



The 4th World Congress on
**CONTROVERSIES TO CONSENSUS IN DIABETES,
OBESITY AND HYPERTENSION (CODHy)**
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NAFLD/NASH: is it an independent predictor of cardiovascular disease?

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Outline

- NAFLD definition and epidemiology
- NAFLD and metabolic diseases
- NAFLD and preclinical CVD
- NAFLD and clinical CVD (MACE)
- NAFLD as an independent predictor (risk factor) of CVD
- Conclusions

Diapositiva preparata da Enzo Bonora e ceduta alla Società Italiana di Diabetologia. Per avere una versione originale, si prega di scrivere a siditalia@siditalia.it

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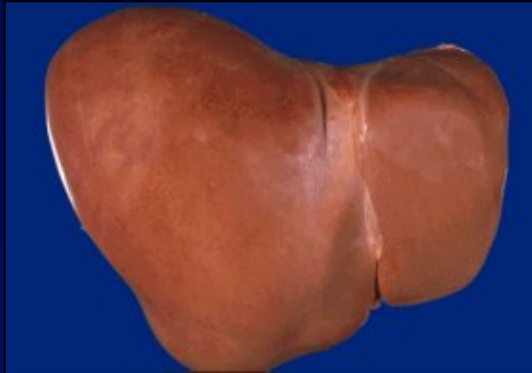
Definition of NAFLD (Non-Alcoholic Fatty Liver Disease)

- Hepatic steatosis (with or without inflammation and fibrosis) occurring **in the absence of:**
 - excessive alcohol consumption
 - other causes of hepatic disease (e.g., virus, medications, iron overload, autoimmunity, etc.)
- **Diagnosis by exclusion (or by assumption?)** because no laboratory test or imaging technique can unequivocally distinguish NAFLD from an hepatic steatosis related to alcohol or other causes

Pitfalls in Diagnosis of NAFLD

- Alcohol intake threshold (e.g. 20 g/day women; 30 g/day men) is arbitrary and questionable (many people are above the threshold)
- Past and not only current alcohol intake might be relevant
- Screening for viral causes of hepatic disease is not so common
- Previous use of hepatotoxic drugs might be underreported and/or overlooked
- Iron overload with liver damage is often underestimated
- A substantial fraction of subjects diagnosed with NAFLD might have a different liver disease

The Spectrum of Pathologic Conditions in NAFLD



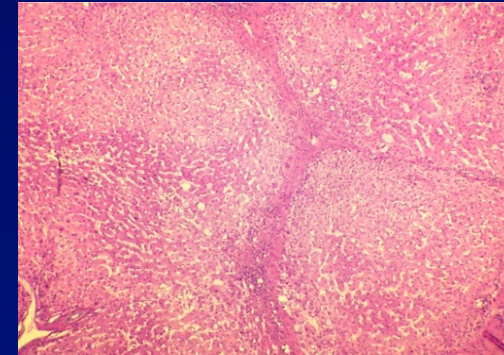
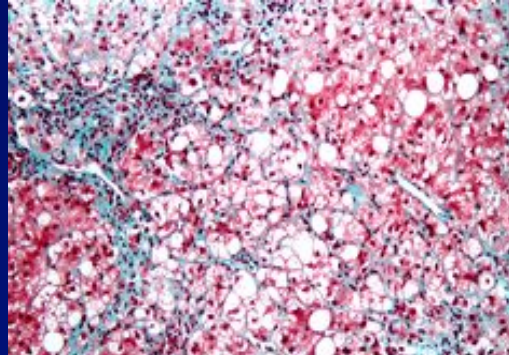
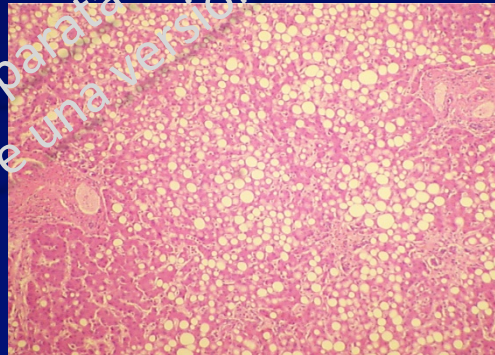
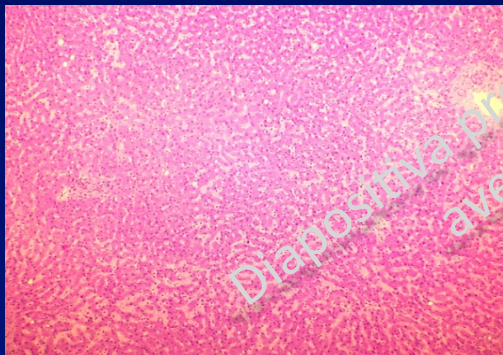
Normal liver



Fatty liver



Liver cirrhosis



Tools for Diagnosing NAFLD

- **Mild-moderate elevation of serum liver enzymes**

Elevated serum liver enzymes is only a surrogate marker of NAFLD

Liver enzymes may be in the normal range in up to 70% of patients with NAFLD

- **Imaging (Ultrasonography, CT, MRI-MRS)**

Imaging has a good sensitivity and specificity for the detection of moderate and severe hepatic steatosis

Imaging cannot be used to accurately determine the severity of liver damage (fatty liver vs. NASH)

- **Liver Biopsy (“gold standard”)**

Prevalence of NAFLD in the General Population According to Diagnostic Tool

- Elevated liver enzymes and clinical features 2-10%
- Brighter liver on ultrasound examination 5-20%
- IHTG >5.5% on MRS 30-35%
- Excess triglycerides on liver histology up to 50%

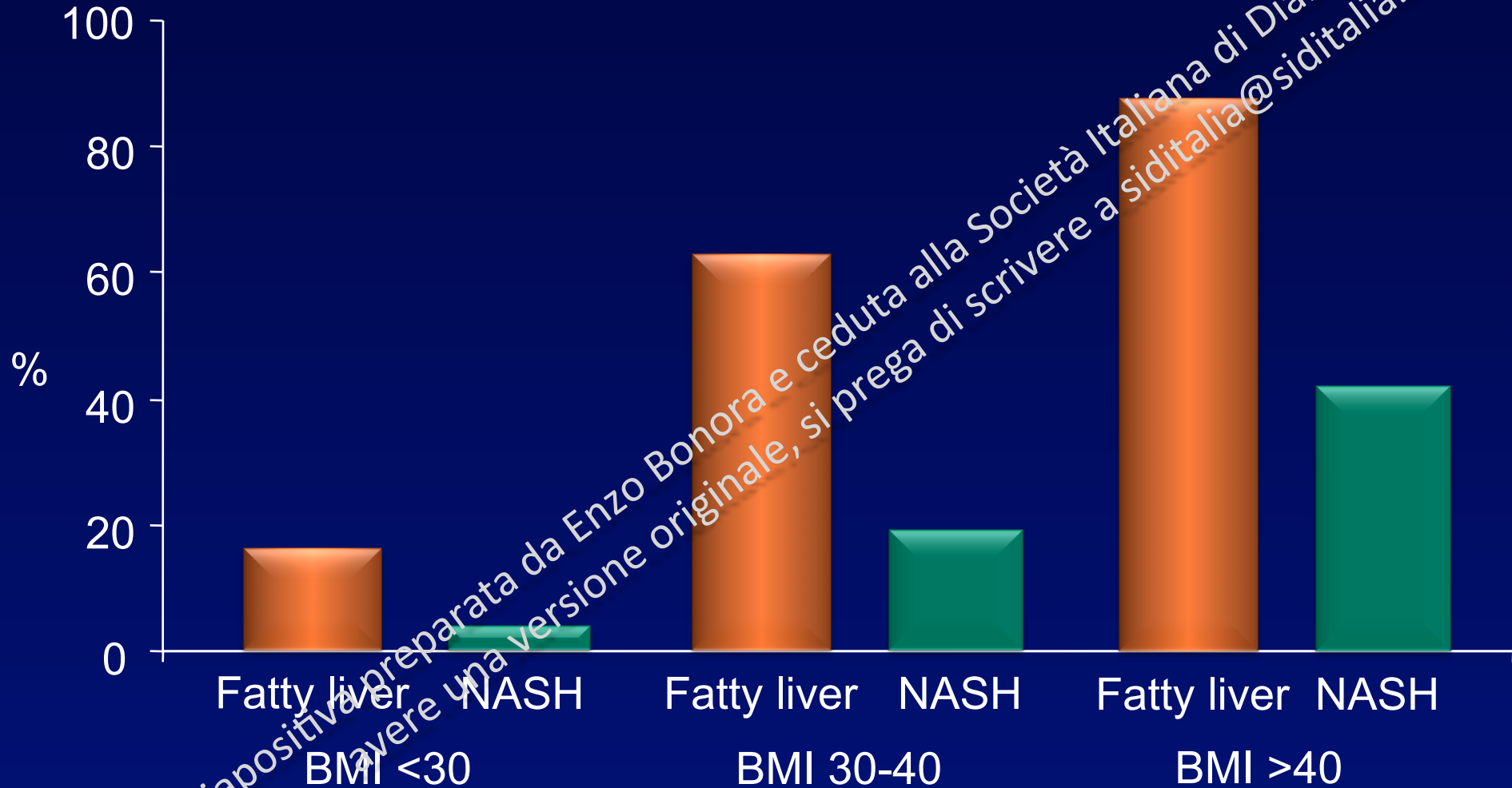
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Prevalence of Fatty Liver and NASH in Obesity from Autopsy and Liver Biopsy Studies



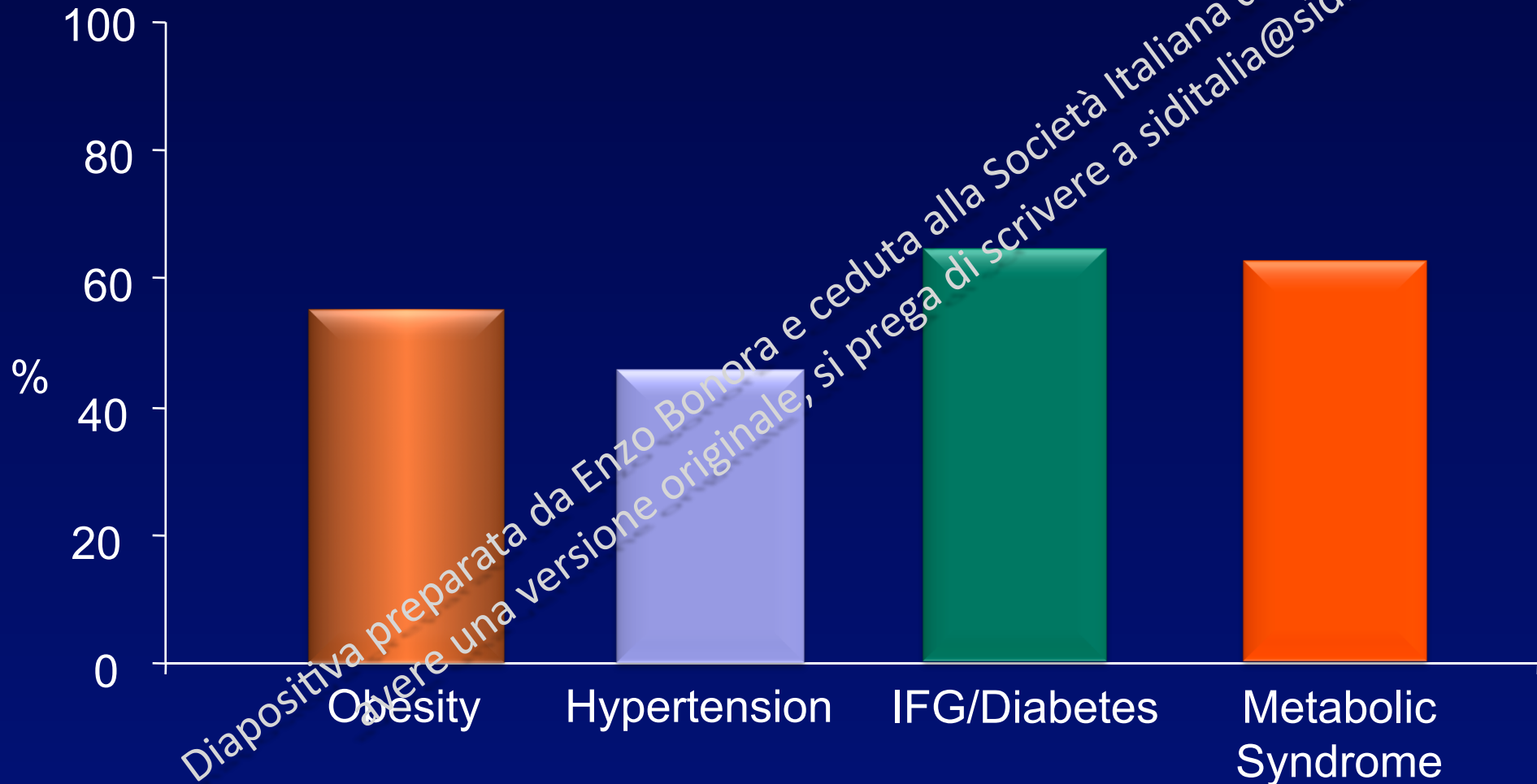
Marcos et al - *Transplantation* 2000; Hilden et al - *Scand J Gastroenterology* 1977;
Lee - *Hum Pathol* 2000; Gholam et al - *Obes Surg* 2002

Prevalence of NAFLD in T2DM

Author	Reference	No. subjects Prevalence	Method
Jimba et al	<i>Diabetic Med</i> 2005; 22:1141-1145	N=342 62%	Ultrasound
Targher et al	<i>Diabetes Care</i> 2007; 30: 1212-1218	N=2,839 69%	Ultrasound
Williams et al	<i>Gastroenterology</i> 2011; 140: 124-131	N=64 74%	Liver biopsy

Prevalence of Obesity, Hypertension, Dysglycemia and Metabolic Syndrome in NAFLD

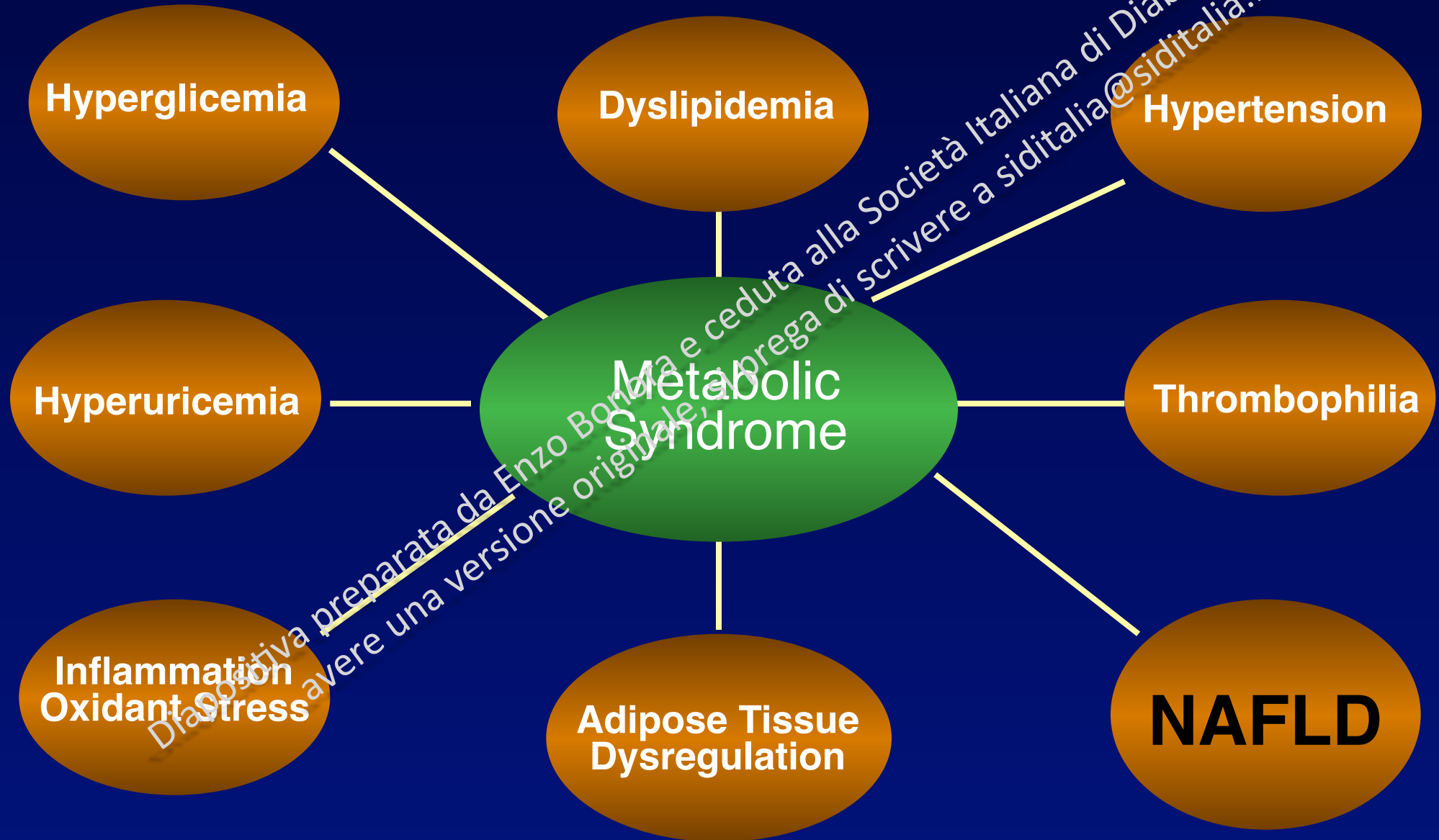
Framingham Heart Study – Speliotes et al - *Hepatology* 2010;51:1979-1987



N=2,589; NAFLD diagnosed by ultrasonography

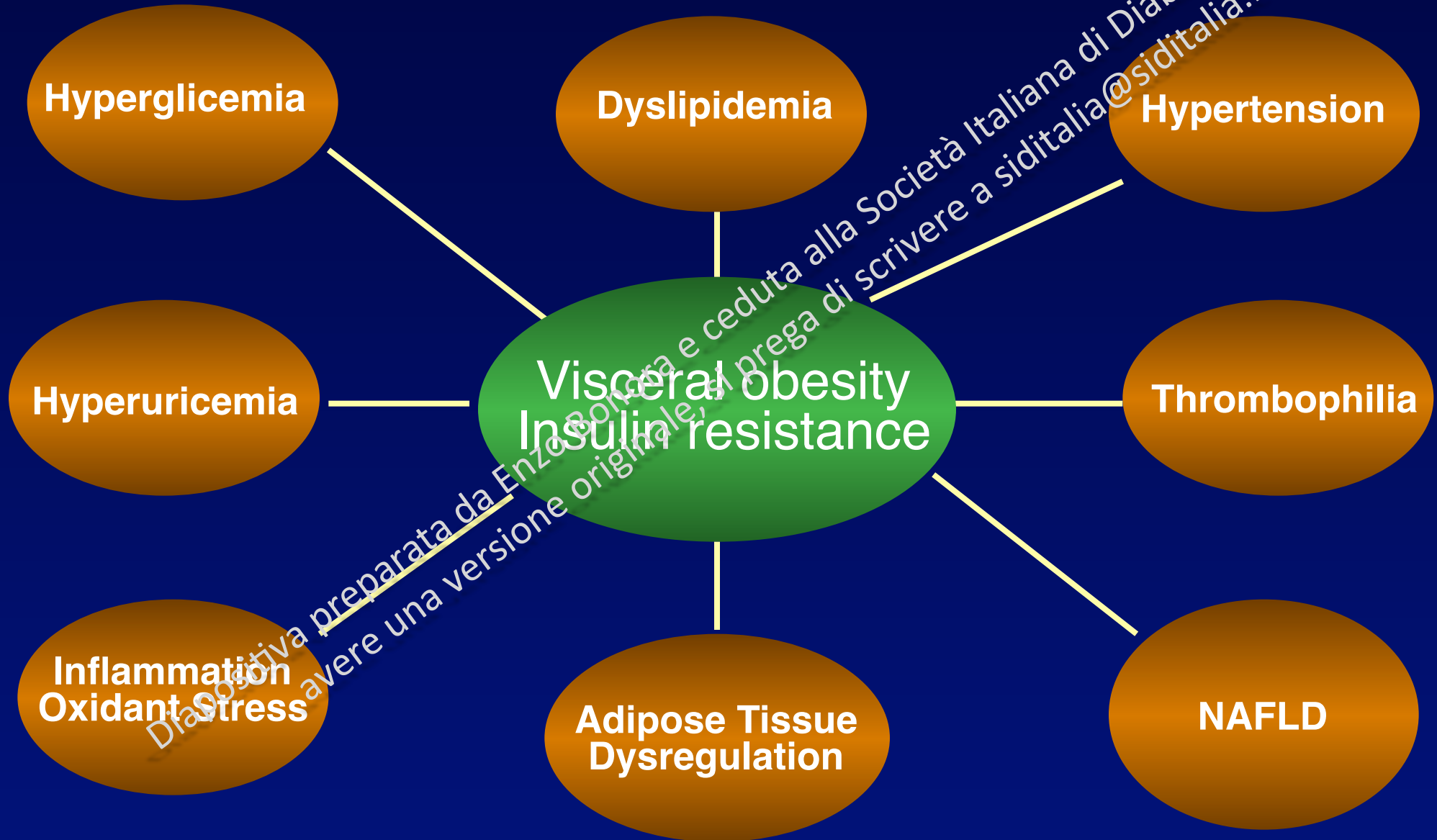
NAFLD is Another Feature of the Metabolic Syndrome

Bonora E & Targher G - *Nat Rev Gastroenterol Hepatol* 2012; 9:372-381



Main Underlying Disorders in the Metabolic Syndrome

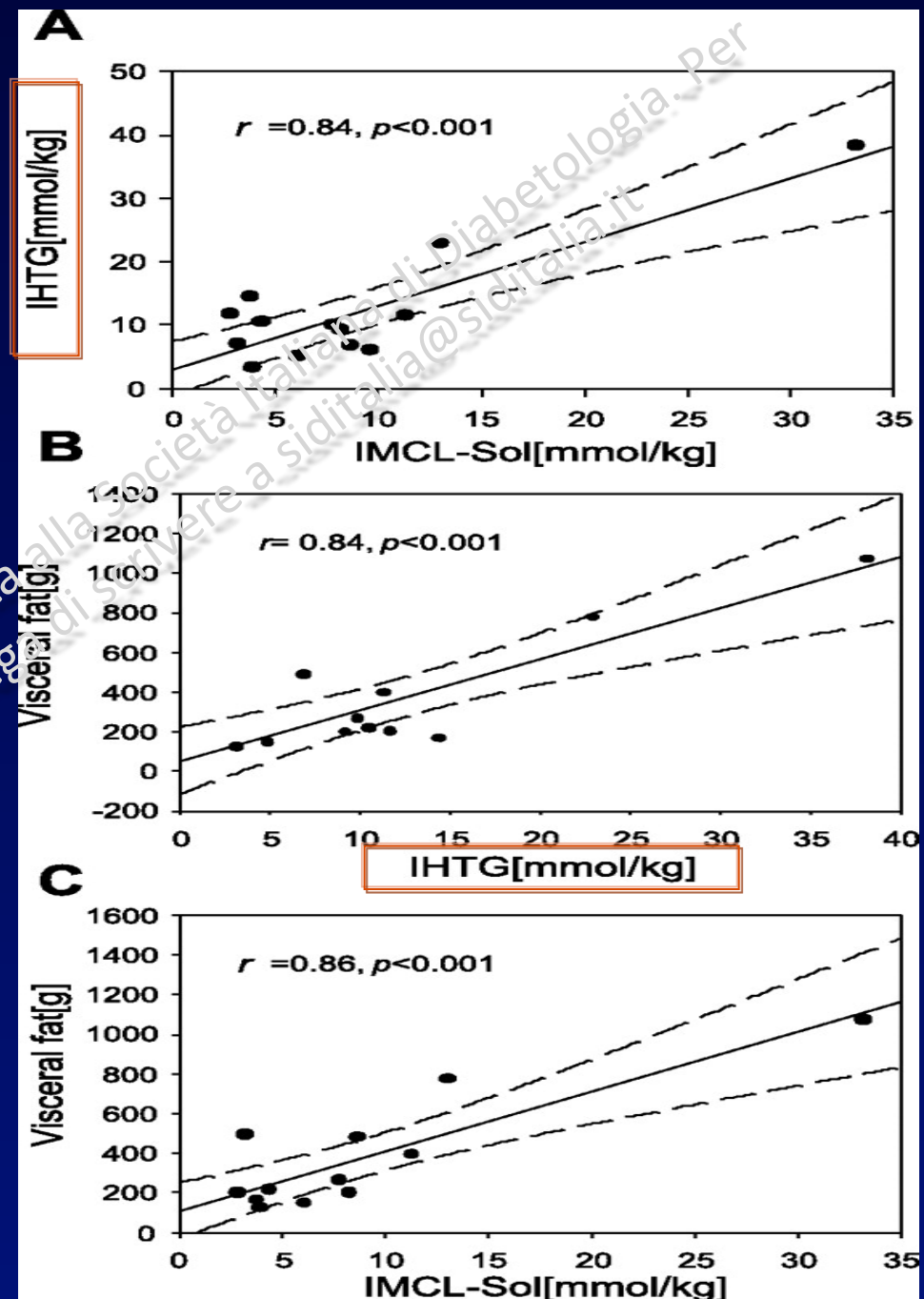
Bonora E & Targher G - *Nat Rev Gastroenterol Hepatol* 2012; 9: 372-381



Intrahepatic Triglycerides are Correlated to Intramyocellular Triglycerides and to Visceral Fat in Humans

Hwang et al
Am J Physiol Endo Metab
2007; 293: E1663-E1669

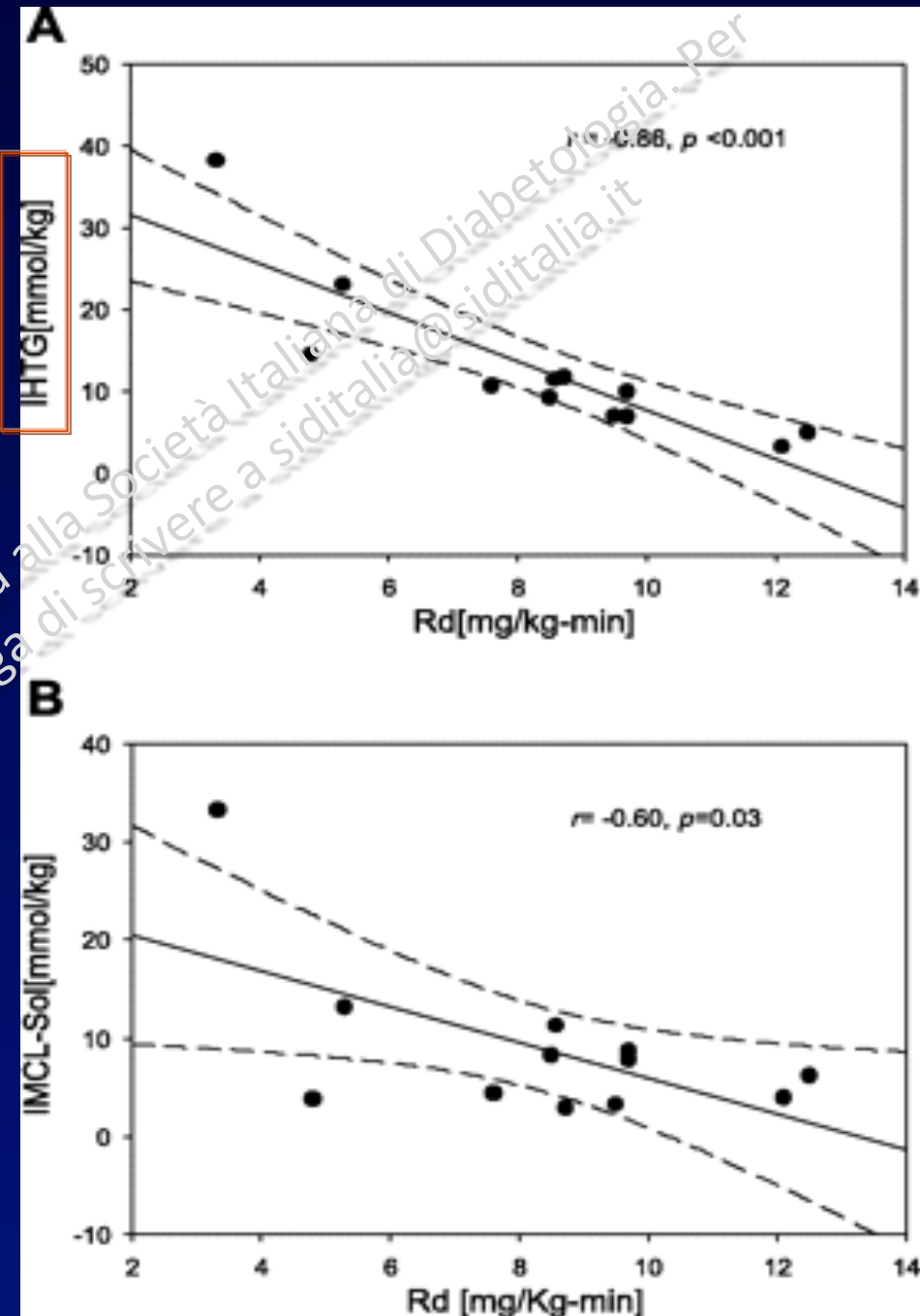
Visceral fat assessed by MRI
IHTG and IMCL assessed by MRS



Intrahepatic Triglycerides and Intramyocellular Triglycerides are Correlated to Insulin Sensitivity in Humans

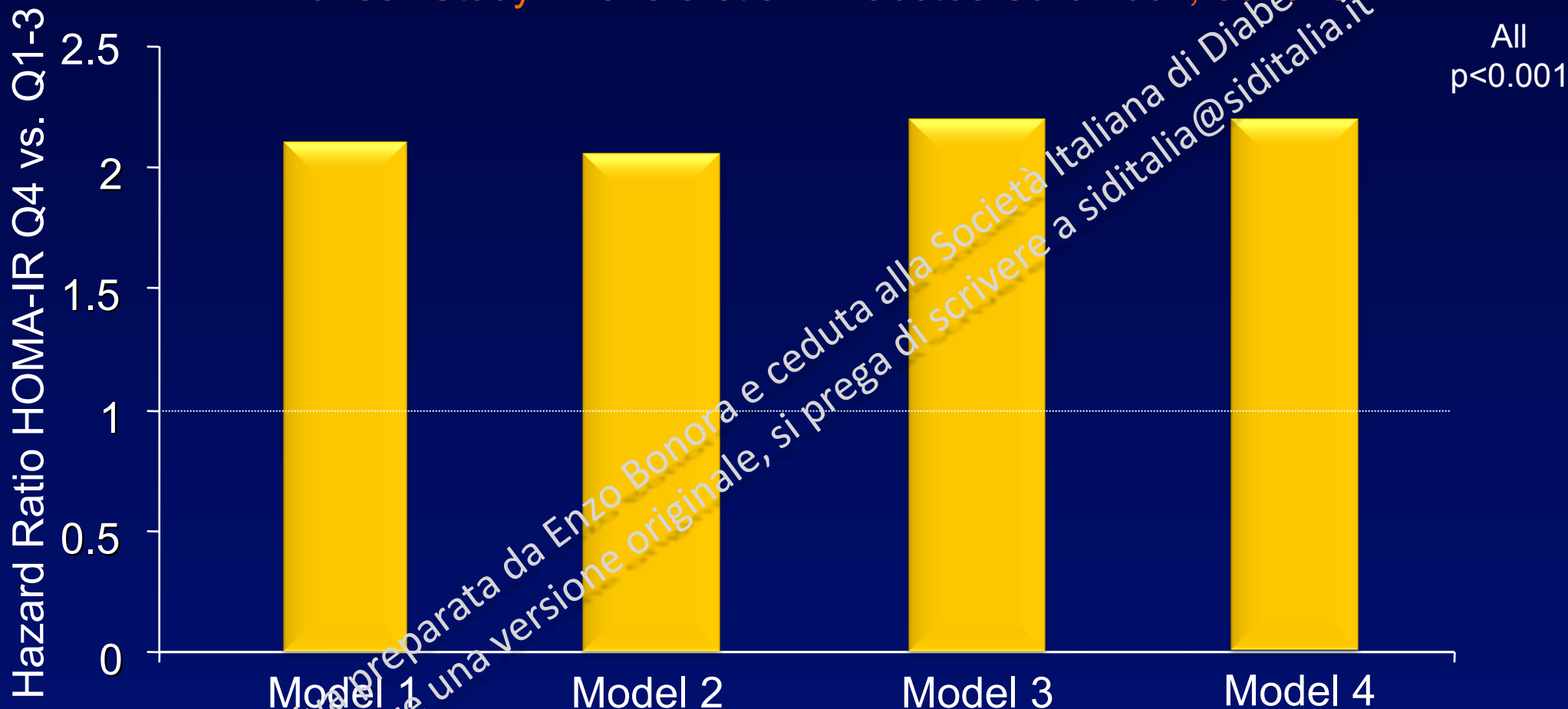
Hwang et al
Am J Physiol Endo Metab
2007; 293: E1663-E1669

IHTG and IMCL assessed by MRS
Insulin sensitivity measured by insulin clamp + tracer technique



Insulin Resistance is an Independent Predictor of Incident CVD in Caucasian Subjects from the General Population

Bruneck Study - Bonora et al - *Diabetes Care* 2007; 30: 2018



N=839, age 40-79, follow-up 15 years; subjects with symptomatic CVD at baseline excluded
CVD=CV death, MI, stroke, TIA, symptomatic PVD, any revascularization. Cases n=118.

Model 1: sex, age, smoking, HOMA-IR; **Model 2:** + physical activity, LDL-C, hypertension, HbA1c;
Model 3: + HDL-C, triglycerides, BMI; **Model 4:** + fibrinogen, oxidized LDL, hsCRP, VCAM-1, adiponectin.

Plasma Inflammatory Markers and Hemostatic Factors in Patients with NASH

Targher G et al – *Obesity* 2008; 16:1394-1399

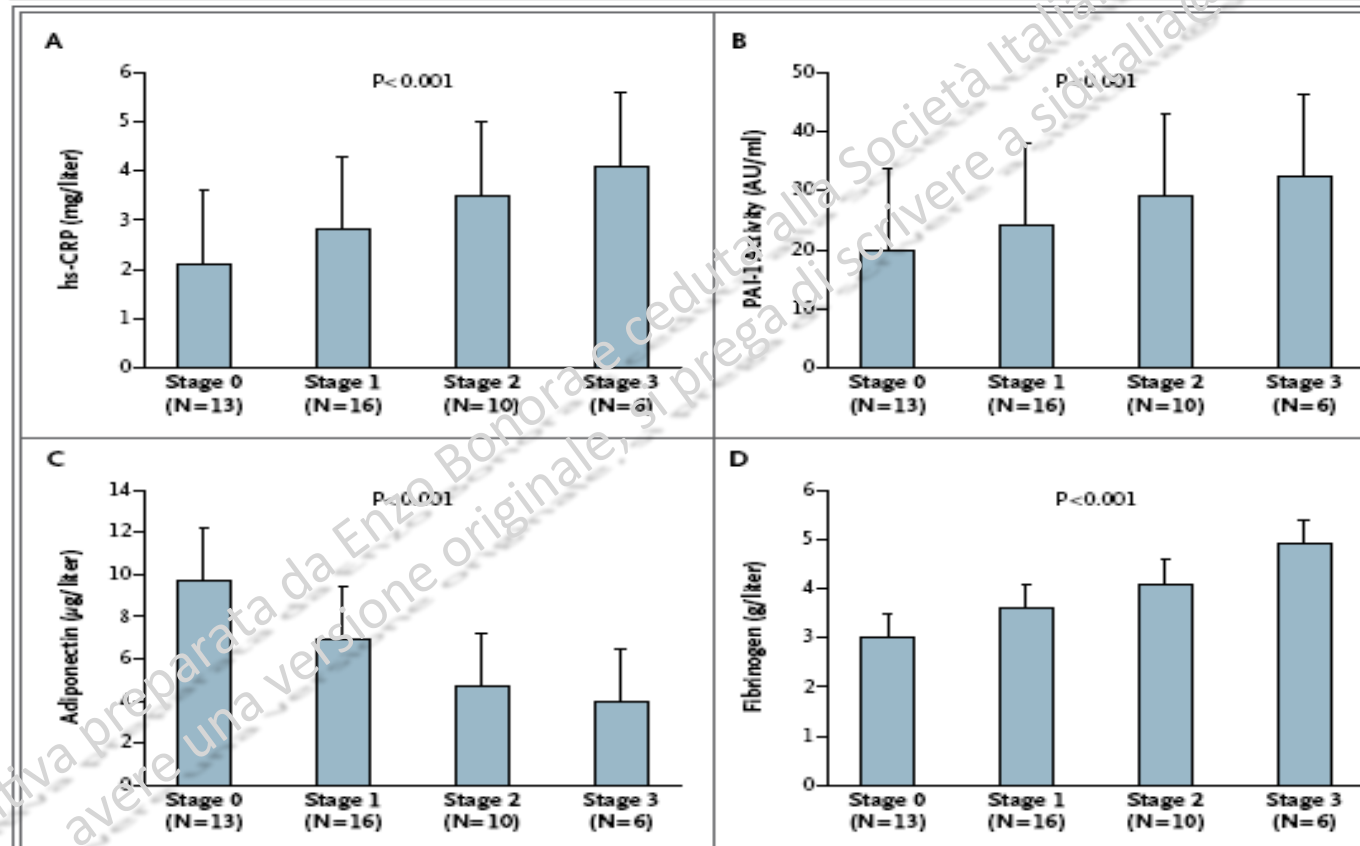
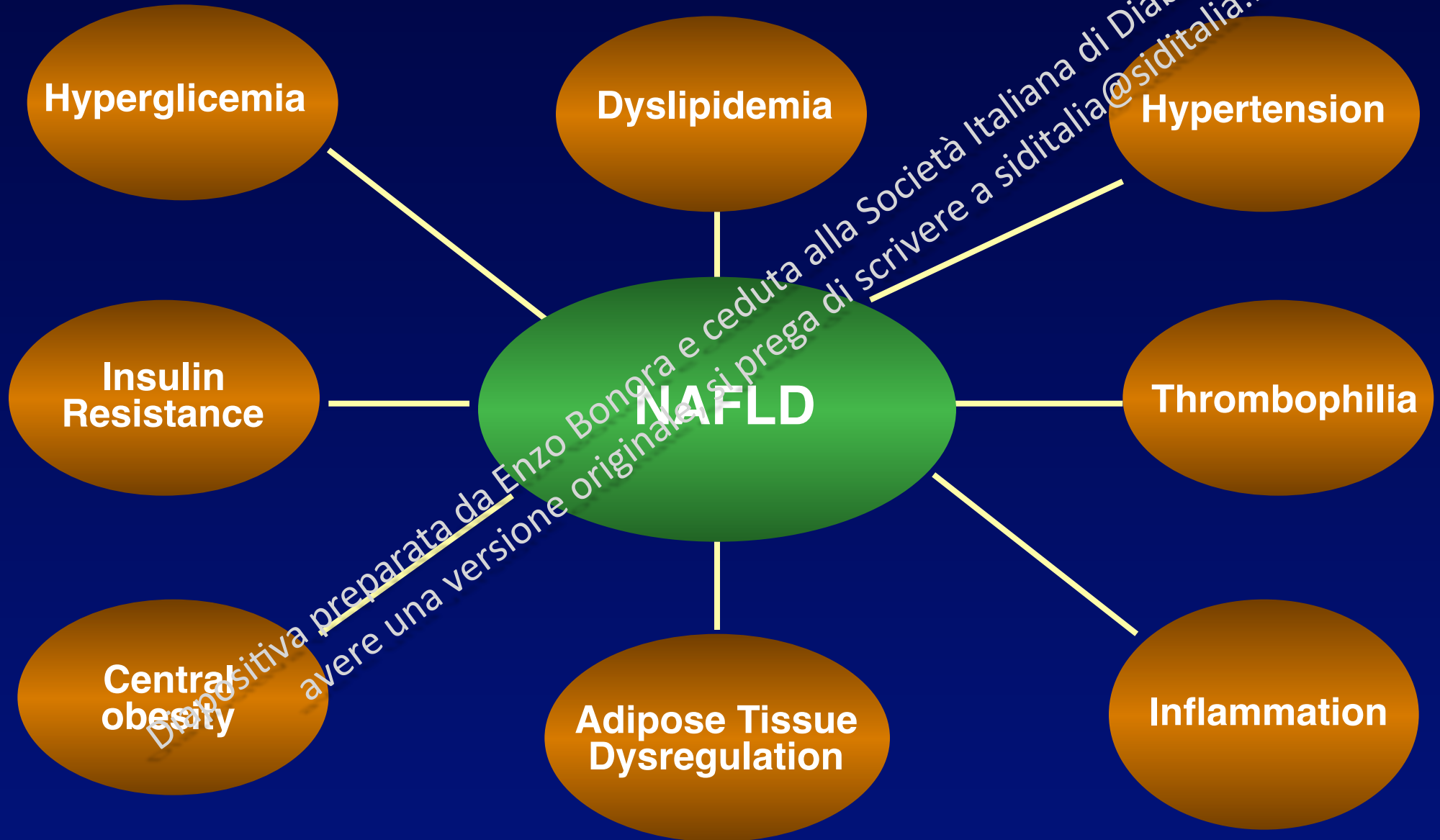


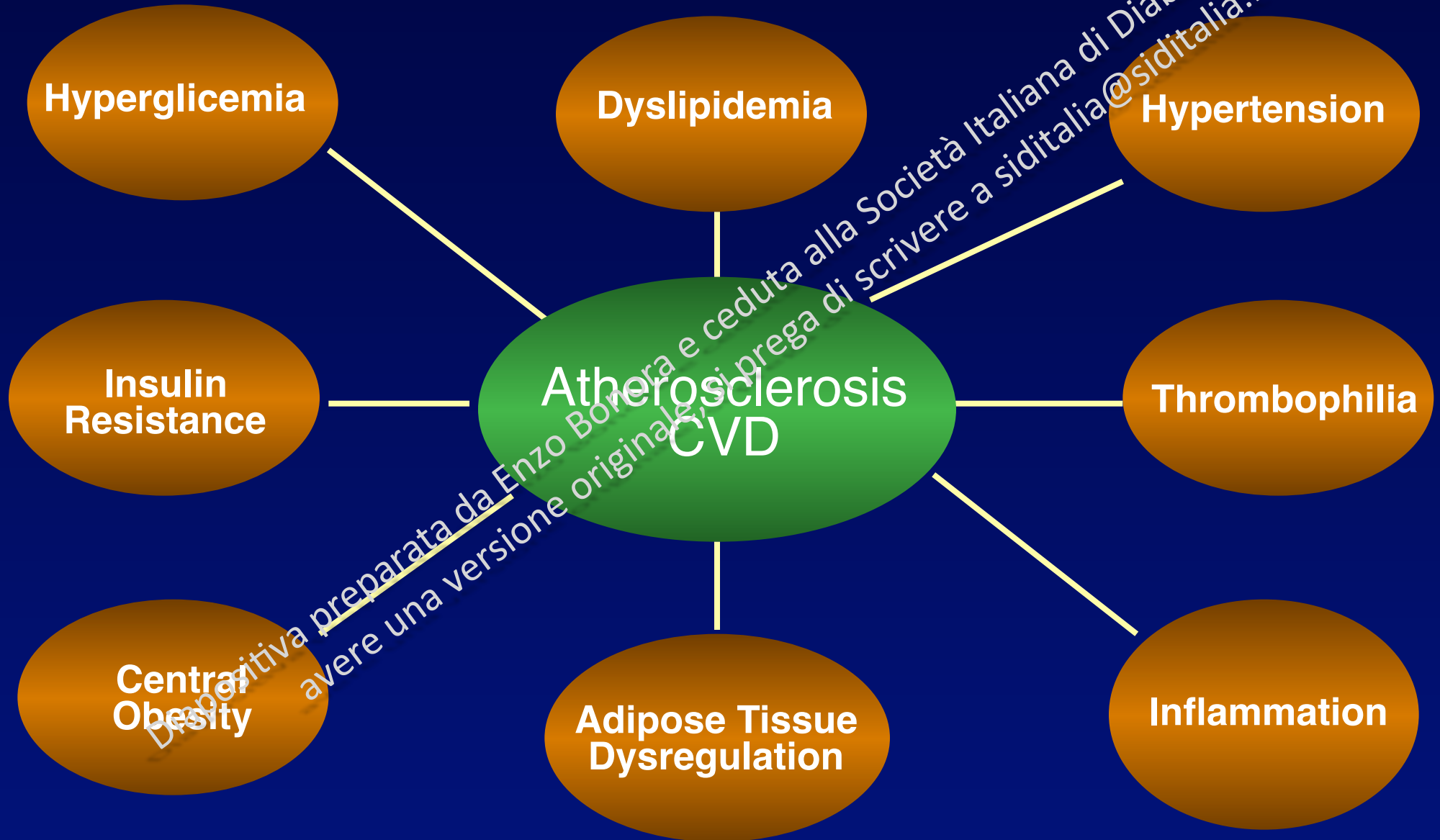
Figure 3. Inflammatory and Procoagulant Biomarkers in Patients with Nonalcoholic Steatohepatitis.

Mean ($\pm$ SD) plasma concentrations of high-sensitivity C-reactive protein (hs-CRP), plasminogen-activator inhibitor 1 (PAI-1) activity, adiponectin, and fibrinogen in relation to the stage of fibrosis are shown for 45 overweight male patients with histologically defined nonalcoholic steatohepatitis (NASH). P values for trends were determined by means of one-way analysis of variance. Data are from Targher et al.¹⁹

The Wide Spectrum of Pro-Atherogenic Disorders in NAFLD



The Wide Spectrum of Pro-Atherogenic Disorders in NAFLD



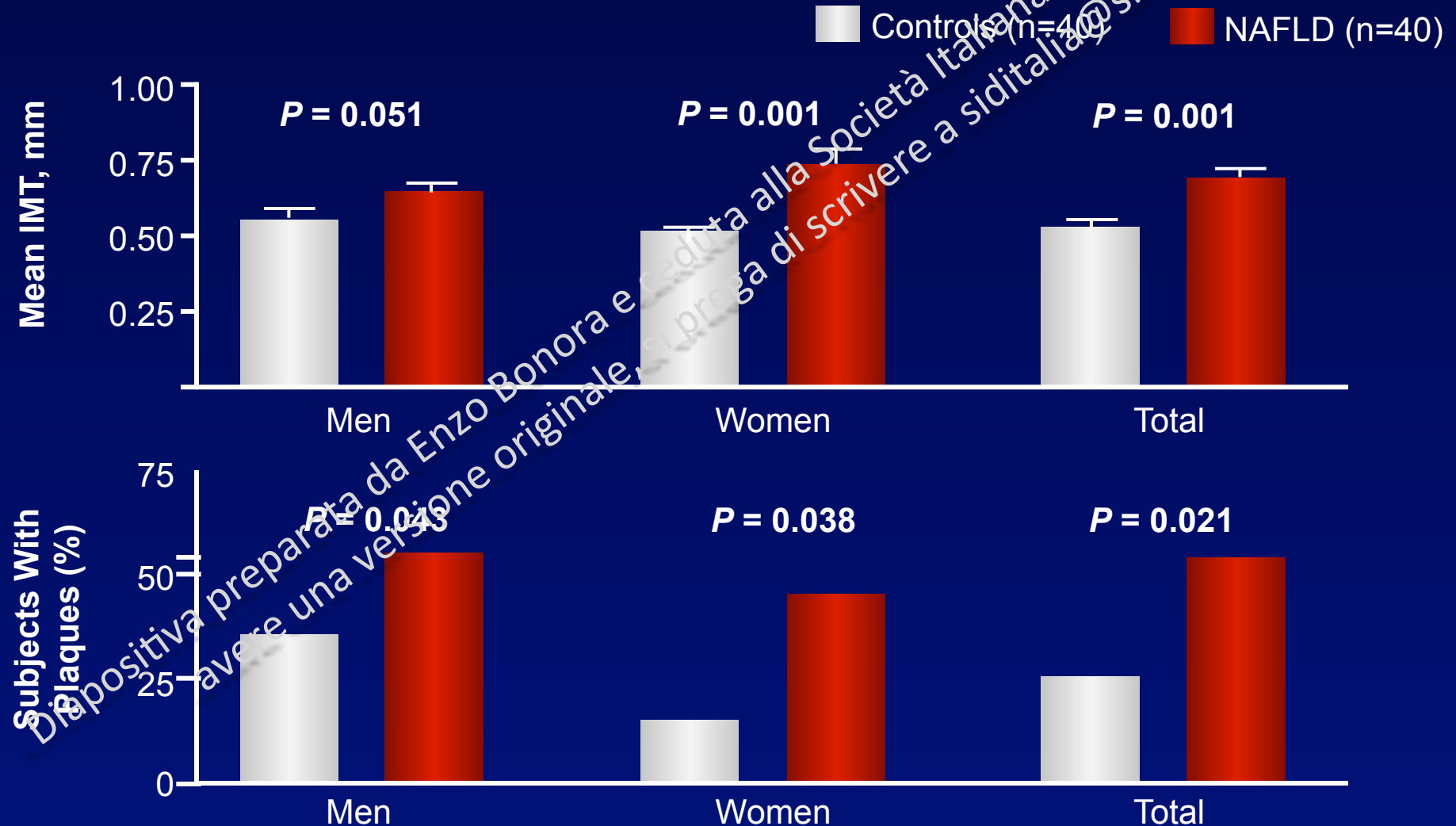
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Carotid IMT and Carotid Plaques in Ultrasonography-Diagnosed NAFLD

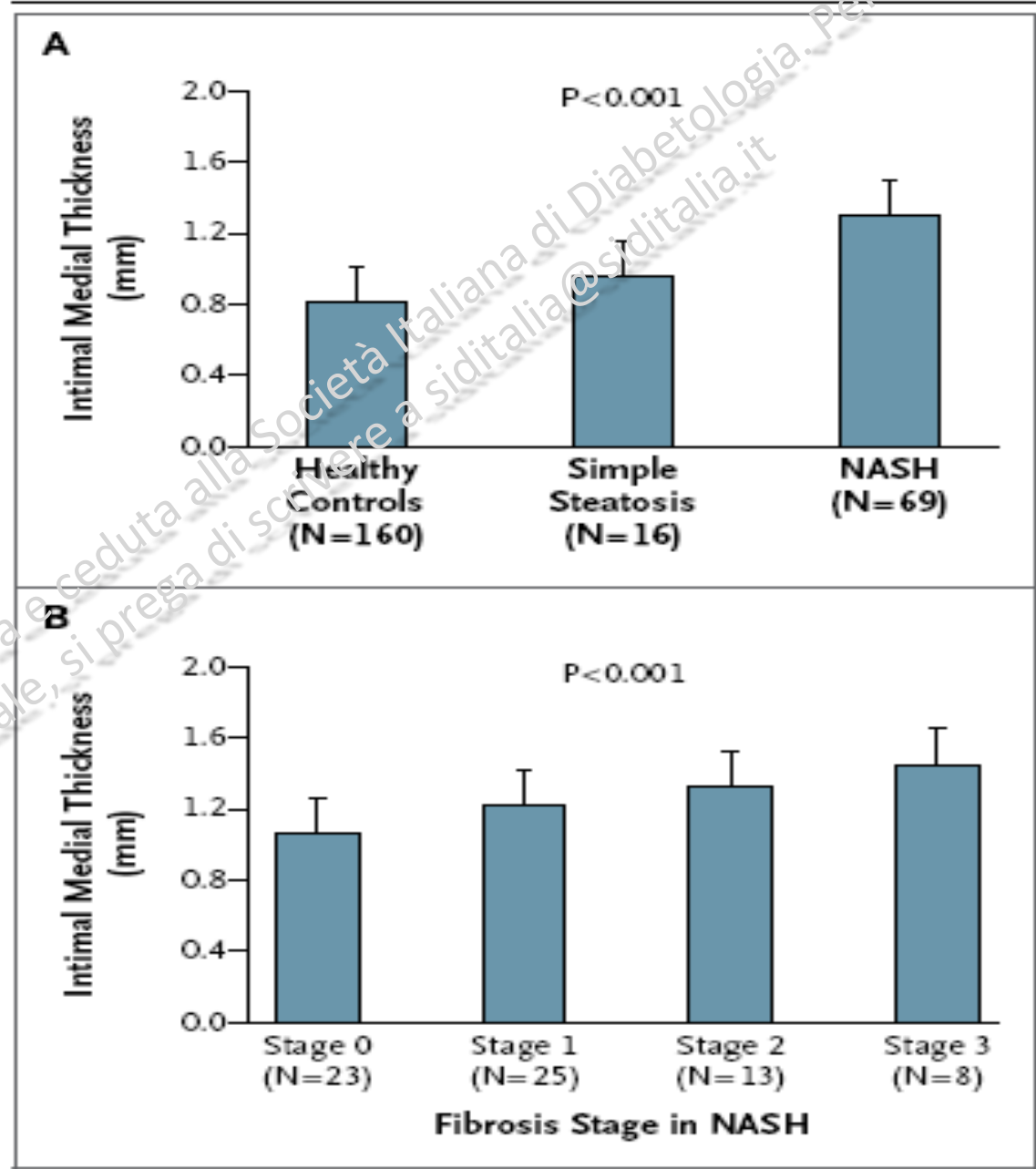
Brea A et al - *Arterioscler Thromb Vasc Biol* 2005; 25:1045-1050



Carotid IMT According to Severity of NAFLD and NASH

Targher G et al
Diabetes Care 2006; 29:1325-1330

Data from liver histology adjusted
for age, sex, smoking, BMI, waist,
hypertension, diabetes, lipids,
HOMA-IR



Coronary Angiogram Findings With and Without Fatty Liver

Wong VW et al - *Gut* 2011; 60: 1721-1727

N=612 consecutive coronary angiography study; significant CAD = 76%

Fatty liver by ultrasonography = 58.2%

CAD in fatty liver = 84.6%; CAD in normal liver = 64.1%; $p < 0.001$

Fatty liver predicted CAD = adjusted OR 2.31 (95% CI 1.46-3.64)

Parameters	Fatty liver	No fatty liver	p Value
Left main stem stenosis (%)	0 (0, 0)	0 (0, 0)	0.17
Left main stem steatosis $\geq 50\%$, n (%)	29 (8.1)	22 (8.6)	0.84
Left anterior descending artery stenosis (%)	80 (30, 90)	50 (0, 80)	<0.001
Left anterior descending artery stenosis $\geq 50\%$, n (%)	232 (65.2)	135 (52.7)	0.002
Left circumflex artery stenosis (%)	50 (0, 90)	0 (0, 70)	<0.001
Left circumflex artery stenosis $\geq 50\%$, n (%)	176 (49.4)	88 (34.4)	<0.001
Right coronary artery stenosis (%)	50 (0, 90)	20 (0, 80)	<0.001
Right coronary artery stenosis $\geq 50\%$, n (%)	188 (52.8)	95 (37.1)	<0.001
Stenosis $\geq 50\%$ in any coronary artery, n (%)	301 (84.6)	164 (64.1)	<0.001
Triple vessel disease, n (%)	100 (28.1)	60 (23.4)	0.20

The percentage stenosis of each coronary artery with respect to its diameter was expressed as the median (IQR).

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Ultrasonography-Diagnosed NAFLD is an Independent Predictor of CVD in Nondiabetic Subjects

Author	Cases	Follow-up	Measured Outcome	CVD risk
Jepsen et al <i>Hepatology</i> 2003; 50: 2101-2104	NAFLD vs. General Population	Up to 16 years	CVD death	SMR 2.1 (1.8-2.5)
Hamaguchi et al <i>W J Gastroenterol</i> 2007; 13: 1579-1584	NAFLD vs. No NAFLD	7 years	Fatal and non fatal CVD	OR 4.12* (1.6-10.7)
Haring et al <i>Hepatology</i> 2009; 50: 1403-1411	NAFLD vs. No NAFLD	7.3 years	CVD death	HR 6.22* (1.22-31.6)

*Multiple-adjusted

Ultrasonography-Diagnosed NAFLD is an Independent Predictor of CVD in T2DM

Targher G et al – *Diabetes* 2005; 12: 3541-3546

Variable	Model 1	Model 2	Model 3
Age (per 10 yr)	1.13 (1.07-1.14)	1.13 (1.07-1.14)	1.12 (1.06-1.14)
Sex (M vs F)	1.48 (1.1-2.0)	1.46 (1.2-1.9)	1.46 (1.2-1.9)
Smoking (yes vs. no)	1.42 (1.1-2.0)	1.40 (1.1-1.9)	1.40 (1.1-1.9)
NAFLD (yes vs. no)	1.80 (1.4-2.2)	1.84 (1.4-2.1)	1.53 (1.1-1.7)

N=744, follow-up 5 yrs

Model 1: age and sex

Model 2: + smoking history, diabetes duration, HbA1C, LDL cholesterol, GGT levels, and use of medications (i.e., hypoglycemic, antihypertensive, lipid-lowering, or antiplatelet drugs)

Model 3: + metabolic syndrome

Biopsy-Diagnosed NAFLD as an Independent Predictor of CVD

Author	No. Cases	Follow-up (yrs)	Measured Outcome	High CVD risk
Matteoni et al <i>Gastroenterology</i> 1999; 116: 1413-1419	132	13.7	Death	Probably yes
Dam-Larsen et al <i>Gut</i> 2004; 53: 750-755	215	16.7	Death	No
Adams et al <i>Gastroenterology</i> 2005; 129: 113-122	420	7.6	Death	Probably yes
Ekstedt et al <i>Hepatology</i> 2006; 44: 865-873	129	14	Death	NASH only
Rafiq et al <i>Clin Gastroenterol Hepatol</i> 2009; 7: 234-238	173	13	Death	Probably yes
Sodeberg DC et al <i>Hepatology</i> 2010; 51: 595-602	256	28	Death	Probably yes

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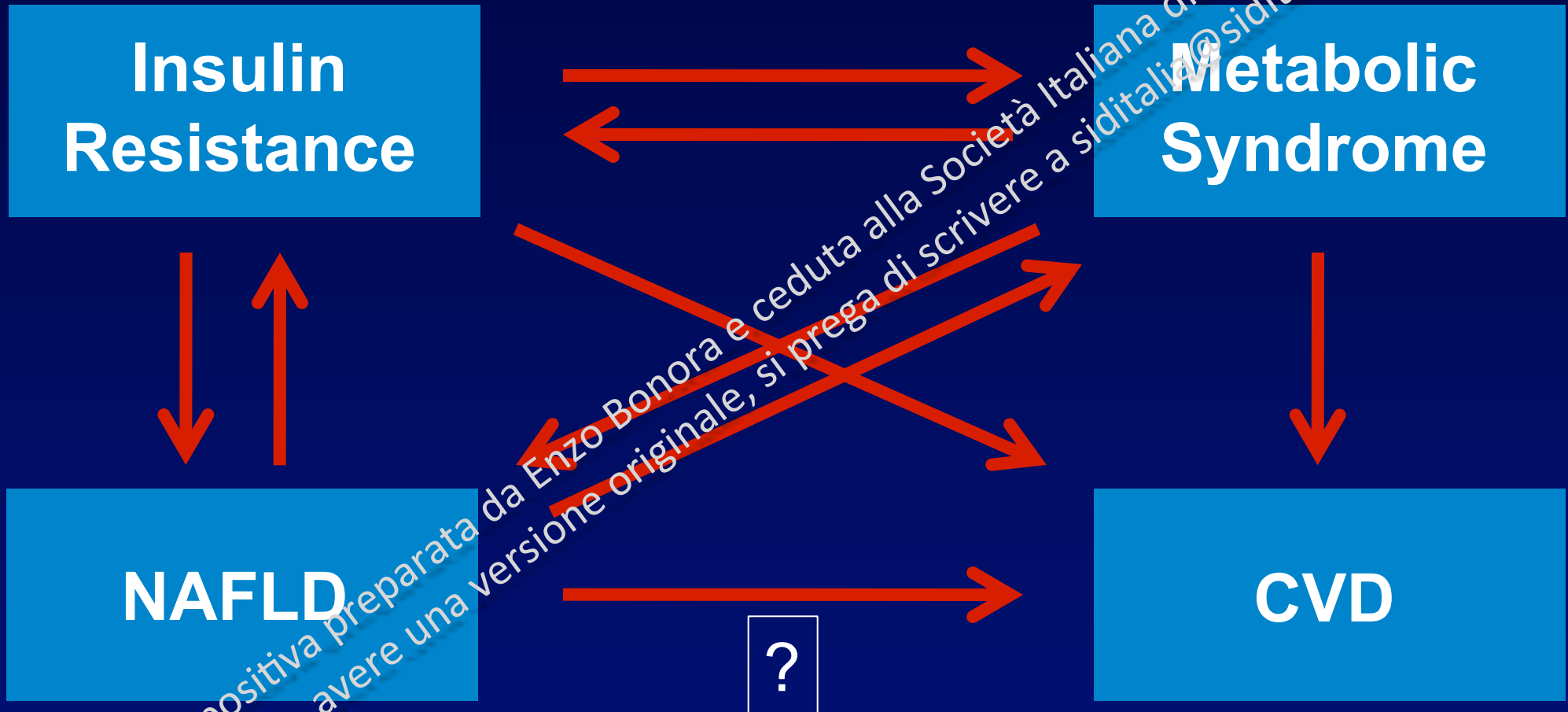
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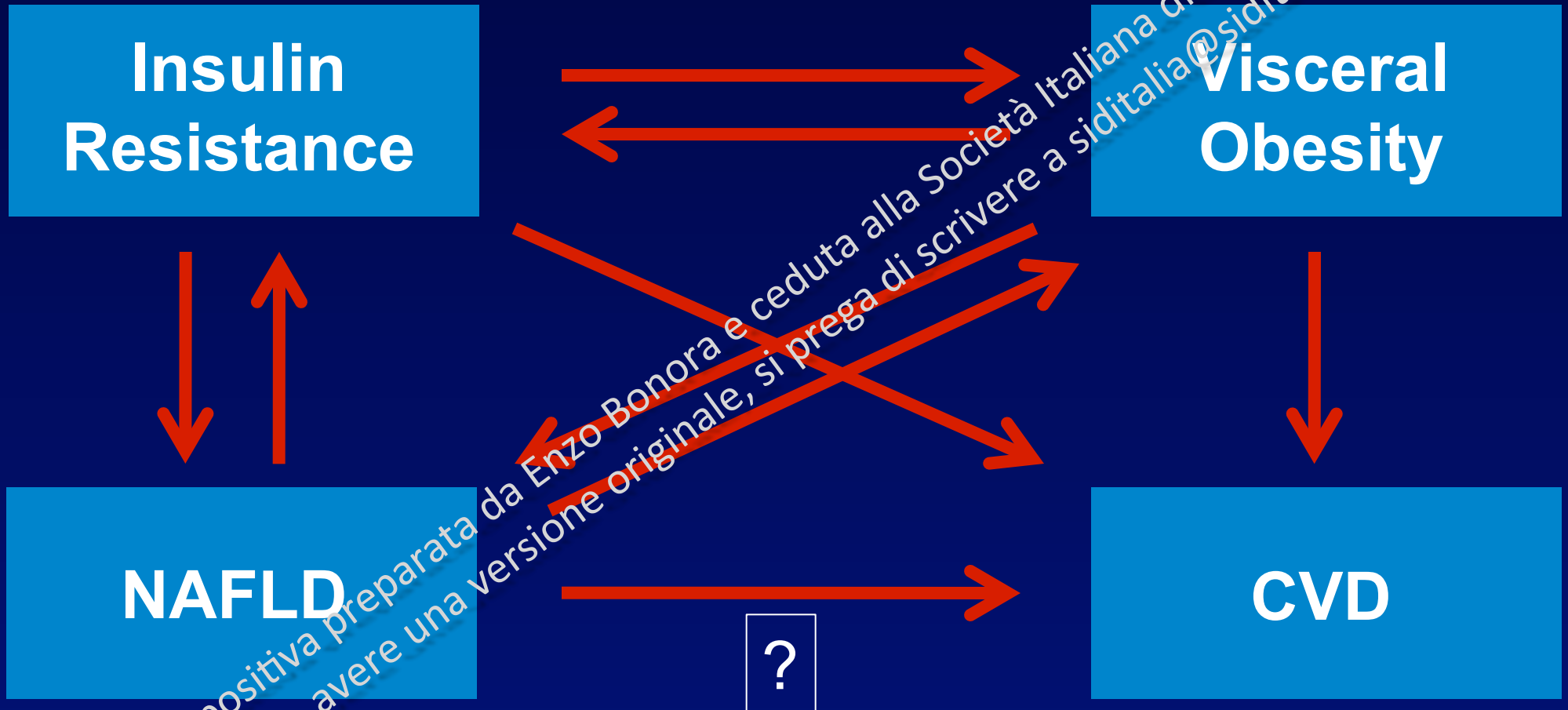
NAFLD and CVD: an Intriguing Network

- NAFLD and CVD share multiple clinical and pathophysiological features (e.g. visceral obesity and insulin resistance)
- Close correlations of NAFLD with traditional and nontraditional CVD risk factors (mainly those featuring the Metabolic Syndrome) make it extremely difficult understanding if NAFLD is just a statistical marker or a true causal factor of CVD

NAFLD and CVD: an Intriguing Network of the *Four Deadly Sisters*

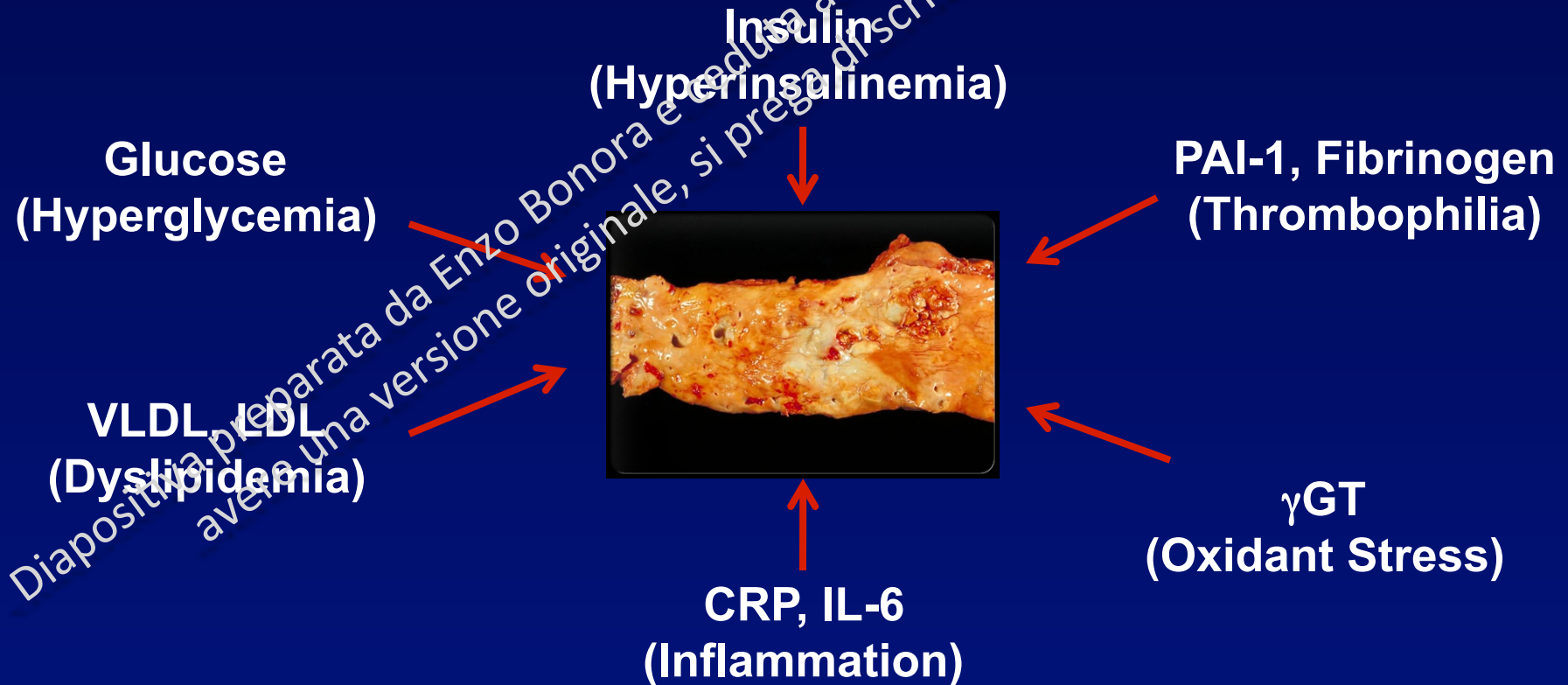
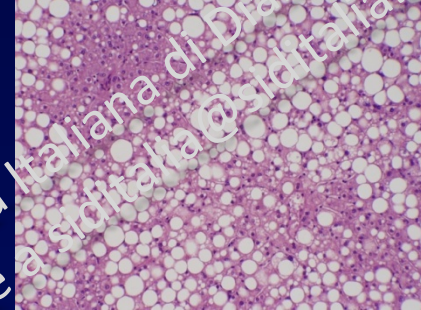


NAFLD and CVD: an Intriguing Network of the *Four Deadly Sisters*



From Fatty Liver to Atherosclerosis: the Links

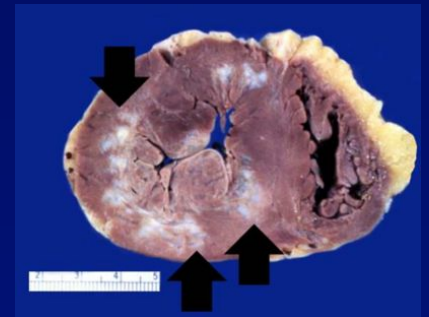
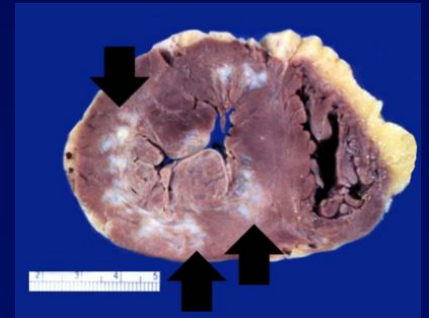
Targher G, Day C, Bonora E – *NEJM* 2010; 363:1341-1349



NAFLD and CVD: Marker or Causal Factor?

Common Factor(s)

Visceral Fat
Insulin Resistance
Metabolic Syndrome

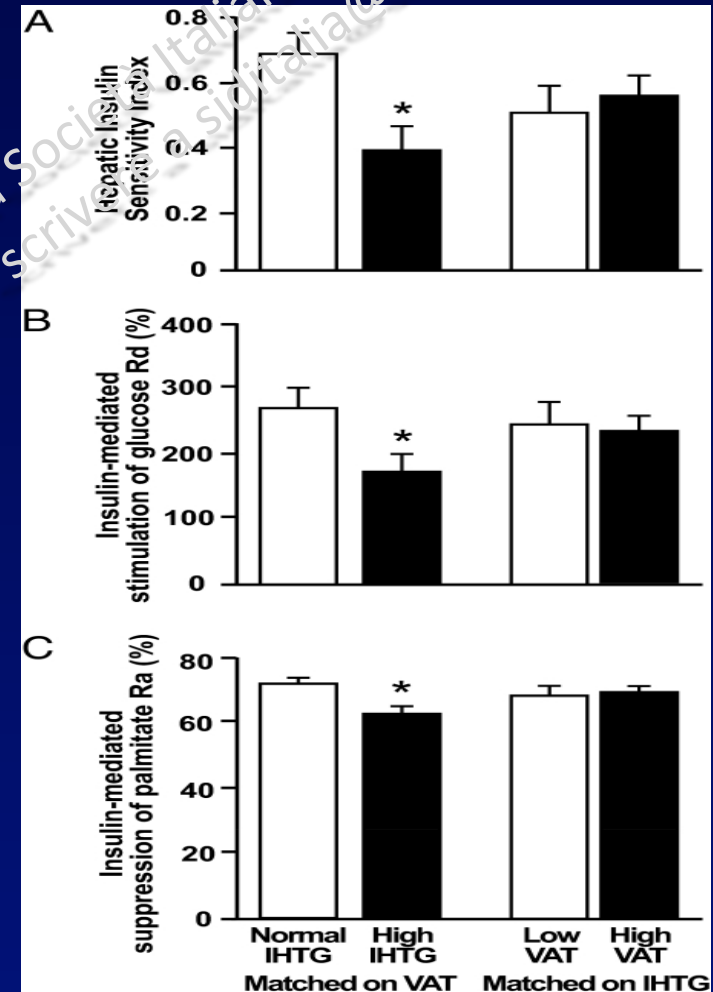
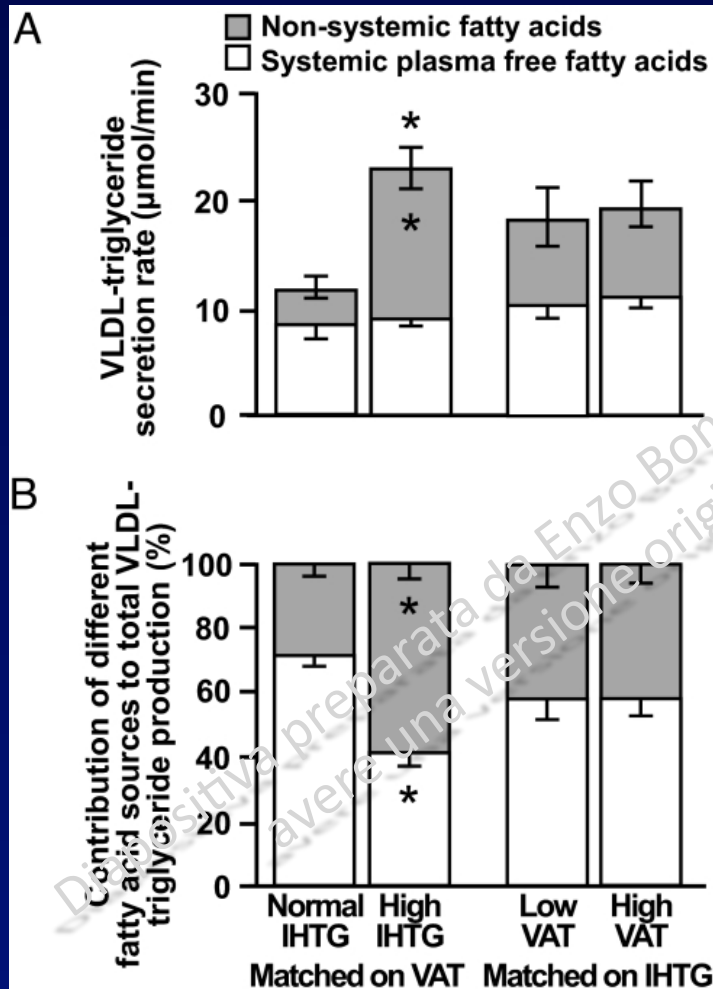


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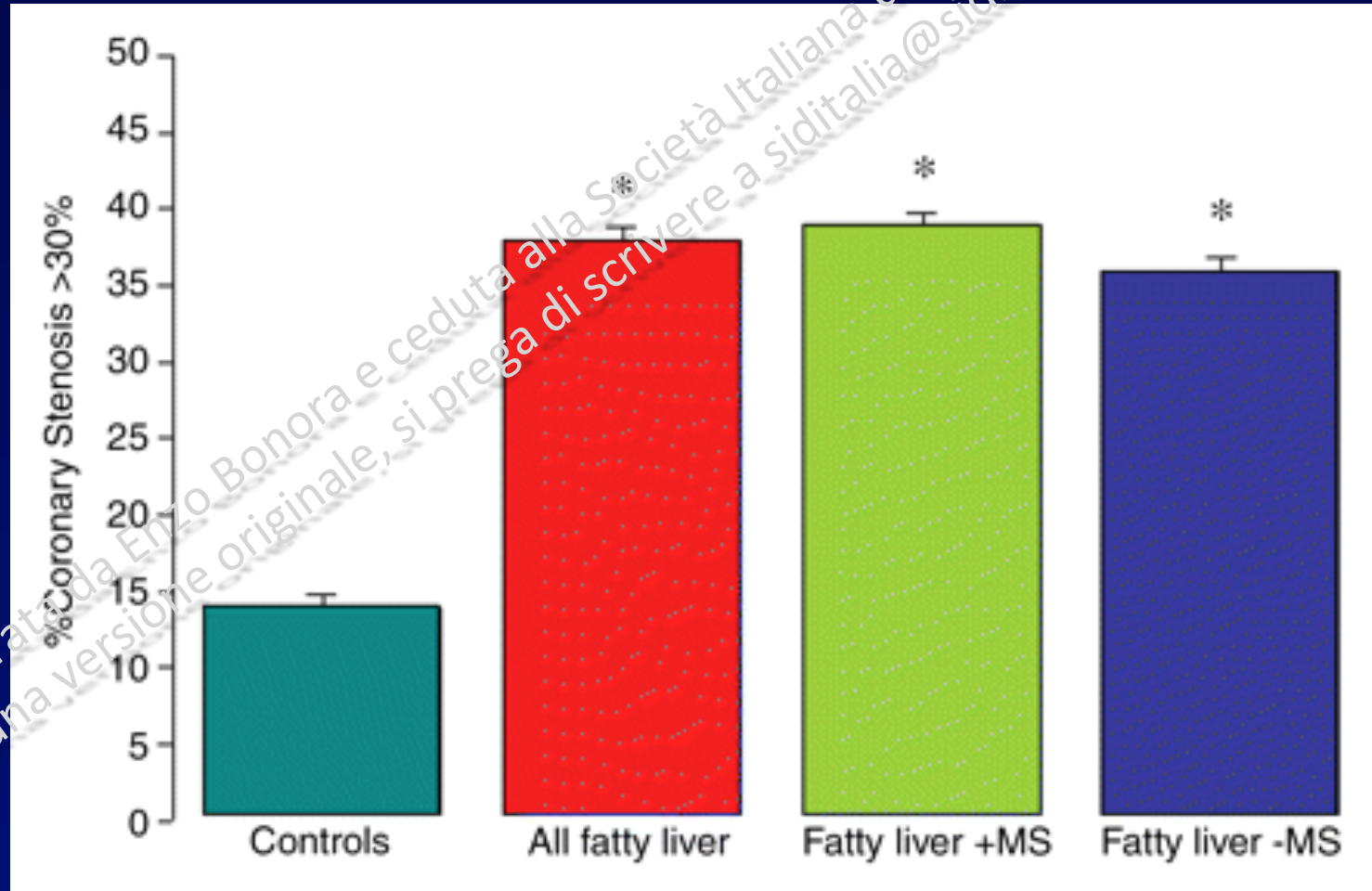
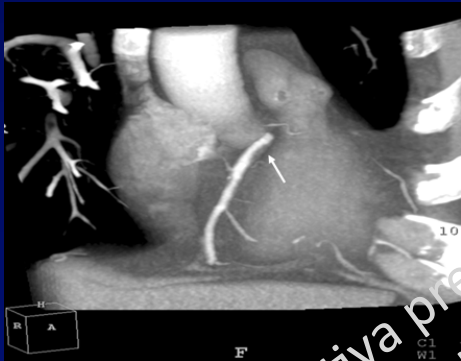
Intra-Hepatic Rather than Visceral Fat is Linked to Increased VLDL Secretion Rate and Insulin Resistance in Skeletal Muscle and Adipose Tissue

Fabbrini et al – *PNAS* 2009; 106: 15430-15435



Coronary Stenosis and Fatty Liver With or Without the Metabolic Syndrome

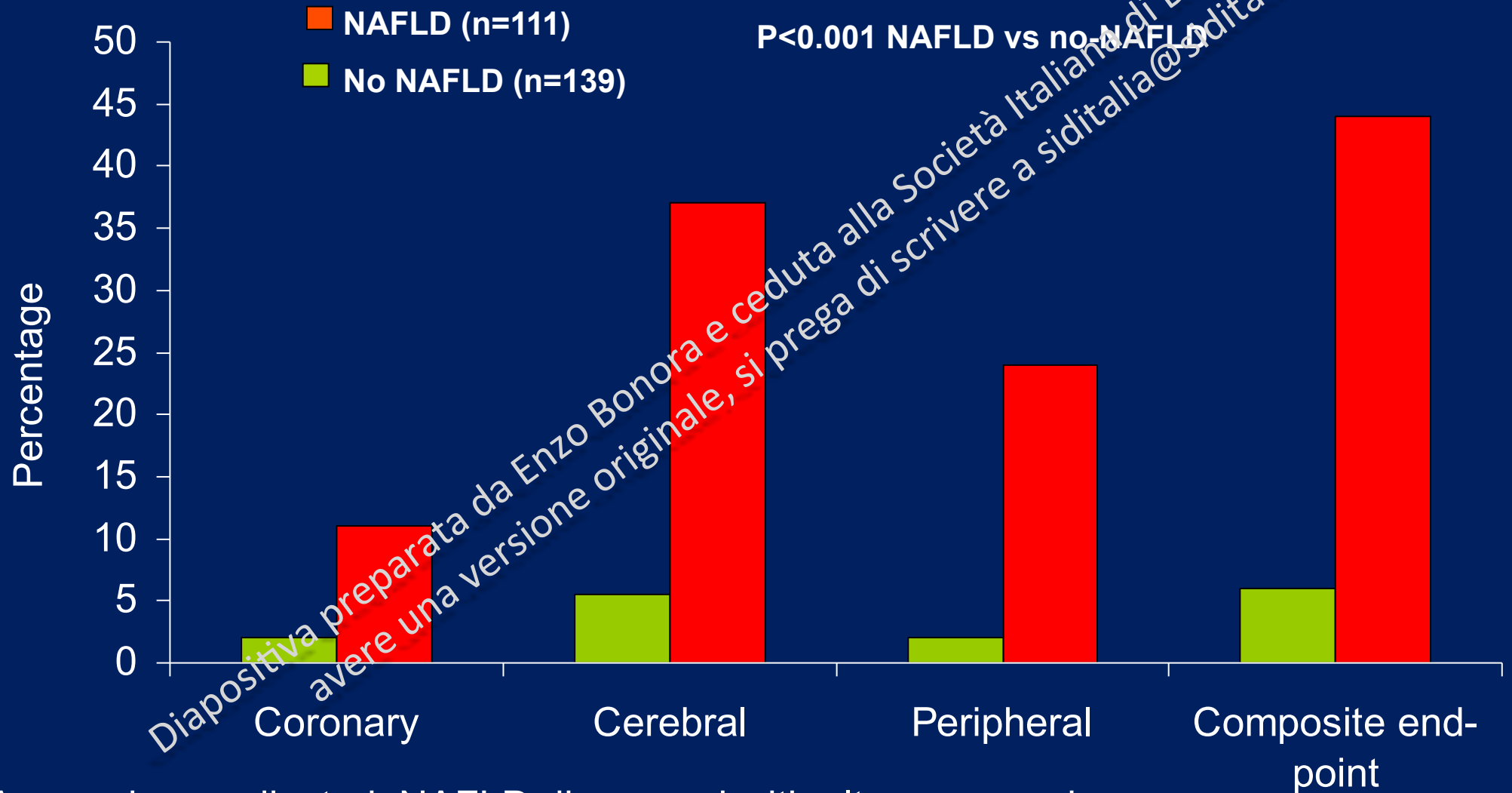
Assy et al - *Radiology* 2010; 254: 393-400



N= 61; fatty liver by CT scan; CAD by CT coronary angiography

Prevalence of CVD in T1DM with NAFLD

Targher G et al – *J Hepatol* 2010; 53: 713-718



Age and sex-adjusted; NAFLD diagnosed with ultrasonography

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NAFLD and CVD – Conclusions (1)

- Many prospective population-based studies have limitations because they only used surrogate indexes of NAFLD (e.g., serum GGT or ALT).
- Ultrasonography-based studies are more reliable but many of them were not exactly population-based and they often did not adjust for all potential confounding factors.
- In these studies a substantial number of subjects might have a different kind of liver disease, and among those with NAFLD a remarkable fraction has NASH.
- Histology-based studies were restricted to selected subjects and included relatively few individuals so they had insufficient statistical power.
- Nevertheless....

NAFLD and CVD – Conclusions (2)

- The association of NAFLD with preclinical and clinical CVD seems to have strength, consistency, temporality and biological plausibility.
- The association is certainly mediated by the concomitant presence of visceral obesity, insulin resistance, dyslipidemia, hypertension, dysglycemia (i.e., conditions featuring the metabolic syndrome).
- There is some epidemiological, clinical and experimental evidence that the association might be partially independent of these conditions.
- Many factors might play a role in the direct link between NAFLD and CVD. Among them, inflammation, oxidant stress and thrombophilia might be crucial.

NAFLD and CVD – Conclusions (3)

- Although the finding of NAFLD should prompt to a more careful surveillance of subjects also from a CVD perspective, the opportunity to carefully identify NAFLD in order to improve CVD risk assessment and/or to reduce CVD outcomes with a targeted treatment (once available) needs to be substantiated by more data and by specific trials.
- Meanwhile it is reasonable to believe that finding NAFLD in a subject without any feature of the metabolic syndrome should deserve the greatest attention.

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The end
Thank you so much



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Verona
The Opera at the Roman Arena