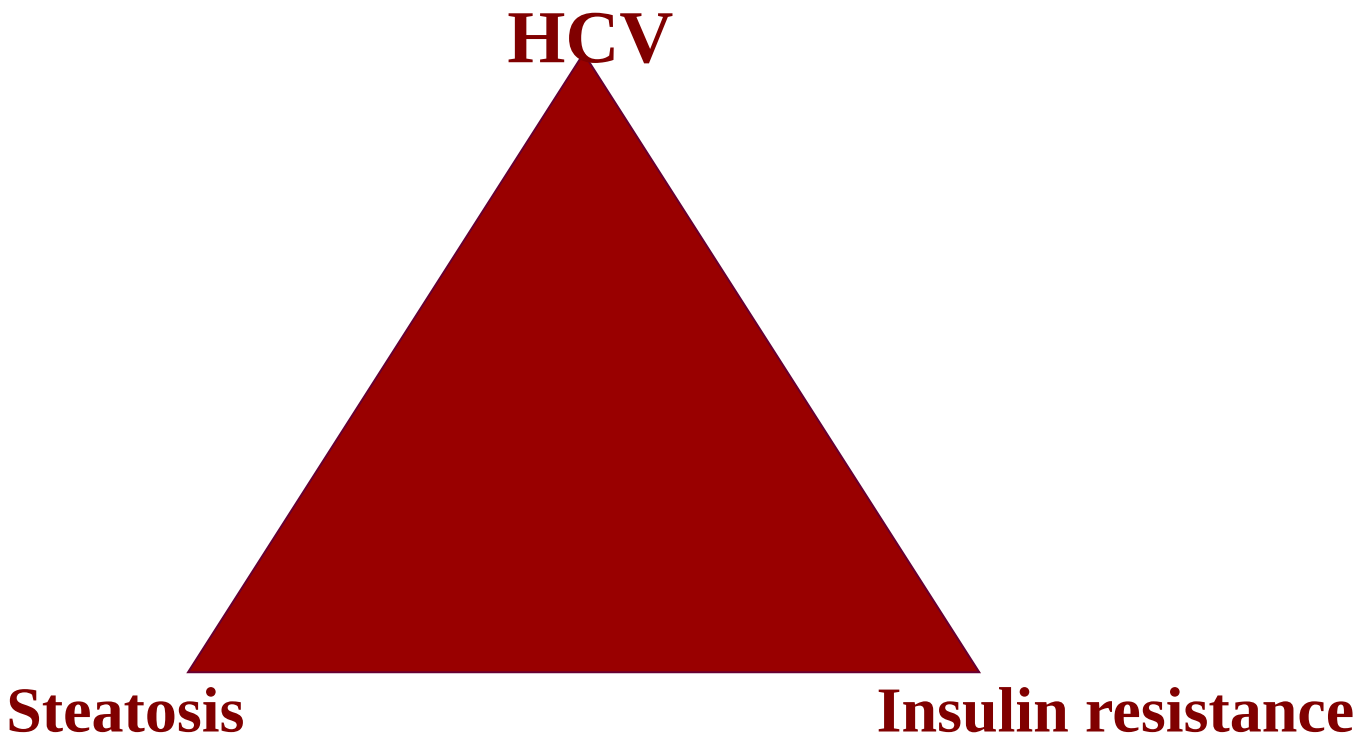
METABOLIC SYNDROME AND HCV: FROM THEORY TO PRACTICE



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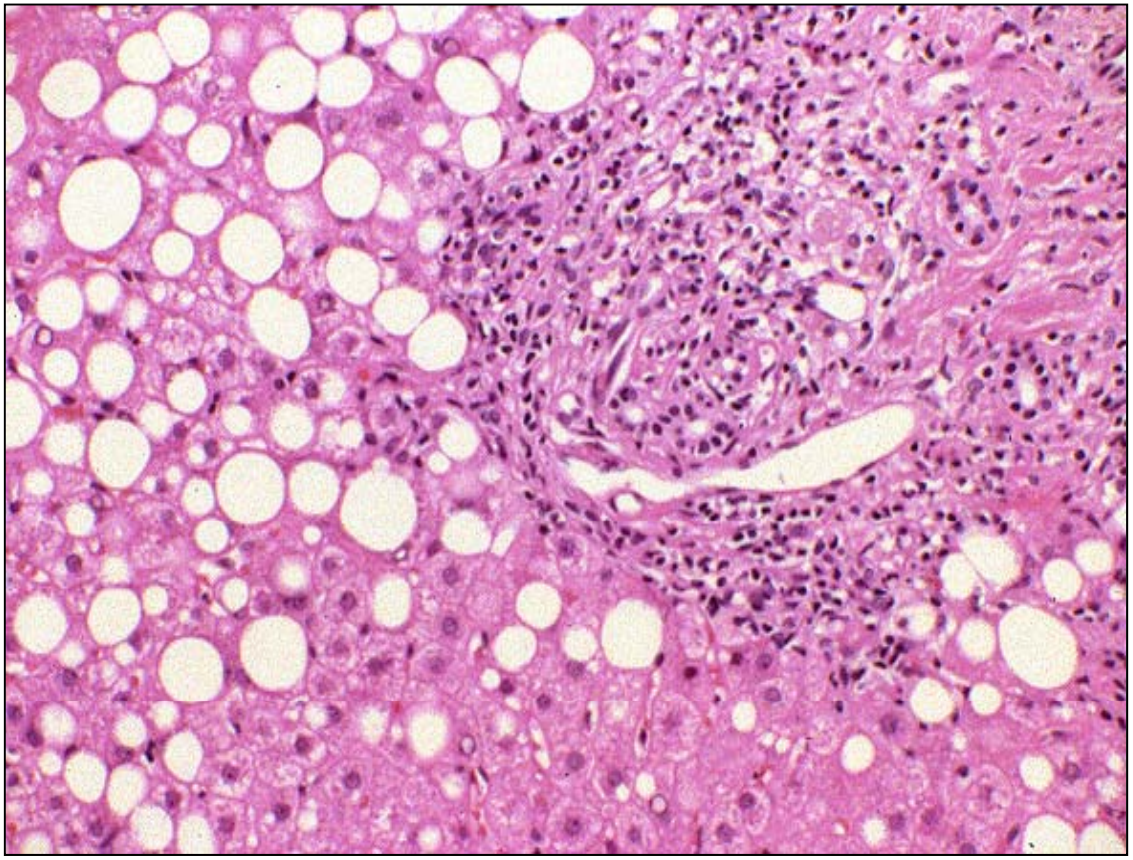
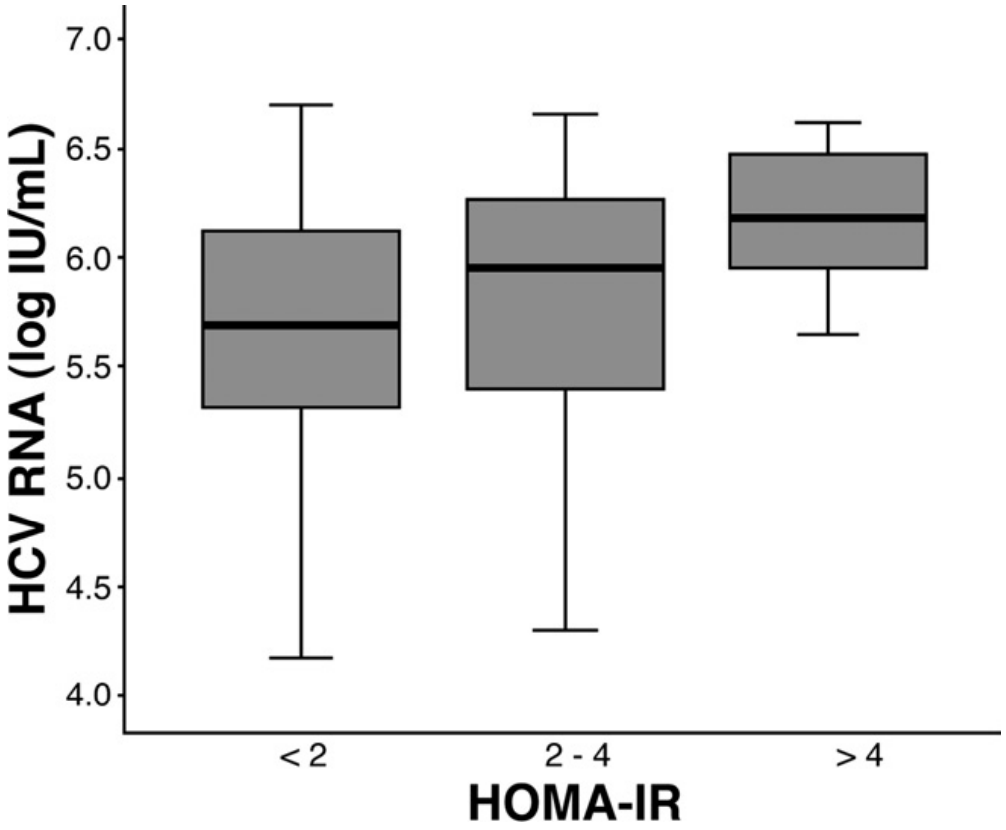
Conflicts: no financial relationships to declare for this presentation

Fatty Liver Disease in HCV



- Genotype 3
- In genotype 1
  - BMI
  - Diabetes
  - Insulin resistance

HCV virus and steatosis affect insulin resistance



Factors associated with IR:

- Age > 40
- Male gender
- genotype 1 and 4
- advanced fibrosis
- steatosis > 30%

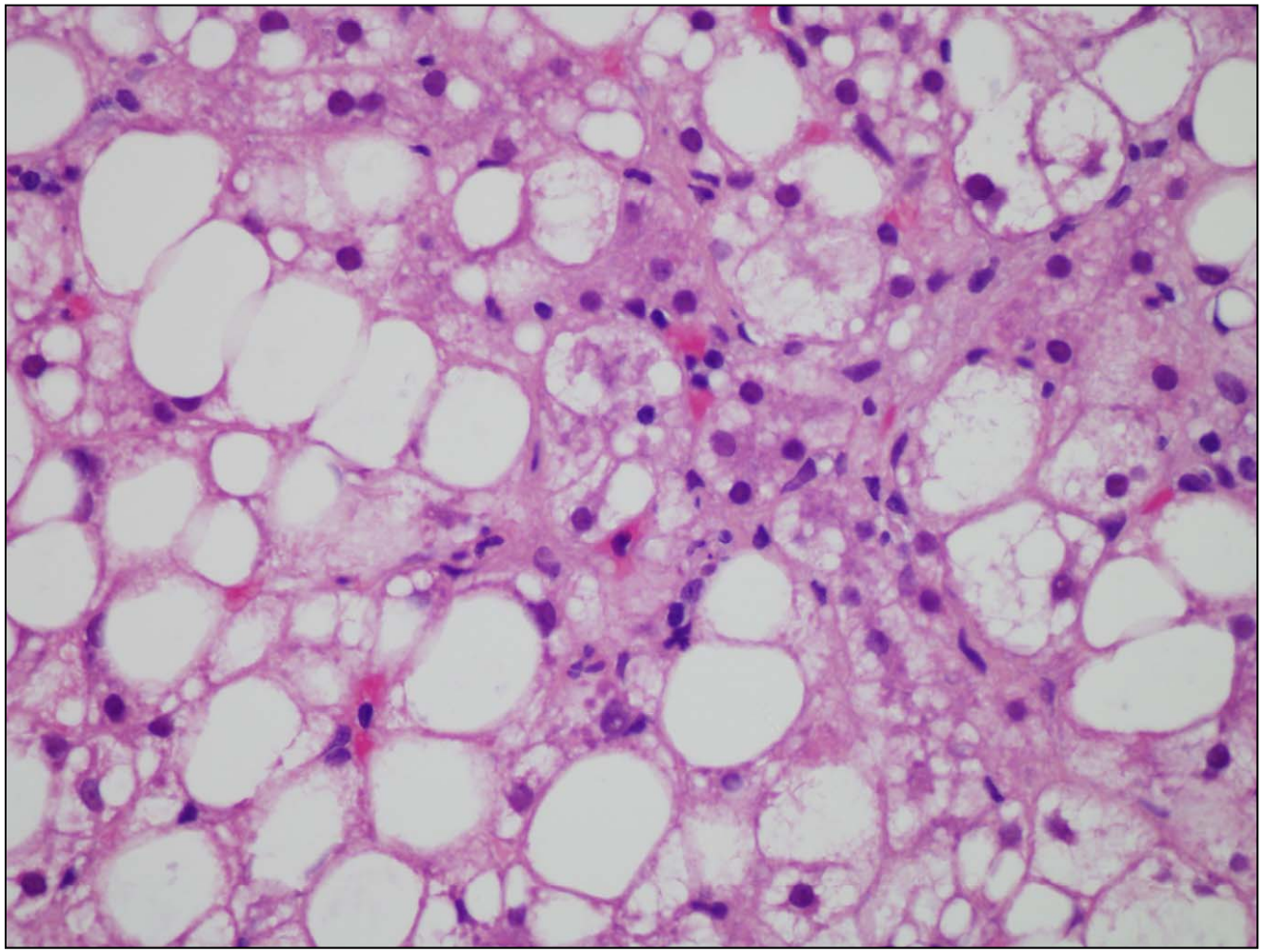
Moucari et al, Gastroenterology, 2008, 134:416-423

Hepatitis C and the Metabolic Syndrome

- **Insulin resistance and its consequences contribute to morbidity and mortality in patients with HCV**

- It is feasible to reduce the impact of insulin resistance and the metabolic syndrome on the burden of disease due to HCV

How to diagnose steatosis vs steatohepatitis in a patient with HCV



Effect of steatosis on HCV fibrosis: cross-sectional studies

Author	Effect of steatosis on fibrosis	Risk factors for fibrosis
Adinolfi	↑	BMI, genotype3
Hourigan	↑	BMI
Ruggiero	↑	BMI, genotype 3
Romero-Gomez	↑	Leptin, visceral obesity
Rubbia-Brandt	↑	Metavir activity
Ong	↑	Metabolic syndrome
Sanyal	↑	Cytologic Ballooning
Patton	↑	BMI, HCV RNA

Contribution of MetS and NAFLD to HCV-related burden of HCC

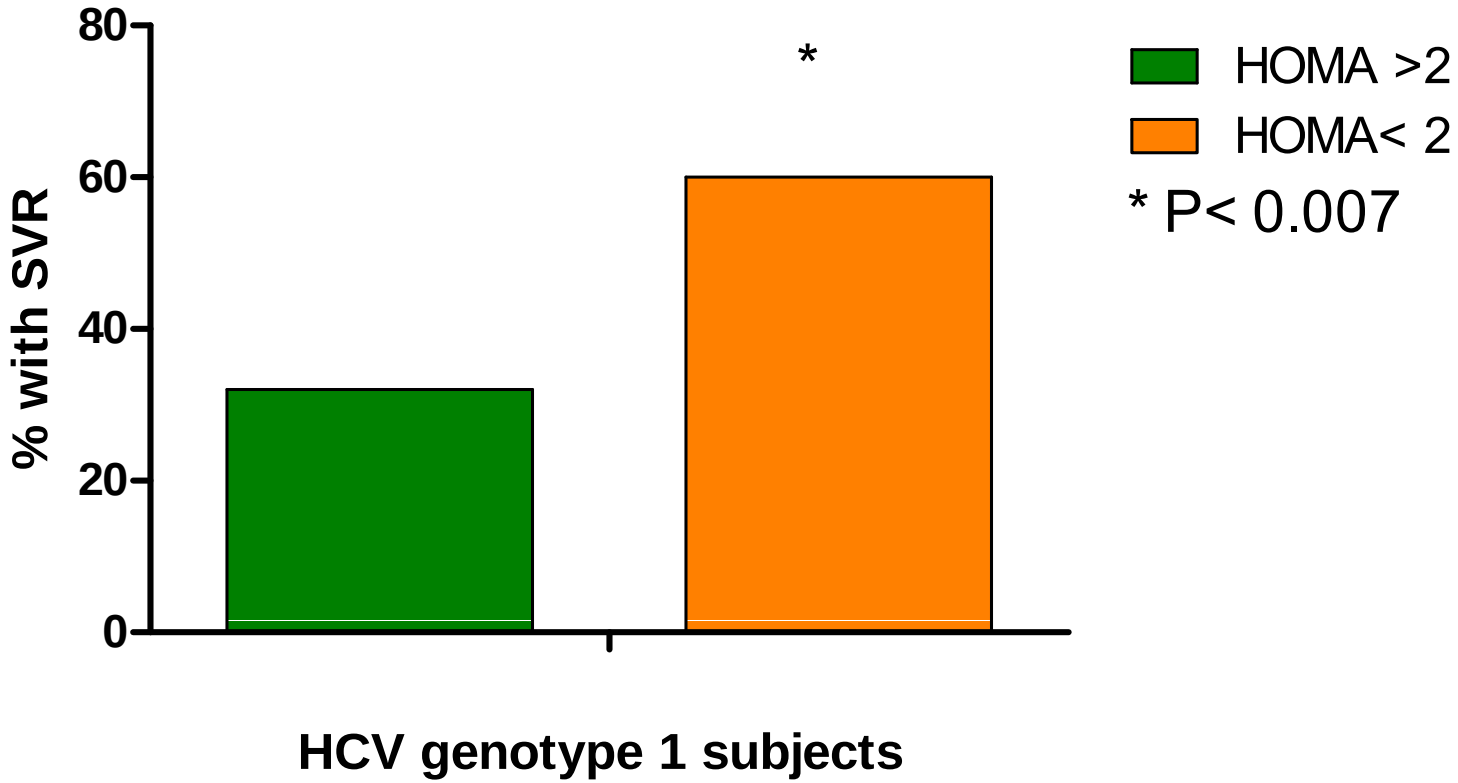
Prevalence of HCC in HCV: 7.9/1000
Prevalence of HCC in NAFLD/NASH: 4.7/1000

Risk Factor (ICD-9-CM code)	HCC Patients (%)	Control (%)	*P* Value	
HCV (070.41, 070.44, 070.51, 070.54, V02.62)	22	0.4	< 0.0001	→ Cirrhosis*: 69% Diabetes: 32% NASH: 68%
NAFLD/NASH (571.8, 571.9, 573.4, 573.8, 573.9)	54.6	2.9	< 0.0001	→ Cirrhosis*: 42% Diabetes: 36% HCV: 28%
Diabetes (250)	33.9	18.6	< 0.0001	→ HCV: 21% NASH: 58%
Alcohol (571.0, 571.1, 571.2, 571.3)	11.6	0.2	< 0.0001	

***ICD-9-CM code 571.5 or 571.6**

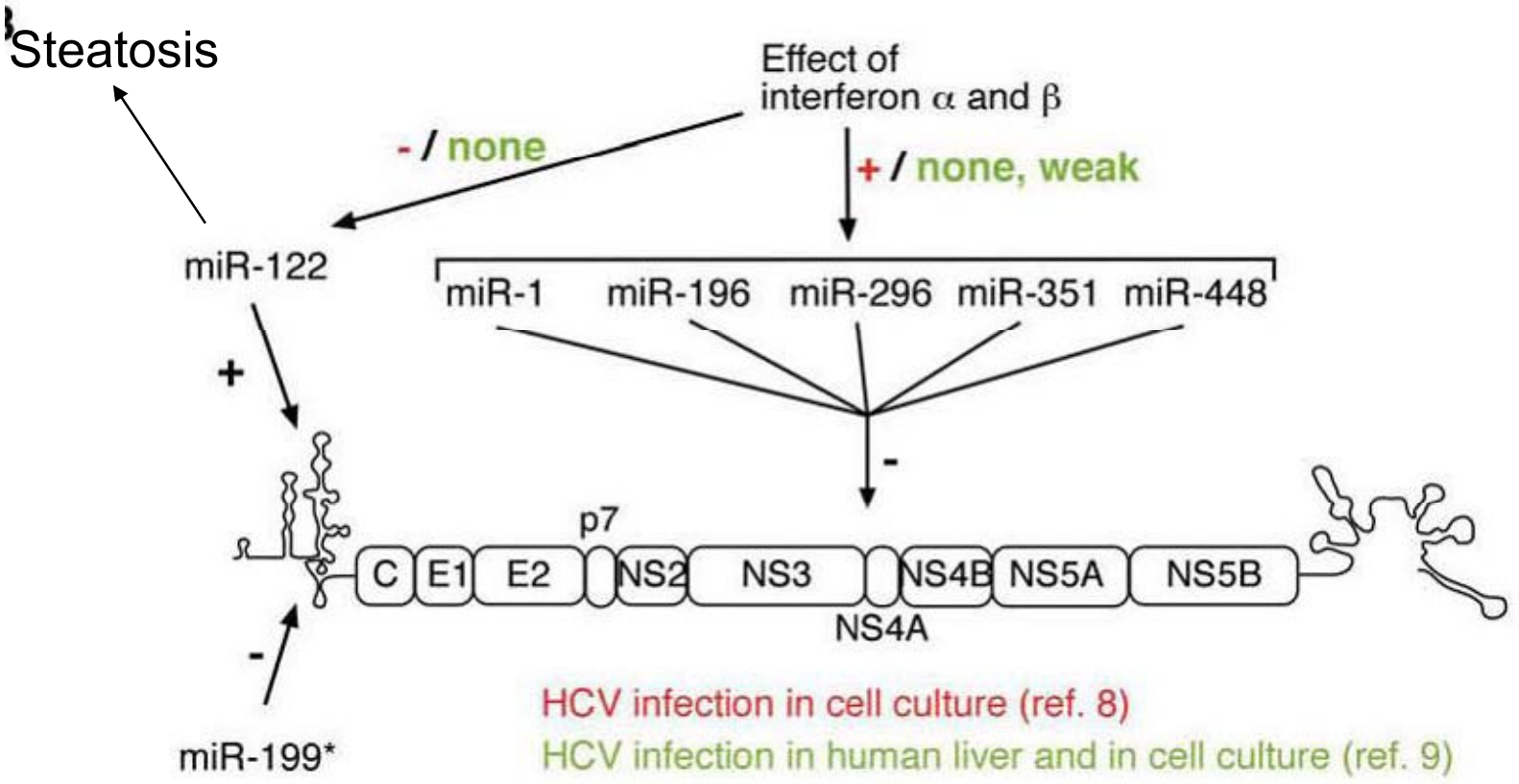
Sanyal et al, CMRO, 2010

Insulin resistance and SVR



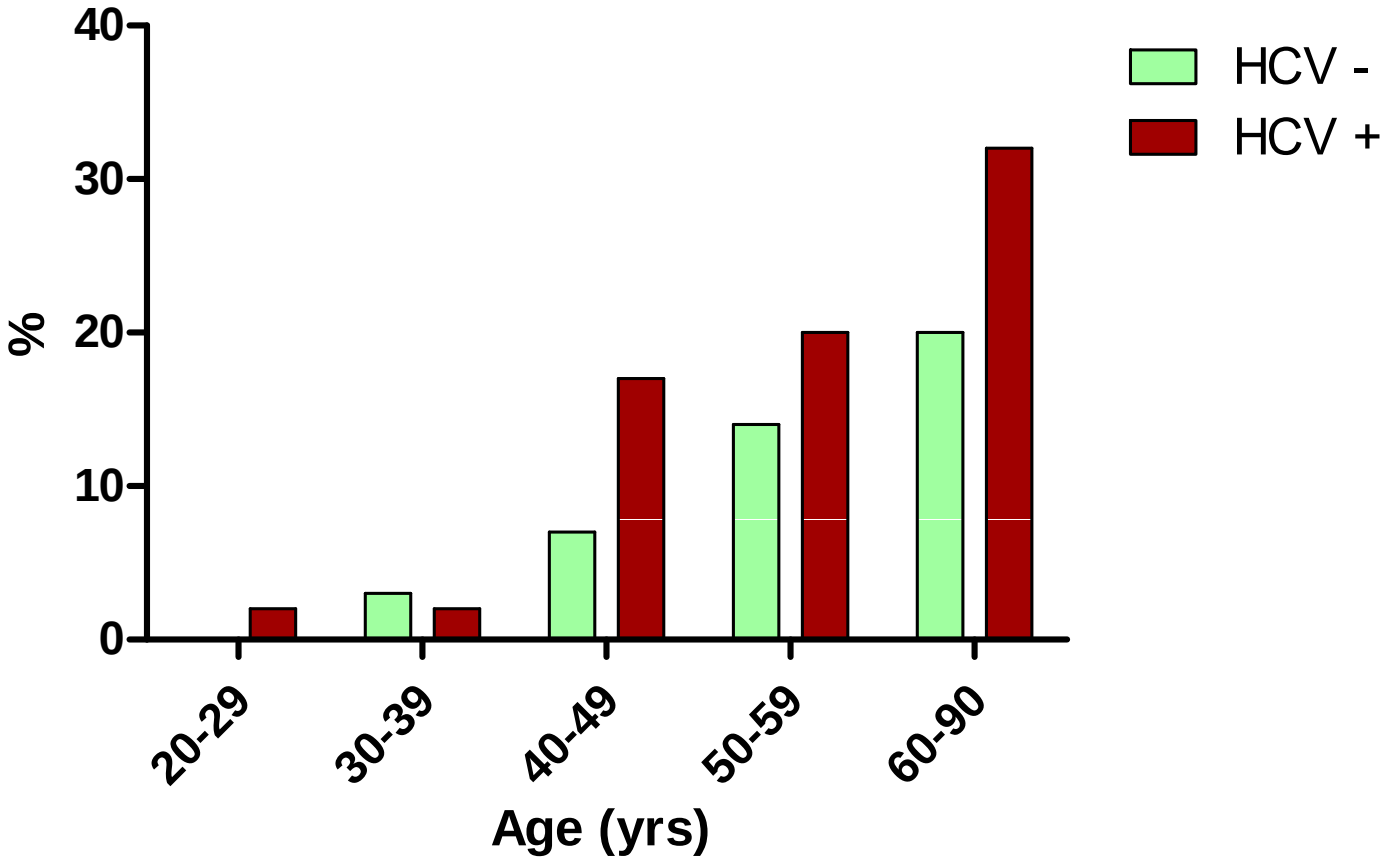
Romero Gomez et al, Gastroenterology, 2005, 128:636-41

MicroRNAs and HCV



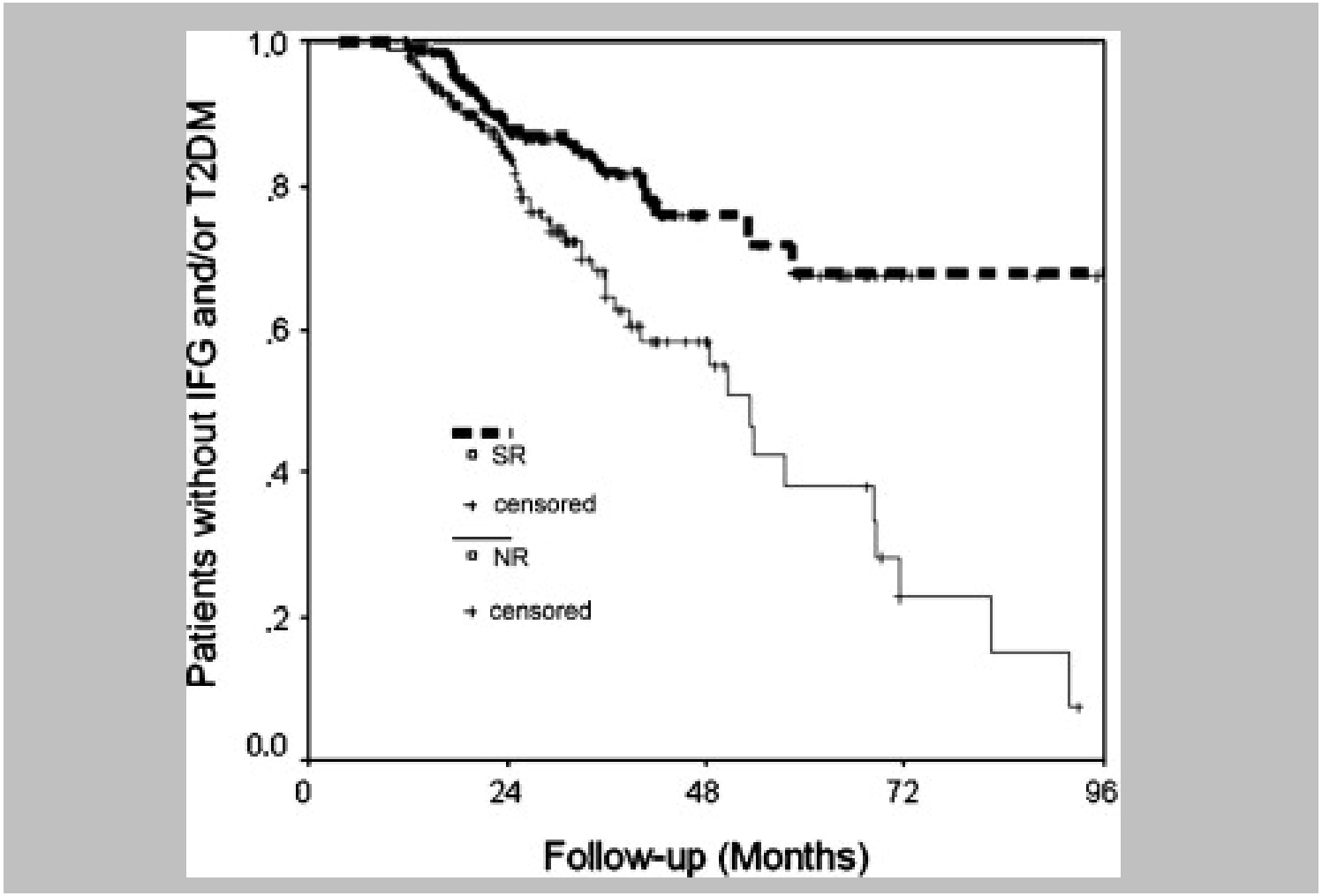
Pfeffer and Baumert, J Hepatology, 2008, 59:606-611

Impact of HCV on development of Type 2 Diabetes Mellitus



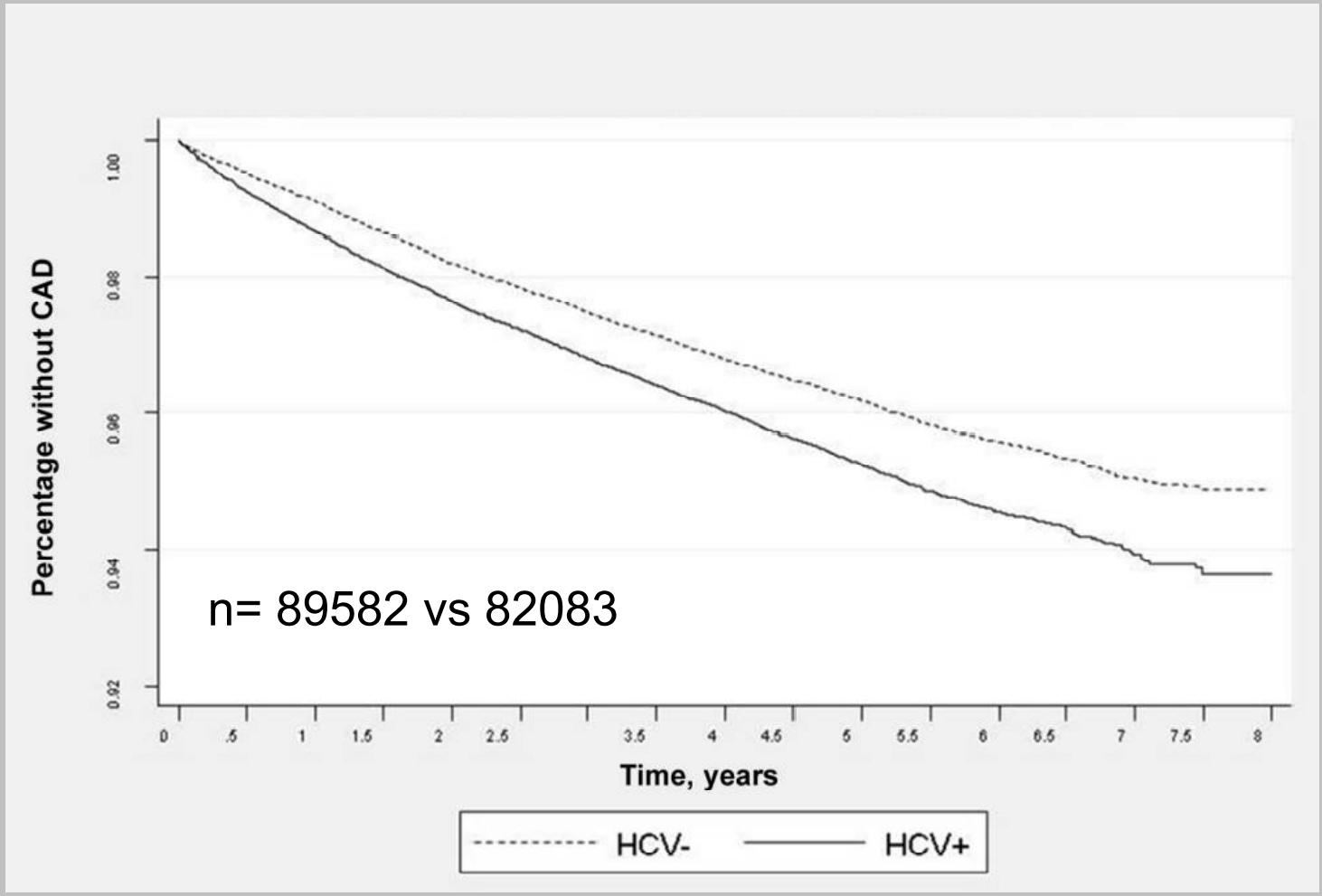
Mehta et al, Ann Intern Med, 2000, 133:592-599

SVR decreases risk of type II diabetes mellitus



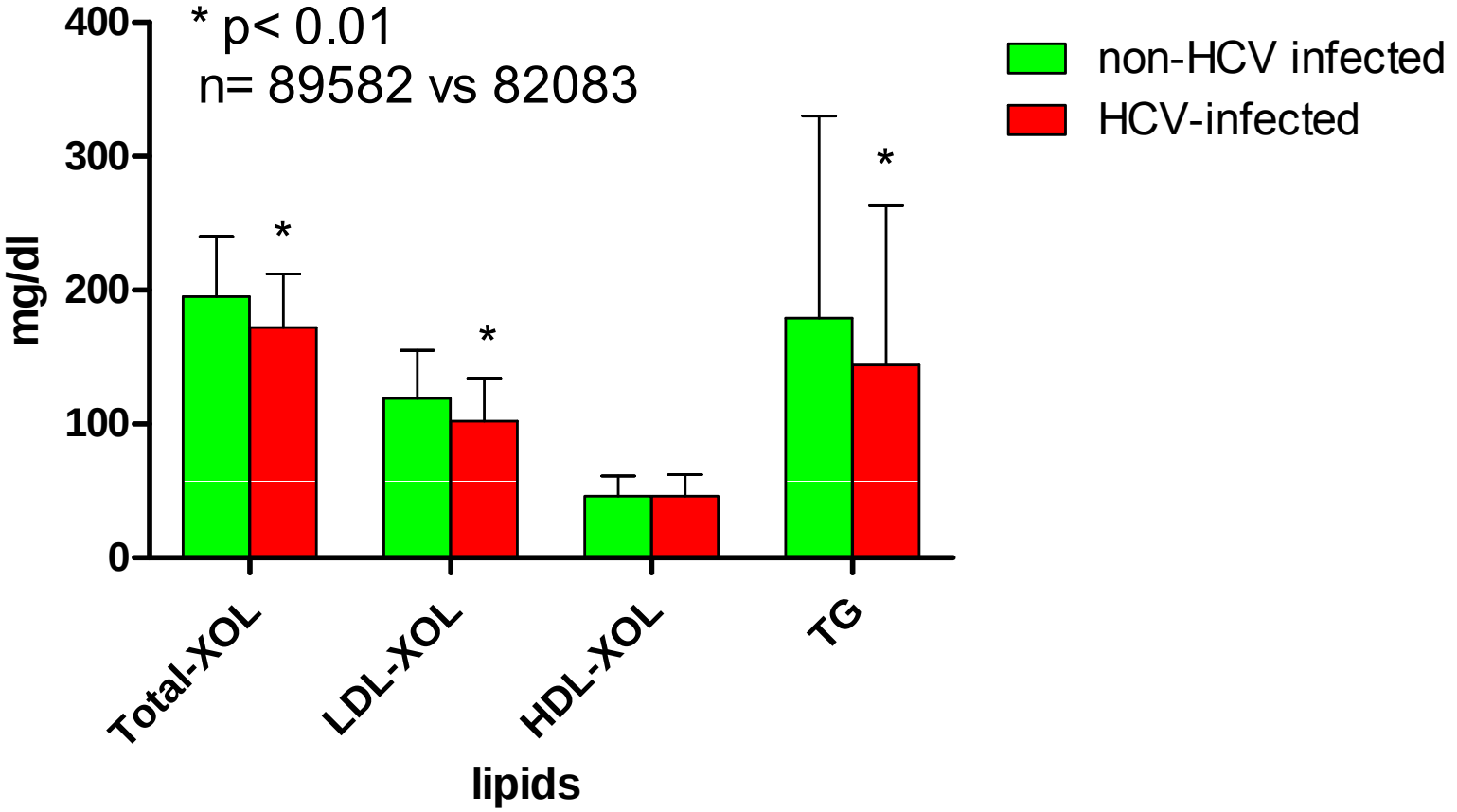
Romero Gomez et al, J Hepatol, 2008, 48:721-727

HCV: a risk factor for coronary artery disease



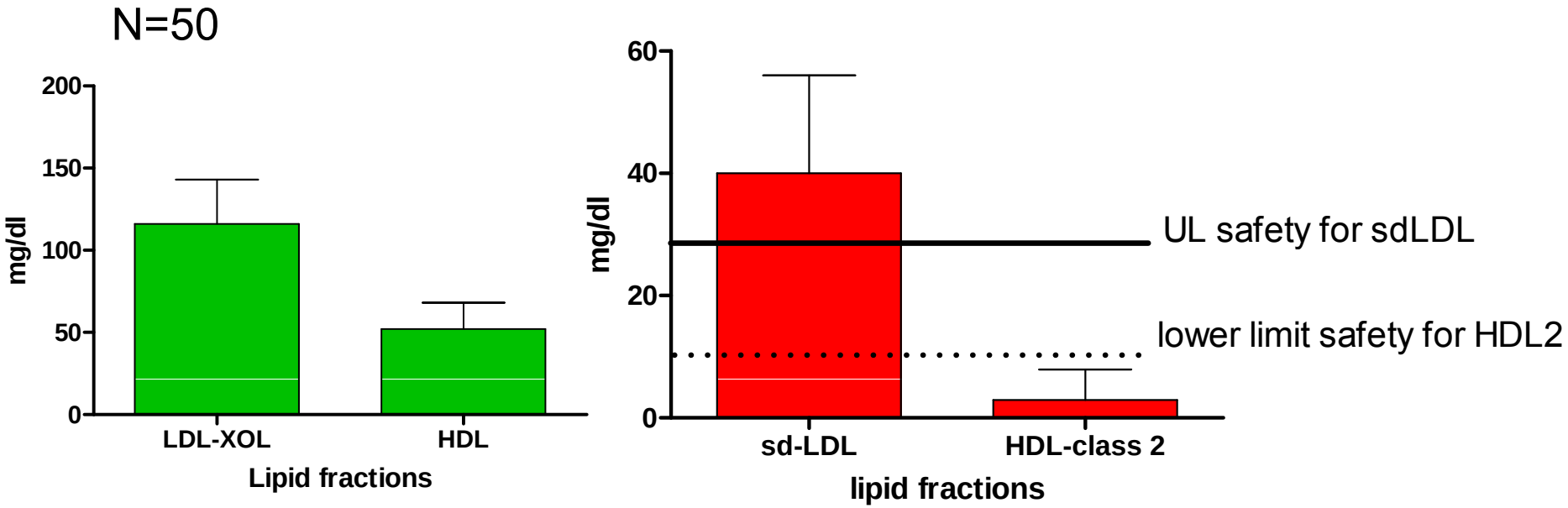
Butt et al, ***CID 2009:49 (15 July)*** • *225*

Is HCV associated with dyslipidemia?



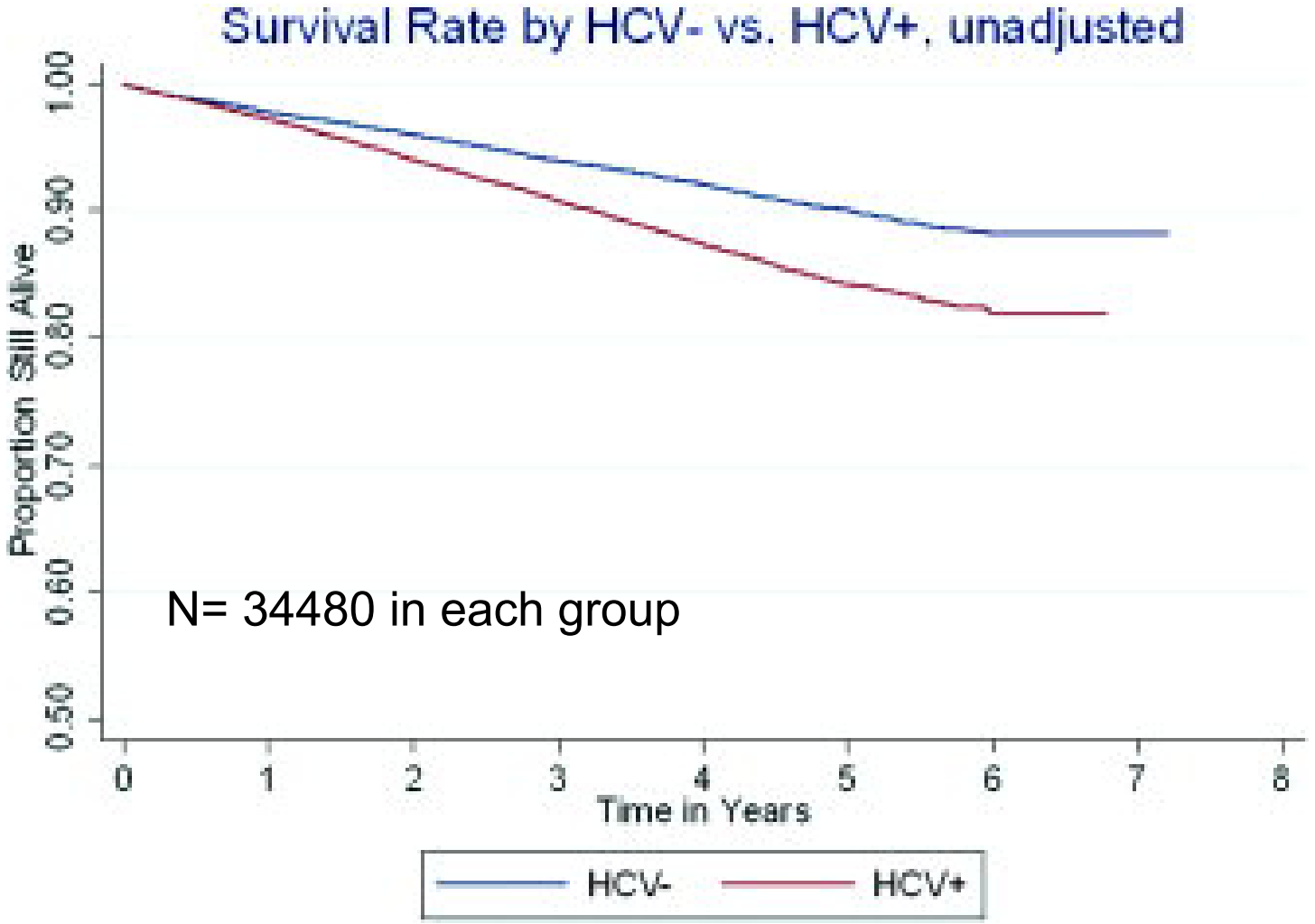
Butt et al, CID 2009:49 (15 July) • 225

Simple Lab tests are misleading for atherogenic risk in this population



Sd-LDL vs FLD activity (steatosis-ballooning-lob inflam) r= 0.53, p< 0.0006

HCV impairs survival

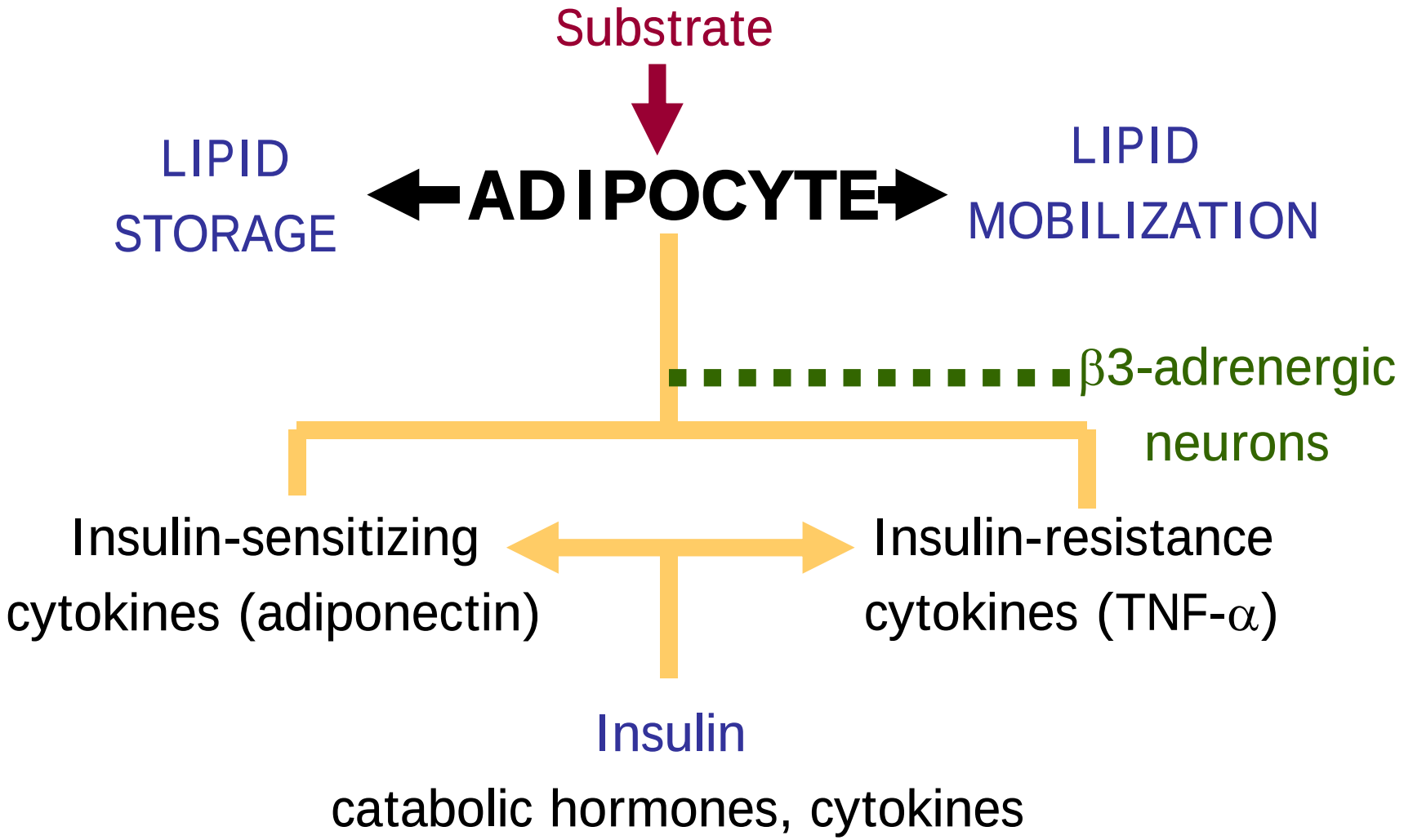


Butt et al, HEPATOLOGY 2009;50:387-392

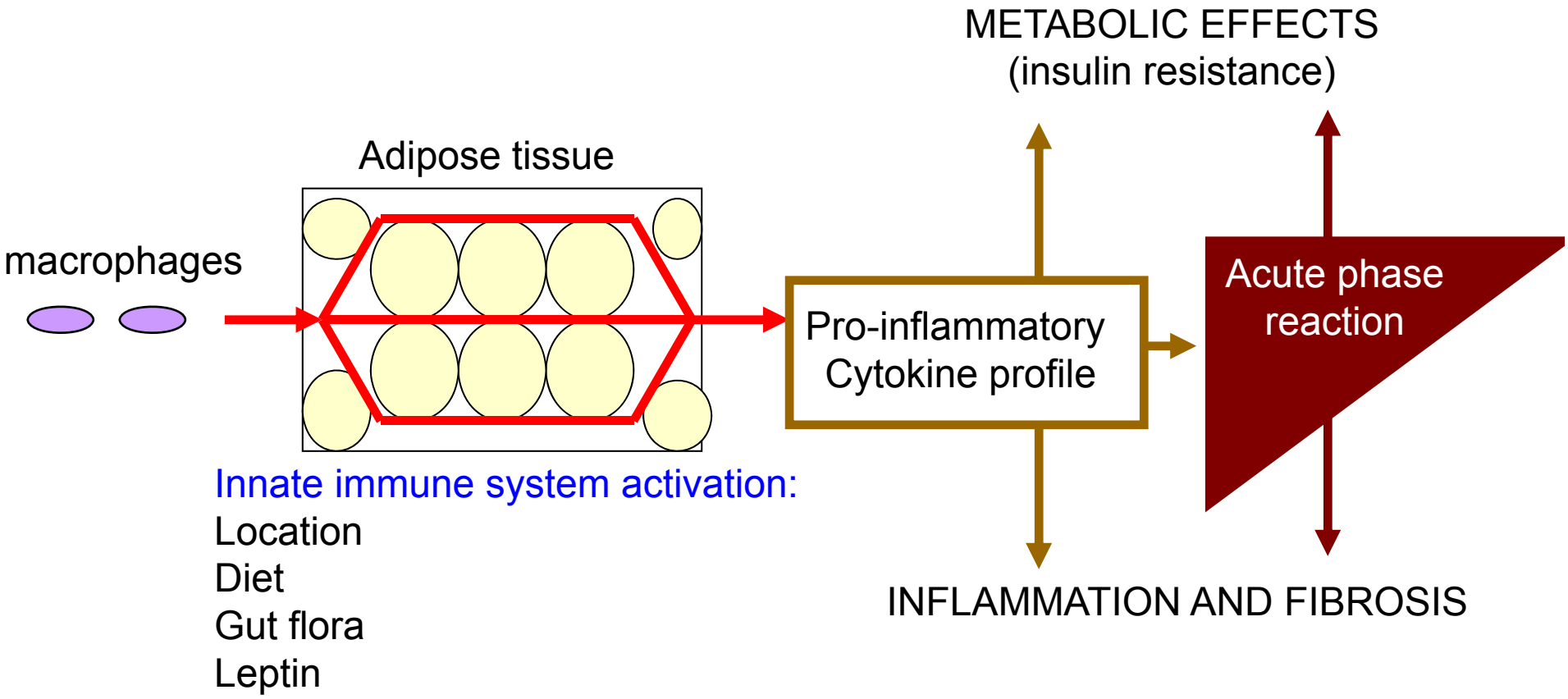
Hepatitis C and Metabolic Syndrome: Clinical implications

- Hepatitis C is associated with the metabolic syndrome
- Subjects with HCV have a higher risk of developing diabetes, chronic kidney disease, coronary artery disease
- In subjects with HCV, the presence of insulin resistance and MetS is associated with steatosis, increased progression to cirrhosis and HCC
- Insulin resistance confers resistance to PEG-IFN and ribavirin therapy

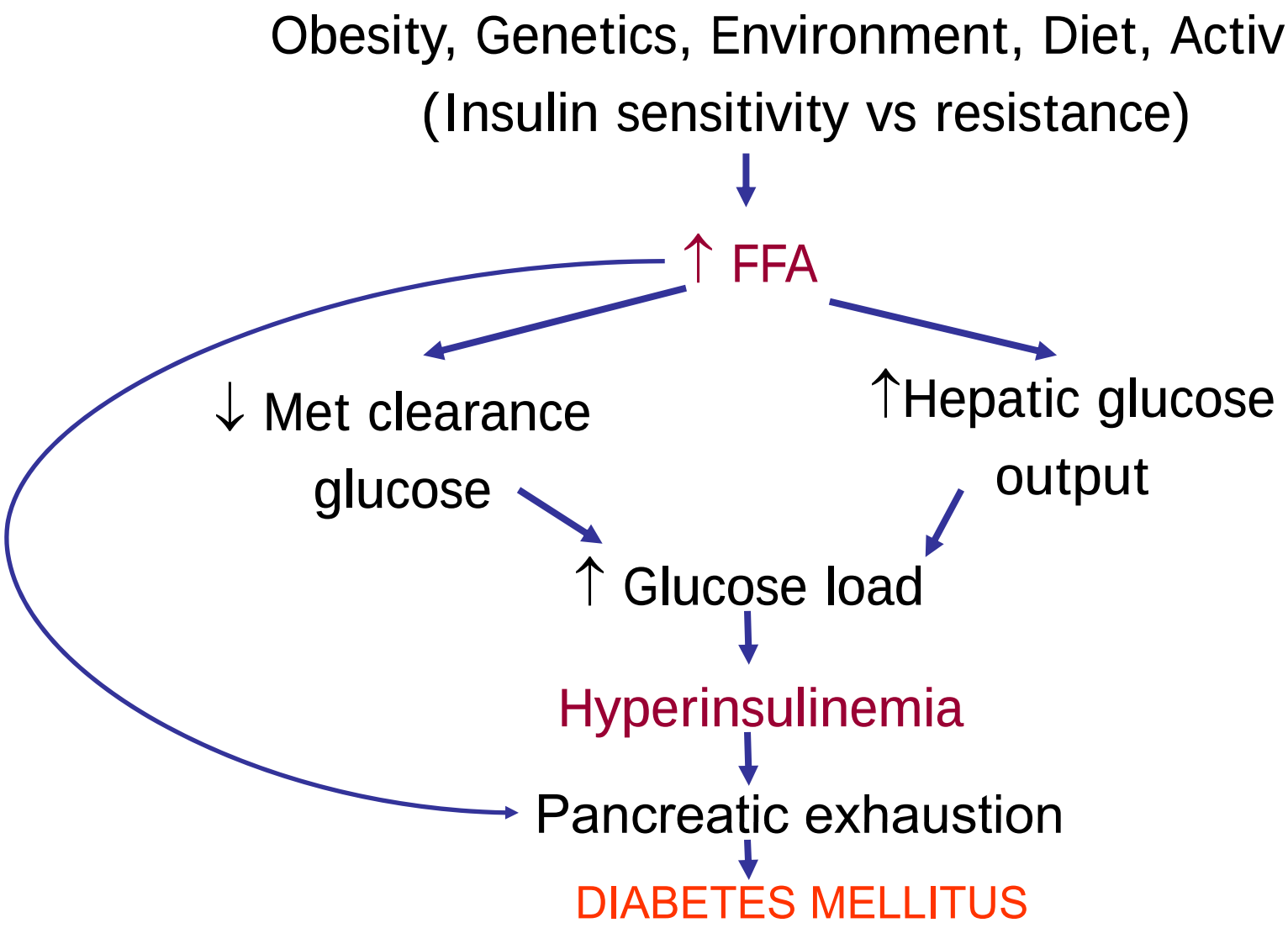
Insulin resistance: a vital physiologic phenomenon



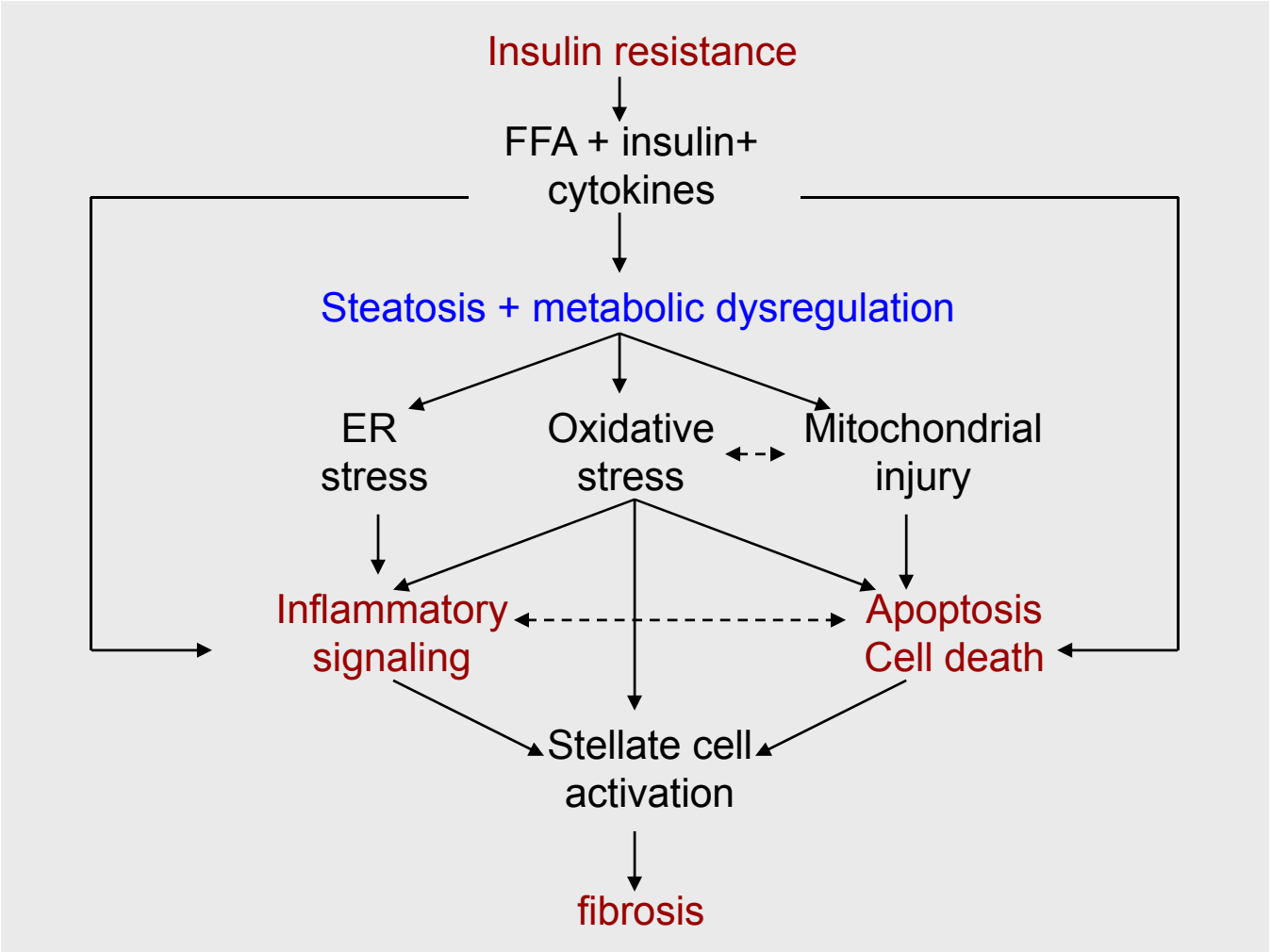
Pathogenesis of insulin resistance



Pathophysiology of insulin resistance



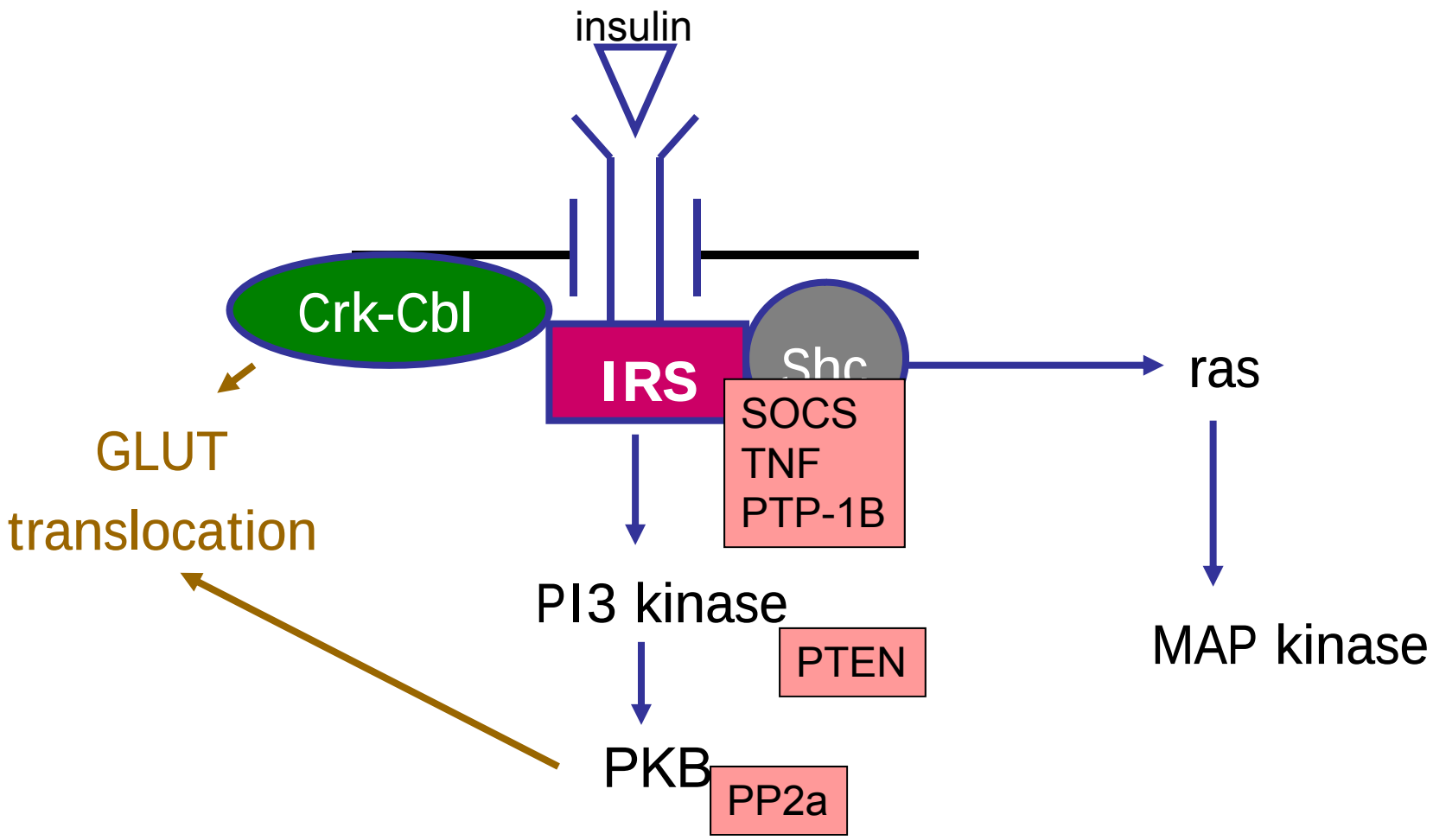
Pathogenesis of NASH



Multiple sources

M

Mechanisms of impaired insulin signaling in HCV



Hepatitis C and the Metabolic Syndrome

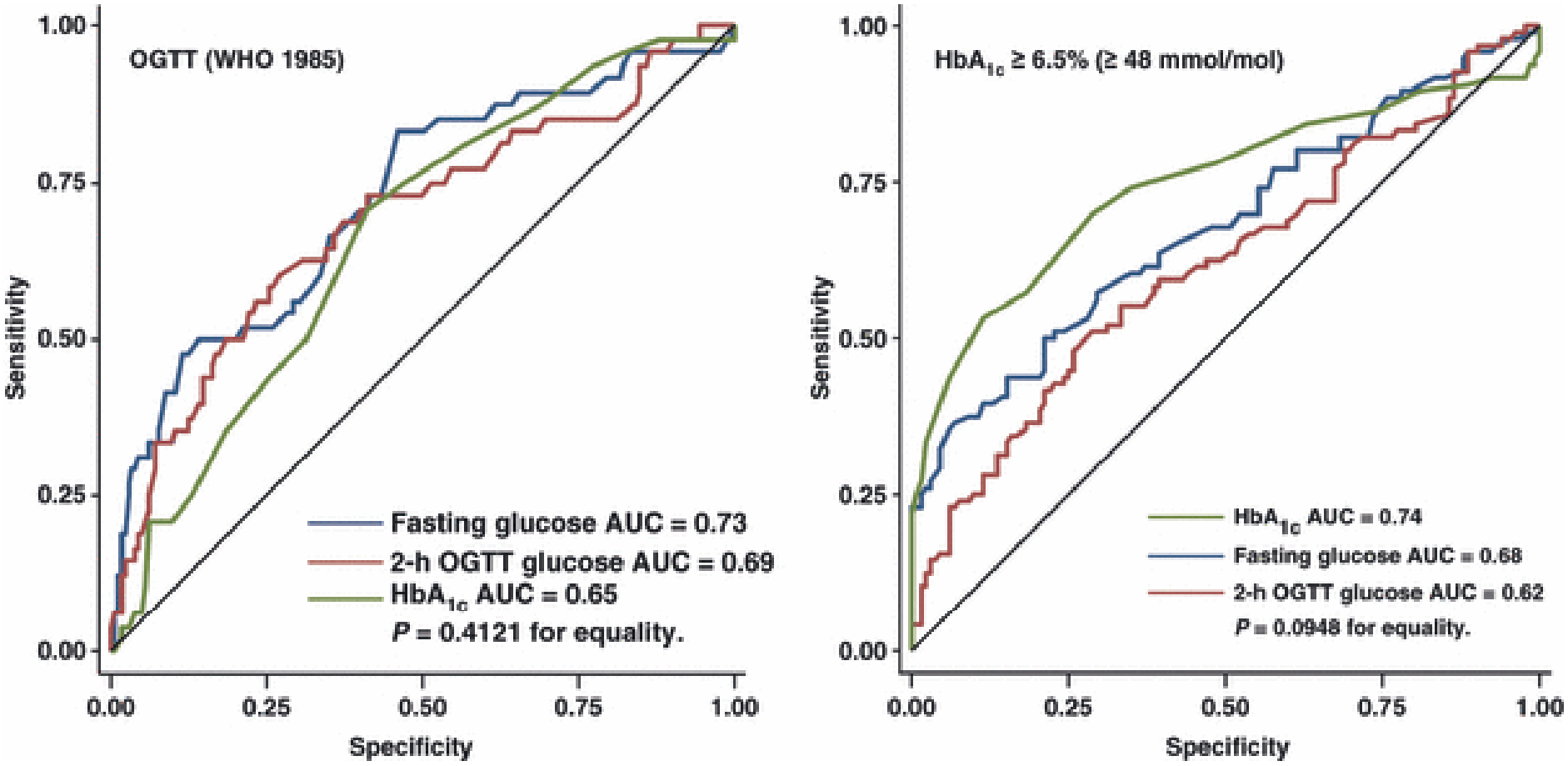
- Insulin resistance and its consequences contribute to morbidity and mortality in patients with HCV

- **It is feasible to reduce the impact of insulin resistance and the metabolic syndrome on the burden of disease due to HCV**

Hepatitis C and the Metabolic Syndrome: Implications for Management

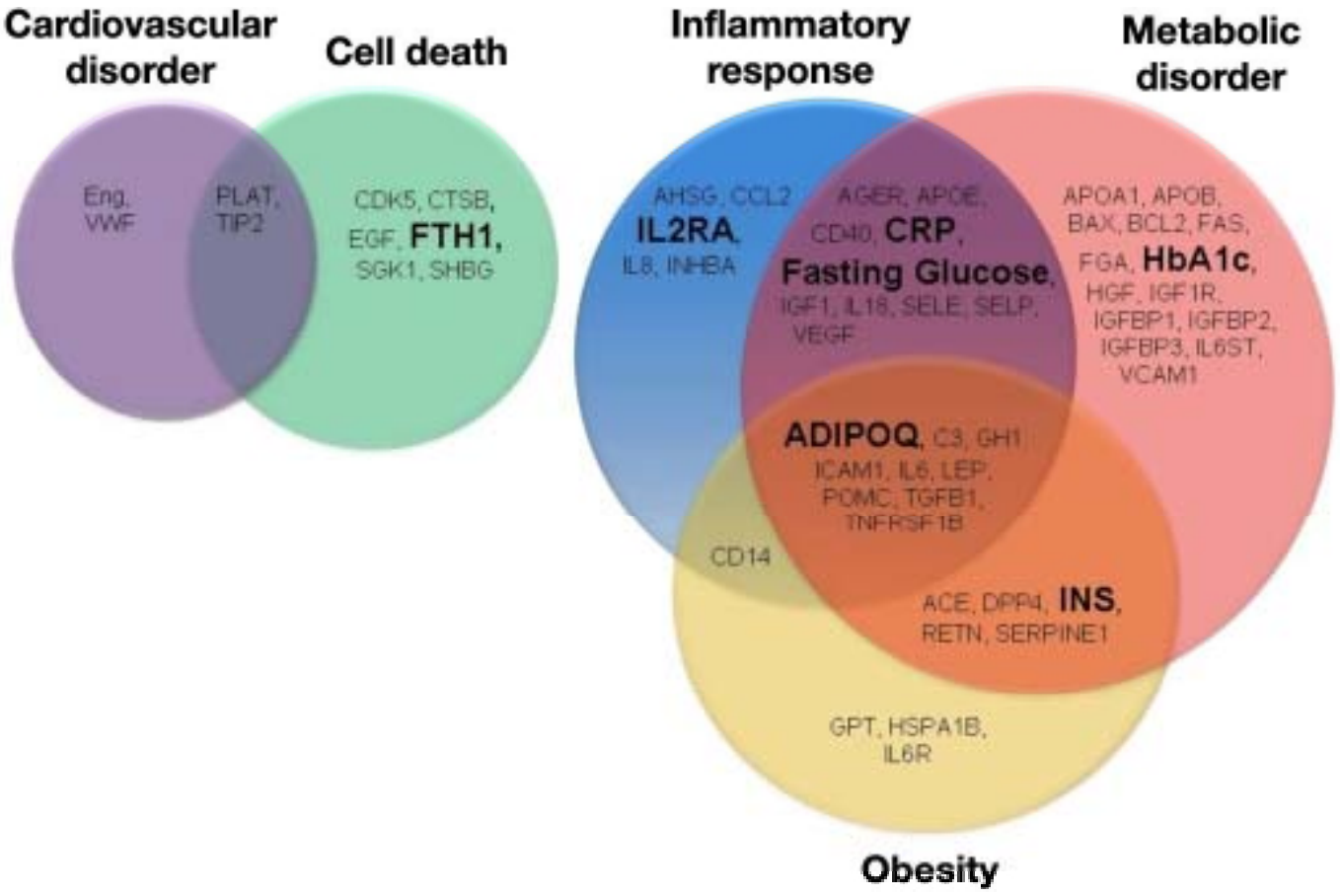
- Assess presence of or risk of:
  - type 2 diabetes mellitus (www.diabetes.fi)
  - coronary artery disease
- Lifestyle intervention
- Drugs to prevent diabetes
- Drugs to prevent coronary artery disease
- Should insulin resistance be treated prior to anti-HCV treatment

Can diabetes be predicted by usual glycemic measures?



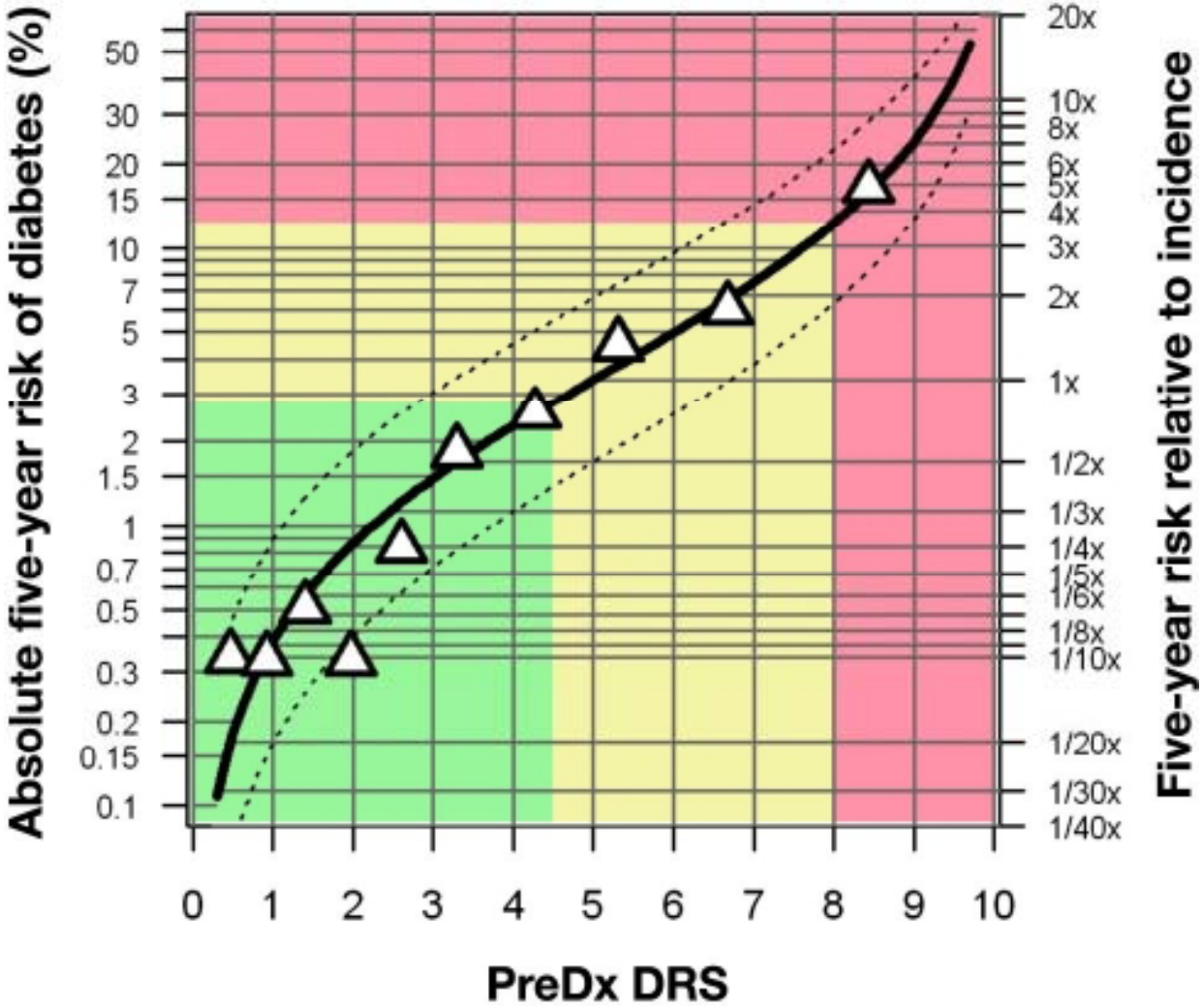
Pajunen et al, Diabet Med. 2011 Jan;28(1):36-42.

Biomarkers predictive of development of Type 2 diabetes



Urdea et al, J Diabetes Sci Technol. 2009 Jul 1;3(4):748-55.

Performance of PreDx for prediction of Type 2 DM

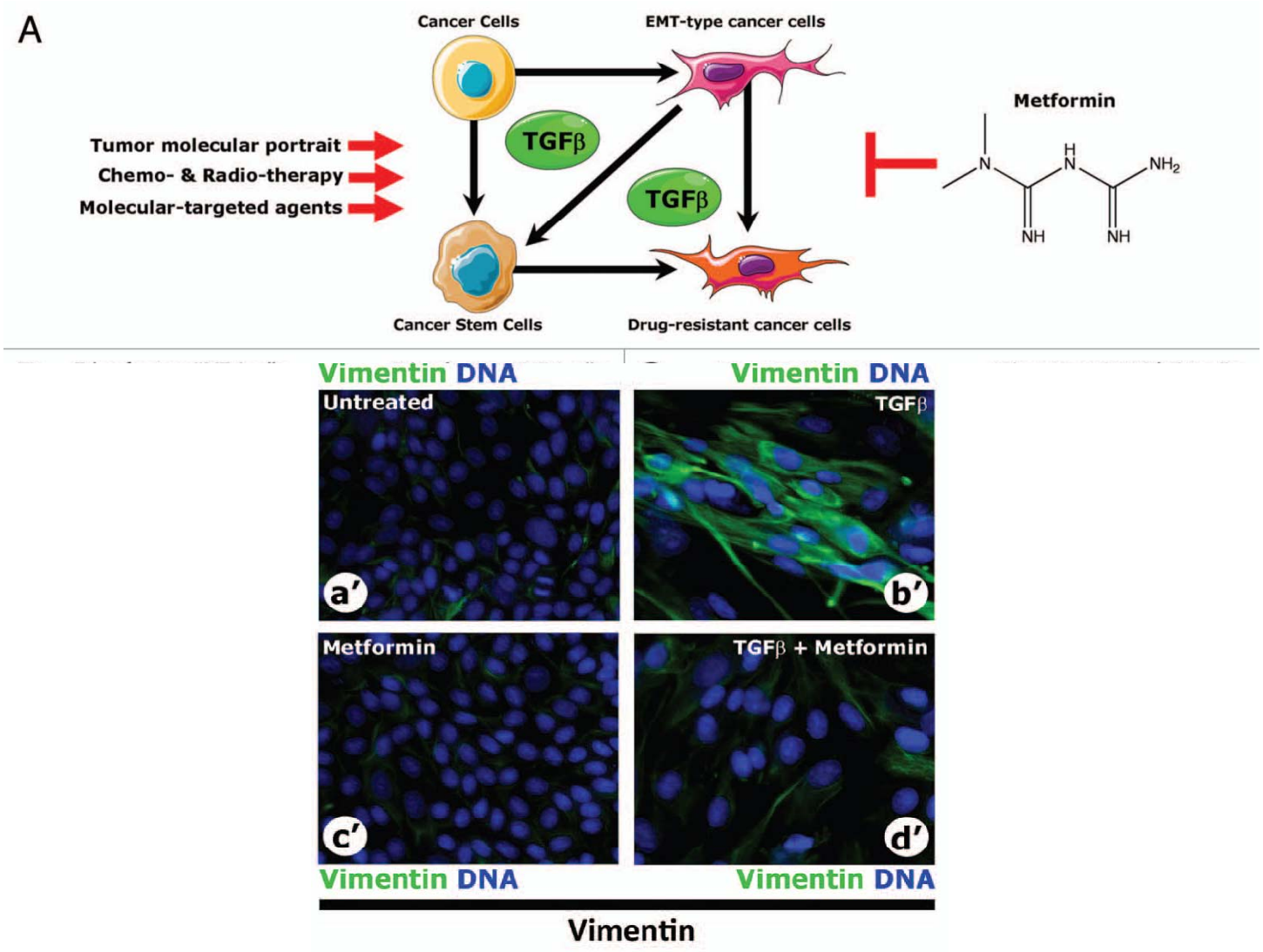


Urdea et al, J Diabetes Sci Technol. 2009 Jul 1;3(4):748-55.

Approaches to reduce risk of T2DM in subjects at risk

- Lifestyle changes:
  - 58% reduction with intense changes
  - 60% risk of new onset T2DM after intense intervention is stopped.
- Drugs:
  - Metformin
  - Glitazones
  - ? Acarbose
- Bariatric surgery (for BMI > 40 kg/m2)

Metformin: potential uses in HCV



Cufi et al, Cell Cycle 2010, 9:22, 4461-4468

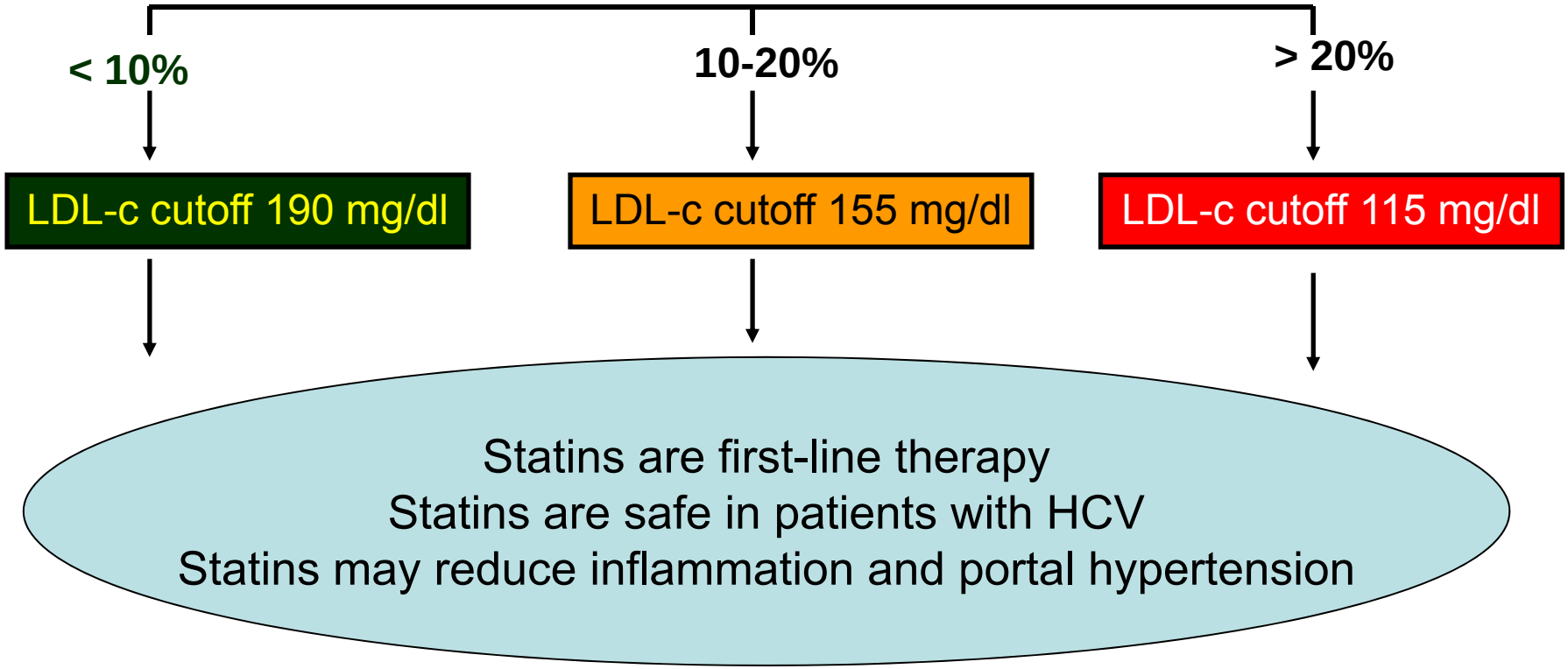
Is metformin protective against HCC?

	n	Metformin (%)	Sufonylurea (%)	Insulin (%)
HCC	190	9.5	53	40
Controls	215	24	51	22
Cirrhosis	144	40	16	43

Donadon et al, Liver Int. 2010 May;30(5):750-8.

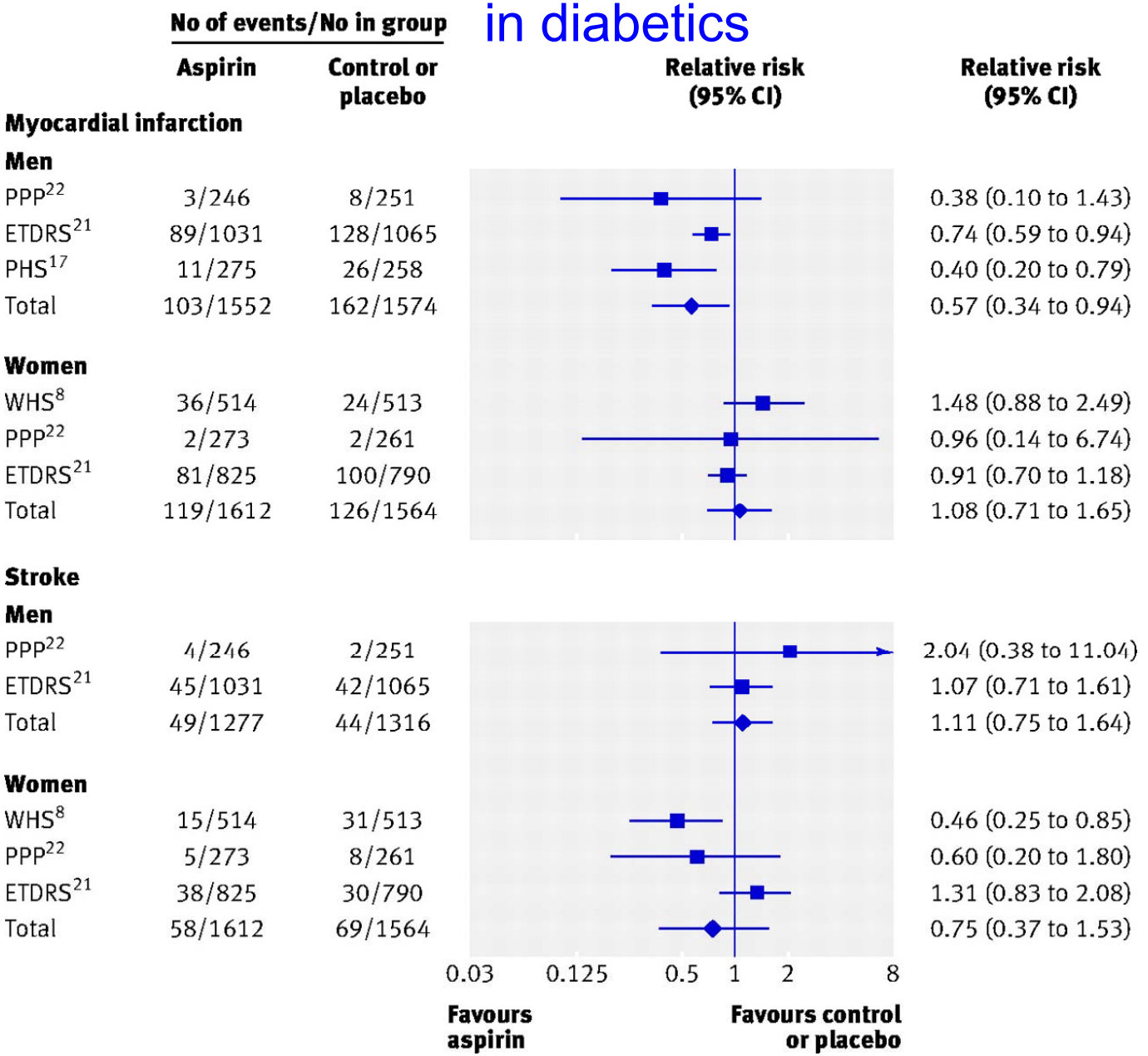
Approach to management of dyslipidemia

Estimate 10 yr risk of coronary heart disease
http://hp2010.nhlbihin.net/atpiii/calculator.asp?usertype=prof
(lifestyle recommendations)



ATP III recommendations for management of atherogenic dyslipidemic

Is Aspirin beneficial for prevention of cardiovascular events in diabetics



DeBerardis et al, BMJ, BMJ 2009; 339:b4531

Pioglitazone + PEG-IFN + Ribavirin for HCV

- N= 5
- All nonresponders
- Treated with pioglitazone (30 mg/day) + standard PEG/Riba
- None of the subjects responded although insulin sensitivity improved.

J Hep 2009

Future Directions

- Long-term studies to reduce the burden of non-hepatic complications related to MetS in subjects with HCV.
- Validation of the value of personalized approaches to reduce the risk of diabetes, CAD, HCC in subjects with HCV
- Define the role of insulin resistance in treatment resistance to triple therapy
- Define the role of modulating MetS to further boost the response to PEG-IFN and ribavirin.

THANK YOU FOR YOUR ATTENTION