drugs (except beta-blockers)**

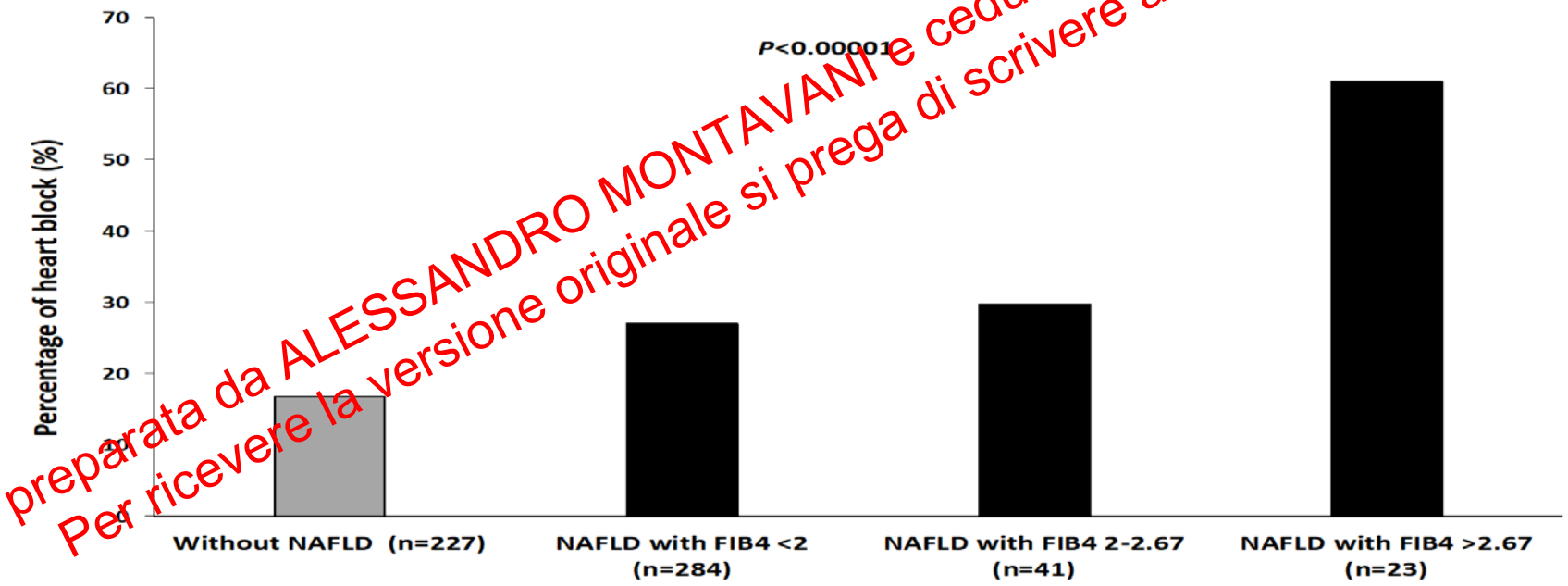


**Fig. Prevalence of heart block in relation to advanced NAFLD fibrosis (by using FIB4 score)**

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Mantovani A *et al.* PLoS ONE 12(10): e0185459.

RESEARCH ARTICLE

# Nonalcoholic fatty liver disease is associated with an increased risk of heart block in hospitalized patients with type 2 diabetes mellitus

**Table 2. Logistic regression models—Association between NAFLD and the risk of prevalent heart block in patients with T2DM.**

| Logistic Regression Models | Odds Ratio | 95% CI | *p* value |
|---|---|---|---|
| **NAFLD (yes *vs.* no)** | | | |
| Unadjusted model ($n = 751$) | 2.27 | 1.53–3.36 | <0.001 |
| Adjusted model 1 ($n = 751$) | 2.65 | 1.75–4.01 | <0.001 |
| Adjusted model 2 ($n = 751$) | 2.82 | 1.73–4.57 | <0.001 |
| Adjusted model 3 ($n = 731$) | 3.04 | 1.81–5.10 | <0.001 |
| **Other independent predictors of heart block in regression *model 3*** | | | |
| Age (years) | 1.03 | 1.01–1.06 | <0.001 |
| Sex (men *vs.* women) | 1.67 | 1.10–2.44 | <0.01 |
| Mild-moderate heart valve disease (yes *vs.* no) | 1.59 | 1.01–2.98 | <0.05 |
| Serum creatinine (mmol/l) | 0.98 | 0.97–0.99 | <0.05 |

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**Model 1**: adjusted for age and sex; **model 2:** adjusted for age, sex, BMI, diabetes duration, HbA1c, eGFR, macroalbuminuria, hypertension (*i.e.,* blood pressure 140/90 mmHg or drug treatment, including beta-blockers), prior IHD and mild-to-moderate VHD; **Model 3:** adjusted for the same variables included in model 2 ***plus*** peripheral artery disease, diabetic retinopathy, lower-extremity sensory neuropathy, statins and anti-platelet agents.

Mantovani A e*t al.* PLoS ONE 12(10): e0185459.

# KEY MESSAGE - 2

- Accumulating cross-sectional and prospective studies have suggested that imaging-diagnosed NAFLD is *independently* associated with an increased risk of cardiac arrhythmias (mainly permanent/persistent atrial fibrillation) in both non-diabetic individuals and those with type 2 diabetes.

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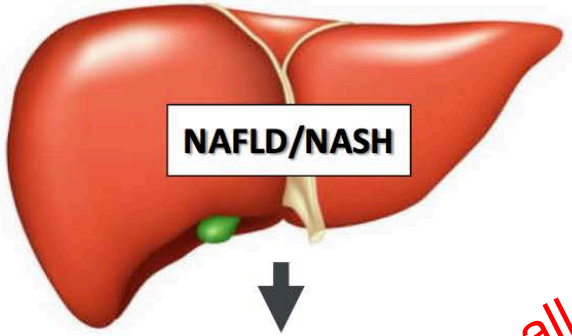
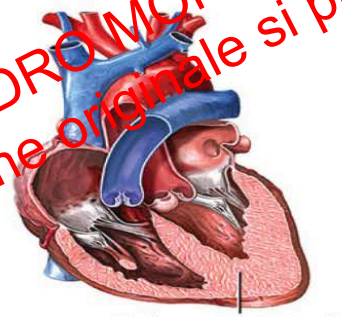
# NAFLD AND MYOCARDIAL DYSFUNCTION




**NAFLD-related cardiac complications**



Enlargement of heart muscle

**Cardiac Dysfunction**
**Cardiac Hypertrophy**

**Heart Failure**

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Mantovani A *et al.* Dig Dis Sci 2016;61:1246-1267

RESEARCH ARTICLE

# Nonalcoholic Fatty Liver Disease Is Independently Associated with Early Left Ventricular Diastolic Dysfunction in Patients with Type 2 Diabetes

**Cross-sectional study: n=222 consecutive T2DM outpatients (mean age 64±6 yrs; 71 % with NAFLD on US) without history of CHD, HF, moderate-to severe VHD, and hepatic diseases**

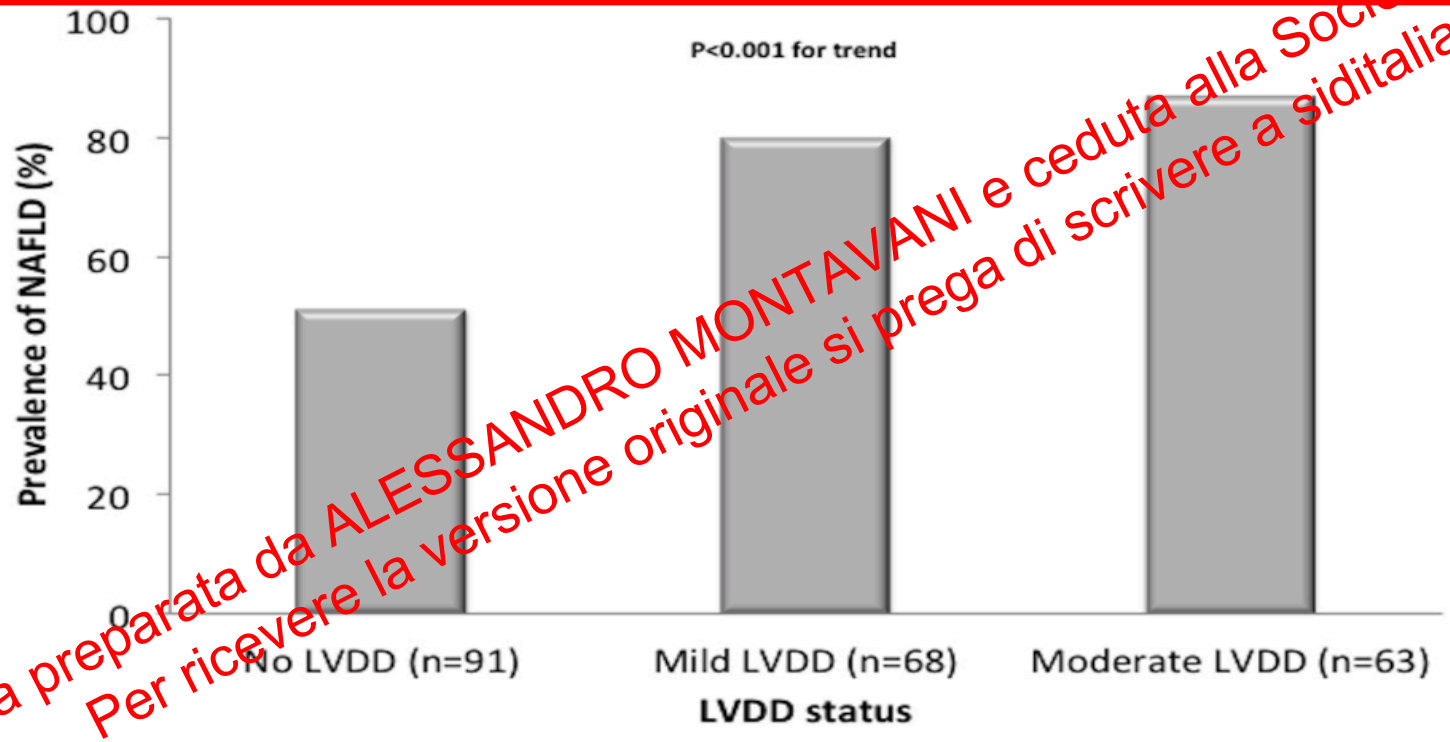


**Fig 1. Prevalence of NAFLD in relation to echocardiographic grades of left ventricular diastolic dysfunction (LVDD) in patients with type 2 diabetes.** *P*-value <0.001 for the trend among the three groups of patients (as assessed by the $\chi^2$ test).

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Mantovani A *et al*. Plos One 2015;10:e0135329

RESEARCH ARTICLE

# Nonalcoholic Fatty Liver Disease Is Independently Associated with Early Left Ventricular Diastolic Dysfunction in Patients with Type 2 Diabetes

**Table 3. Independent predictors of the presence of mild and/or moderate LV diastolic dysfunction in patients with type 2 diabetes.**

| Logistic Regression Models | Odds ratio | 95% CI | *P* value |
|---|---|---|---|
| **NAFLD (yes *vs*. no)** | | | |
| Unadjusted model | 4.89 | 2.6–9.2 | <0.001 |
| Adjusted model 1 | 4.17 | 2.1–8.1 | <0.001 |
| Adjusted model 2 | 3.50 | 1.7–7.2 | <0.001 |
| Adjusted model 3 | 3.08 | 1.5–6.4 | = 0.003 |
| **Other independent predictors of LVDD in adjusted model 3** | | | |
| Diabetes duration (years) | 1.07 | 1.03–1.1 | <0.005 |
| Male sex | 3.21 | 1.4–7.3 | <0.005 |
| LV ejection fraction (%) | 0.91 | 0.86–0.96 | <0.001 |

**Model 1: adjusted for age and sex; model 2: adjusted for age, sex, BMI, duration of diabetes, hemoglobin A1c, eGFR and hypertension; model 3: adjustment for the same variables included in model 2 *plus* LV ejection fraction and LV mass index.**

Mantovani A *et al*. Plos One 2015;10:e0135329

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# Association of Nonalcoholic Fatty Liver Disease With Subclinical Myocardial Remodeling and Dysfunction: A Population-Based Study

**Community-based study: n= 2,713 US adult participants (10% with NAFLD detected by computed tomography)**

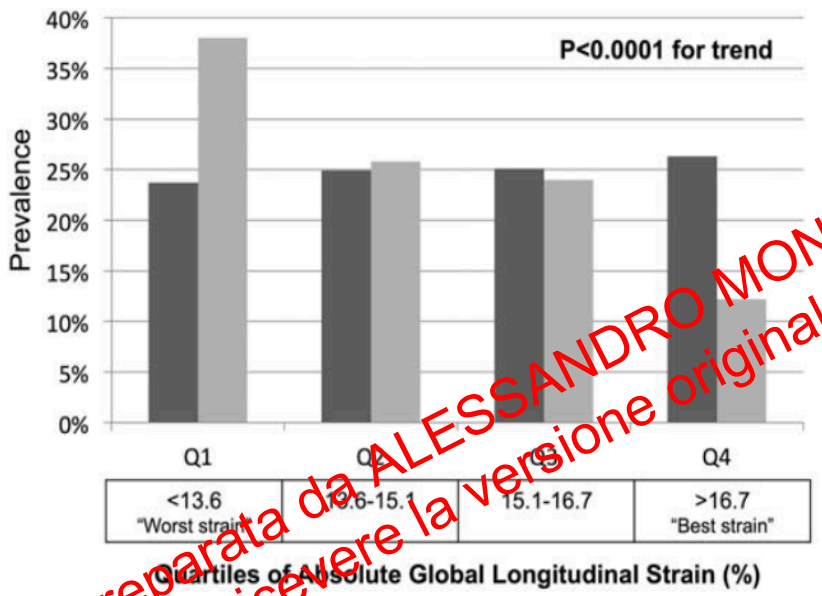


Fig. 2. Quartiles of global longitudinal strain in NAFLD participants compared to non-NAFLD. NAFLD was associated with worse global longitudinal strain, compared to non-NAFLD ($P < 0.0001$ for trend).

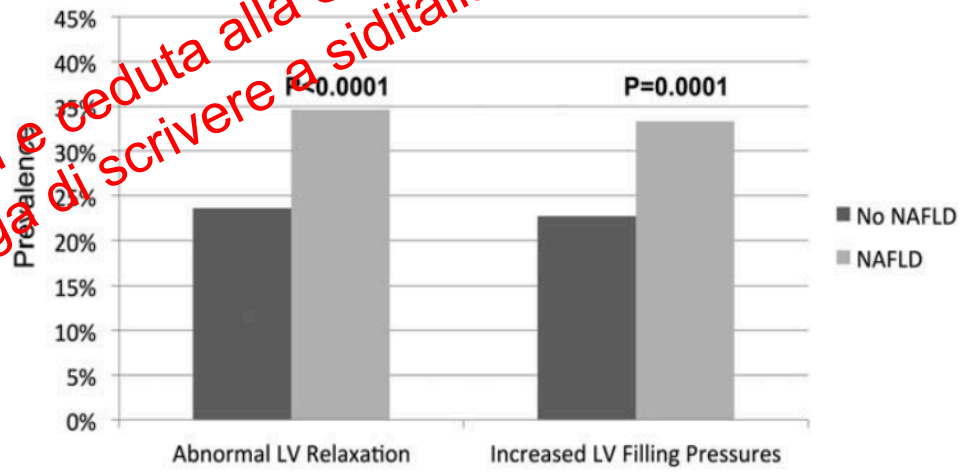


Fig. 3. Markers of subclinical diastolic dysfunction in NAFLD participants compared to non-NAFLD. Abnormal LV relaxation = lateral tissue Doppler e' velocity <10 cm/s. Increased LV filling pressures = lateral E/e' ratio ≥12 or left atrial volume index ≥34 mL/m$^2$. NAFLD was associated with both abnormal LV relaxation ($P < 0.0001$) and increased LV filling pressures ($P = 0.0001$), compared to non-NAFLD.

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VanWagner LB *et al*. Hepatology 2015; 62: 773-83

# Non-alcoholic fatty liver disease is independently associated with left ventricular hypertrophy in hypertensive Type 2 diabetic individuals

Cross-sectional study: n= 116 older T2DM patients (mean age 68±6 yrs; 53% with NAFLD on US) without prior history of CHD and liver diseases

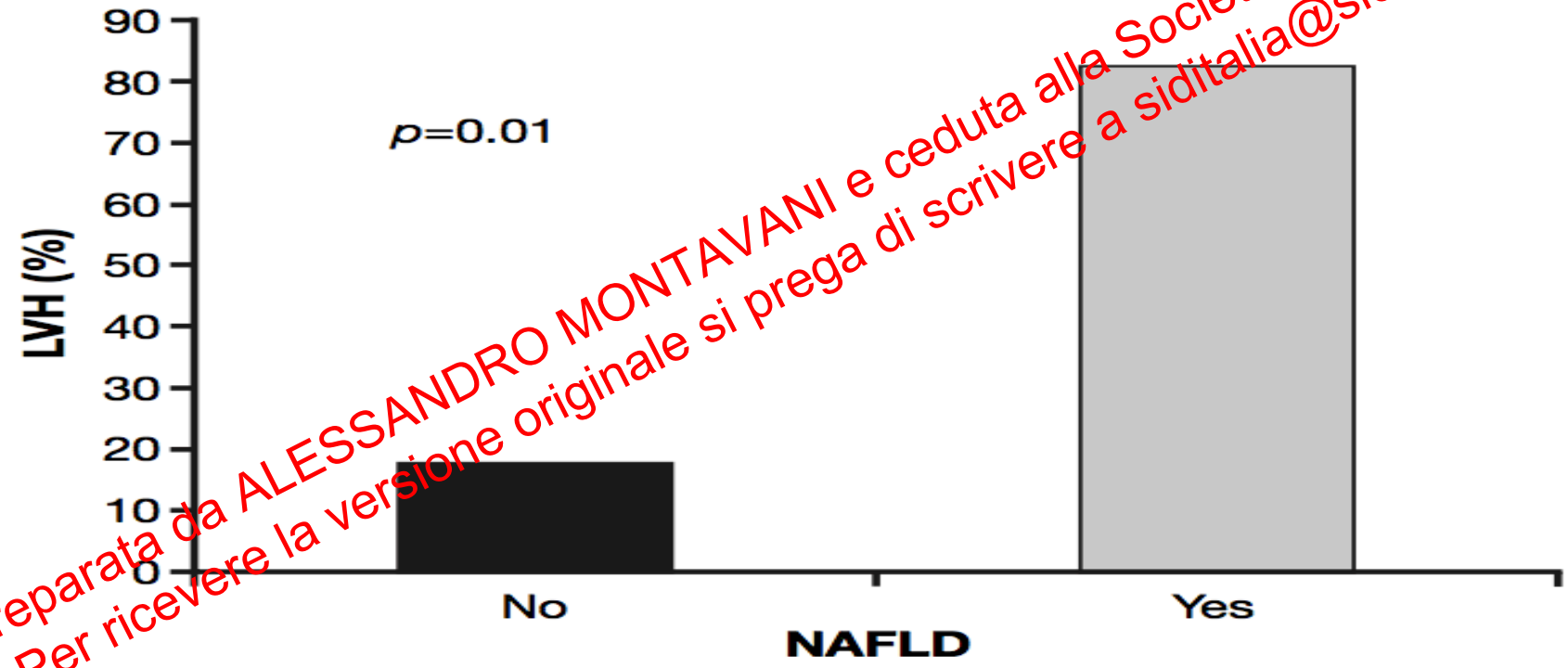


Fig. 1 - *Prevalence of left ventricular hypertrophy (LVH) (as detected by echocardiography) according to the presence of ultrasound-diagnosed non-alcoholic fatty liver disease (NAFLD) in Type 2 diabetic patients (no.=116).*

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Mantovani A *et al*. J Endocrinol Invest 2012;35:215-18

# KEY MESSAGE - 3

- There is strong evidence of a significant relationship between NAFLD (detected by imaging or histology) and myocardial abnormalities both in obese adolescents and in adults with and without type 2 diabetes.

- This relationship appears to be statistically significant even after adjusting for overweight/obesity, hypertension, and other coexisting MetS features.

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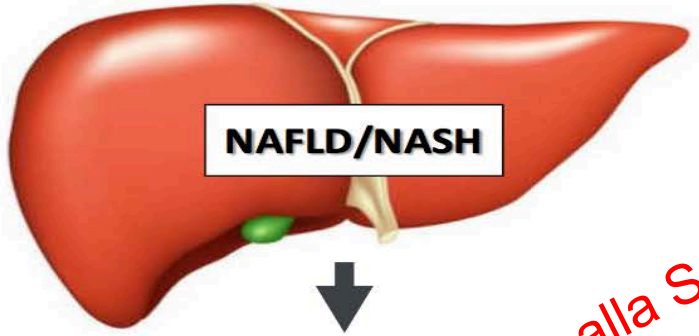
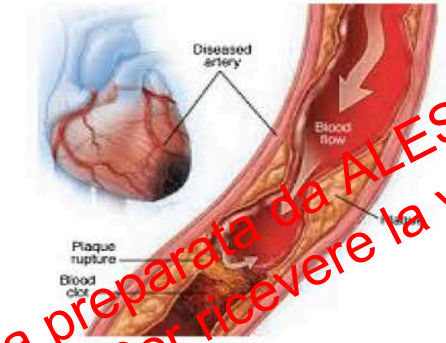
# NAFLD AND CORONARY HEART DISEASE




**NAFLD-related cardiac complications**




**Coronary Heart Disease**

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Mantovani A *et al.* Dig Dis Sci 2016;61:1246-67

Review

# A systematic review: Burden and severity of subclinical cardiovascular disease among those with nonalcoholic fatty liver; Should we care?

Ebenezer T. Oni [a], Arthur S. Agatston [a,b], Michael J. Blaha [c], Jonathan Fialkow [d], Ricardo Cury [d,k], Andrei Sposito [e], Raimund Erbel [f], Ron Blankstein [g], Ted Feldman [a], Mouaz H. Al-Mallah [h], Raul D. Santos [i], Matthew J. Budoff [j], Khurram Nasir [a,b,c,l,*]

**In total, 27 cross-sectional study included in the meta-analysis:**

- **16 studies for association between NAFLD and *carotid IMT/plaques***
- **7 studies for association between NAFLD and *coronary artery calcification***
- **7 studies for association between NAFLD and *arterial stiffness***
- **6 studies for association between NAFLD and *endothelial* dysfunction**

*Conclusion:* There is evidence to support the association of NAFLD with subclinical atherosclerosis independent of traditional risk factors and metabolic syndrome. However, there is need for future longitudinal studies to review this association to ascertain causality and include other ethnic populations.

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Oni ET, et al. *Atherosclerosis.* 2013;230:258-267.

# Prevalence of Nonalcoholic Fatty Liver Disease and Its Association With Cardiovascular Disease Among Type 2 Diabetic Patients

**Cross-sectional study: n=2,839 T2DM outpatients (mean age 65±6 yrs; 69% NAFLD on US)**

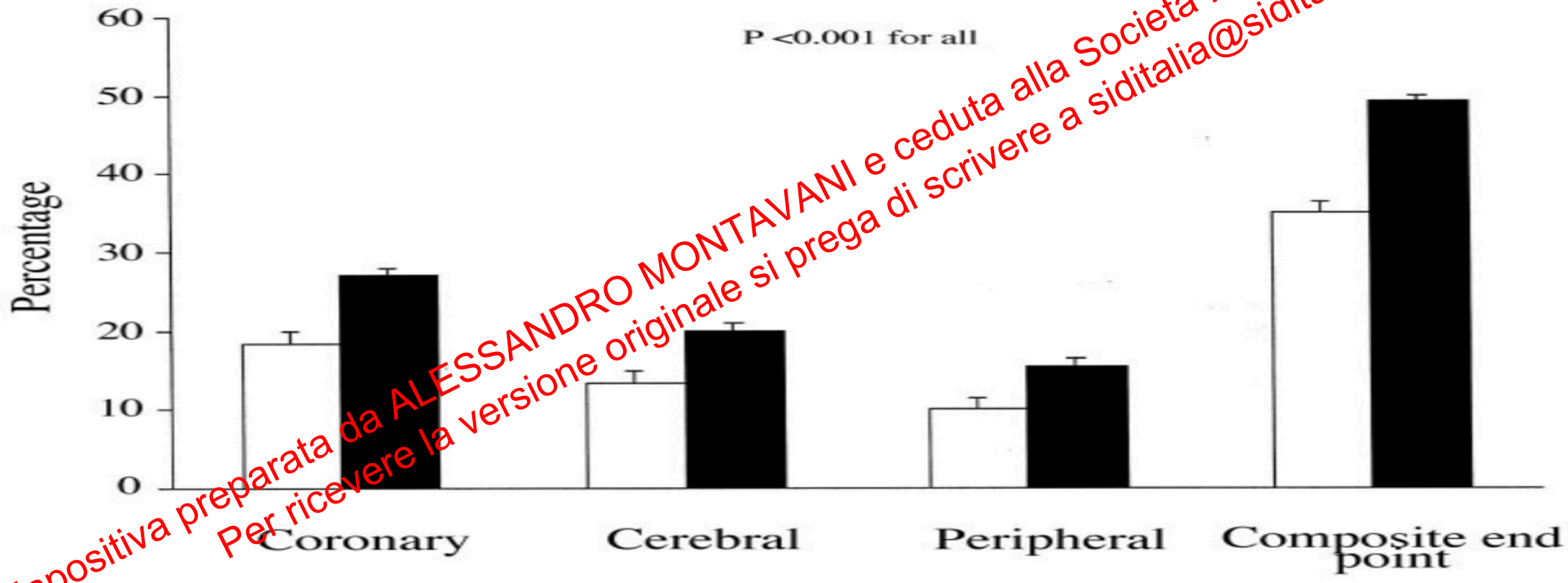


**Figure 2**—*Age- and sex-adjusted prevalence of CVD in type 2 diabetic adults with (■) and without (□) NAFLD. Data are expressed as percentages ± SE. P < 0.001 for differences between the groups.*

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Targher *et al*. Diabetes Care 2007 30:1212–18

# Prevalence of Nonalcoholic Fatty Liver Disease and Its Association With Cardiovascular Disease Among Type 2 Diabetic Patients

**Cross-sectional study: N=2,839 T2DM patients (mean age 65±6 yrs; 69% NAFLD on US)**


**Figure 3**—*Association between NAFLD and prevalent CVD in type 2 diabetic adults with and without NAFLD (n = 2,392). Data are expressed as ORs ± 95% CI. *The multiple adjustment reported in the third and fourth bars was as follows: age, sex, BMI, smoking status, diabetes duration, A1C, LDL cholesterol, and current use of medications (hypoglycemic, antihypertensive, lipid-lowering, or antiplatelet drugs).*

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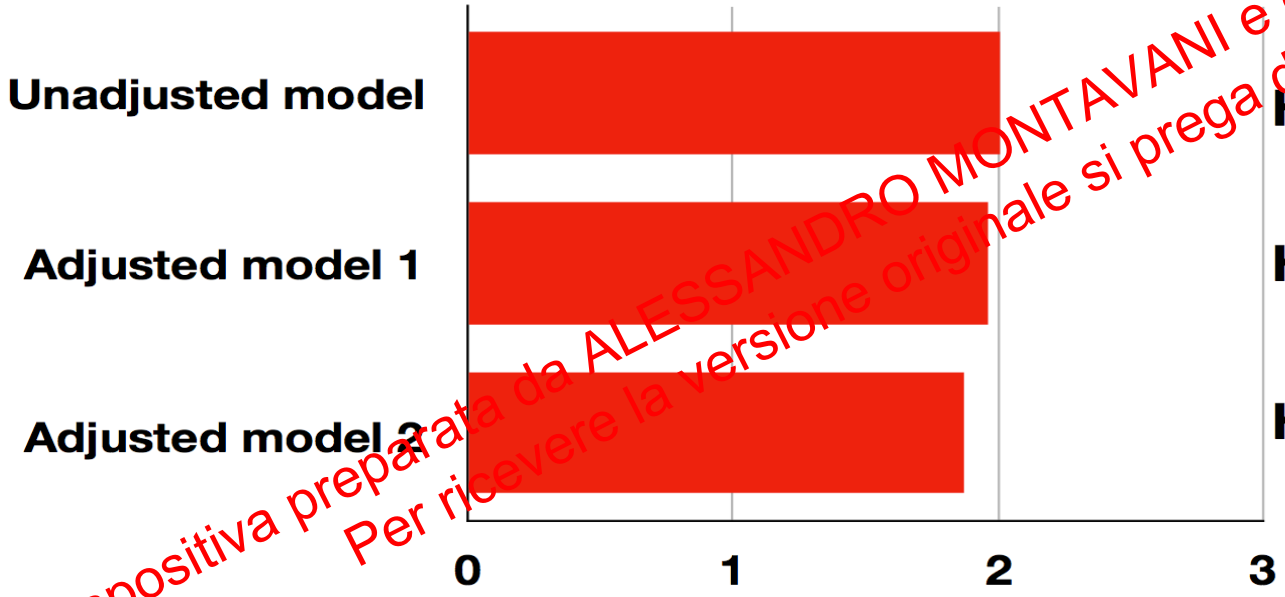
Targher *et al*. Diabetes Care 2007 30:1212–1218

# Nonalcoholic Fatty Liver Disease Is Independently Associated With an Increased Incidence of Cardiovascular Events in Type 2 Diabetic Patients

Longitudinal study: N=2,103 T2DM outpatients (mean age 60±4 yrs; 63.3% NAFLD on US) without manifest CVD and/or secondary causes of chronic liver disease; mean follow-up 6.5 years

**Logistic Regression Analysis - Association between NAFLD and incident CVD events (myocardial infarction, ischemic stroke, coronary revascularization, or cardiovascular death)**




HR 2.01 (95% CI 1.4-2.9), P<0.01

HR 1.96 (95% CI 1.4-2.7), P<0.01

HR 1.87 (95% CI 1.2-2.6), P<0.01

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**Model 1:** adjusted for sex, age, smoking, diabetes duration,HbA1C, LDL, and medications (hypoglycemic, antihy-pertensive, lipidowering, or antiplatelet drugs; **model 2:** model 1 plus metabolic syndrome.

Targher *et al*. Diabetes Care 2007 30:2119–2121

# NAFLD Predicts Incident CVD Events

**Table 2. Principal prospective and retrospective studies of the risk of CVD mortality and morbidity in patients with NAFLD (defined by biopsy or imaging only).**

| Study and year | Study design, sample size, population and mean follow up | Diagnosis of NAFLD | Main findings |
|---|---|---|---|
| Ekstedt M *et al.* 2006 [23] | Retrospective cohort<br>129 Sweden NAFLD patients, 13.7 years | Biopsy* | Patients with NASH, but not those with simple steatosis, had higher rates of all-cause (~2-fold), CVD (~2-fold) and liver-related (~10-fold) mortality than the general population matched for age and sex |
| Ekstedt M *et al.* 2014 [24] | Retrospective cohort<br>229 Sweden NAFLD patients, 26.4 years | Biopsy* | NAFLD patients had increased risk of death (HR 1.29, 95% CI [illegible]-1.59), with a high risk of death from CVD (HR 1.55, 95% CI 1.11-2.15) and liver-related disease (HR 3.2, 95% CI 1.05-9.81). NAFLD activity score (NAS) was not able to predict all-cause death, whereas fibrosis stage predicted all-cause, CVD and liver-related death |
| Stepanova M *et al.* 2012 [80] and Lazo M *et al.* 2011 [91] | National-based cohort<br>11,371 US adults from the Third National Health and Nutrition Examination Survey 1988-94, 14.5 years | Ultrasound* | No significant association between NAFLD and all-cause and cause-specific (CVD, cancer and liver) mortality |
| Wong VW *et al.* 2011 [82] | Prospective cohort<br>465 Chinese patients with coronary heart disease as diagnosed by coronary angiography, 1.8 years | Ultrasound‡ | NAFLD was independently associated with an increased prevalence of CVD at baseline but there was no significant association between NAFLD and risk of incident CVD events |
| Zhou YJ *et al.* 2012 [85] | Community-based cohort<br>3543 Chinese adult individuals, 4 years | Ultrasound* | Patients with NAFLD had ~3-fold higher rates of all-cause and CVD mortality than those without NAFLD |
| Treeprasertsuk S *et al.* 2012 [86] | Retrospective community-based cohort<br>309 US NAFLD patients, 11.5 years | Ultrasound/ computed tomography¶ | Framingham risk score accurately predicted the higher 10-year coronary heart disease risk in NAFLD patients and was the only variable significantly associated with the risk of developing new-onset coronary heart disease events in this patient cohort |
| Targher G *et al.* 2007 [87] | Prospective cohort<br>2103 Italian outpatients with type 2 diabetes without viral hepatitis and CVD at baseline, 6.5 years | Ultrasound§ | NAFLD was associated with an increased risk of fatal and nonfatal CVD events (HR 1.87, 95% CI 1.2-2.9) independently of age, sex, body mass index, smoking, diabetes duration, hemoglobin A1c, LDL-cholesterol, metabolic syndrome features, medication use |
| Söderberg C *et al.* 2010 [88] | Retrospective cohort<br>118 Sweden NAFLD patients, 24 years | Biopsy* | Patients with NASH, but not those with simple steatosis, had higher rates of all-cause (~2-fold), CVD (~2-fold) and liver-related mortality than the general population matched for age and sex |
| Rafiq N *et al.* 2009 [89] | Retrospective cohort<br>173 US NAFLD patients, 13 years | Biopsy* | CVD, cancer and liver-related complications were the most common causes of mortality in this cohort of NAFLD patients |
| Matteoni CA *et al.* 1999 [90] | Retrospective cohort<br>132 US NAFLD patients, 18 years | Biopsy* | Patients with NASH had higher rates of all-cause and liver-related mortality than those without the disease. CVD mortality did not differ between the groups |
| Kim D *et al.* 2013 [92] | National-based cohort study<br>11,154 US adults from the Third National Health and Nutrition Examination Survey, 14.5 years | Ultrasound and advanced fibrosis score systems * | NAFLD was not associated with increased all-cause mortality. However, NAFLD with advanced hepatic fibrosis (defined by NAFLD fibrosis score, APRI index or FIB-4) was independently associated with a 69% increased risk of all-cause mortality. Increase in mortality was almost entirely from CVD causes (for NFS: HR 3.46, 95% CI 1.91-6.25; for APRI: HR 2.53, 95% CI 1.33-4.83; for FIB-4: HR 2.68, 95% CI 1.44-4.99) |
| Jepsen P *et al.* 2003 [93] | Retrospective cohort<br>1804 Danish hospitalized patients with NAFLD, 6.2 years | Ultrasound* | Patients with NAFLD had higher rates of all-cause (2.6-fold), CVD (2.1-fold) and liver-related (19.7-fold) mortality than the general population |
| Haring R *et al.* 2009 [94] | Population-based cohort<br>4160 German individuals, 7.3 years | Ultrasound* | NAFLD was associated with an increased risk of all-cause and CVD (HR 6.22, 95% CI 1.2-31.6) mortality in men, independently of age, sex, waist circumference, alcohol consumption, physical activity, civil status, equalized income, functional comorbidity index, blood pressure, diabetes status |
| Hamaguchi M *et al.* 2007 [95] | Community-based cohort<br>1637 Japanese individuals, 5 years | Ultrasound‡ | NAFLD was associated with an increased risk of nonfatal CVD events (HR 4.10, 95% CI 1.6-10.7), independently of age, sex, body mass index, alcohol intake, smoking history, LDL-cholesterol and metabolic syndrome features |
| Dunn MA *et al.* 2013 [96] | Retrospective cohort<br>2343 US type 2 diabetics seen in the primary care and specialty clinics of a large integrated delivery network, 5 years | Computed tomography§ | No significant association was found between NAFLD and risk of all-cause mortality and cause-specific (CVD, cancer and liver) mortality and morbidity. NAFLD patients (steatosis >30% on imaging) averaged 8 years younger than those without NAFLD |
| Dam-Larsen S *et al.* 2004 [97] | Retrospective cohort<br>109 Danish NAFLD patients (without NASH at baseline), 16.7 years | Biopsy* | No significant difference in mortality rates between patients with simple steatosis and the general population |
| Adams LA *et al.* 2005 [98] | Retrospective cohort<br>420 US NAFLD patients, 7.6 years | Biopsy/imaging* | Patients with NAFLD (especially those with cirrhosis and NASH) had higher rates of all-cause, CVD and liver-related mortality than the age and sex-matched general population |

*Study outcome was all-cause and cause-specific mortality.
‡Study outcome was nonfatal coronary heart disease and stroke.
§Study outcome was a combined end point of CVD mortality and nonfatal myocardial infarction, ischemic stroke and coronary revascularization procedures.
‖Study outcome was a combined end point of CVD mortality and nonfatal myocardial infarction and coronary revascularization procedures.
¶Study outcome was a combined end point of CVD mortality and nonfatal congestive heart failure, angina, myocardial infarction and coronary revascularization procedures.

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Byrne CD, Targher G. *J Hepatol.* 2015; 62:S47-S64.

# Nonalcoholic fatty liver disease is independently associated with an increased incidence of cardiovascular disease in adult patients with type 1 diabetes

**Retrospective cohort of 286 outpatients with T1DM (mean age 43±14 yrs; mean BMI 25±4 kg/m$^2$; 52% with NAFLD on US) without secondary causes of chronic liver diseases; mean follow-up: 5.3 years**


**Fig. 2.** Cumulative incidence rates of CVD (combined endpoint) in 286 adult patients with type 1 diabetes stratified by NAFLD on ultrasonography at baseline. p-Values < 0.001 for between-group difference by the $\chi^2$ test.

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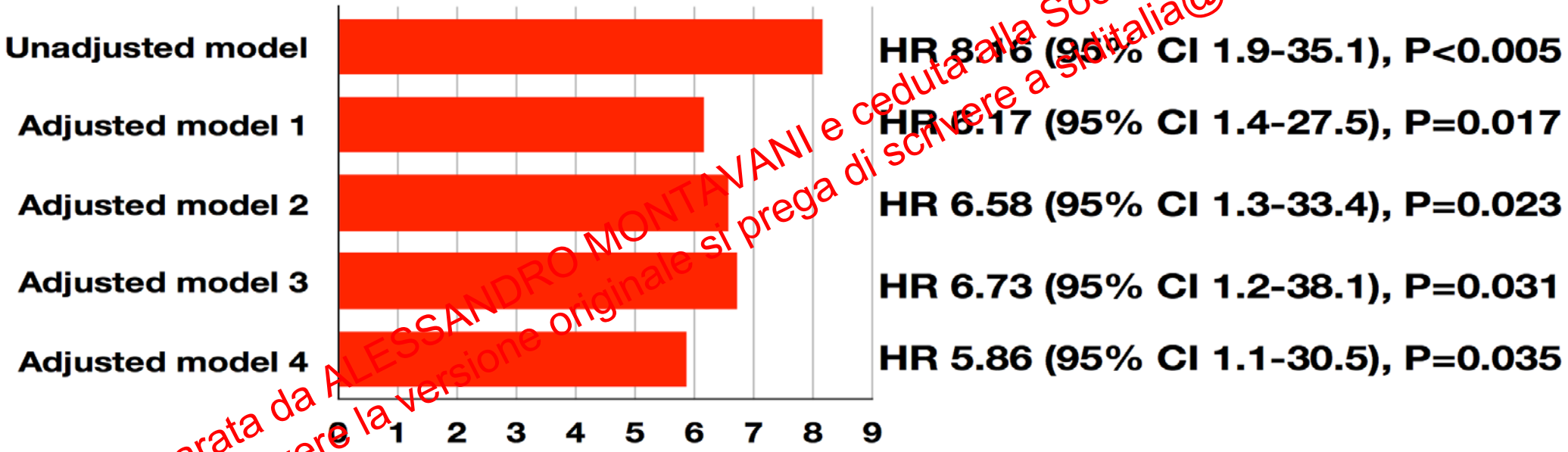
**CVD events**: **a combined endpoint** ***inclusive*** **of nonfatal IHD, nonfatal ischemic stroke or revascularization procedures**

Mantovani A *et al*. Int J Card 2016;225:387–91

# Nonalcoholic fatty liver disease is independently associated with an increased incidence of cardiovascular disease in adult patients with type 1 diabetes

## Cox regression analyses – Association between NAFLD and risk of incident CVD events in T1DM adults

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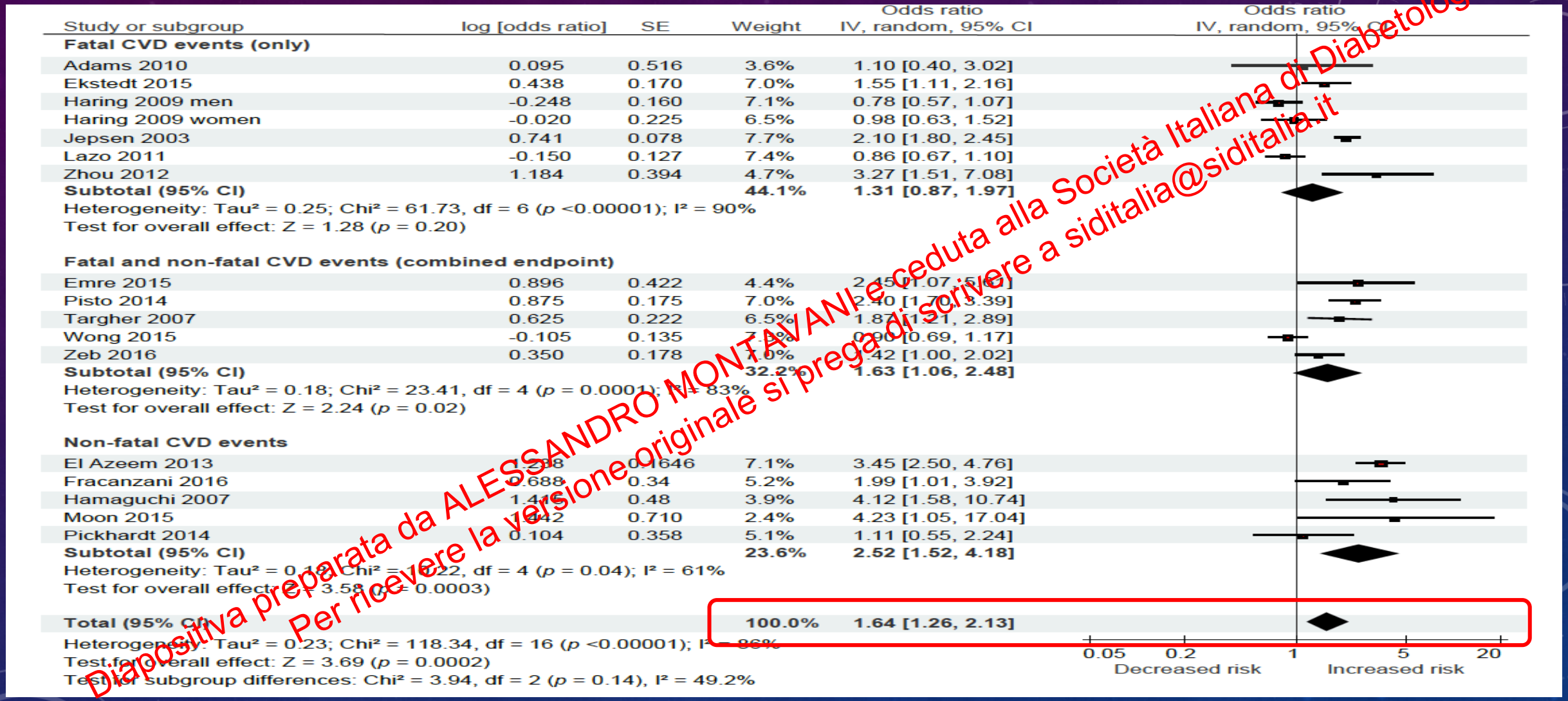
**Model 1:** adjusted for age and sex; **Model 2:** adjusted for age, sex, BMI, smoking, diabetes duration, HbA1c, hypertension, dyslipidemia and CKD; **Model 3:** adjustment for the same variables included in model 2 ***plus*** prior history of IHD and serum GGT; **Model 4**: adjusted for age, sex, diabetes duration, smoking and temporal changes in BMI, HbA1c, eGFR, hypertension and dyslipidemia over the follow-up.

Mantovani A *et al*. Int J Card 2016;225:387–91

# Ultrasound- or Biopsy-Diagnosed NAFLD Predicts Fatal and Non-fatal CVD Events: Meta-analysis

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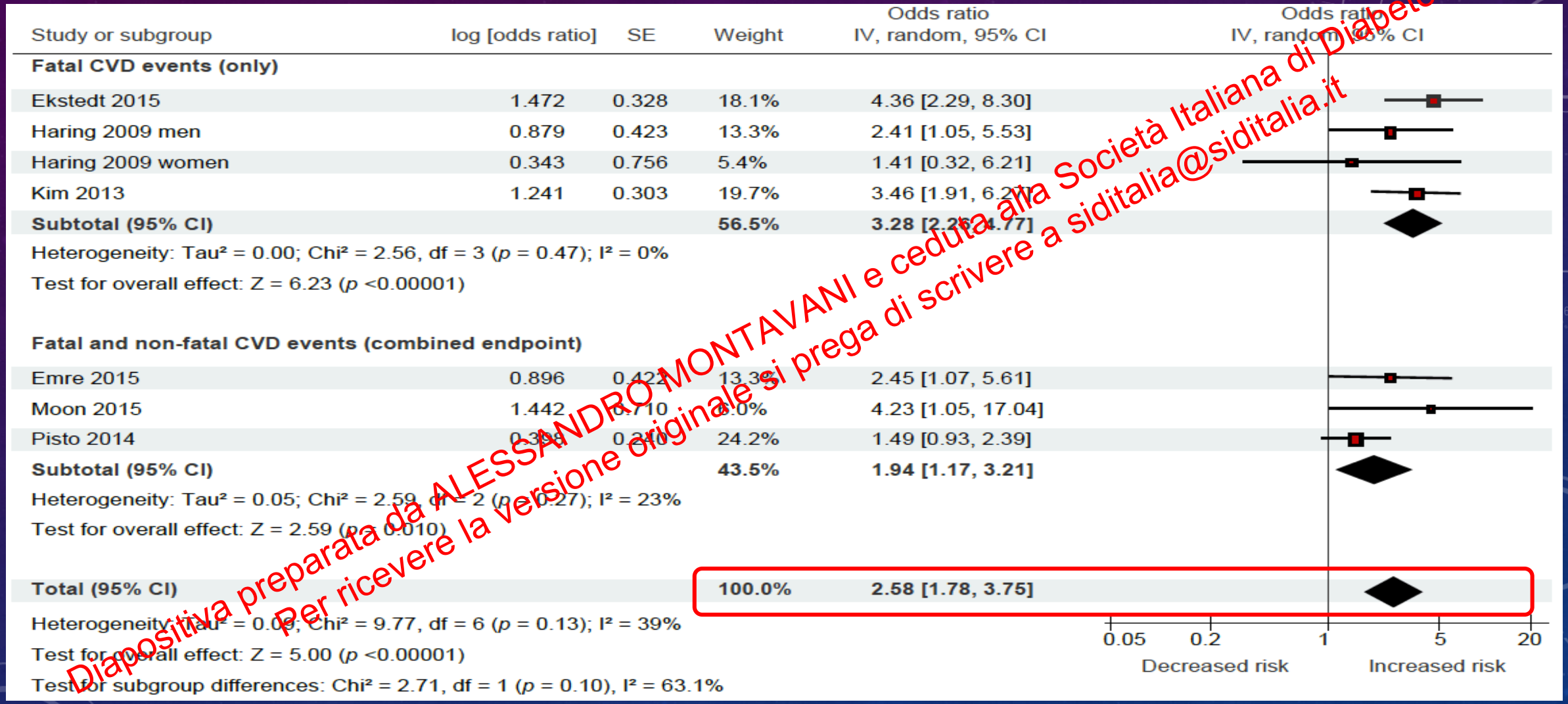
***N*** **=16 observational studies with 34,043 adult individuals (36.3% with NAFLD)**
**Approximately 2,600 CVD outcomes (>70% CVD deaths)**

Targher G, et al. *J Hepatol.* 2016;65:589-600

# Severity of NAFLD (either by imaging ± biomarkers or by histology) Predicts Fatal and/or Non-fatal CVD Events: Meta-analysis

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***N*** **=16 observational studies with 34,043 adult individuals (36.3% with NAFLD)**
**Approx. 2,600 CVD outcomes (>70% CVD deaths)**

Targher G, et al. *J Hepatol.* 2016;65:589-600

# KEY MESSAGE - 4

- **Clear epidemiological evidence supports the notion that NAFLD (regardless of the method used for diagnosing it) is significantly and independently associated with an increased risk of CVD morbidity and mortality in both patients with and without diabetes.**

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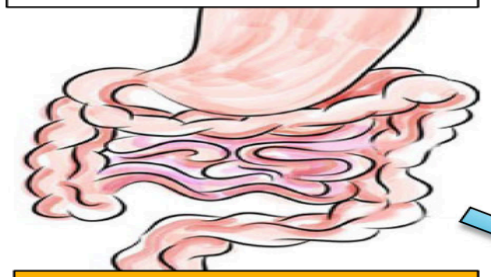
# PUTATIVE MECHANISMS LINKING NAFLD WITH CARDIOVASCULAR, CARDIAC AND ARRHYTMIC COMPLICATIONS

**ALTERED GUT MICROBIOTA**



GLP-1
Endotoxin/bacteria
SCFAs

Fiaf
Endotoxin/bacteria
SCFAs

**EXPANDED AND INFLAMED ADIPOSE TISSUE**

↑ Nov-esterified fatty acids
↑ Inflammatory adipocytokines
↑ Thrombospondin-1
↓ Adiponectin

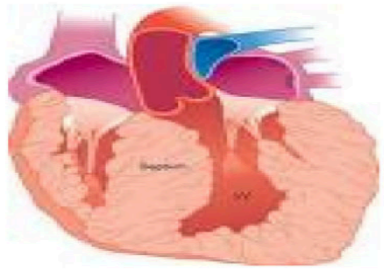
**NAFLD/NASH**

**Lipids and Lipoproteins & Insulin resistance**
(e.g.↑ VLDL, ↓ HDL-C, ↑ small, dense LDL-C, ↑ non-esterified fatty acids)

**Pro-inflammatory molecules**
(e.g. ↑ C-reactive protein, IL-6, TNF-alpha and other cytokines )

**Vasoactive and Thrombogenic molecules**
(e.g. ↑ endothelin, TGF-beta, fibrinogen, factor VIII, PAI-1, ↓ FGF-21)


**Structural and electrical remodelling**



**CARDIAC STEATOSIS, INCREASED PERICARDIAL FAT**
**AORTIC-VALVE SCLEROSIS, MITRAL ANNULUS CALCIFICATION**
**CORONARY HEART DISEASE**

**LEFT VENTRICULAR DYSFUNCTION & HYPERTROPHY**
**CONGESTIVE HEART FAILURE**
**CARDIAC ARRHYTHMIAS (ATRIAL FIBRILLATION)**

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Mantovani A *et al.* Dig Dis Sci 2016;61:1246-67

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# HOW SHOULD CLINICIANS USE THESE RESULTS IN CLINICAL PRACTICE?

Caravaggio, San Girolamo, 1605-1606, detail

CLINICAL PRACTICE GUIDELINES

# EASL–EASD–EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease

**European Association for the Study of the Liver (EASL) · European Association for the Study of Diabetes (EASD) · European Association for the Study of Obesity (EASO)**

## Recommendations

- Cardiovascular complications frequently dictate the outcome of NAFLD and screening of the cardiovascular system is mandatory in all persons, at least by detailed risk factor assessment (**A1**)

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Diabetologia 2016;59:1121–40

# CONCLUSIONS - 1

- Mounting evidence indicates that NAFLD is associated with an increased risk of cardiovascular disease, independently of multiple cardio-metabolic risk factors.

- Convincing evidence also substantiates a link between NAFLD and functional and structural myocardial abnormalities in adults with and without coexisting features of the metabolic syndrome.

- Clinicians who manage patients with NAFLD (especially those with NASH) should not focus only on liver disease, but should also recognize the increased risk of cardiovascular, cardiac and arrhythmic complications and undertake early, aggressive risk factor modification.

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# CONCLUSIONS - 2

- However, it is not yet established whether addition of NAFLD to the currently available risk assessment calculators improves CVD risk prediction.
- Randomized controlled trials with CVD outcomes that focus on treatments for liver disease in NAFLD are also required in order to definitely establish a causal relationship between NAFLD and risk of incident CVD events.
- The ***key question*** of whether the prognostic value of NAFLD in the development and progression of CHD/cardiac diseases is restricted to NASH and advanced fibrosis or is also associated with simple steatosis remains (partly) unresolved.
- Finally, more research is needed to gain mechanistic insights into the pathophysiology linking NAFLD to CHD/cardiac diseases.

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# RINGRAZIAMENTI


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# THANK YOU FOR YOUR ATTENTION!

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# Non-alcoholic fatty liver disease is associated with an increased prevalence of atrial fibrillation in patients with type 2 diabetes

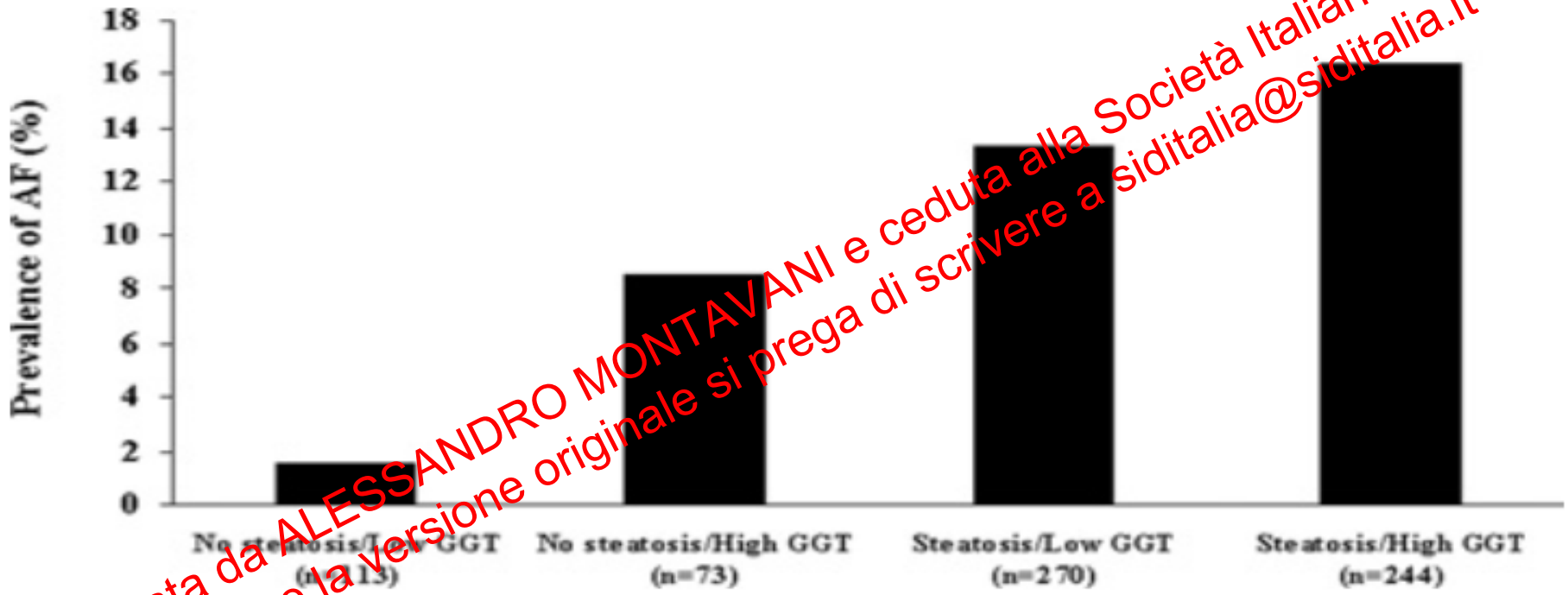


**Figure 1 Prevalence of AF in hospitalized Type 2 diabetic patients stratified by NAFLD status on ultrasound and the median serum GGT concentration**

*P* value <0.001 for trend by the $\chi^2$ test.

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Targher G, Mantovani A et *al.* Clinical Science 2013;125:301–309

# Non-alcoholic fatty liver disease is independently associated with left ventricular hypertrophy in hypertensive Type 2 diabetic individuals

Table 2 - *Multivariate logistic regression analysis. Independent predictors of left ventricular hypertrophy (LVH) in Type 2 diabetic patients.*

| | Odds ratio (95% confidence intervals) | *p* |
|---|---|---|
| Gender (male *vs* female) | 0.66 (0.24-1.87) | 0.44 |
| Age (yr) | 1.03 (0.99-1.08) | 0.15 |
| Diabetes duration (yr) | 1.03 (0.96-1.10) | 0.37 |
| Body mass index (kg/m²) | 0.93 (0.86-1.01) | 0.07 |
| Systolic blood pressure (mmHg) | 1.03 (1.00-1.06) | 0.05 |
| Glycated hemoglobin (%) | 0.95 (0.76-1.16) | 0.62 |
| e-GFR (ml/min/1.73 m²) | 1.01 (0.98-1.05) | 0.38 |
| GGT (U/l) | 1.00 (0.98-1.01) | 0.53 |
| NAFLD (yes/no) | 5.94 (1.47-24.01) | 0.01 |

Cohort size, no.=116. e-GFR: estimated glomerular filtration rate; GGT: γ-glutamyltransferase; NAFLD: non-alcoholic fatty liver diseases.

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Mantovani A *et al*. J Endocrinol Invest 2012;35:215-18