Is NAFLD a driver or simple marker of cardiovascular risk?

The cardiologist’s perspective

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Conflicts of interest

• Board: Amgen, Sanofi

• Research grants: Boeringher, Amgen, Sanofi, Astra Zeneca

• Lectures fees: Abbott, ViiV Healthcare, MSD, Novartis, Gilead, Servier

• Travel grants: MSD, ViiV Healthcare, Amgen
Summary

• Epidemiological association
• Genetic association?
• Intervventional studies?
• Conclusions
NAFLD is associated with CVD, and the 2 disorders share several cardiometabolic risk factors.

The specific contribution of NAFLD to increased CVD risk, especially in clinical studies, is difficult to discern from the combination of these shared risk factors.

The population of NAFLD patients is heterogeneous.

The liver is particularly involved in the pathophysiology of the metabolic syndrome (MetS), and the subsequent development of CVD and other complications, whereas in others, NAFLD is a manifestation of end-organ damage due to MetS.
This is what we need to prove that NAFLD is causal in CVD. The example of LDLc and CVD.

Association between LDLc and cardiovascular diseases

Nordetgaard BG et al. Eur Heart J. 2018
Is the association of NAFLD and CVD independent of other CV risk factors?

• Yes
  → Many large population-based cohorts.

• No
  → In contrast, some studies did not.
After controlling for DM and BMI, NALFD is no more an independent risk factor (70-75% DM have NAFLD)

# Epidemiology. CVD events

**Disparities**: How NAFLD is diagnosed in those studies? What are the CVD endpoints?

<table>
<thead>
<tr>
<th>Studies</th>
<th>N</th>
<th>Non fatal and fatal CVD events</th>
<th>Severity of NAFLD or NASH</th>
<th>CVD Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Meta-analysis of Targher (2016)</strong></td>
<td>n = 34,043</td>
<td>OR: 1.64 95% CI: 1.26 to 2.13</td>
<td>OR: 2.58 95% CI: 1.78 to 3.75</td>
<td>No association</td>
</tr>
<tr>
<td>16 studies*</td>
<td></td>
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</tr>
<tr>
<td><strong>Meta-analysis of Haddad (2017)</strong></td>
<td>n = 25,837</td>
<td>Clinical CVD evts RR: 1.77 95% CI: 1.26 to 2.48</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>6 studies) NAFLD (diagnosed via ultrasound)</td>
<td></td>
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<tr>
<td><strong>Meta-analysis of Wu (2016)</strong></td>
<td>n = 165,000</td>
<td>OR: 1.81 95% CI: 1.23 to 2.66</td>
<td>HR: 2.97 95% CI: 1.03 to 8.52</td>
<td>No association with either overall mortality or CVD mortality in both NAFLD and NASH.</td>
</tr>
<tr>
<td>34 studies</td>
<td></td>
<td>Incident CVD HR: 1.37 95% CI: 1.10 to 1.72</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*NAFLD by imaging/by histology in one study

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Mahfood Haddad T, et al. Diabetes Metab Syndr 2017
Association of NAFLD with atherosclerosis

• NAFLD is independently associated with increased CIMT and CAC.

• **Meta-analysis** \( (n=85\,395\) with \(29\,493\) NAFLD) increased risk of subclinical atherosclerosis compared with individuals without NAFLD \( (OR: 1.60; 95\%\ CI: 1.45\) to 1.78)  

  CIMT \( (OR: 1.74; 95\%\ CI: 1.47\) to 2.06) 
  Arterial stiffness \( (OR: 1.56; 95\%\ CI: 1.24\) to 1.96) 
  CAC \( (OR: 1.40; 95\%\ CI: 1.22\) to 1.60) 
  Endothelial dysfunction (FMD) \( (OR: 3.73; 95\%\ CI: 0.99\) to 14.09).

• **Longitudinal study** \( (n=8,020,\) FU 8 years)  
  Regression of CIMT in those with regression of NAFLD compared with those with persistent NAFLD was **HR 0.82 (95\%\ CI: 0.69\) to 0.96; \(p= 0.013)\**

Cardiomyopathy

- Increased left ventricular wall thickness and myocardial mass
- Lower early diastolic relaxation velocity (and worse absolute global longitudinal strain)
- NAFLD independently associated with valvular heart disease, specifically aortic valve sclerosis (AVS) and mitral annulus calcification
- NAFLD (n= 180 D) associated with increased risk of AVS (adjusted OR: 3.04; 95% CI: 1.3 to 7.3).
- Increased Epicardial adipose tissue

_Trovato FM et al. Int J Cardiol 2016;221:275–9._
Diabetes, NAFLD and QTc prolongation

Italy, n= 400
Ultrasonographic NAFLD
Bazett computerized EKG

Logistic regression models for NAFLD as a predictor for increased QTc interval duration.

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

NAFLD is associated with Ventricular Arrhythmias in Diabetics

### SVT or AF

<table>
<thead>
<tr>
<th></th>
<th>Without NAFLD (n = 92)</th>
<th>With NAFLD (n = 238)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paroxysmal SVT</td>
<td>33.6</td>
<td>47.4</td>
<td>0.023</td>
</tr>
<tr>
<td>Paroxysmal atrial fibrillation</td>
<td>2.2</td>
<td>7.6</td>
<td>0.044</td>
</tr>
</tbody>
</table>

### nVT or PVC

<table>
<thead>
<tr>
<th>Logistic regression models</th>
<th>ORs</th>
<th>95% CIs</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NAFLD (yes vs. no)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted model</td>
<td>3.47</td>
<td>1.65–7.30</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Adjusted model 1</td>
<td>3.39</td>
<td>1.60–7.20</td>
<td>0.001</td>
</tr>
<tr>
<td>Adjusted model 2</td>
<td>3.26</td>
<td>1.44–7.37</td>
<td>0.005</td>
</tr>
<tr>
<td>Adjusted model 3</td>
<td>3.01</td>
<td>1.26–7.17</td>
<td>0.013</td>
</tr>
</tbody>
</table>

Other independent predictors of ventricular arrhythmias in model 3

<table>
<thead>
<tr>
<th>Predictor</th>
<th>ORs</th>
<th>95% CIs</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>3.03</td>
<td>1.31–7.01</td>
<td>0.008</td>
</tr>
<tr>
<td>Serum GGT (units/L)</td>
<td>1.02</td>
<td>1.01–1.03</td>
<td>0.009</td>
</tr>
<tr>
<td>LV ejection fraction (%)</td>
<td>0.96</td>
<td>0.93–0.99</td>
<td>0.028</td>
</tr>
</tbody>
</table>

*Italy, N= 330 diabetics*  
*Retrospective, Cross-sectional*  
*without AF, ESRD, LD*  
*24-h Holter monitoring for clinical reasons (2013-2015)*  
*Ventricular arrhythmias= nonsustained VT, or >30 premature ventricular complexes (PVCs) per hour*  
*Ultrasonography NAFLD*

NAFLD and Atrial fibrillation

Persistent or permanent AF

Italy
N= 702 patients with Type 2 diabetes
NAFLD on ultrasonography

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 χ² test.

<table>
<thead>
<tr>
<th>Logistic regression model</th>
<th>OR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NAFLD (yes compared with no)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted model</td>
<td>3.04 (1.54–6.02)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Adjusted model 1</td>
<td>4.45 (2.17–9.11)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Adjusted model 2</td>
<td>5.88 (2.72–12.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Adjusted model 3</td>
<td>5.17 (2.05–13.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Other independent predictors of AF in model 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>1.06 (1.03–1.09)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Estimated GFR (ml/min per 1.73 m²)</td>
<td>0.98 (0.97–0.99)</td>
<td>=0.013</td>
</tr>
<tr>
<td>History of HF (yes against no)</td>
<td>3.29 (1.60–6.79)</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>History of hyperthyroidism (yes against no)</td>
<td>5.01 (1.42–17.7)</td>
<td>=0.012</td>
</tr>
</tbody>
</table>

NAFLD and atrial fibrillation

- NAFLD is a marker of ectopic fat accumulation in other organs, including the myocardium and pericardium → left atrial remodeling
- Adipocytes from epicardial, retrosternal or abdominal adipose tissues may modulate the electrophysiological properties and ion currents, causing higher arrhythmogenesis (ANS dysfunction)
- NAFLD may release a variety of pro-inflammatory and pro-coagulant mediators and other inflammatory cytokines possibly inducing structural and/or electrical remodelling of the atria

Jmaly S et al, JACC 2016
Mechanisms NAFLD increases CVD

- ↑ Hepatic Insulin Resistance
- ↑ Hepatic Fatty Acid Accumulation
- ↑ Hepatic Glucose Production
- ↓ Hepatic Insulin Signaling

- ↑ Homocysteine
- Impaired Redox Status

- ↑ Plasma Free Fatty Acid Level
- ↑ Liver Fat Content
- ↑ Hepatic Lobular Inflammation

- ↑ ADMA
- Impaired Redox Status
- ↑ Homocysteine
- ↑ Platelet Activation
- ↑ Systemic Inflammation

- ↑ IL-6
- ↑ M1/M2
- ↑ hsCRP
- ↑ CCL3
- ↑ sICAM-1
- ↑ TNFα
- ↑ IL-1β

CVD CV Events/Mortality Atherosclerosis Cardiomyopathy Arrhythmias

Oxidative Stress

Systemic Insulin Resistance

Altered Lipid Metabolism

Systemic Inflammation

Plaque Formation/Instability

Endothelial Dysfunction

Altered Vascular Tone

↑ Systemic Inflammation

↑ Prothrombotic Factors
- ↑ Hepatic Angiogenesis & ↑ VEGF
- ↑ Intestinal Dysbiosis and ↑ Secretion of Bile Acids, TMA, and Short Chain Fatty Acids into Bloodstream

Two missense genetic variants have been identified by GWAS studies of NAFLD:

1/ **PNPLA3** related to TG metabolism.
Carriers of this mutation: increased atherosclerosis.

In a cohort study of the Danish general population, using Mendelian randomization, high liver fat content was not found to be causally associated with increased risk of ischemic heart disease (OR: 0.95; 95% CI: 0.86 to 1.04; p= 0.46).

2/ **Transmembrane 6 superfamily member 2** modulates secretion of TG and cholesterol in the liver via VLDL excretion. Carriers of this mutation are at risk for NAFLD due to increased retention of TG and lipids in the liver but may experience some degree of cardioprotection with subsequently reduced levels of serum TG, LDL cholesterol, and total cholesterol.

Therapies?

- **Statins**: + effects both CVD and NAFLD
- **Aspirin**: ?
- **Metformin**: limited efficacy in NAFLD
- **Pioglitazone**: decrease hepatic fat content; increase hepatic insulin sensitivity; decrease serum ALT levels; and improve fibrosis, steatosis, inflammation, and ballooning necrosis (concern with HF)
- **Liraglutide** (GLP-1 analogue) reduces NASH (LEAN: weight loss dependant)
- **Angiotensin II receptor blockers** (ARBs) weak proof
- **Vitamin E** no CV effect

- **Future**: Ongoing Phase III clinical trials with Farnesoid X receptors (FXRs) agonist: Obeticholic Acid (LDLc increased), Elafibranor (dual PPAR-α/delta agonist)
- **Phase IIb**: Cenicriviroc is an antagonist of C-C motif chemokine receptor (CCR) types 2 and 5: decreases fibrosis in NASH

*JAMA Intern Med 2017;177:633–40.*
Conclusions

Patients with NAFLD develop increased atherosclerosis, cardiomyopathy, and arrhythmia, which clinically result in increase cardiovascular morbidity and mortality.

CVD and NAFLD are associated with each other through multiple pathophysiological mechanisms (inflammation, ED, hepatic IR, OS and altered lipid metabolism).

A genetic basis for the disease is under study with SNP associations that warrant further validation.

The candidate medications under study for NAFLD should be thoroughly evaluated using cardiovascular endpoints and subclinical CVD.
Thank you

Fernando Botero
Dancers 1987
Back up
This is what we need to prove that NFLD is causal in CVD. The example of LDLc and CVD. Association between LDLc and cardiovascular diseases.
Do we need to screen all patients at high risk for NAFLD?

• No for USA: uncertainties in diagnostic work up and limited treatment options

• Yes for Europe in Obese, MetS and high risk CVD (liver enzymes and/or ultrasound because of its prognostic implications)

• The CardioMetabolic Heath Alliance → more comprehensive screening to improve prevention of MetS. Measurable biomarkers such as blood pressure, lipids, body mass index (BMI), and waist circumference.
### Characteristics. NAFLD and QTc

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>No NAFLD n=18 225</th>
<th>NAFLD Mild n=9152</th>
<th>Moderate n=2976</th>
<th>Severe n=796</th>
<th>P Value for Heterogeneity</th>
<th>P Value for Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>48.8 (12.8)</td>
<td>52.2 (11.0)</td>
<td>51.4 (11.0)</td>
<td>48.9 (11.0)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sex, male, n (%)</td>
<td>7843 (42.6)</td>
<td>5660 (61.5)</td>
<td>2139 (71.5)</td>
<td>568 (73.9)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>1133 (6.2)</td>
<td>1210 (13.2)</td>
<td>697 (23.4)</td>
<td>221 (29.0)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>2970 (16.3)</td>
<td>2800 (30.6)</td>
<td>1237 (41.6)</td>
<td>424 (55.6)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Metabolic syndrome, n (%)</td>
<td>1096 (6.0)</td>
<td>1931 (21.1)</td>
<td>1170 (39.3)</td>
<td>440 (57.7)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Coronary artery disease, n (%)</td>
<td>170 (1.0)</td>
<td>106 (1.2)</td>
<td>55 (1.9)</td>
<td>20 (2.7)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Stroke, n (%)</td>
<td>69 (0.4)</td>
<td>60 (0.7)</td>
<td>13 (0.5)</td>
<td>1 (0.1)</td>
<td>0.008</td>
<td>0.325</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease, n (%)</td>
<td>570 (3.3)</td>
<td>307 (3.5)</td>
<td>105 (3.7)</td>
<td>35 (4.8)</td>
<td>0.123</td>
<td>0.037</td>
</tr>
<tr>
<td>Smoking, n (%)</td>
<td>1976 (10.9)</td>
<td>1396 (15.3)</td>
<td>557 (18.7)</td>
<td>146 (19.2)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Anthropometric measures</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>22.4 (2.8)</td>
<td>25.2 (2.8)</td>
<td>27.2 (3.2)</td>
<td>29.6 (4.2)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Waist circumference, cm</td>
<td>81.3 (8.1)</td>
<td>88.7 (7.4)</td>
<td>93.5 (8.2)</td>
<td>99.1 (10.2)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>119.5 (15.4)</td>
<td>127.6 (15.2)</td>
<td>132.8 (14.8)</td>
<td>137.2 (16.5)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>71.6 (10.1)</td>
<td>76.7 (10.4)</td>
<td>80.2 (10.3)</td>
<td>82.9 (11.2)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>QTc interval, ms (by Bazett’s formula)</td>
<td>418.9 (60.4)</td>
<td>422.5 (44.8)</td>
<td>430.9 (49.2)</td>
<td>439.9 (48.2)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>QTc interval, ms (by Hodges’ formula)</td>
<td>411.6 (32.9)</td>
<td>413.4 (32.6)</td>
<td>418.6 (33.3)</td>
<td>424.6 (34.4)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>QTc &gt;440 ms, n (%) (by Bazett’s formula)</td>
<td>5302 (29.1)</td>
<td>2923 (31.9)</td>
<td>1190 (40.0)</td>
<td>366 (48.0)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>QTc &gt;440 ms, n (%) (by Hodges’ formula)</td>
<td>3412 (18.7)</td>
<td>1823 (19.9)</td>
<td>755 (25.4)</td>
<td>239 (31.3)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Left ventricular hypertrophy, n (%)</td>
<td>703 (3.8)</td>
<td>527 (5.7)</td>
<td>186 (6.2)</td>
<td>46 (6.0)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
NAFLD and QTc. Large cohort

Taiwan cohort
Cross sectional study D+/-
N= 31 116

Significant association of blood pressure, hemoglobin A1c, and high-density lipoprotein concentration with QTc interval.

NAFLD : Abdominal ultrasonography and classified as none, mild, moderate, or severe
Physiopathology of QTc prolongation in NASH

NASH

Traditional risk factors: obesity, diabetes, HTN, HDL

Inflammation: elevated CRP, IL6, TNFαR1

Nervous autonomic dysfunction

Cardiomyocytes

Hormones-Hypogonadism: Testosterone?

Prolongation of QTc interval
Obesity and QT in humans and mice

Obesity is associated with long QT, increased frequency of premature ventricular complexes, and sudden cardiac death.

• Diet-induced obese mice have long QT, similar to obese H

• Transcription of potassium channels is reduced because of lower cAMP response element binding protein (CREB) levels.

• Reduced cardiac CREB is a novel mechanism causing electrophysiologic remodeling in obesity.

Haiyan Huang et al. J of Mol and Cell Cardiol 2013;59:151-158
Obesity and QT in relation with the metabolic syndrome

Prevalence increased with each MS component (aOR 1.27, 95% CI 1.22 to 1.32) but not with body mass index (aOR 1.01, 95% CI 0.99 to 1.02).
Clinical implications

• Further confirmation using large cohorts studies to assess whether QTc prolongation among patients with NAFLD independently contributes to future cardiovascular events or all-cause mortality is warranted.

• Given the fact that NAFLD is probably a risk factor for cardiovascular morbidity and mortality, a search for every possible link between NAFLD and cardiovascular disease is key to improving outcomes among these patients.

• The pathophysiological pathways through which NAFLD contributes to chronic inflammation, hypogonadism, hypercoagulation, and insulin resistance might represent potential therapeutic targets for the prevention and treatment of myocardial remodeling and the electrophysiological abnormalities of the myocardium in patients with NAFLD.
Autonomic Nervous System & Obesity

• ANS regulates cardiovascular system and energy expenditure

• 10% increase in body weight = decline in parasympathetic tone = increase in resting heart rate

• Increase of resting HR is associated with high mortality rates

• 10% reduction in body weight in severely obese subject resulted improvement in cardiac function, decrease of QTc interval