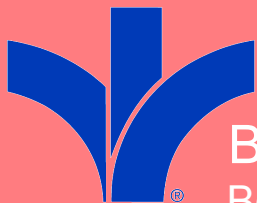


# IMPACT OF HCV THERAPY ON METABOLISM AND PUBLIC HEALTH

Mitchell L Shiffman, MD  
Director  
Liver Institute of Virginia  
Bon Secours Health System  
Richmond and Newport News, VA



Bon Secours Liver Institute of Virginia  
Bon Secours Medical Group

Good Help to Those in Need ®

# DISCLOSURES CONFLICTS OF INTEREST

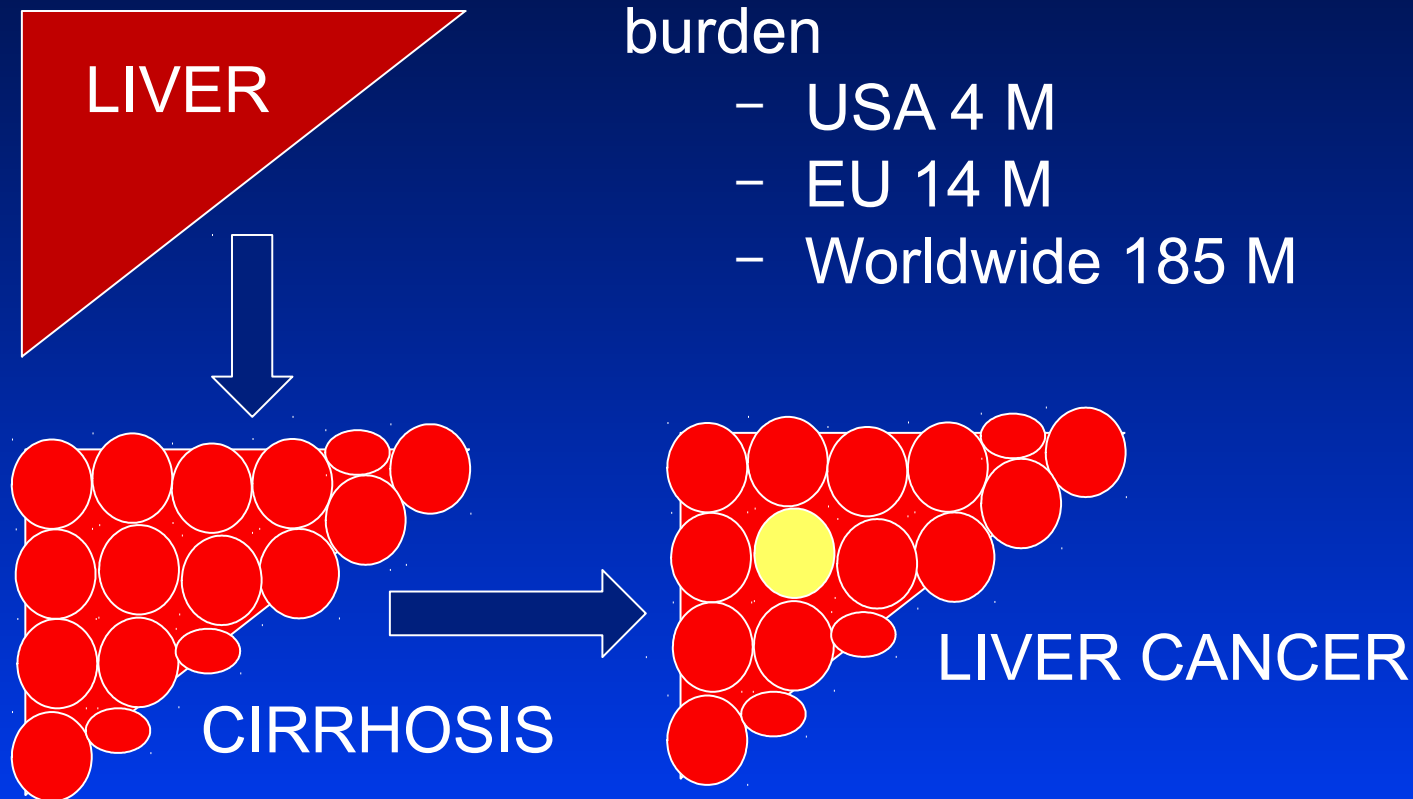
Company	Roles
Abbvie	Advisor meetings, Grant support, Speaker
American Regent	Speaker
Bayer	Speaker
Beckman-Colter	Grant support
Bristol Myers-Squibb	Advisor meetings, grant support, Speaker
Conatus	Grant support
CymaBay	Grant support
Galectin	Grant support
Genfit	Grant support
Gilead	Advisor meetings, Grant support, Speaker
Intercept	Grant support, Advisor meetings, Speaker,
Immuron	Grant support
Merck	Grant support, Advisor meetings, Speaker,
NGMBio	Grant support
Novartis	Grant support

# CHRONIC HCV

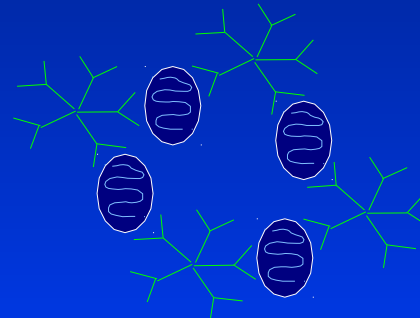
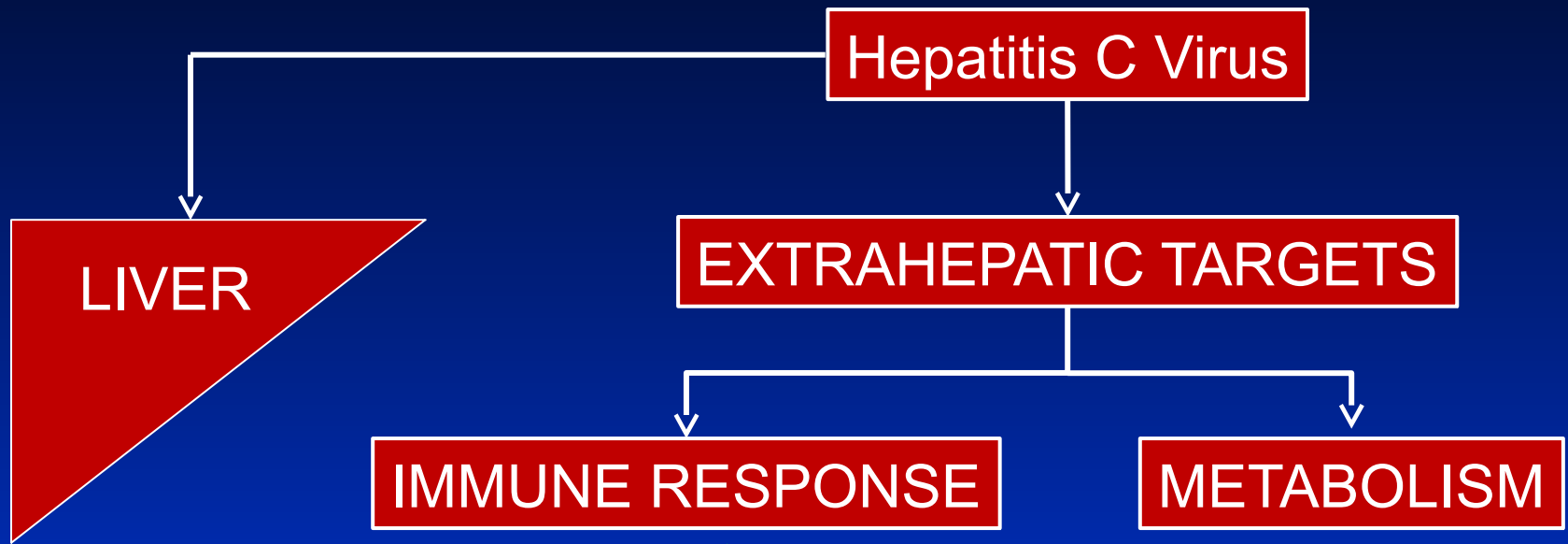
## A GLOBAL HEALTH PROBLEM

Chronic HCV is a significant health burden

- USA 4 M
- EU 14 M
- Worldwide 185 M

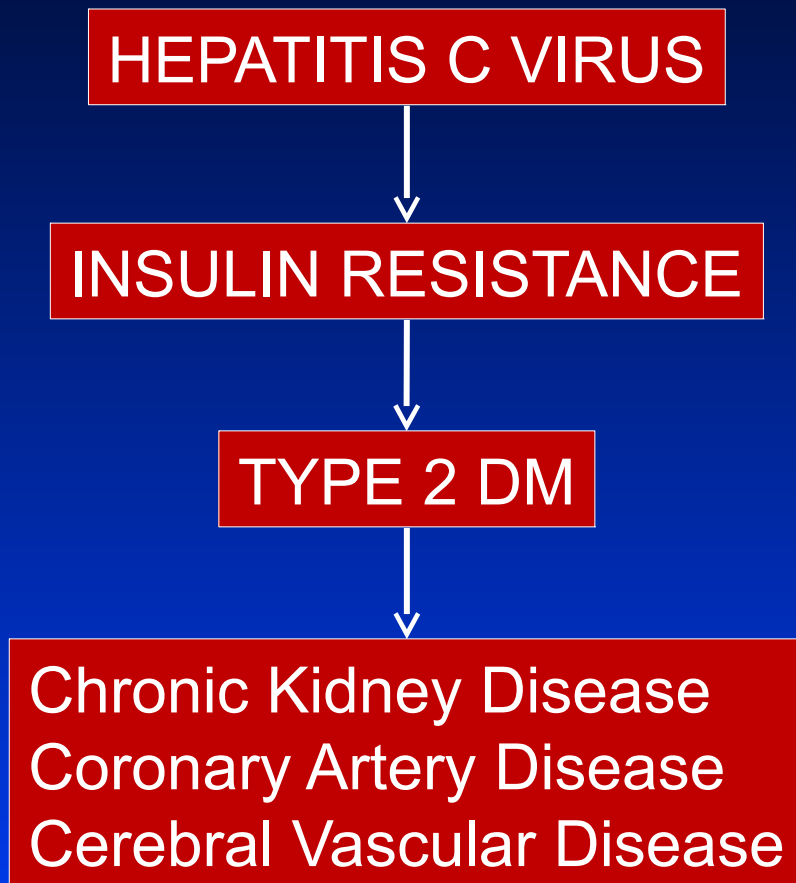


# CHRONIC HCV EXTRAHEPATIC TARGETS



Cryoglobulinemia

# CHRONIC HCV EFFECTS ON METABOLISM



- Estimated 47 M persons have T2DM from HCV
- T2DM is 4x more common in patients with HCV
- HCV precedes appearance of T2DM by 10-20 years
- HCV induced T2DM is a significant public health problem

# HEPATITIS C VIRUS GENETIC SEQUENCE

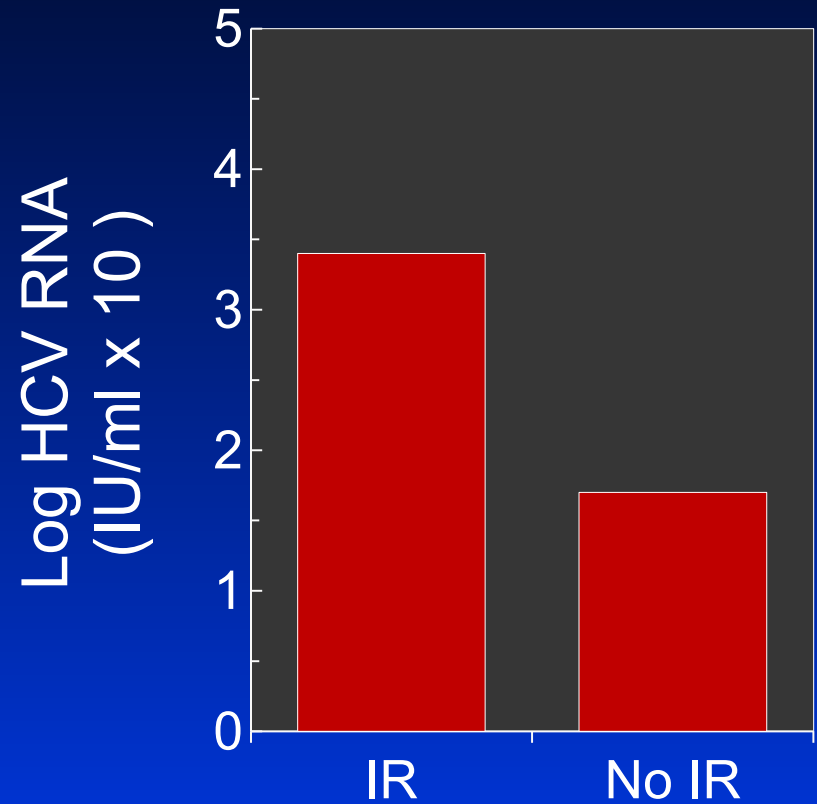
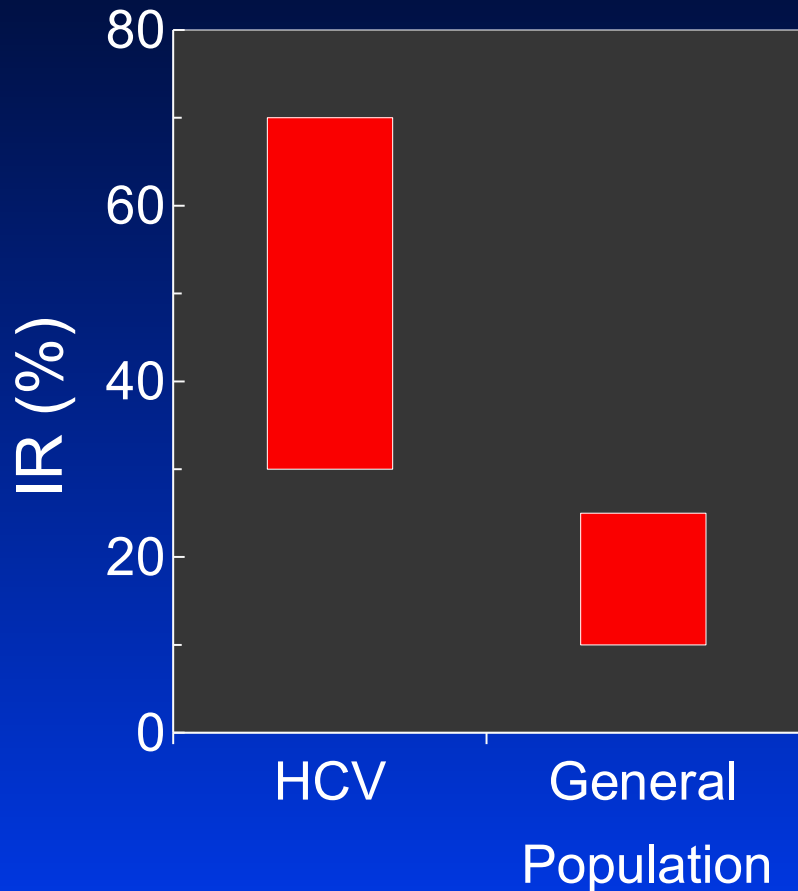
## Structural Proteins



**HCV Core Protein**  
Suppress immune Response  
Alters glucose metabolism

**Non-Structural Proteins**  
Primary role:  
Replication  
Translation

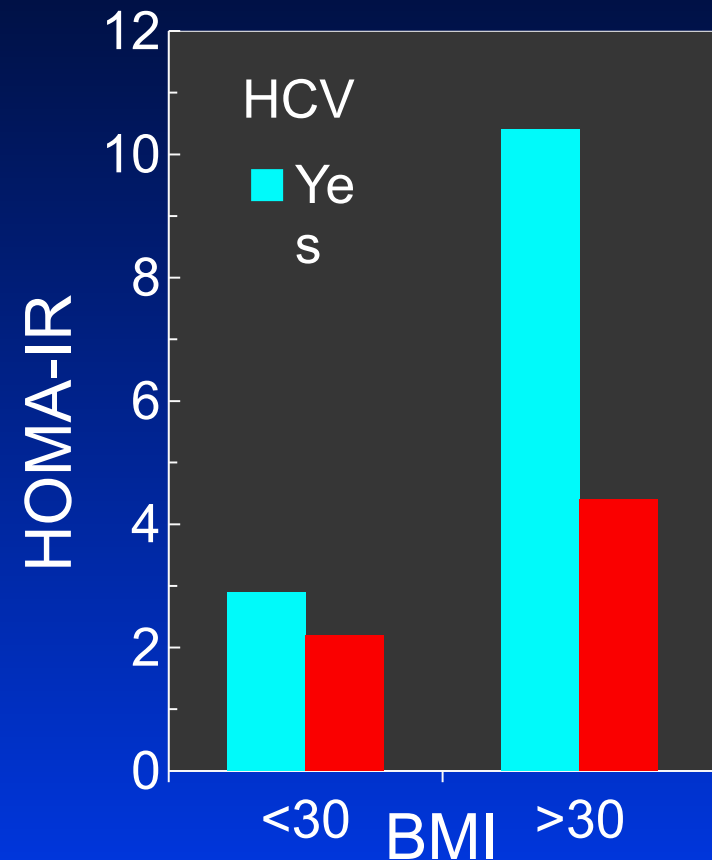
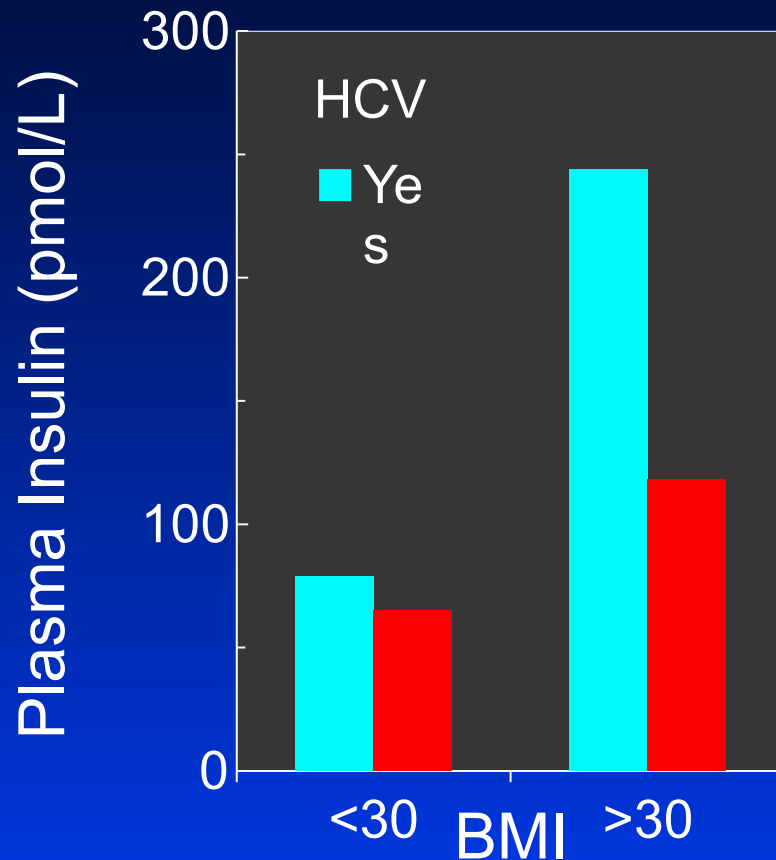
# CHRONIC HCV INSULIN RESISTANCE



S Harrison. Hepatology 2006; 43:1168.

S Harrison et al. Clin Gastroenterol Hepatol 2008; 6:864-876.

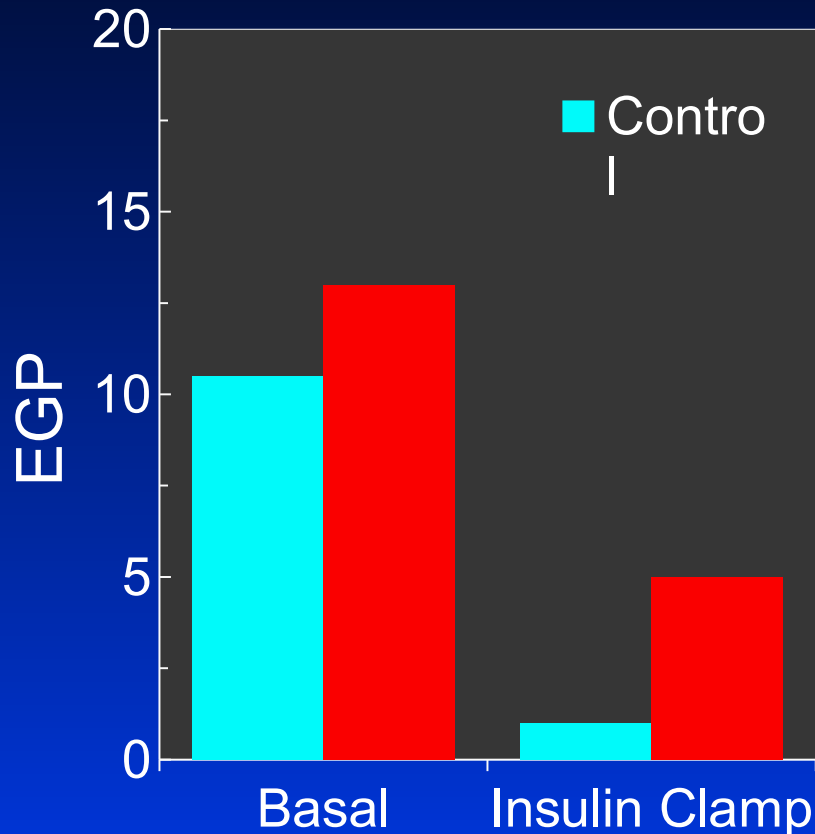
# CHRONIC HCV AND IR IMPACT OF OBESITY





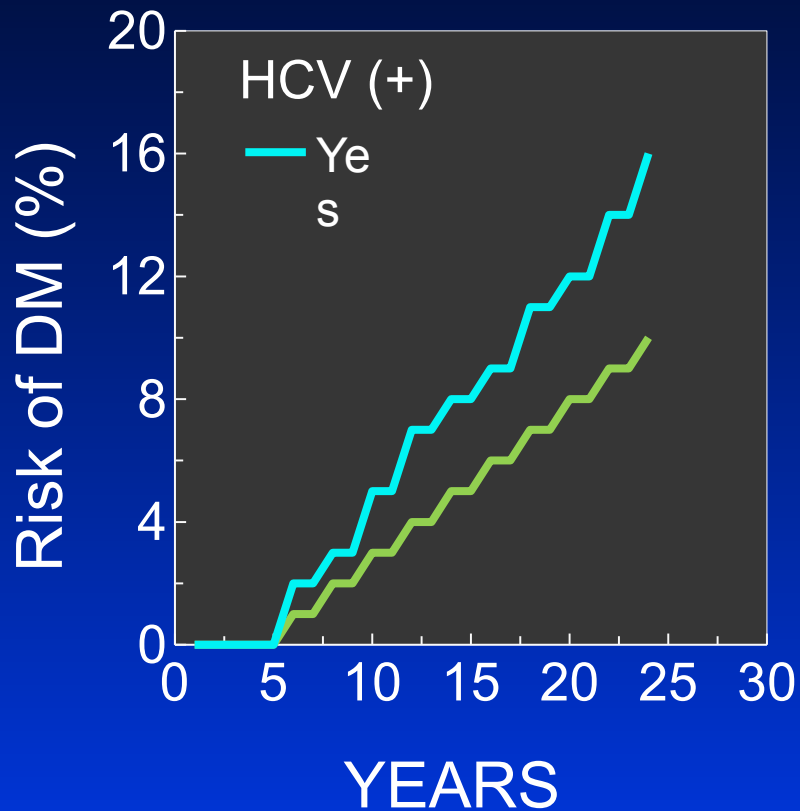
# CHRONIC HCV

## ASSESSING INSULIN RESISTANCE



- 7 Normal weight controls
- 14 Normal weight HCV
- No features of metabolic syndrome
- Endogenous glucose production measured at:
  - Basal state
  - During insulin clamp
- Higher EGP indicative of insulin resistance

# CHRONIC HCV DEVELOPMENT OF DM



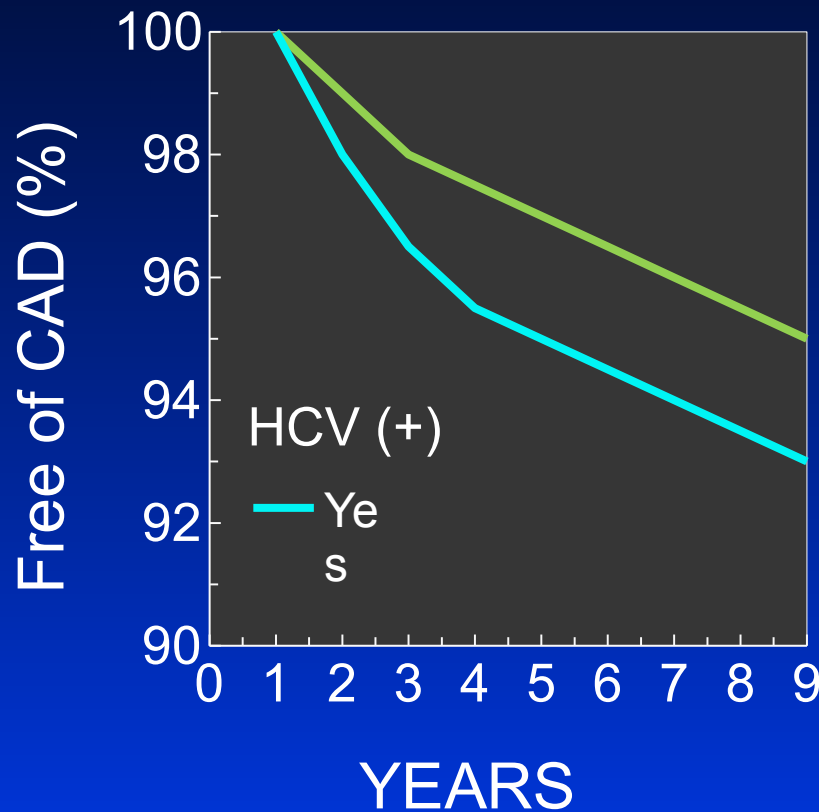
REVEAL Study Cohort  
930 HCV (+)  
16,928 HCV (-)  
Monitored prospectively for  
development of DM

# CHRONIC HCV

## OTHER METABOLIC COMPLICATIONS

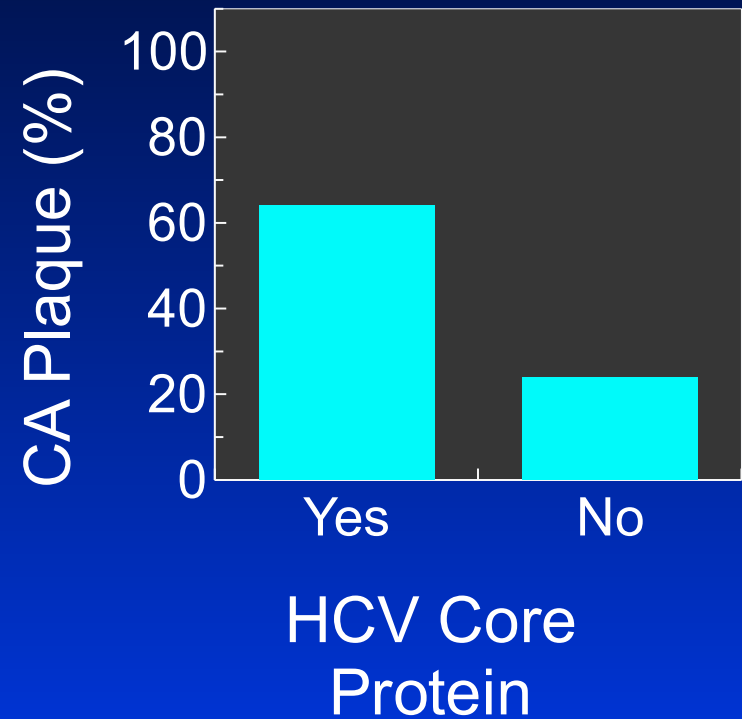
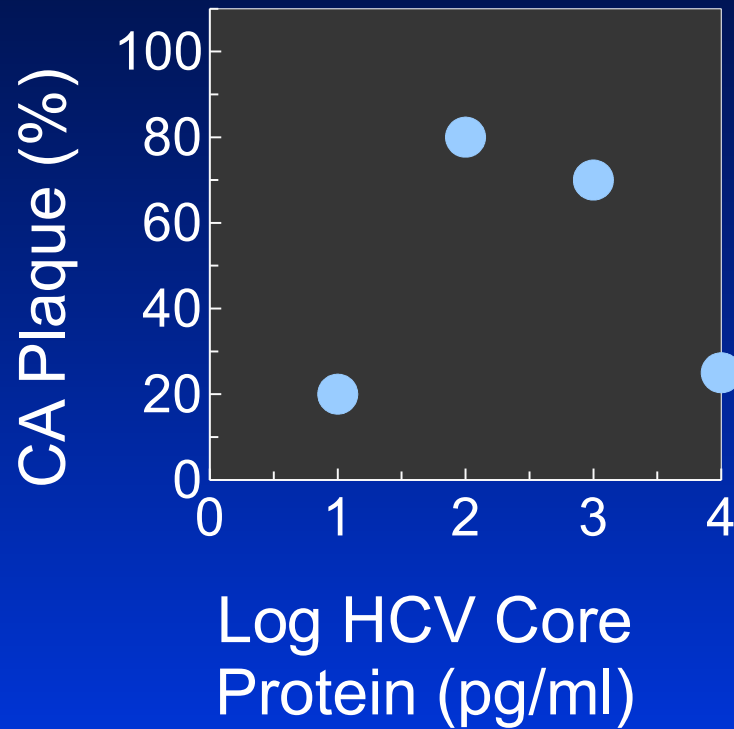
- Since chronic HCV is a risk factor for T2DM
- T2DM is associated with metabolic syndrome
- HCV may contribute to other metabolic complications:
  - Coronary artery disease → Acute coronary syndrome
  - Cerebral vascular disease → Stroke
  - Chronic kidney disease → End Stage Renal Disease

# CHRONIC HCV CORONARY ARTERY DISEASE



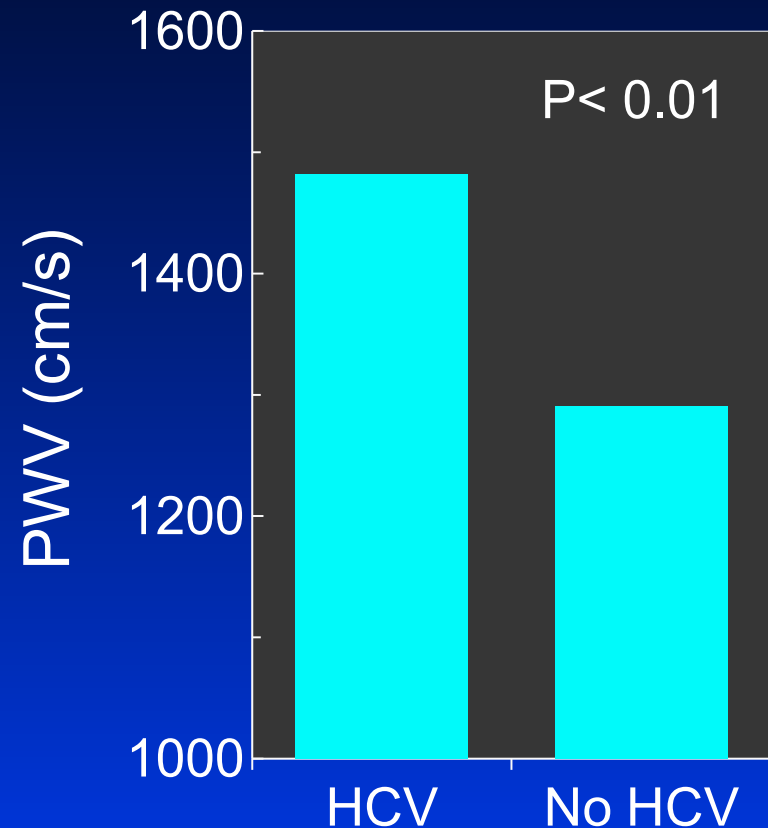
- US VA hospital system
- 82, 083 with HCV
- 89, 582 without HCV
- HCV associated with significantly higher rate of CAD after adjusting for standard risk factors.
- Standard risk factors increased CAD risk in both groups.

# HCV CORE PROTEIN CAROTID ARTERY PLAQUE

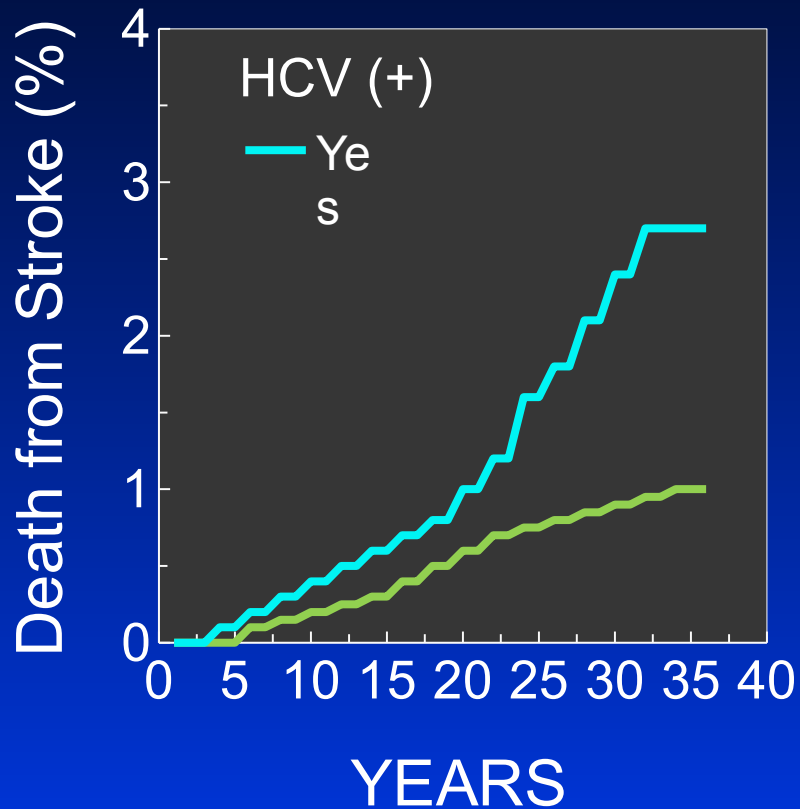


# CHRONIC HCV CAROTID VASCULAR INJURY

- Vascular injury, atherosclerosis and plaque leads to increased carotid artery stiffness
- 87 patients with HCV
- 7,427 without HCV or HBV
- Assessed by Pulse Wave Velocity
- This was not increased with HBV

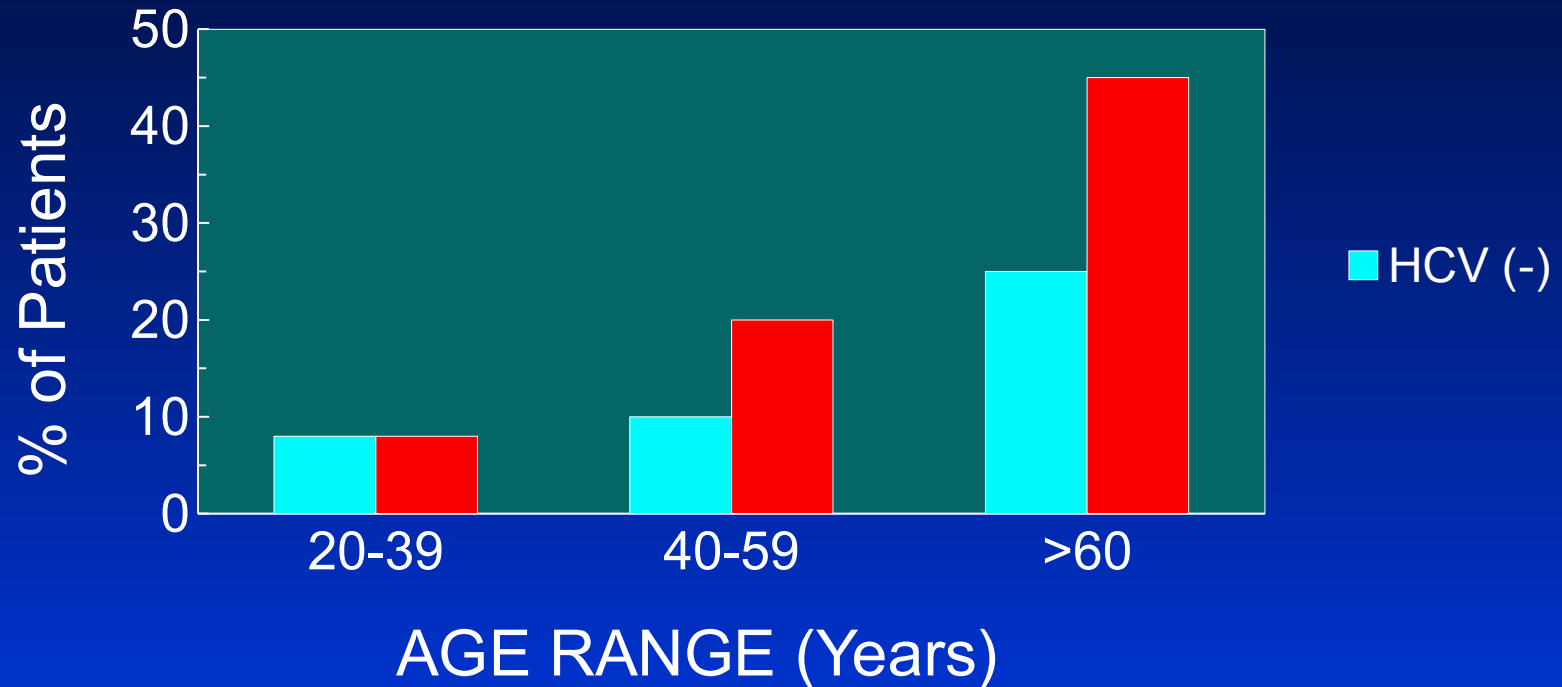


# CHRONIC HCV CEREBROVASCULAR DISEASE



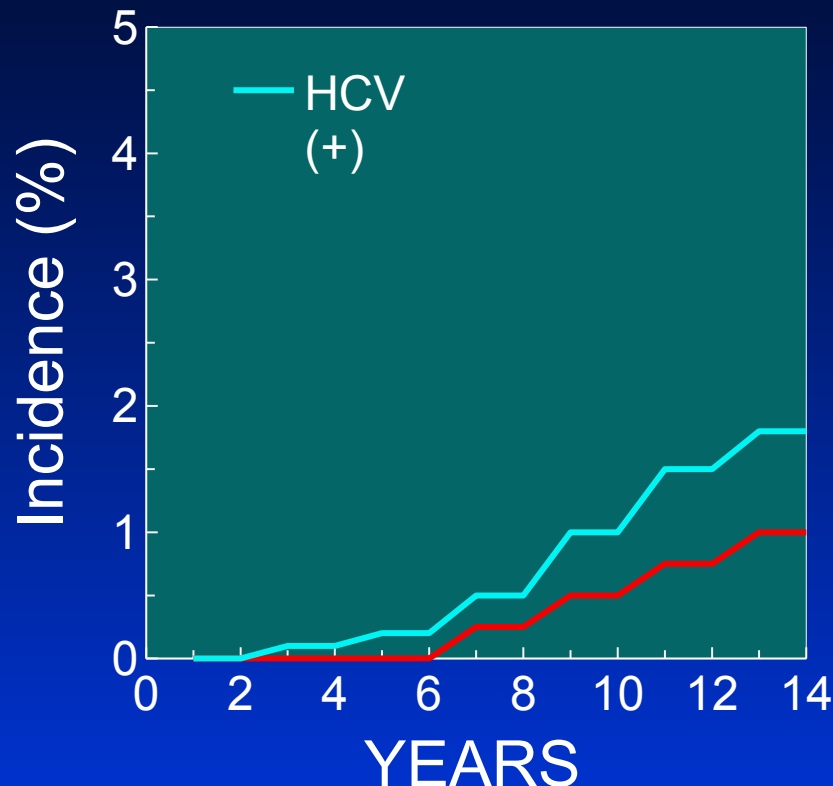
- 1,037 patients with HCV
- 22,358 negative for HCV
- Ages 30-65 years
- All anti-HCV positive confirmed by HCV RNA
- Enrollment 1990-92
- HCV associated with 2.6 fold increased risk for stroke

# CHRONIC HCV ALBUMINUREA





# CHRONIC HCV IMPACT OF DM ON ESRD



- Patients: 19,574  
50% with HCV  
Diabetes for 3.9 years  
Hypertension: 39%  
CAD: 11%  
Hyperlipidemia: 16%
- Factors associated with development of ESRD
- Hypertension
  - Chronic HCV

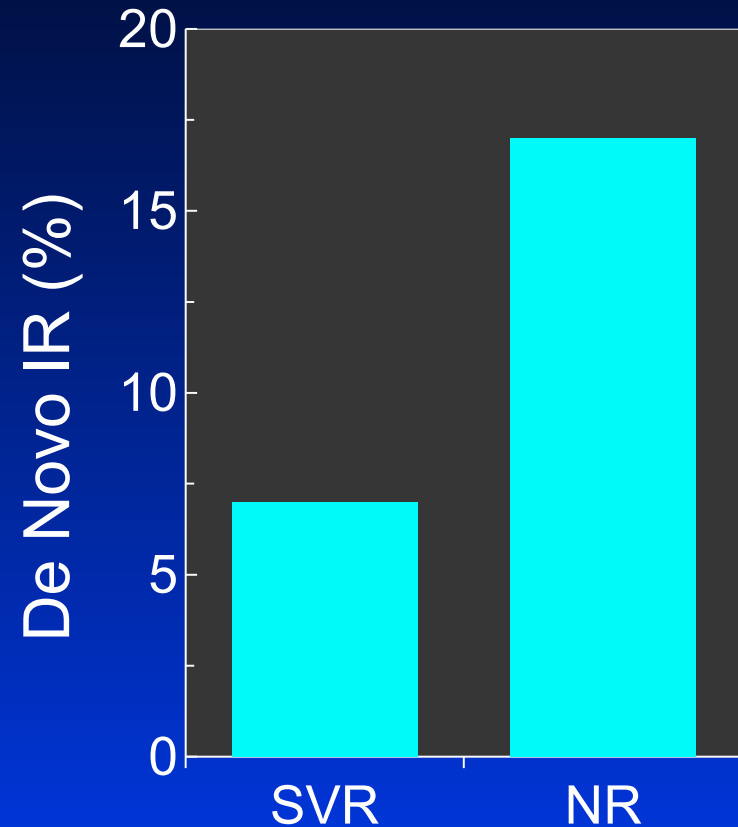
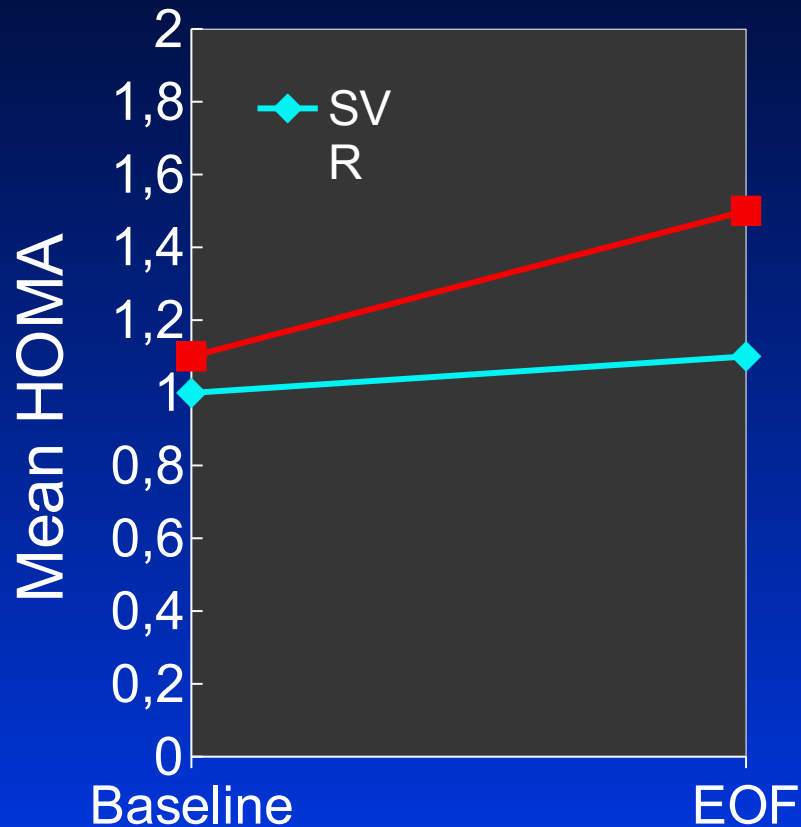
# CHRONIC HCV

## IMPACT OF TREATMENT

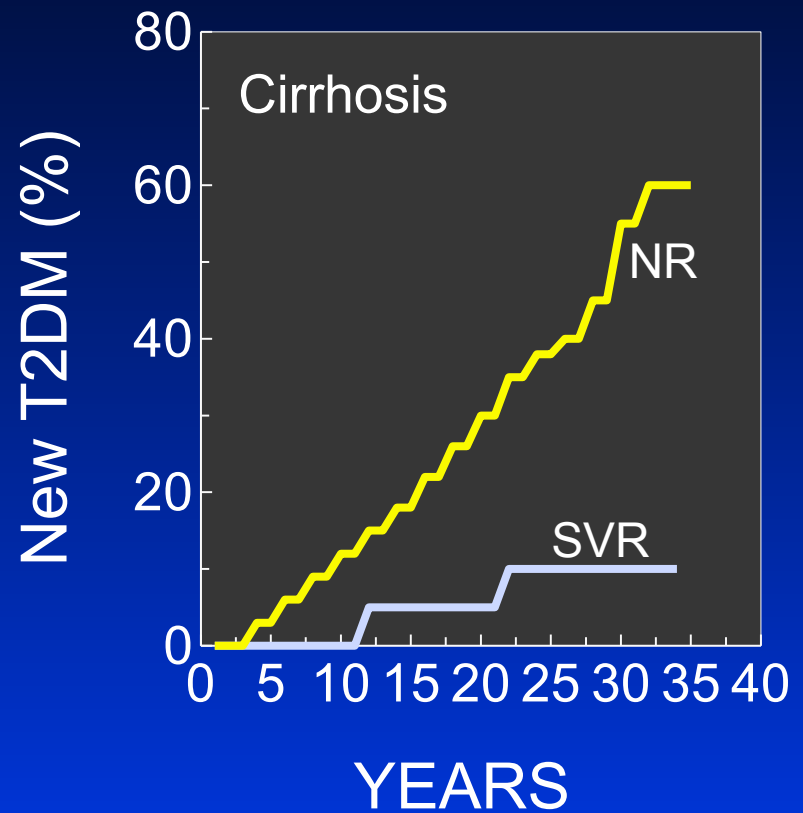
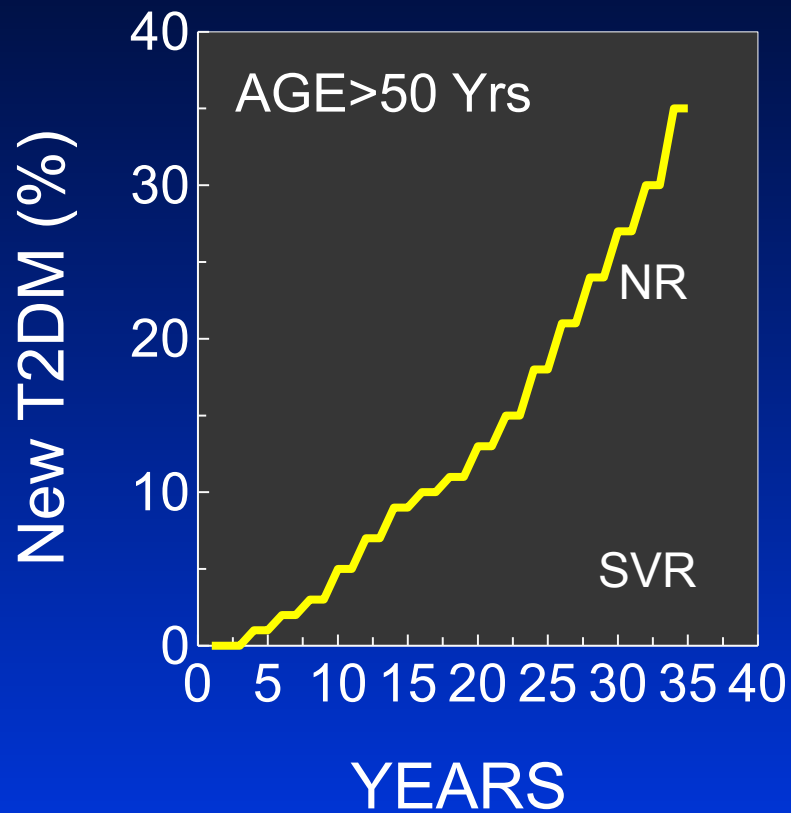
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- The best way to demonstrate that HCV does cause alterations in metabolism and other downstream effects
- Treat and cure HCV
- Demonstrate that these metabolic effects can be prevented or reversed
- Only data available so far is based on interferon therapy

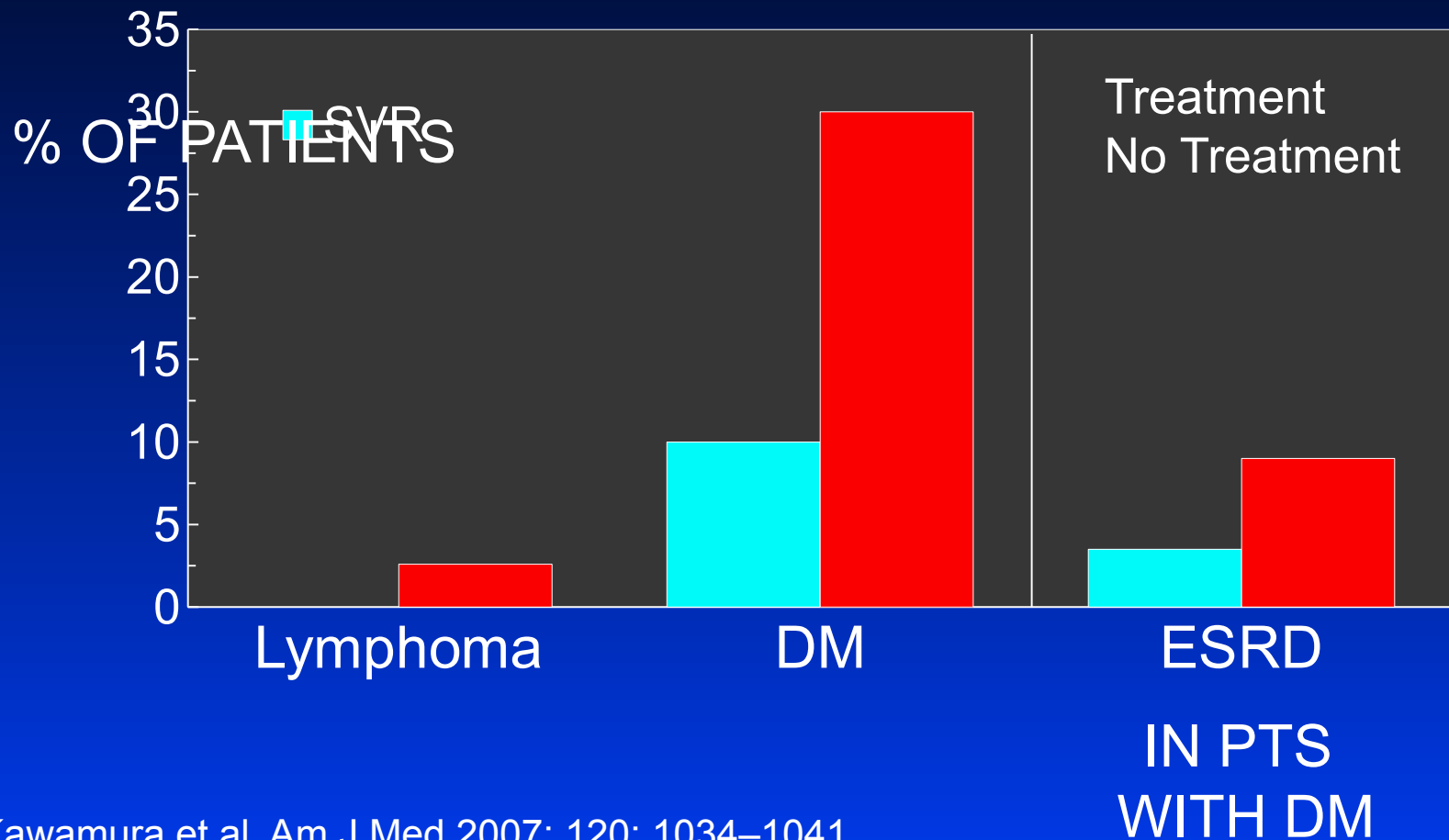
# IMPACT OF HCV TREATMENT HOMA AND IR



# IMPACT OF HCV TREATMENT DEVELOPMENT OF DM



# IMPACT OF HCV TREATMENT EXTRAHEPATIC DISEASE

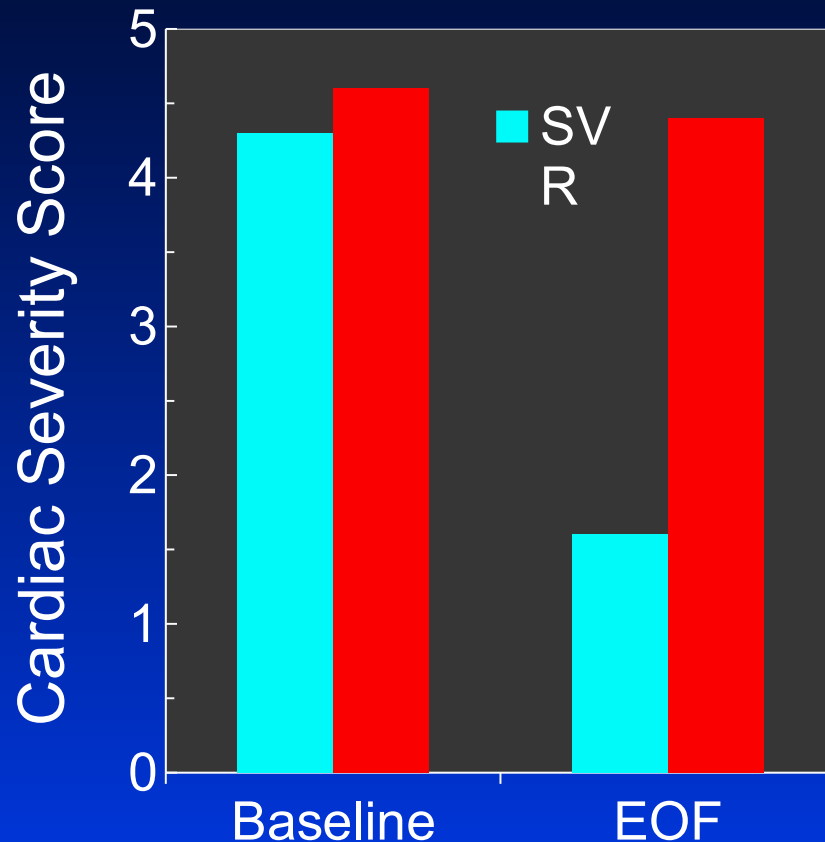


Y Kawamura et al. Am J Med 2007; 120: 1034–1041.

Y Arase et al. Hepatology 2009; 49: 739–744.

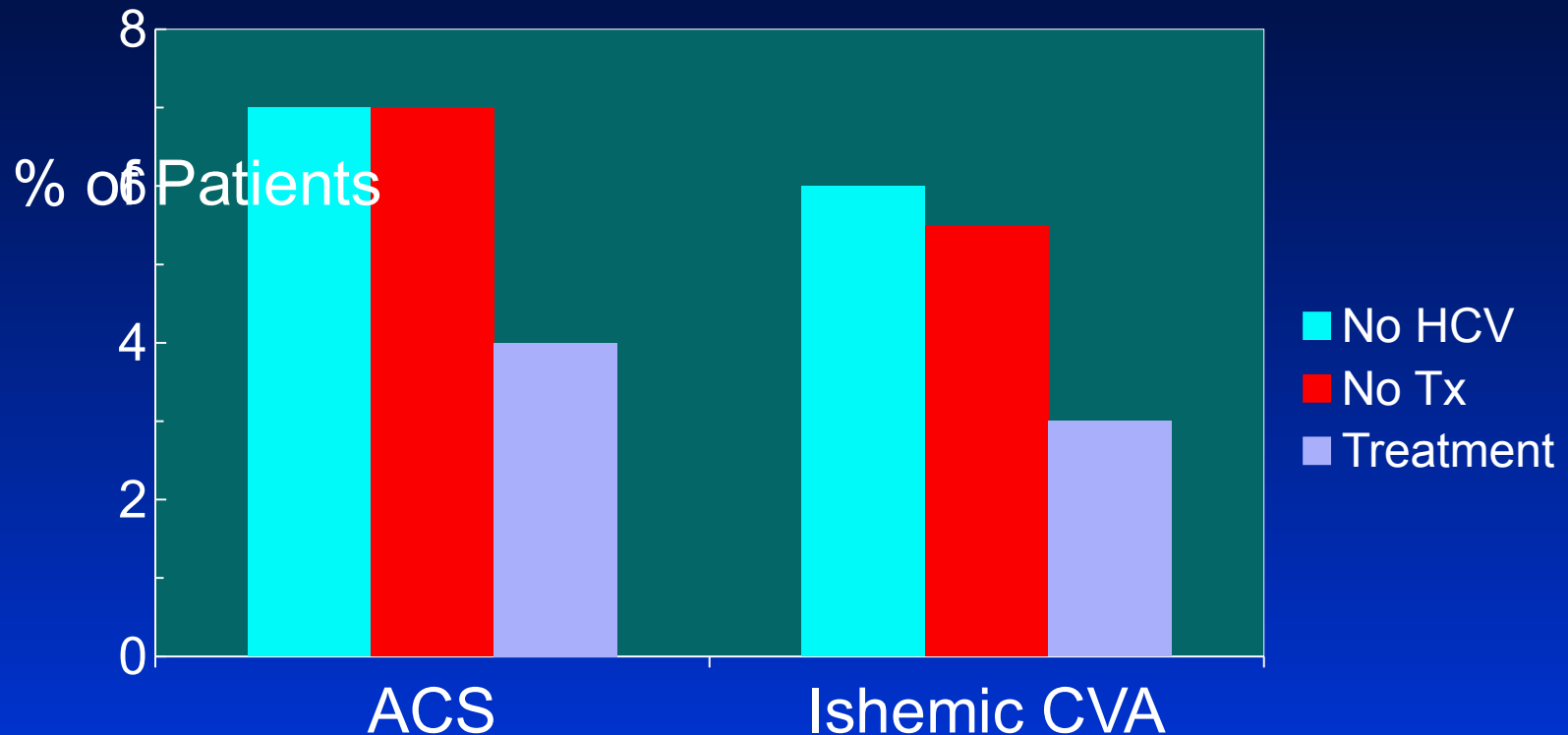
YC Hsu et al. Hepatology 2014; 59: 1293–302.

# HCV TREATMENT IMPACT ON CARDIAC DISEASE

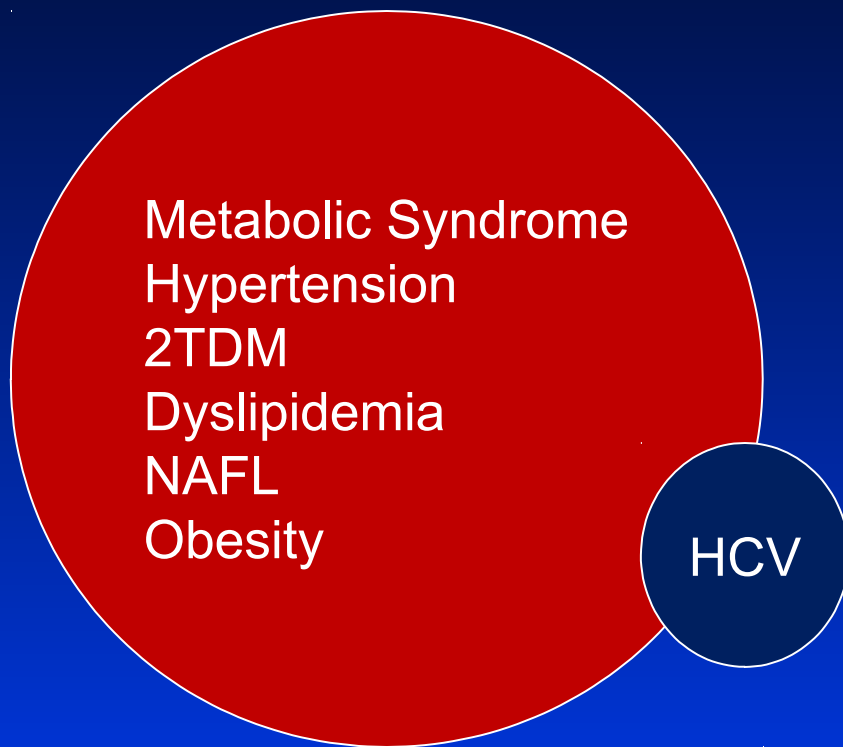


- 210 HCV patients without over cardiac disease
- Evaluated with:
  - ECG
  - Echocardiogram
  - Serum tests of myocardial injury
  - Thallium myocardial perfusion scan
- Cardiac severity score calculated
- Patient treated with PEGINF and RBV
- SVR = 46%

# HCV TREATMENT ACS AND ISCHEMIC CVA



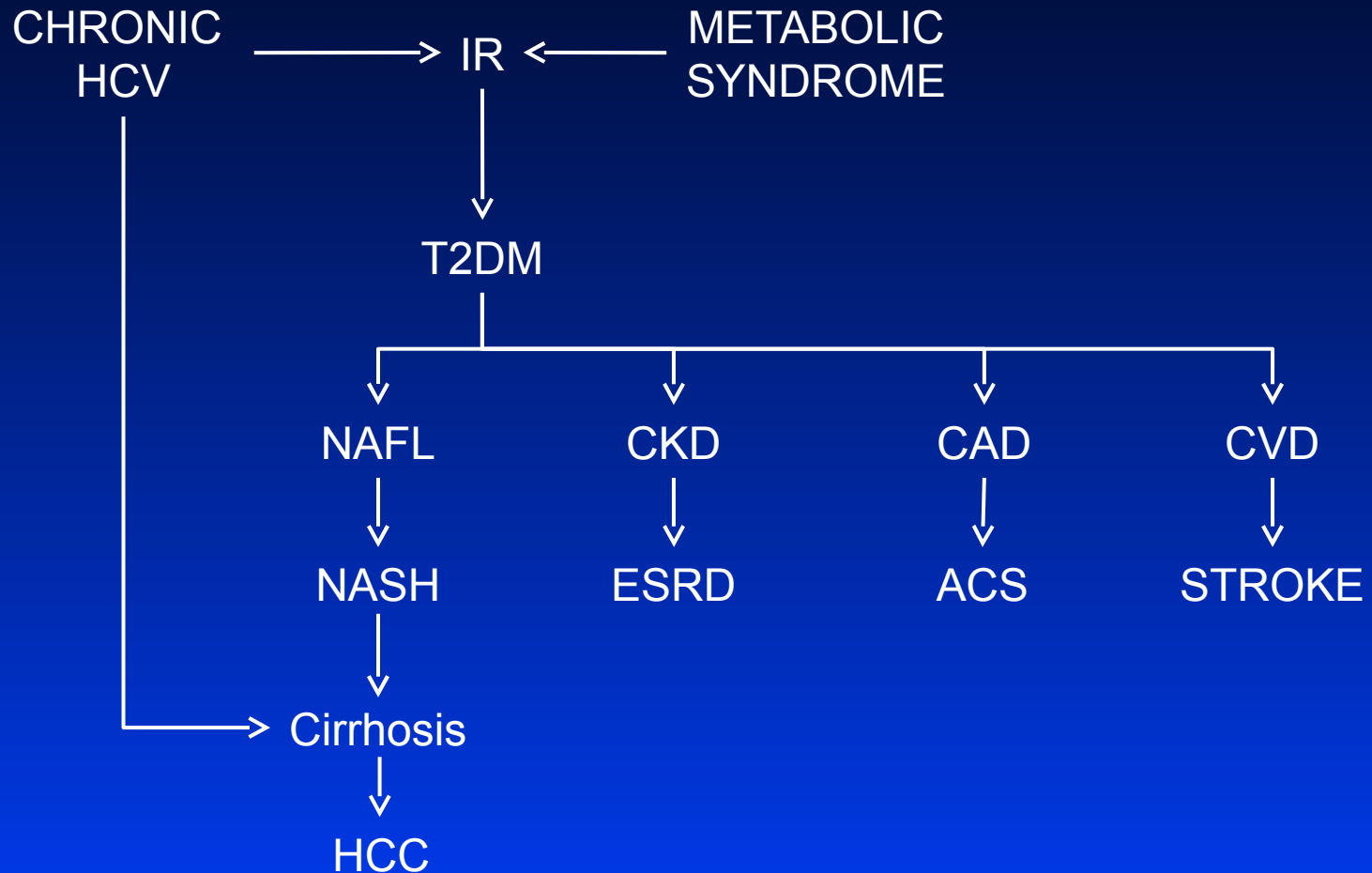
# CHRONIC HCV METABOLIC SYNDROME



- Metabolic syndrome is common in all societies throughout the developed world
- By chance alone 33% of patients with HCV will have metabolic syndrome
- HCV can be cured
- Progressive liver injury may still occur from NASH
- Since liver biopsy is now rarely performed for HCV
- NASH may be missed



# CHRONIC HCV METABOLIC SYNDROME



# HCV AND METABOLISM SUMMARY

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HCV affects not only the liver  
It alters metabolism  
Which is also a killer

The core protein of the virus  
Appears to be driving this bus  
Which causes resistance to insulin  
And leads to diabetes mellitus  
In not only the obese  
But some skinny of us

# HCV AND METABOLISM SUMMARY

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The team of diabetes and HCV  
Can lead to MI through vascular injury  
Increase stroke mortality  
Failure of the kidney  
And this impacts the public health of our city

# HCV AND METABOLISM SUMMARY

So in this year of Brexit and Trump  
There is no reason to be down in the  
dump

The Fantastic 4 have come to town  
Harvoni, Epclusa, Zepetier  
and the new guy from Abbvie

Will put an end to all but a few with  
the C

And this should reduce metabolic  
injury

