

HCV – Treat now !

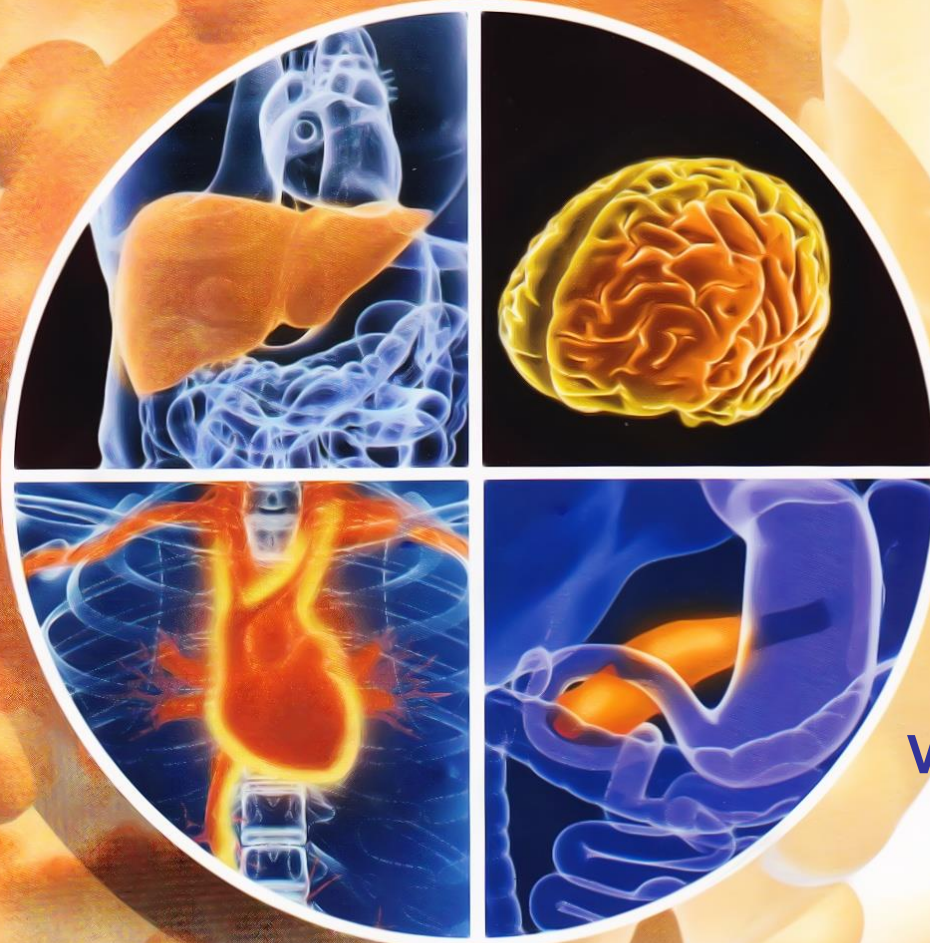
Robert G Gish MD

**Professor Consultant
Stanford University**

**Steering committee and
Executive Board
NVHR
National Viral Hepatitis
Roundtable**

**Founding Member
CEVHAP**

**Singapore
Viral Hepatitis Meeting 2014**



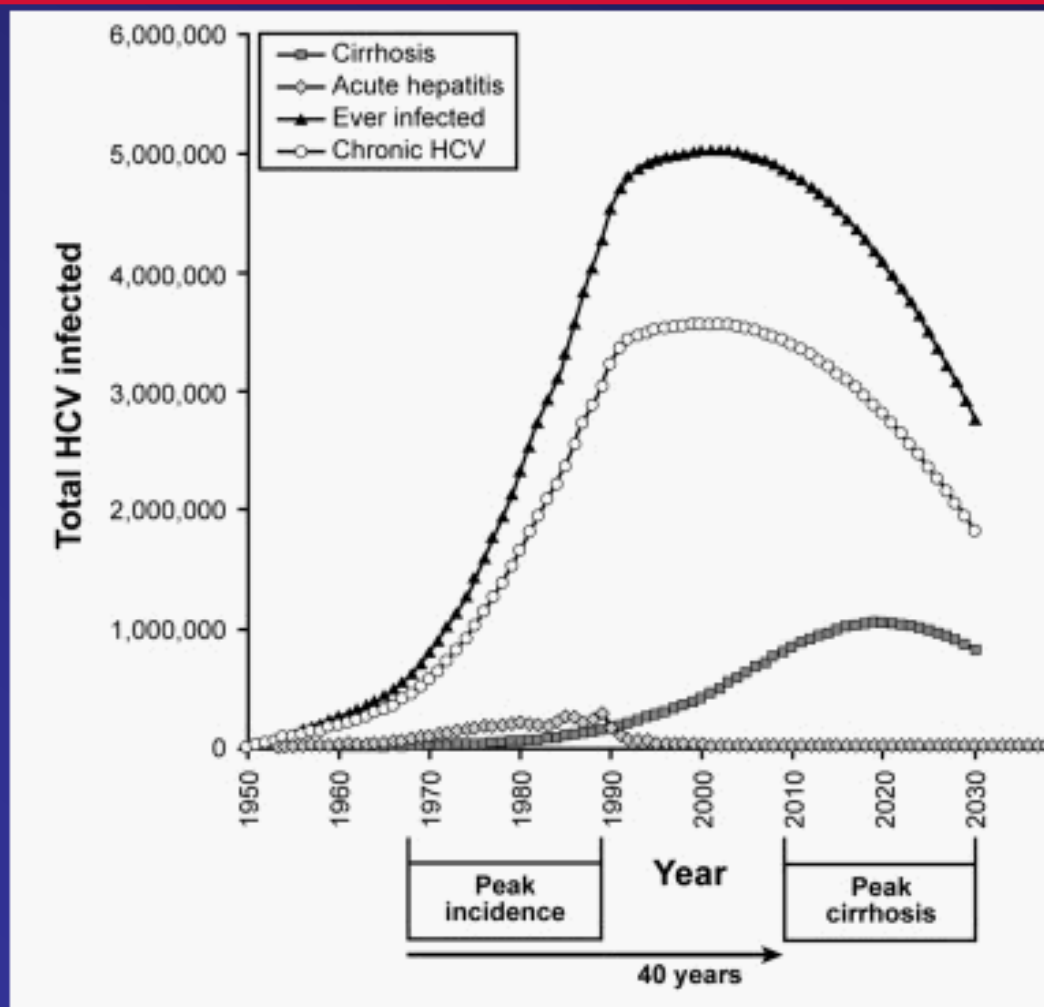
Disclosures

- ▶ **Dr Gish has advisory board relationships, consultancies, and speakers bureaus with Merck, Genentech, Roche, Gilead, BMS and AbbVie**
- ▶ **All pharma funds are expended or donated to research, education and public policy**

HCV current SVR/Cure rates

- ▶ **Genotype 1**
 - Triple PI PEG Based therapy: 70%+
 - Dual PEG therapy: 50-70%
- ▶ **Genotype 2**
 - Dual PEG based therapy: 80%+
- ▶ **Genotype 3**
 - Dual PEG based therapy: 70%+
- ▶ **Genotype 4**
 - Dual PEG based therapy: 50-70%
 - Triple PI PEG based therapy: >70% (Simeprevir)
- ▶ **Genotype 5**
 - TBD
- ▶ **Genotype 6**
 - PEG based therapies 50-70%

Aging of The HCV Population will Lead to a Peak of Cirrhosis in - 2020



OVERVIEW

- Association between chronic HCV infection and:
 - Diabetes/insulin resistance
 - Cardiovascular disease
 - HCV and Brain
 - Cancer
 - Renal impairment
- Effects of antiviral therapy on prognosis:
 - Mixed cryoglobulinaemia
 - Liver-related mortality
 - Non-liver-related mortality

Chronic HCV Infection Affects Many Sites Beyond the Liver

Neurological
(e.g. cognitive
impairment)

Pulmonary
fibrosis

Cardiovascular
Diseases
(CAD)

Renal (e.g.
glomerulonephritis)



Metabolic (e.g.
diabetes)

Lymphoproliferative (e.g. B
cell lymphoma)

Autoimmune
(e.g.
cryoglobulinemic)

Dermatological
(e.g. porphyria
cutanea tarda)

Mechanism of Development of Extrahepatic Manifestations

- **Immunological**

- Chronic persistence of virus leads to the circulation of immune complexes and autoimmune phenomenon
- Mixed cryoglobulinemia (Ferri 207)

- **Virological**

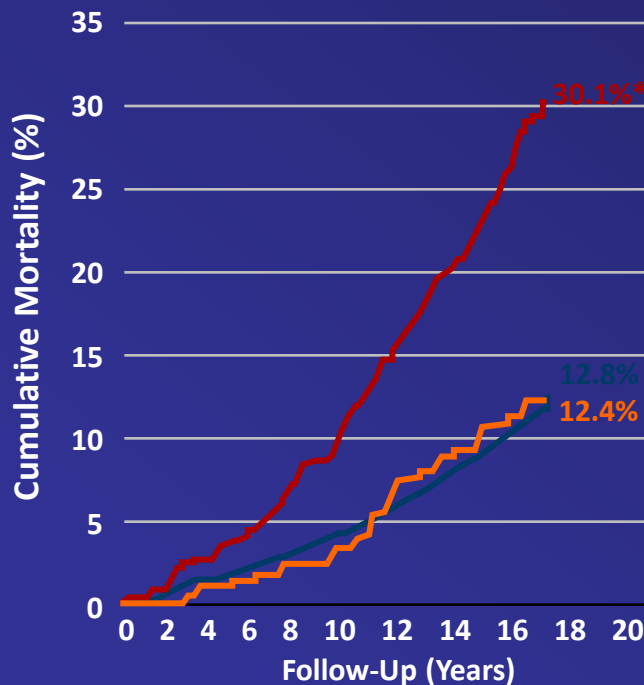
- Extrahepatic tropism of the virus

HCV Viremia Was Associated With Increased Mortality in a Prospective Taiwanese Cohort Study

— Anti-HCV+, HCV RNA detectable — Anti-HCV+, HCV RNA undetectable — Anti-HCV—

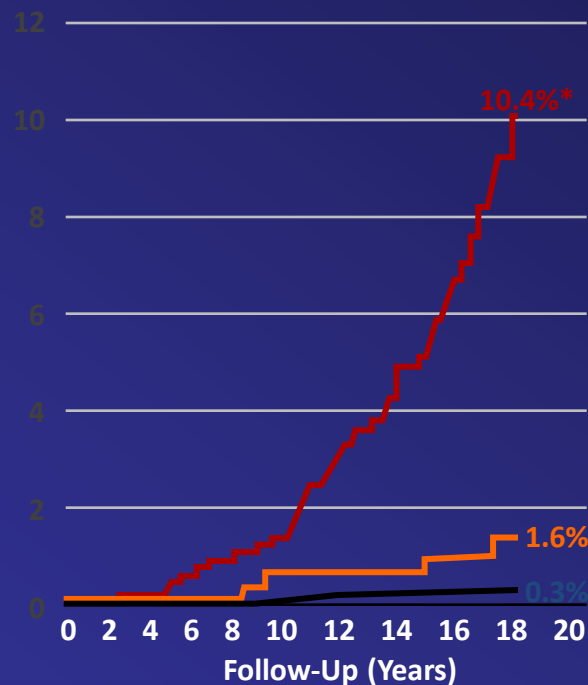
All Causes

(n=2394)



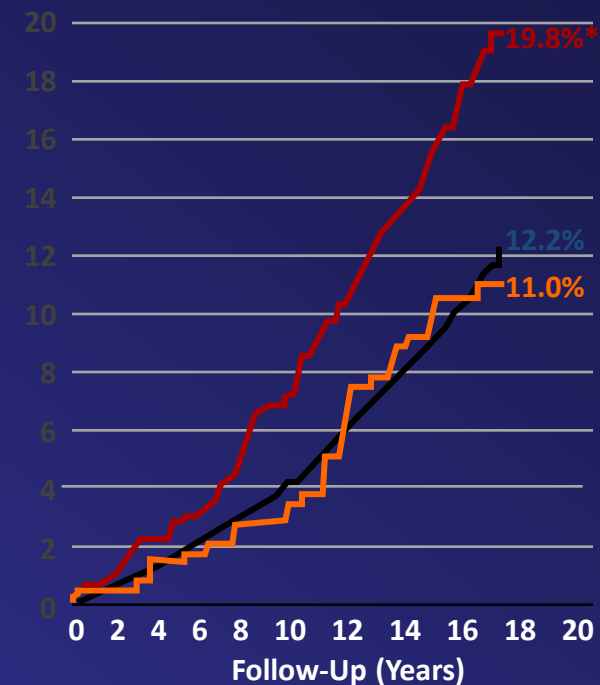
Liver Cancer

(n=115)



Extrahepatic Diseases

(n=2199)



REVEAL HCV: Risk Evaluation of Viral Load Elevation and Associated Liver Disease/Cancer (1991-2008).

Anti-HCV seronegative (n=18,541); anti-HCV seropositive (n=1095; detectable HCV RNA: 69.4%). Average follow-up: 16.2 years.

Among extrahepatic causes of death, 68.5% and 69.3% were noncancer deaths for HCV seronegative and seropositive, respectively.

* $P < .001$ for comparison among all 3 groups and $P < .001$ for HCV RNA detectable vs undetectable.

Lee M-H, et al. *J Infect Dis.* 2012;206:469-477.

HCV and Renal disease

- ▶ HCV infection may lead to renal disease or be associated with renal disease
- ▶ Mixed cryoglobulinemia (type II cryoglobulins, or + RF)
- ▶ Membranoproliferative glomerulonephritis (MPGN)
- ▶ Polyarteritis nodosa

- ▶ Less common
 - Focal segmental glomerular sclerosis
 - Proliferative glomerulonephritis
 - Membranous GN
 - Fibrillary and immunotactoid glomerulopathies

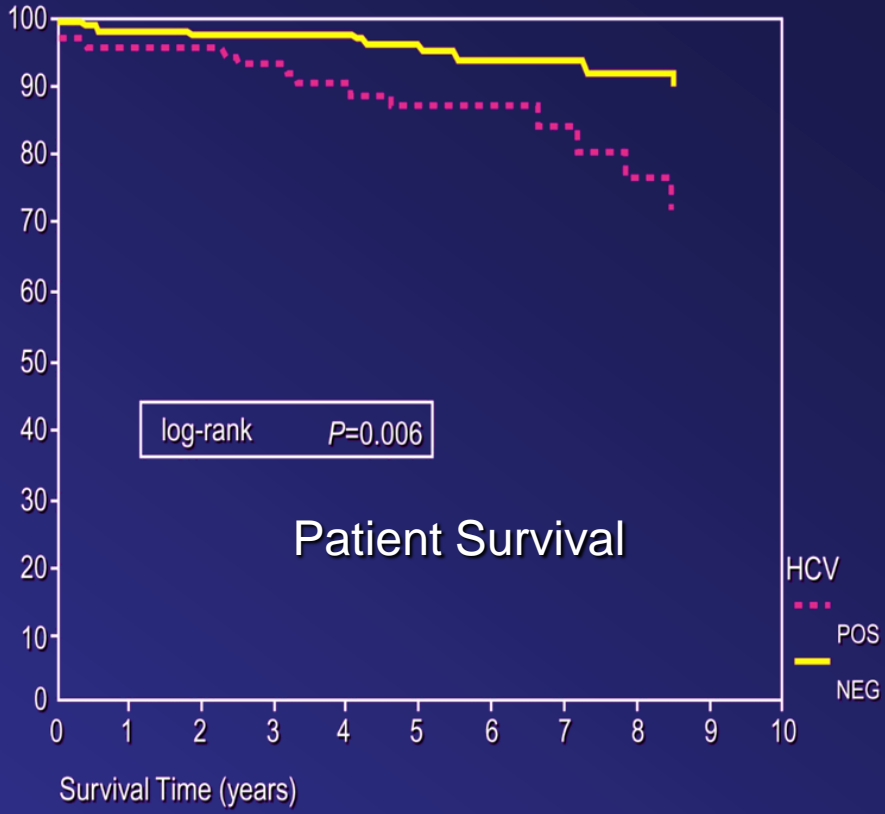
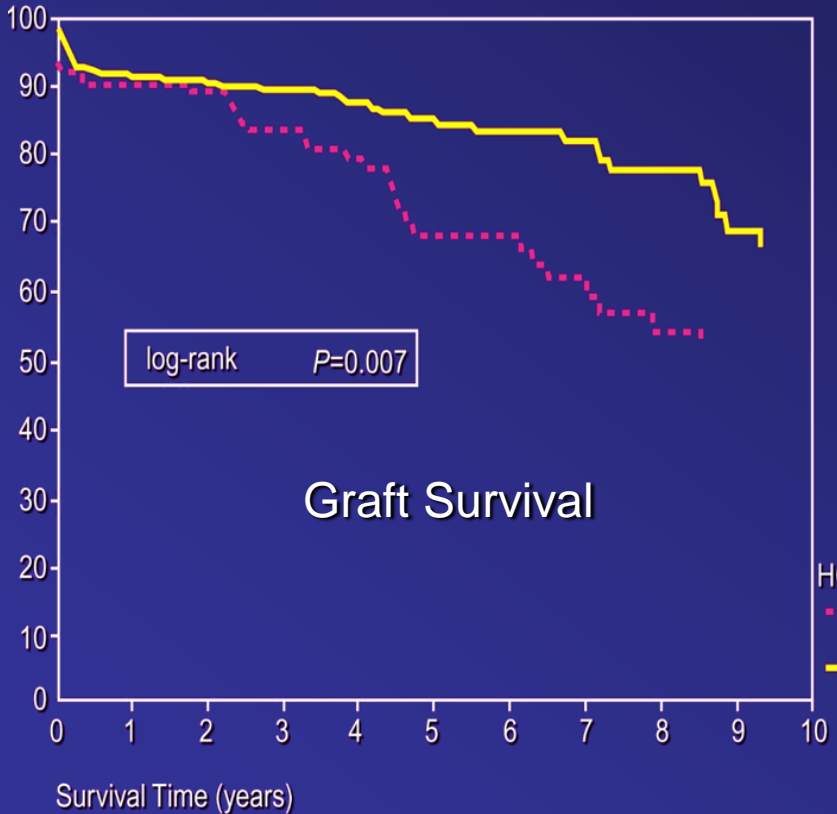
HCV-related Renal Diseases

- **Prevalence - 20-30% of patients have renal involvement**
- **80% of them cryoglobulinemic (CG) MPGN**
- **~ 50% of cases seen moderate urinary syndrome**
- **25% develop severe acute nephritic syndrome**
- **20% develop nephrotic syndrome**

- **For all states nephritis is characterized by severe hypertension.**
- **In one third of patients develop renal failure**

HCV: Virologic Status of Renal Transplant Recipients

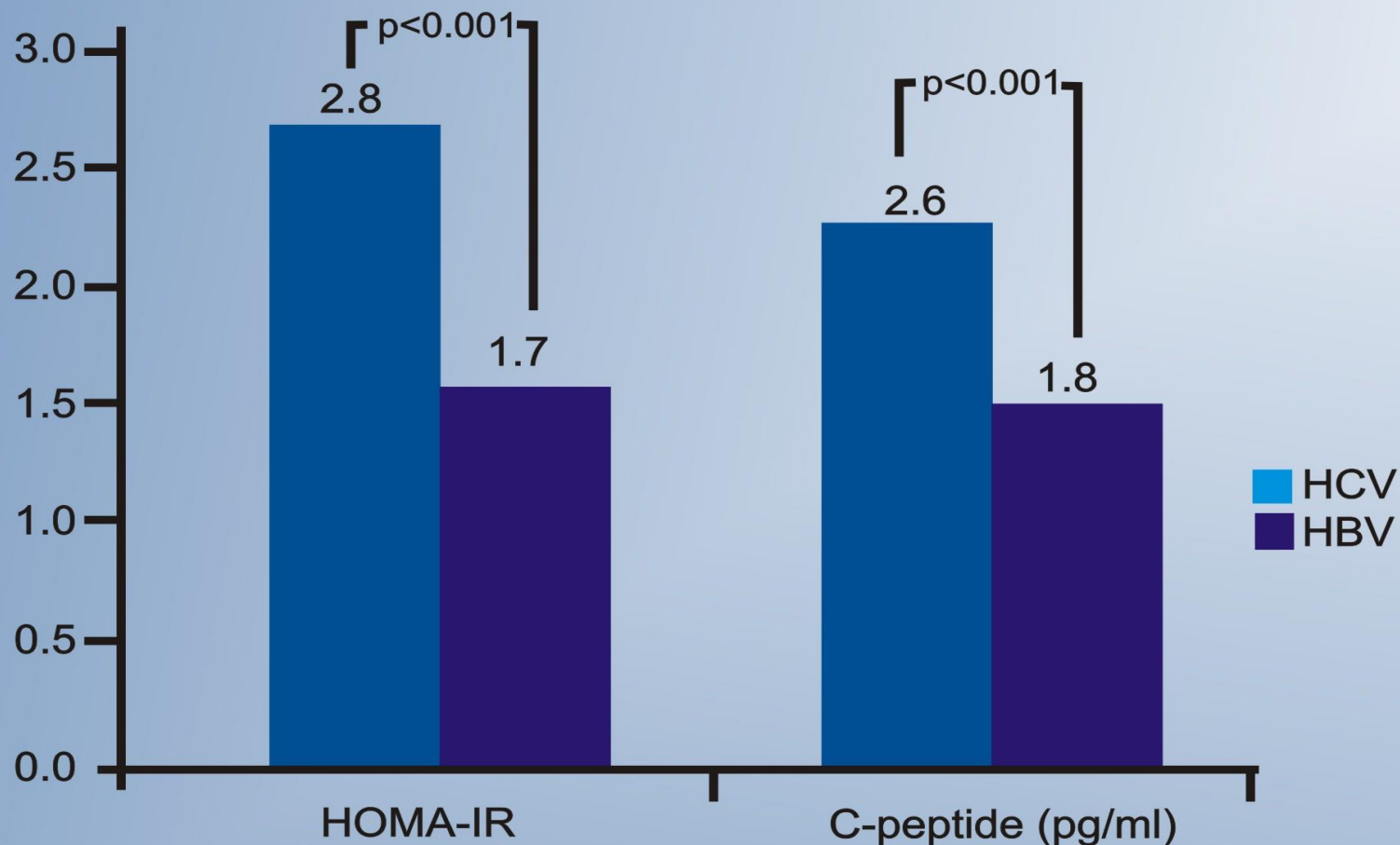
Graft and Recipient Survival



HCV infection is associated with lower graft and recipient survival

Gentil MA et al. *Nephrol Dial Transplant*. 1999;14:2455-2460.

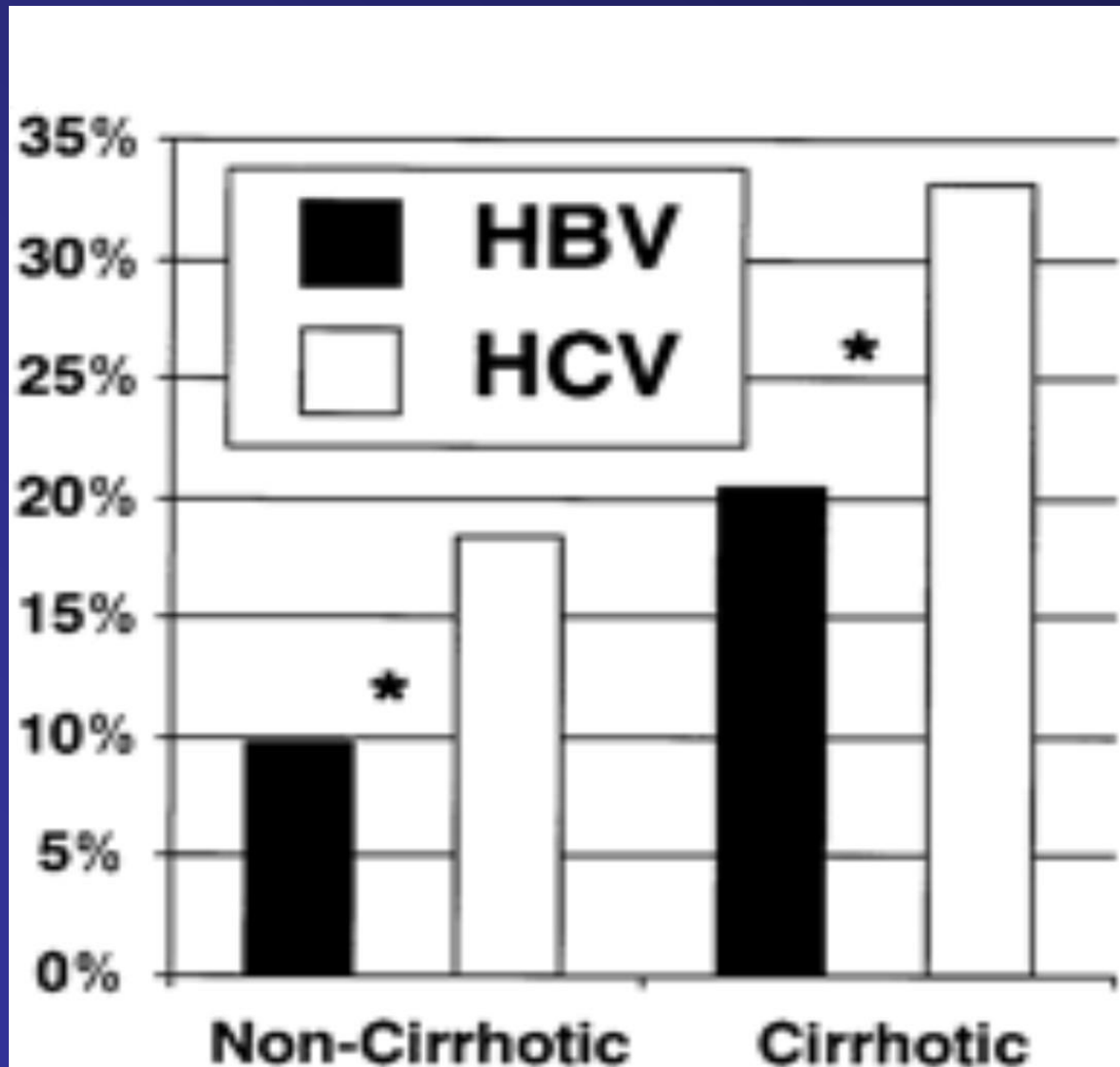
HOMA-IR and C-peptide Levels in Chronic HCV and HBV Infection



Association of Diabetes Mellitus (DM) and HCV Infection

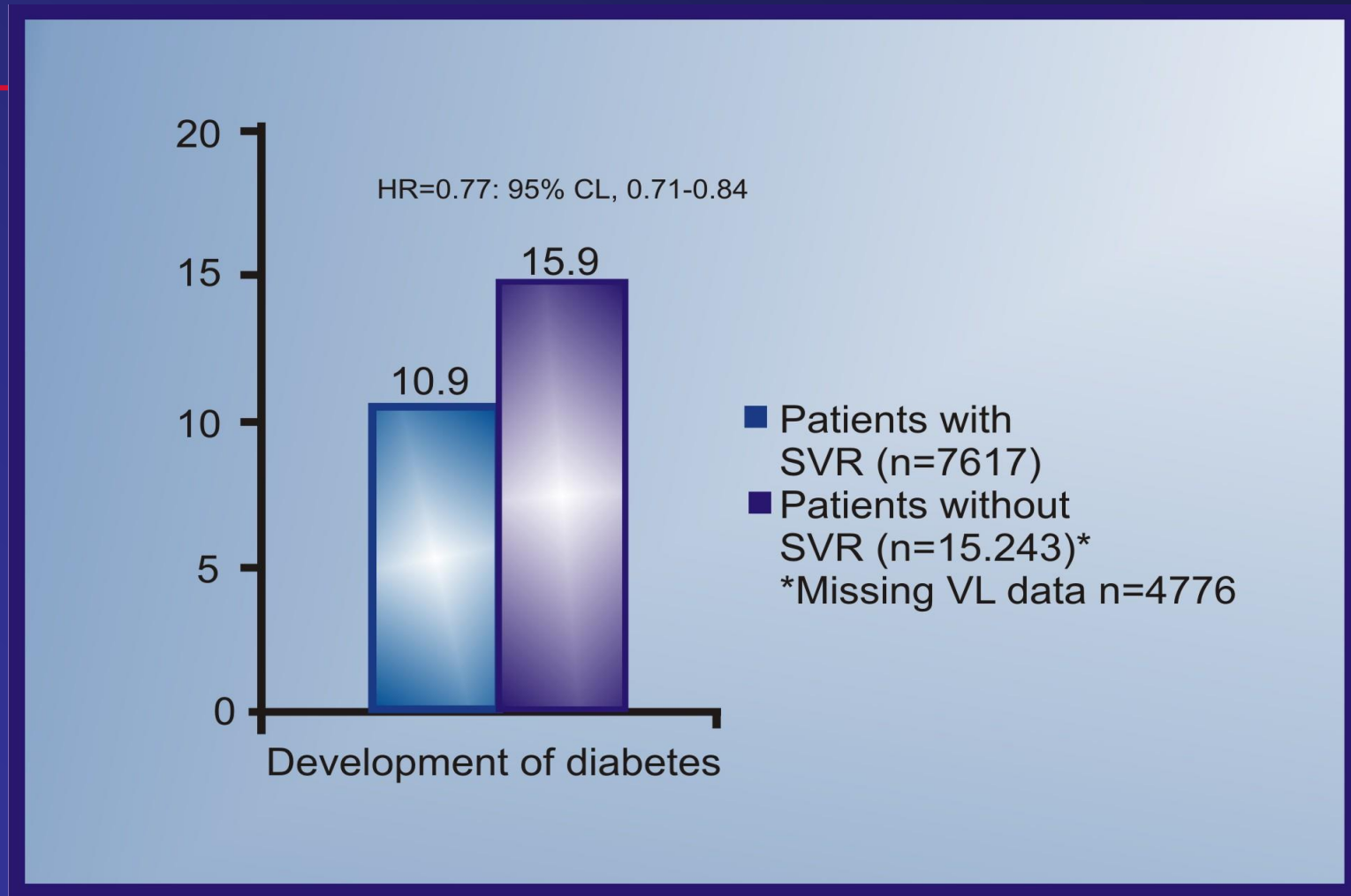
- HCV was second strong predictor of DM2 after obesity.
- In patients with HCV infection DM2 occurred in more than 10 years younger population than in HCV – negative group
- HCV infected patients who displayed any other risk factor for DM2 develop this condition 11 fold more likely compared with HCV-negative group
- HCV is a trigger of DM2 in previously predisposed individuals

Association of Diabetes Mellitus and HCV Infection



*Mason AL et al
Hepatology, 1999*

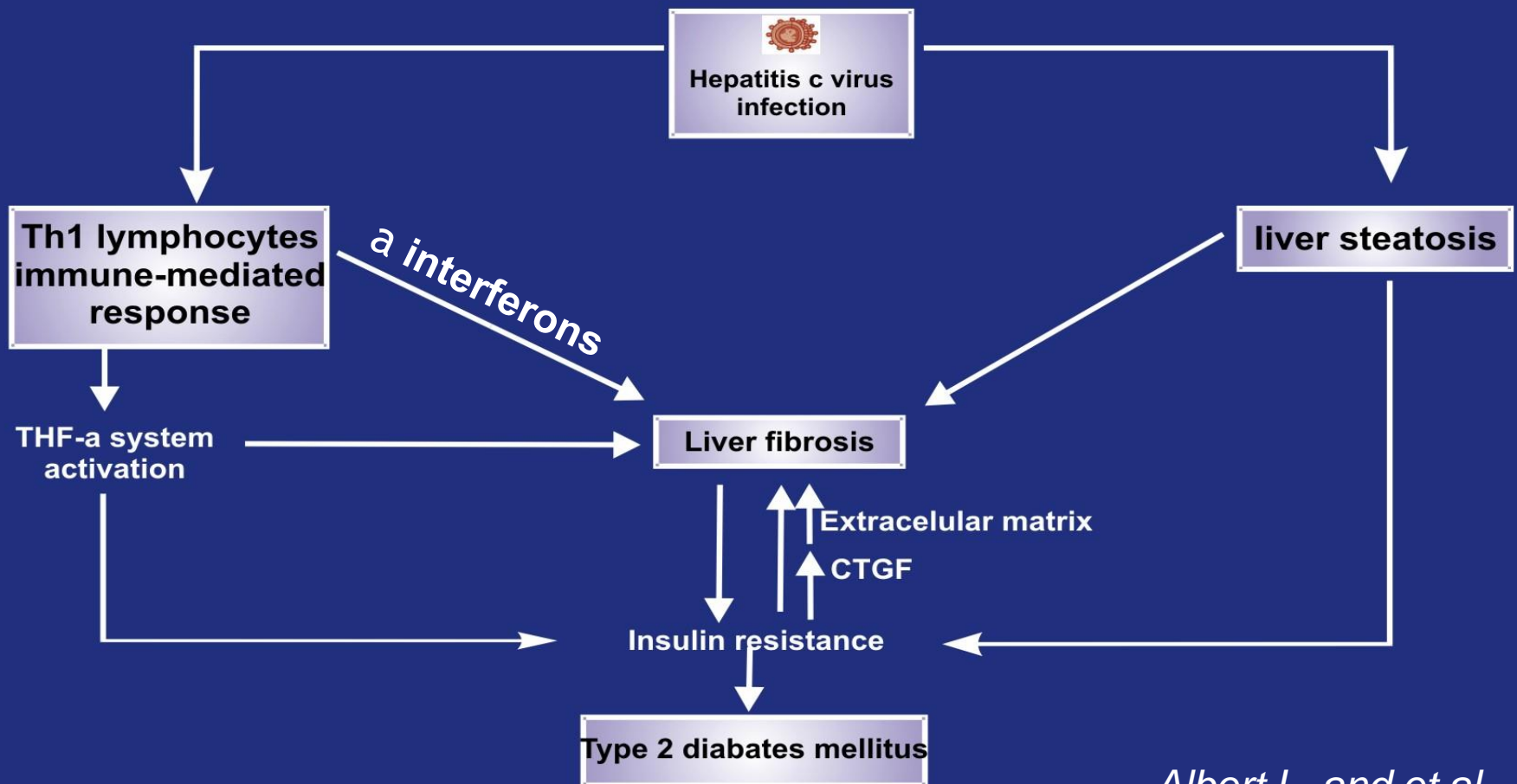
SVR Reduces Risk of Development of Diabetes in Patients with HCV



Veterans Affairs Clinical Case Registry: 27,636 patients with HCV
Followed for median 5 years
Antiviral treatment initiated 1998-2007

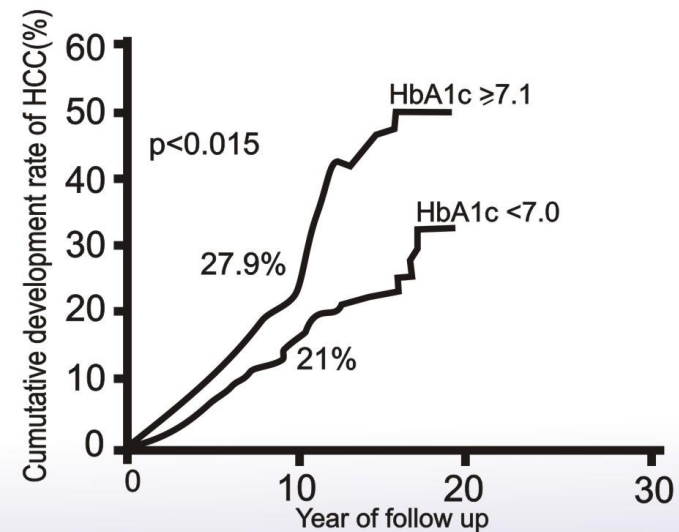
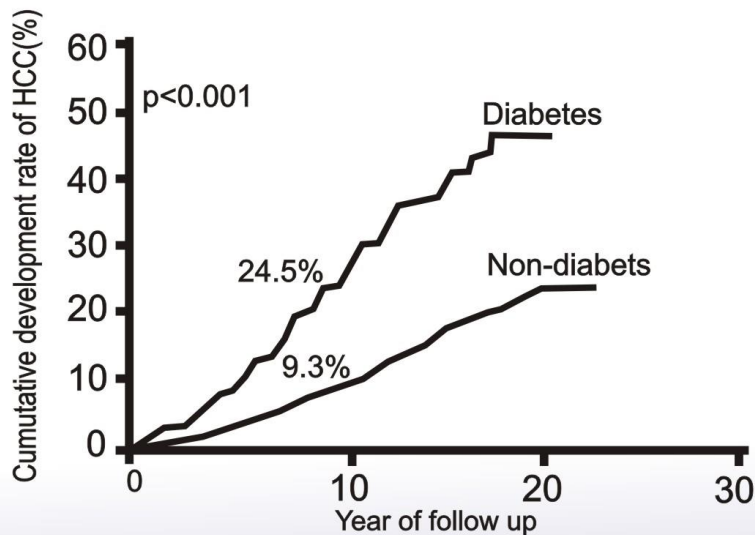
Hyder S. and et al *Digestive Disease week*, 2013

Mechanism Involved in the Diabetogenic Action of HCV



*Albert L. and et al
Diabetes Care, 2006*

Cumulative Development Rate of HCC in HCV – Infected Patients Treated with IFN

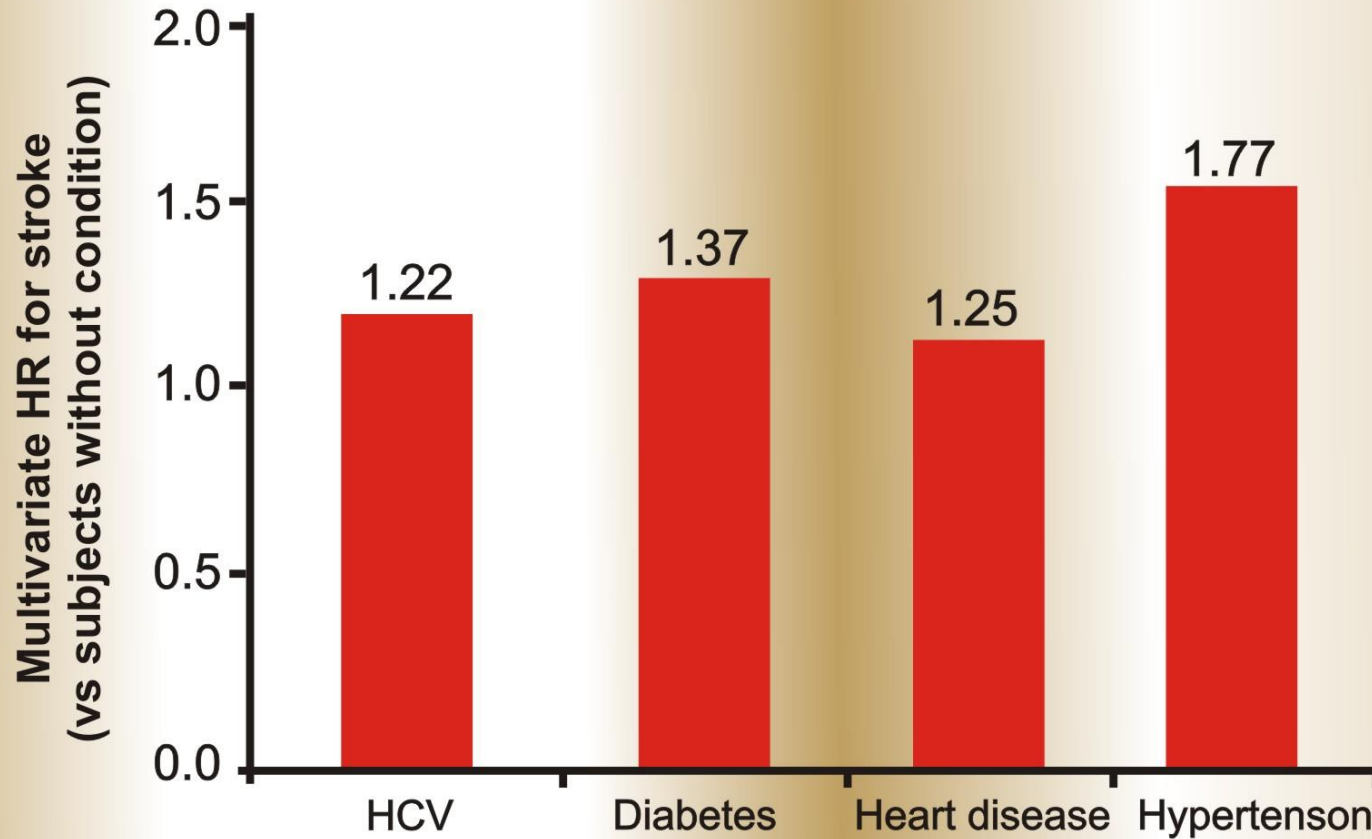


- Retrospective cohort of 4302 Japanese patients treated with IFN- α followed for average 8.1 years
- Cumulative incidence of HCC: 4.3% at 5 years, 10.5% at 10 years, 19.7% at 15 years
- T2DM caused 1.73-fold increase in HCC

HCC, hepatocellular carcinoma; IFN, interferon;
SVR, sustained virological response; T2DM, type 2 diabetes

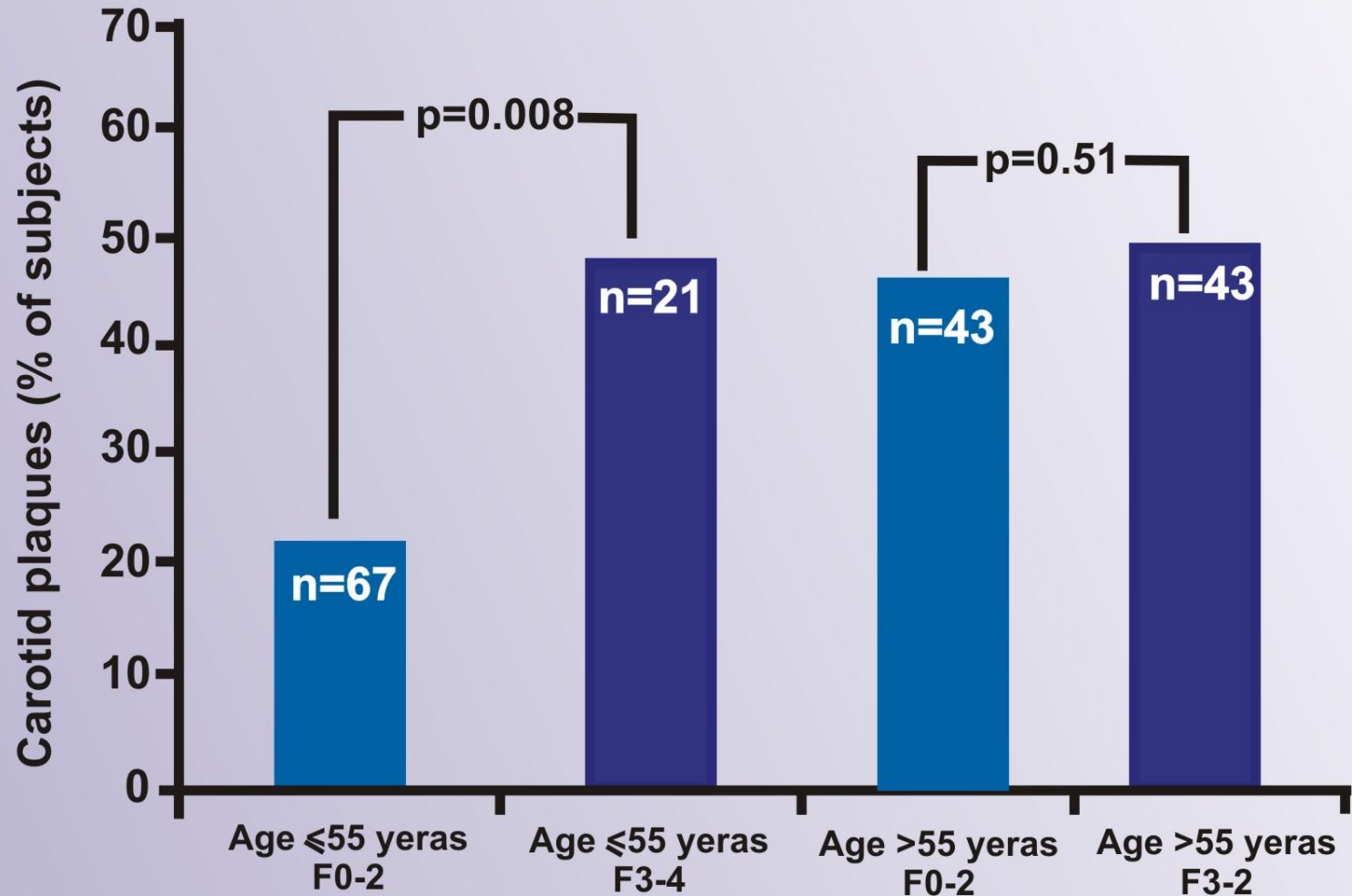
Stroke Incidence and HCV Infection

4094 adults in Taiwan newly diagnosed with HCV infection compared with 16 376 adults without HCV infection and matched by age and sex



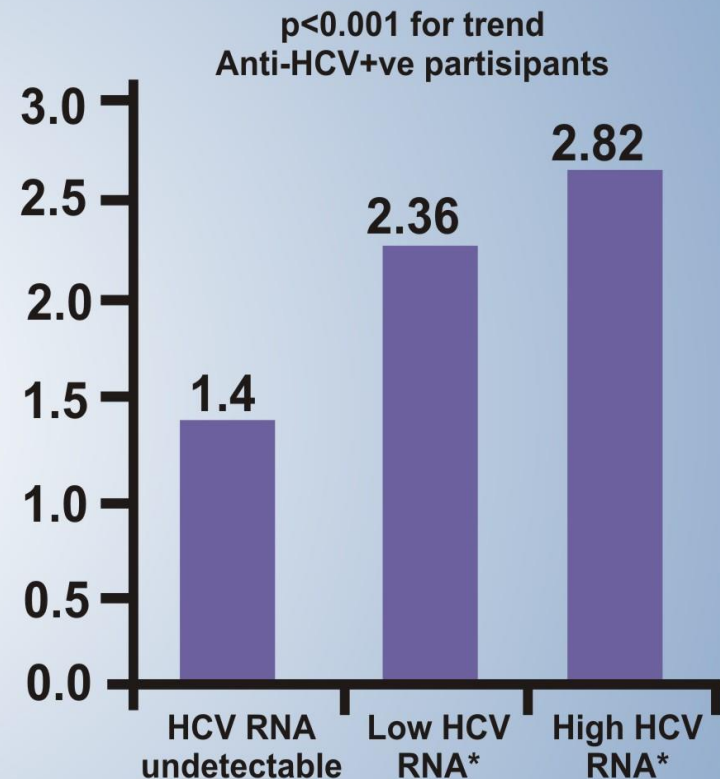
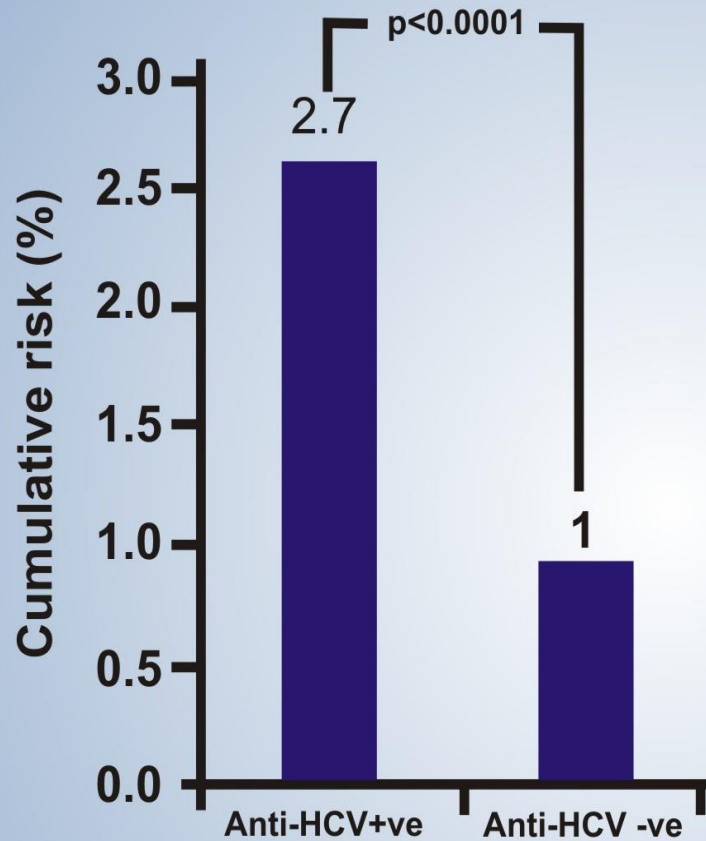
Carotid Atherosclerosis and Chronic HCV

Prevalence of carotid plaques according to age and fibrosis

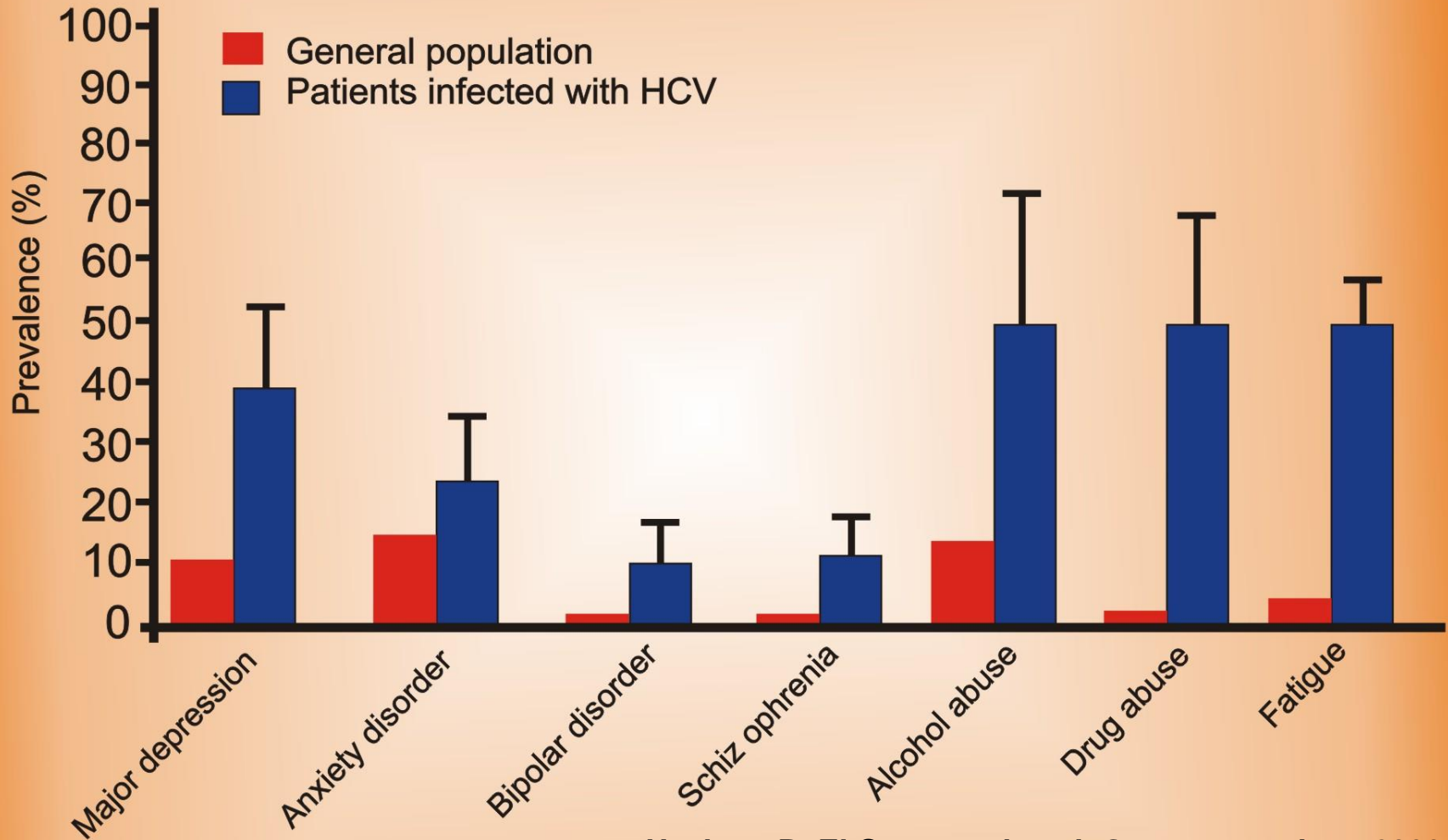


Cerebrovascular Deaths and HCV Infection

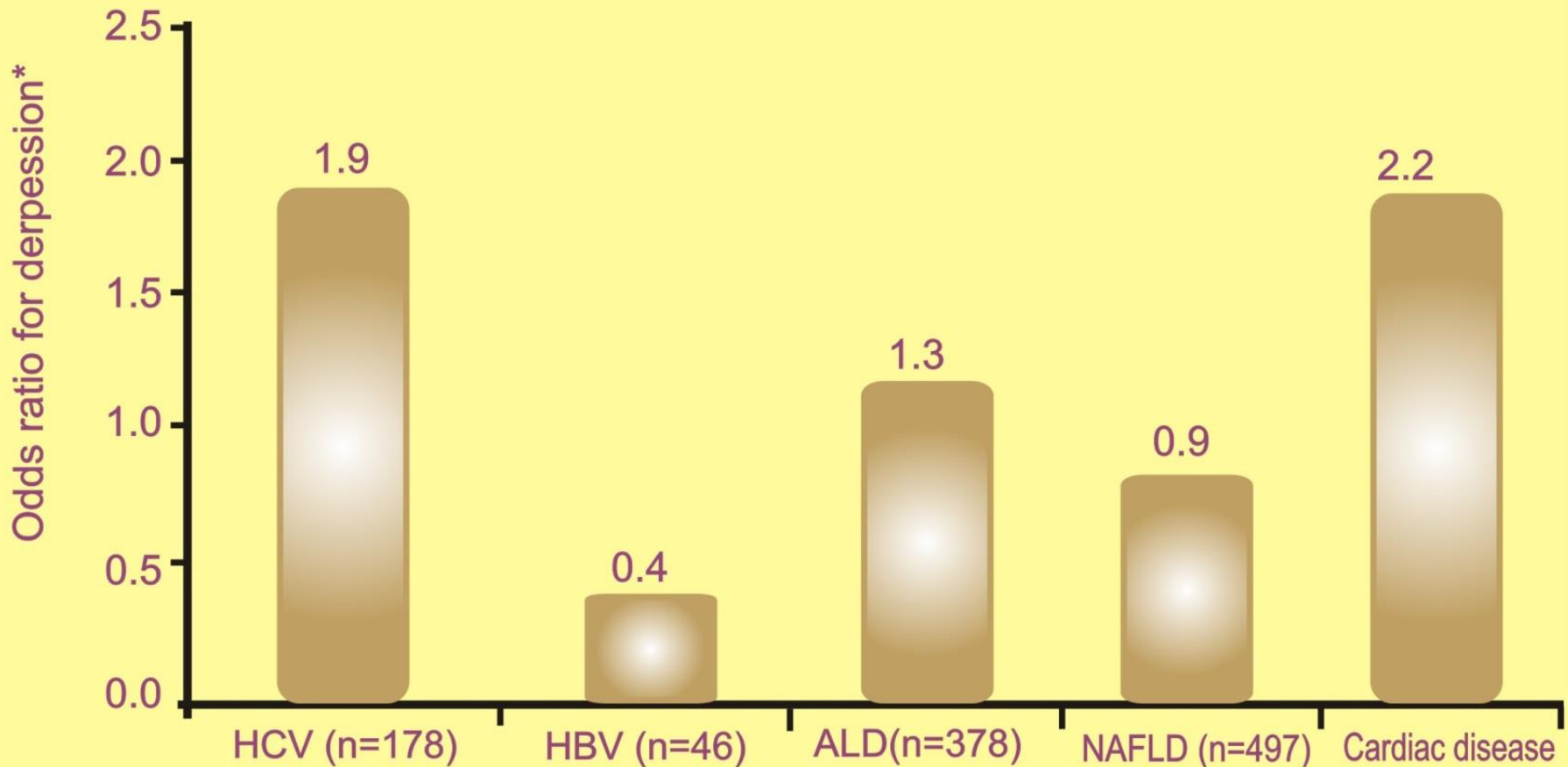
Community-based prospective cohort study: 23665 residents in Taiwan



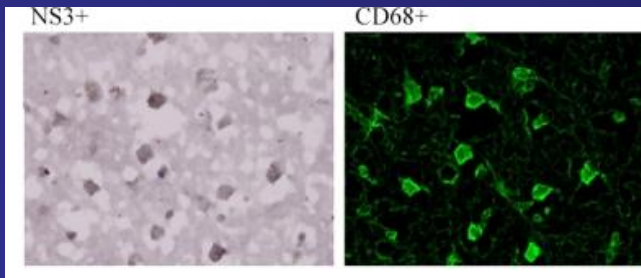
Increased Prevalence of Psychiatric Comorbidity in HCV – Infected Populations



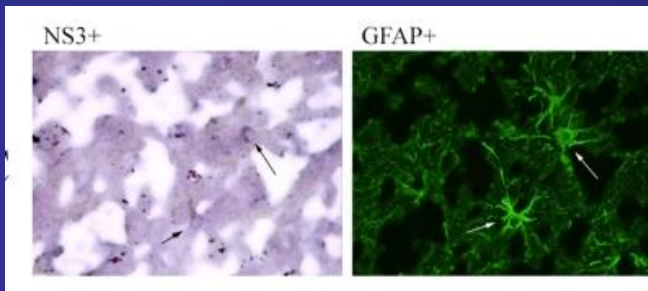
HCV is Strongly Associated with Depression



Cellular Localization Of Hcv Within The CNS: Microglia And Astrocytes



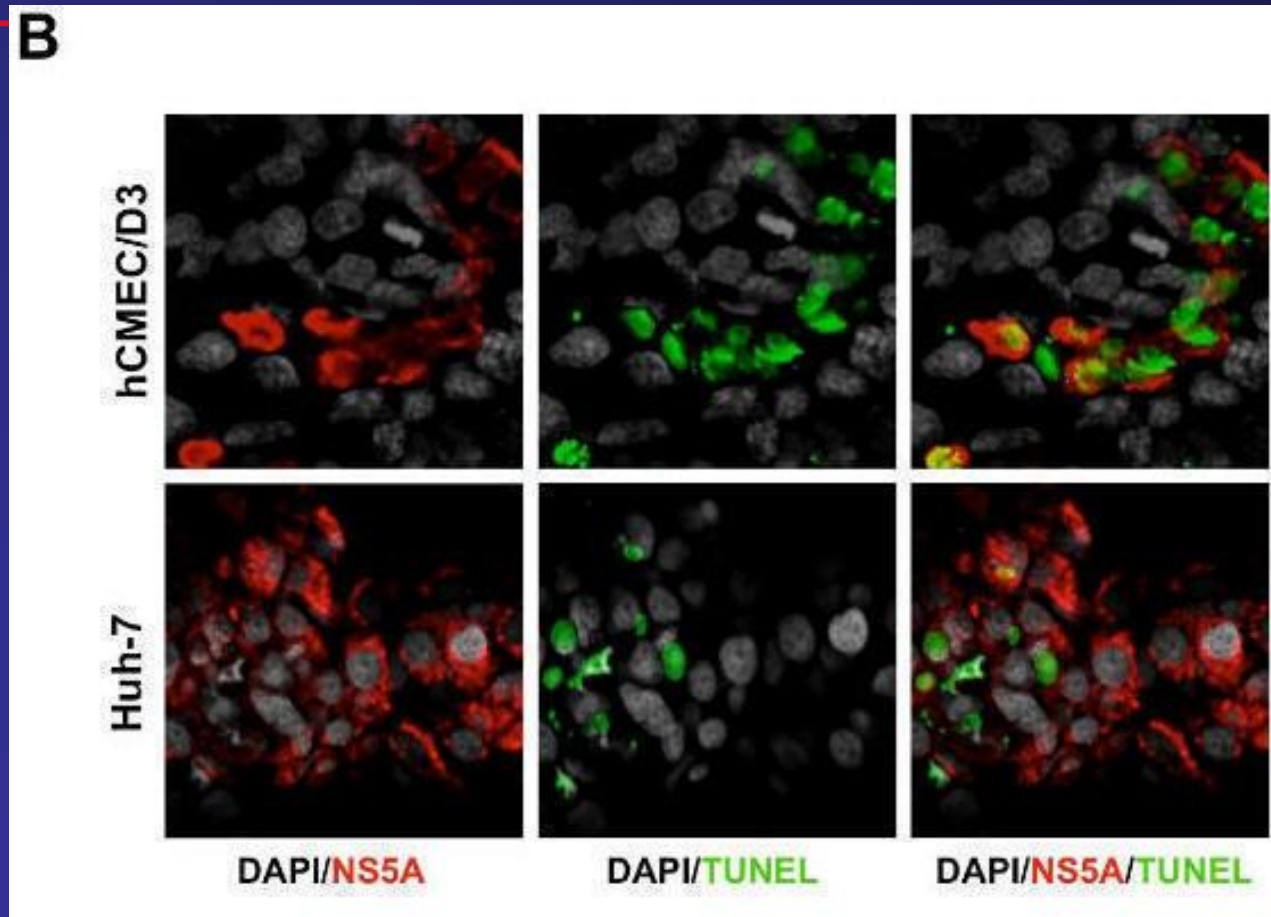
83 -95% of HCV NS3+ cells co-stained for CD68+ (microglia)



4-29 % of NS3+ cells co-stained for GFAP + (astrocytes)

Positive –and negative-strand HCV RNA detected in laser capture microdissected microglia (genomic equiv/400-650 cells)

HCV Infects the Endothelial Cells of the Blood-Brain Barrier



Two brain microvascular endothelial cell lines, hCMEC/D3 and HBMEC, express all the HCV entry factors

HCV Brain Syndrome: Mechanisms

Psychosocial effects

CNS effect of
peripheral immune
response?



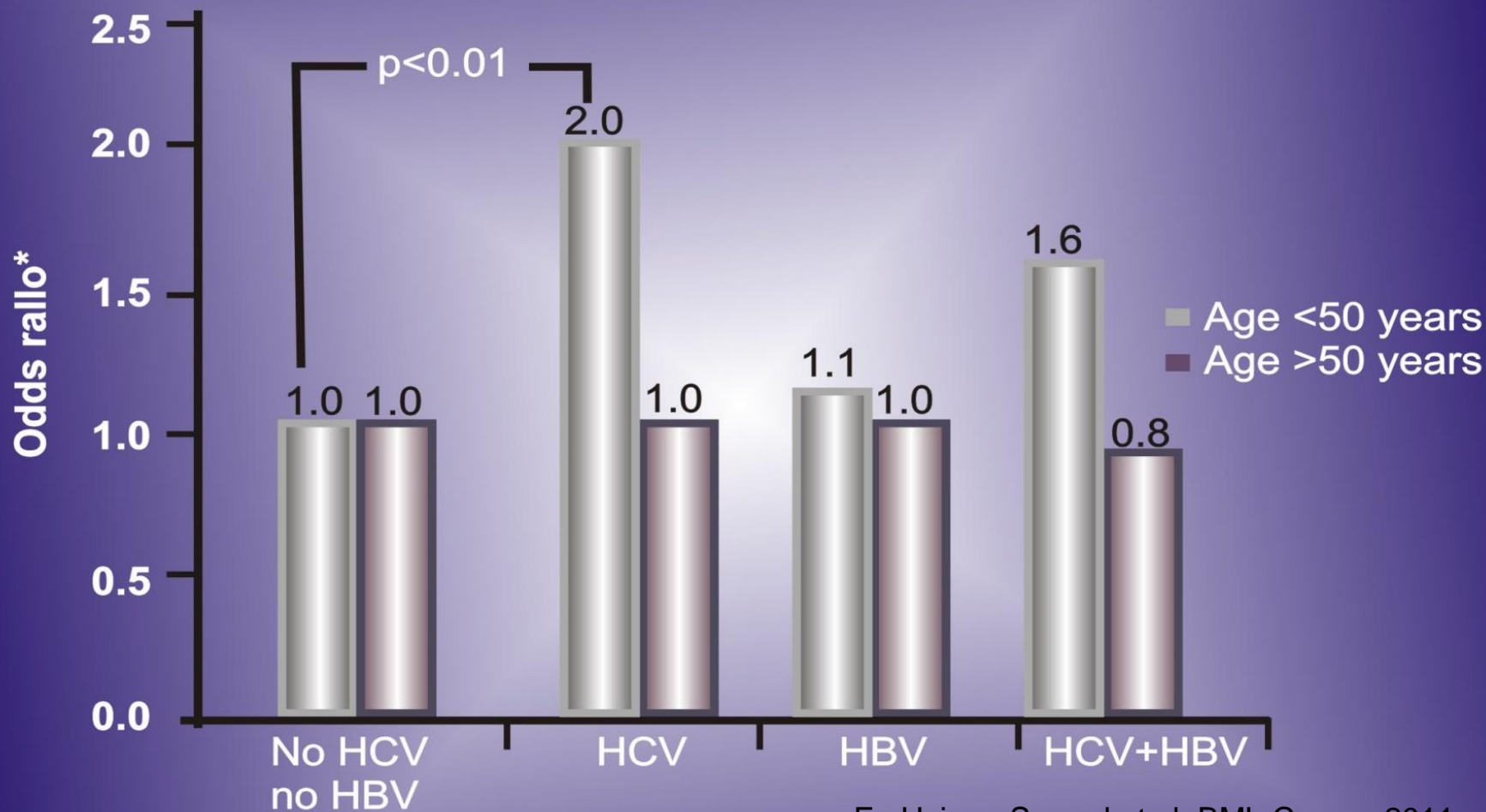
HCV infection of the
CNS?



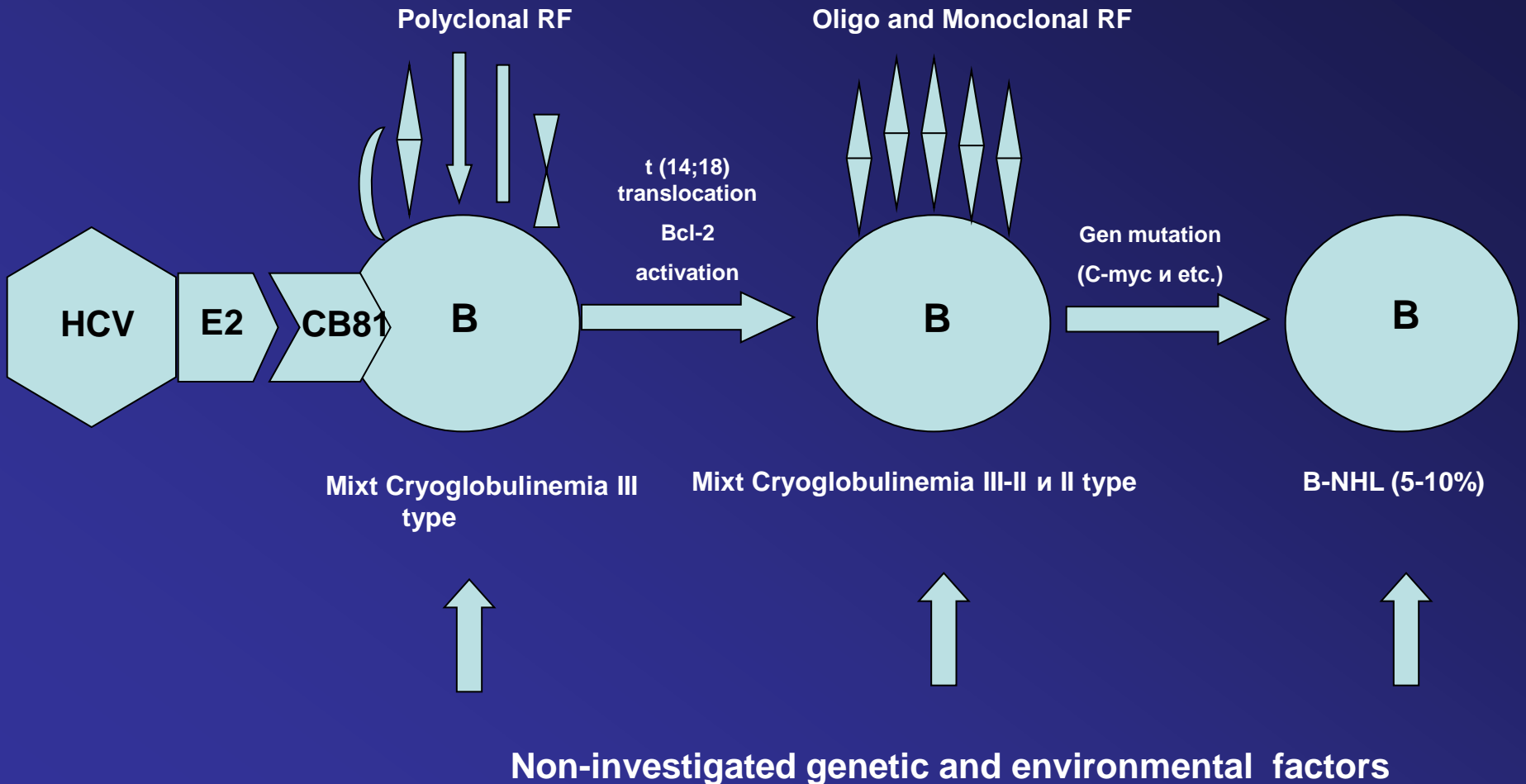
“HCV Brain Syndrome”
Fatigue, Depression, Cognitive impairment

Association Between HCV, HBV and Breast Cancer Risk in Taiwan

Patients newly diagnosed breast cancer (n=1958) Age-matched cohort without cancer (n=7382)



Pathogenesis of HCV-associated B-NHL



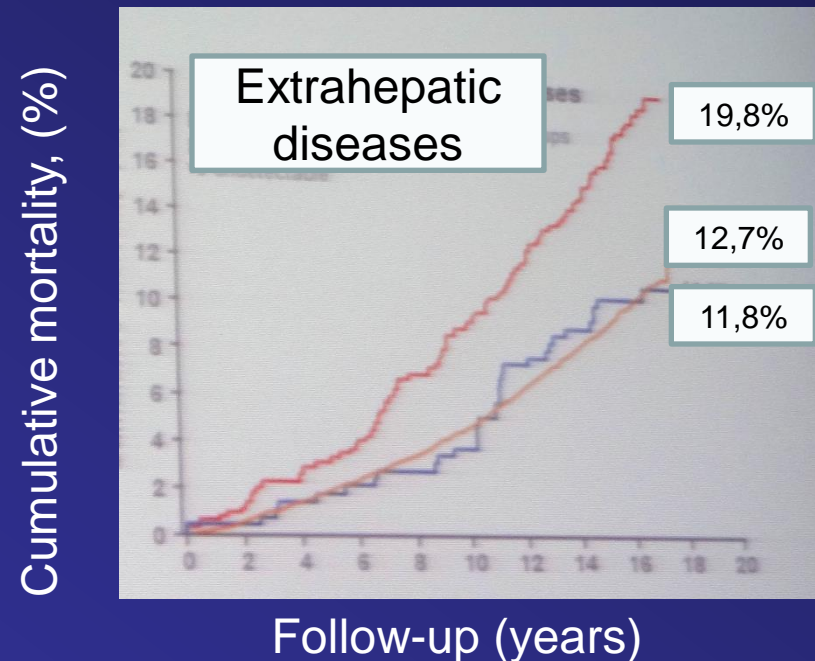
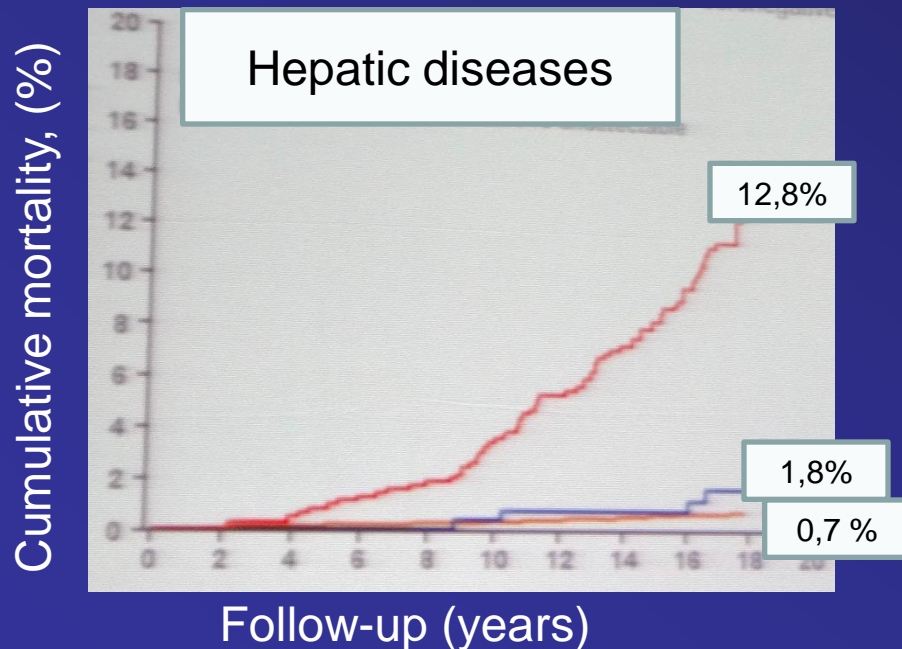
Chronic HCV Increases Mortality from Hepatic and Non-hepatic Diseases

The REVEAL HCV Cohort Study

23820 adults, Taiwan

1095 anti-HCV positive; 69,4% with detectable HCV RNA

- HCV seropositive HCV RNA detectable
- HCV seropositive HCV RNA undetectable
- HCV seronegative

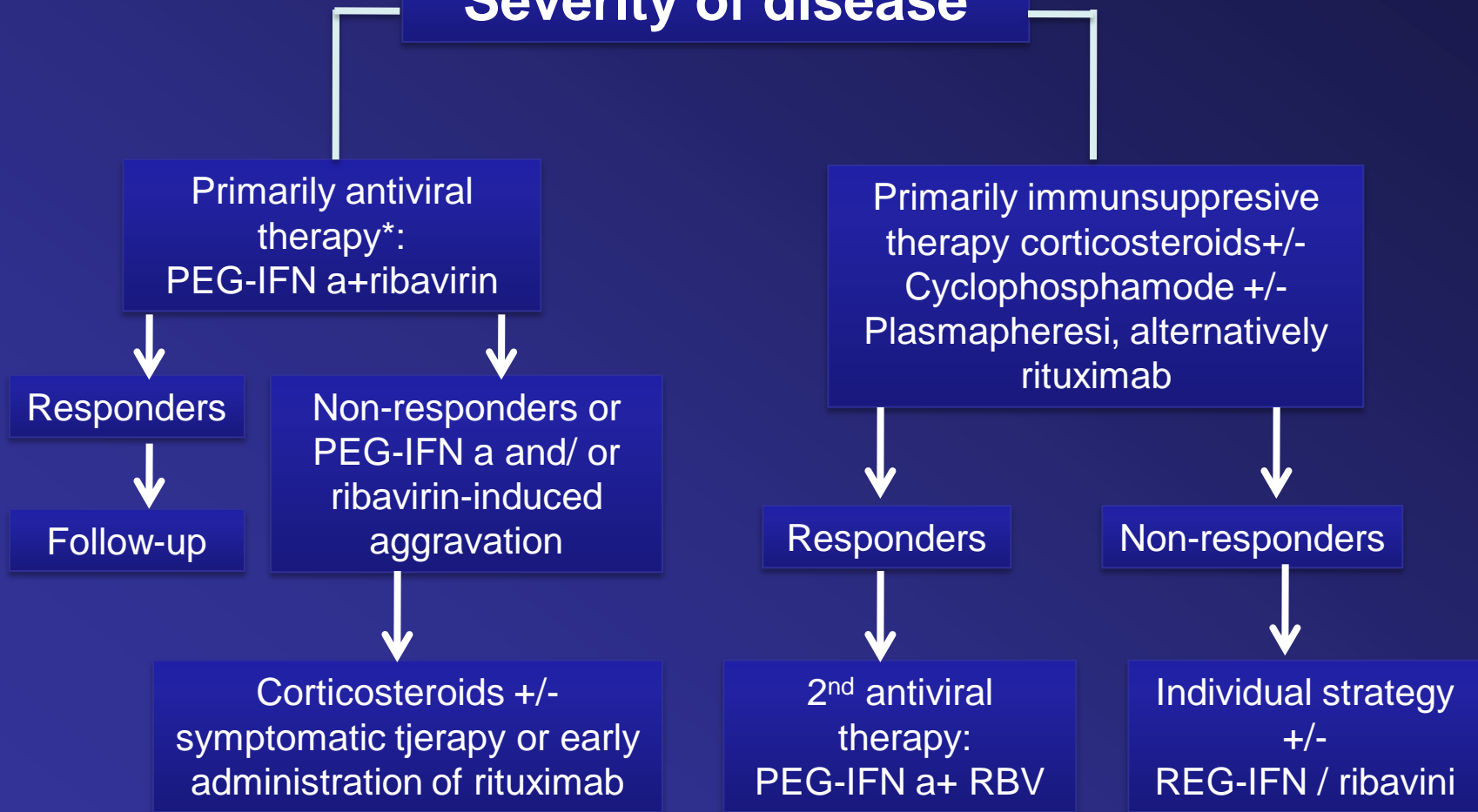


The Management of Extrahepatic Manifestations in Patients with Chronic HCV - Infection

Antiviral treatment	Glucocorticoids
<ul style="list-style-type: none">- Vasculitis: skin, lung, intestines, cerebral- Raynaud's syndrome,- Polyneuropathy- Chronic glomerulonephritis	<ul style="list-style-type: none">- Myocarditis-- Polymyositis-- Granulomatosis of Lungs- Sjogren's syndrome--Tubulointerstitial nephritis
<ul style="list-style-type: none">- Lymphoproliferative diseases- Low-grade NHL	<ul style="list-style-type: none">-Cryoglobulinemic syndrome- with severe renal impairment- Autoimmune hemolytic anemia- Autoimmune thrombocytopenia

Therapy algorithm for HCV extrahepatic manifestations

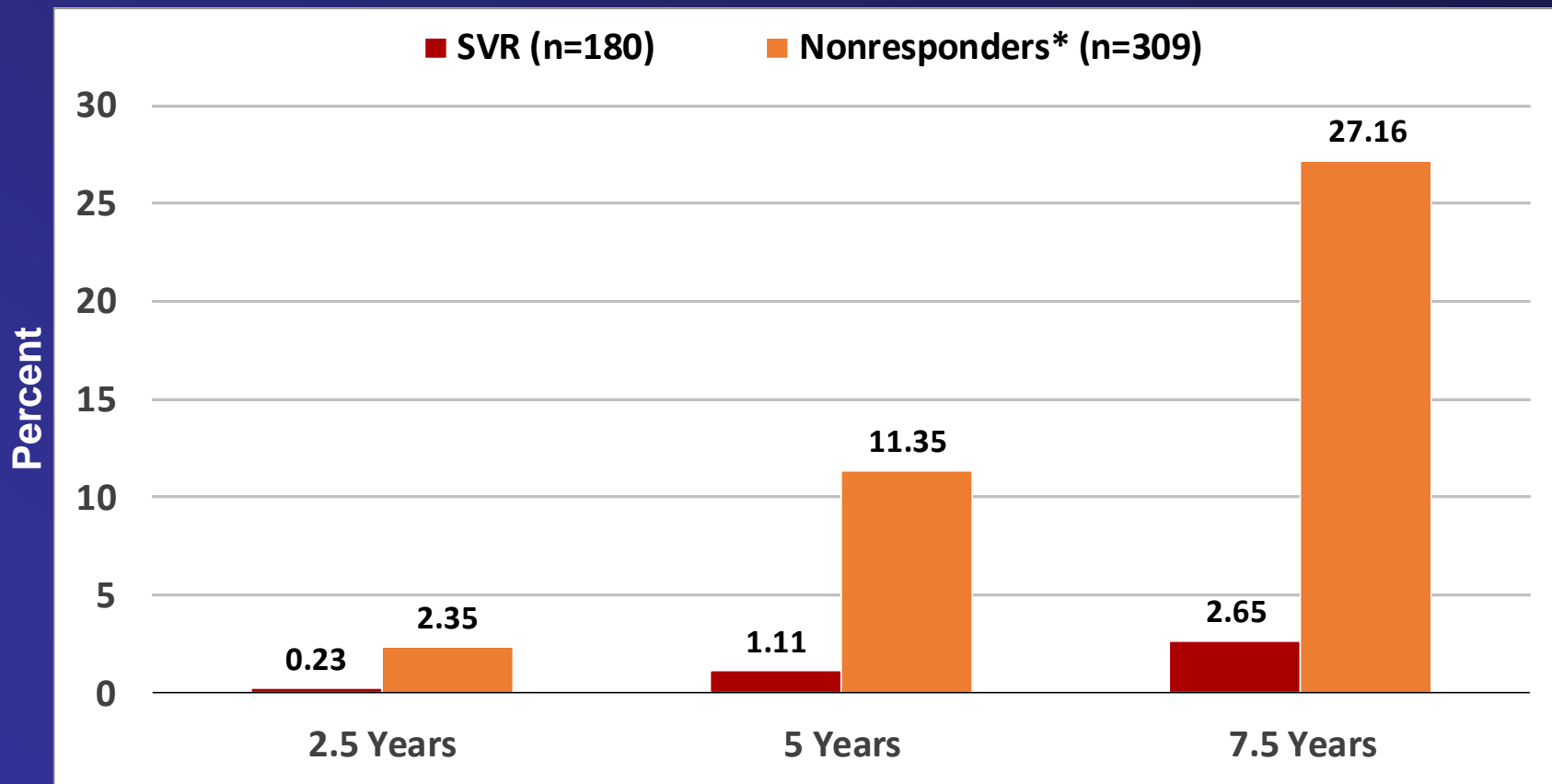
Severity of disease



Modified from Craxi 2008

SVR Was Associated With Improved Long-Term Liver-Related Outcomes in the HALT-C Trial Database

Cumulative Incidence of Any Liver-Related Outcome Among Patients With Bridging Fibrosis or Cirrhosis



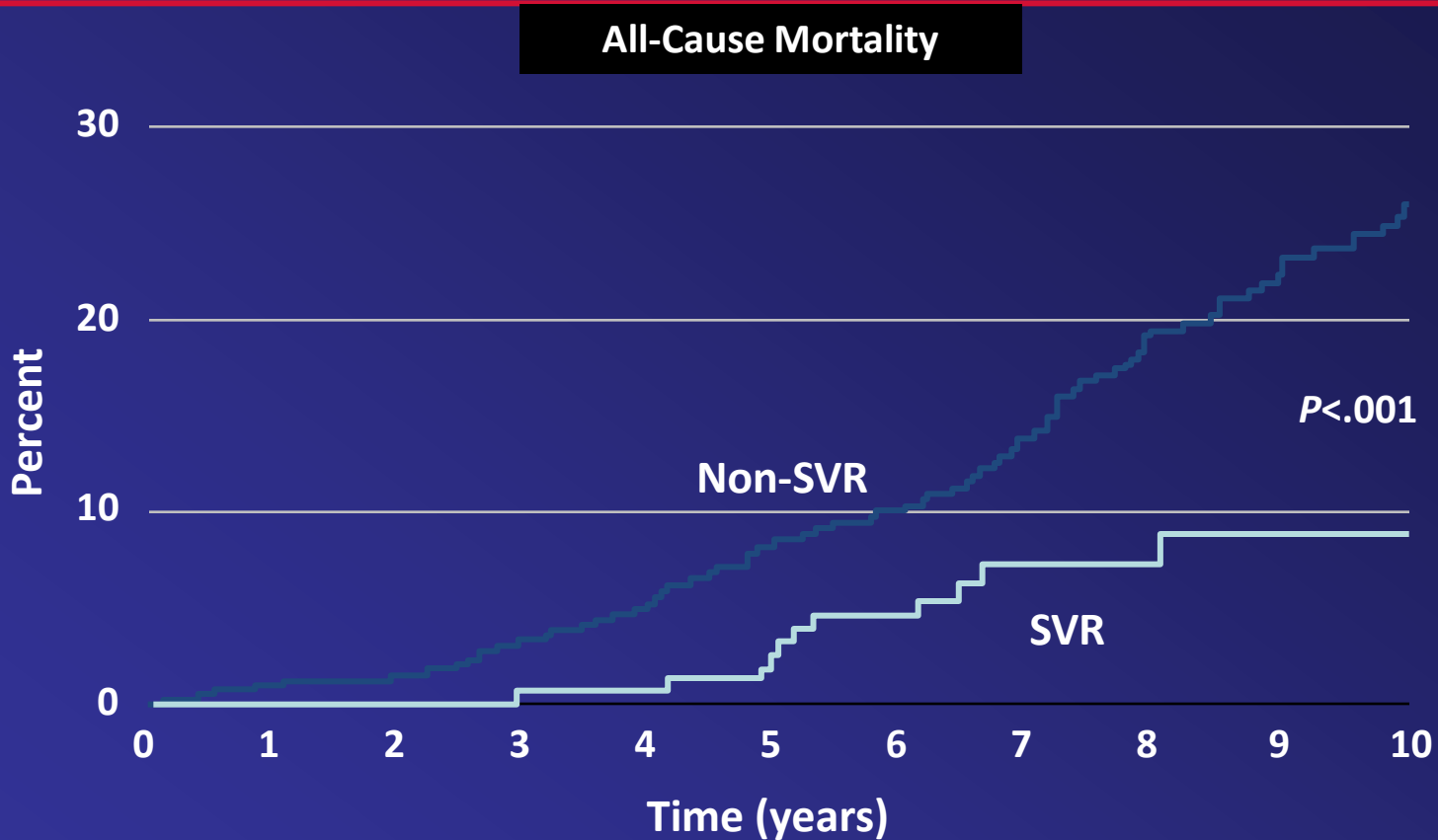
Analysis of liver outcomes (decompensation, HCC, or death) in the HALT-C trial database. All comparisons $P < .0001$.

*Detectable HCV RNA at treatment week 20 (combination therapy was discontinued at week 24).

HALT-C=Hepatitis C Antiviral Long-Term Treatment against Cirrhosis.

Morgan TR, et al. *Hepatology*. 2010;52:833-844.

Term Risk of All-Cause Mortality in an International, Multicenter Study



International, multicenter, long-term follow-up study from 5 large tertiary care hospitals in Europe and Canada. Patients with chronic HCV infection started an interferon-based treatment regimen between 1990 and 2003 (n=530).

van der Meer AJ, et al. *JAMA*. 2012;308:2584-2593.

Conclusions

- Chronic HCV infection has adverse effects on many organ systems outside the liver
- Some of these effects lead to significantly increased mortality
- Improved antiviral efficacy might reduce morbidity and mortality from hepatic and non-hepatic causes

Treat now !