Chronische Hepatitis C
Een Behandelbare Infectieziekte?

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Afdeling Maag-, Darm- en Leverziekten

Erasmus MC

Februari 2024

Slides by: Rob de Knegt, Lisette Krassenburg and Sylvia Brakenhoff.

Wel volgens Pamela

Instagram 2015

YouTube

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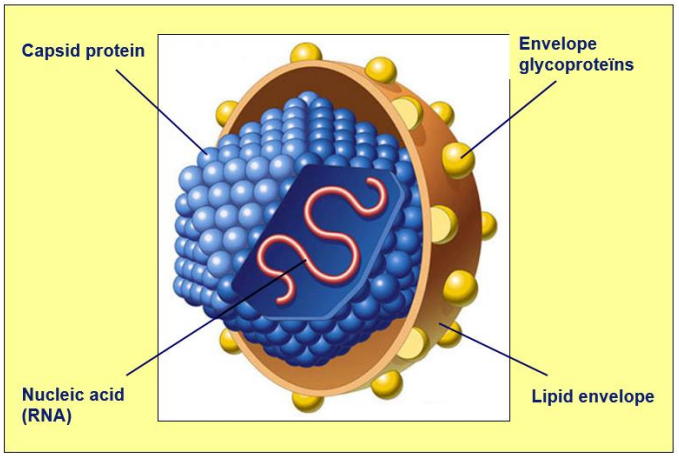
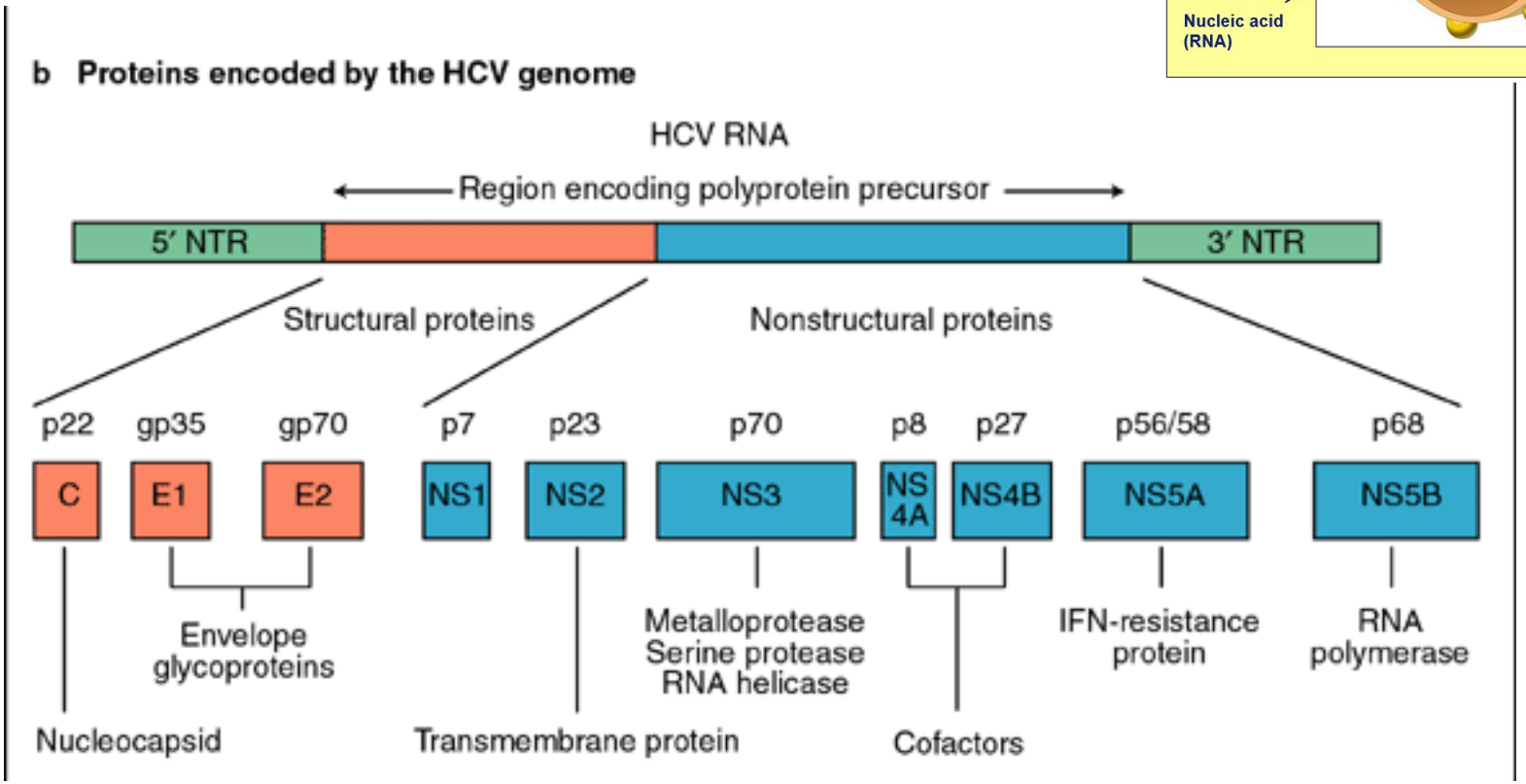
HCV RNA



Small single strand RNA virus of 9600 nucleotides



Single polyprotein → cleaved by host and viral proteases

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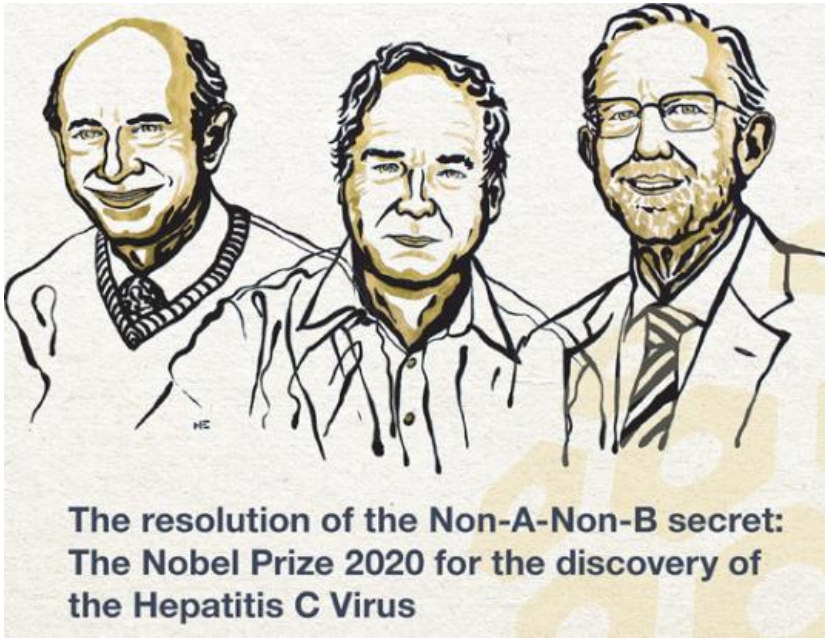
The Hepatitis C virus

Discovered in 1989

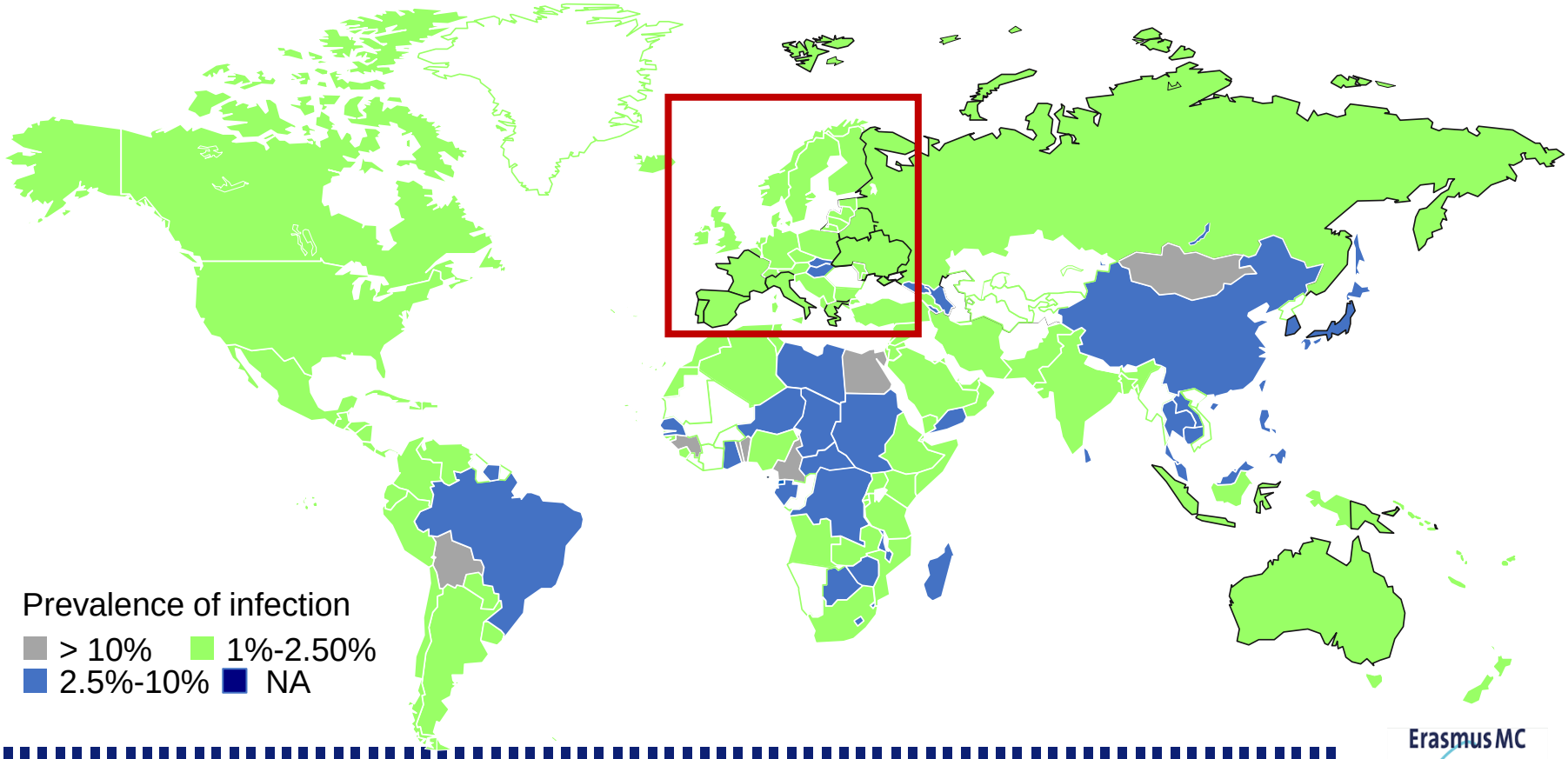
- *Suspected from 1970's → 'non-A non-B Hepatitis'*

Family: *Flaviviridae*, genus: hepacivirus



Estimated 71 Million Persons With HCV Infection Worldwide

1-2 million newly infected each year

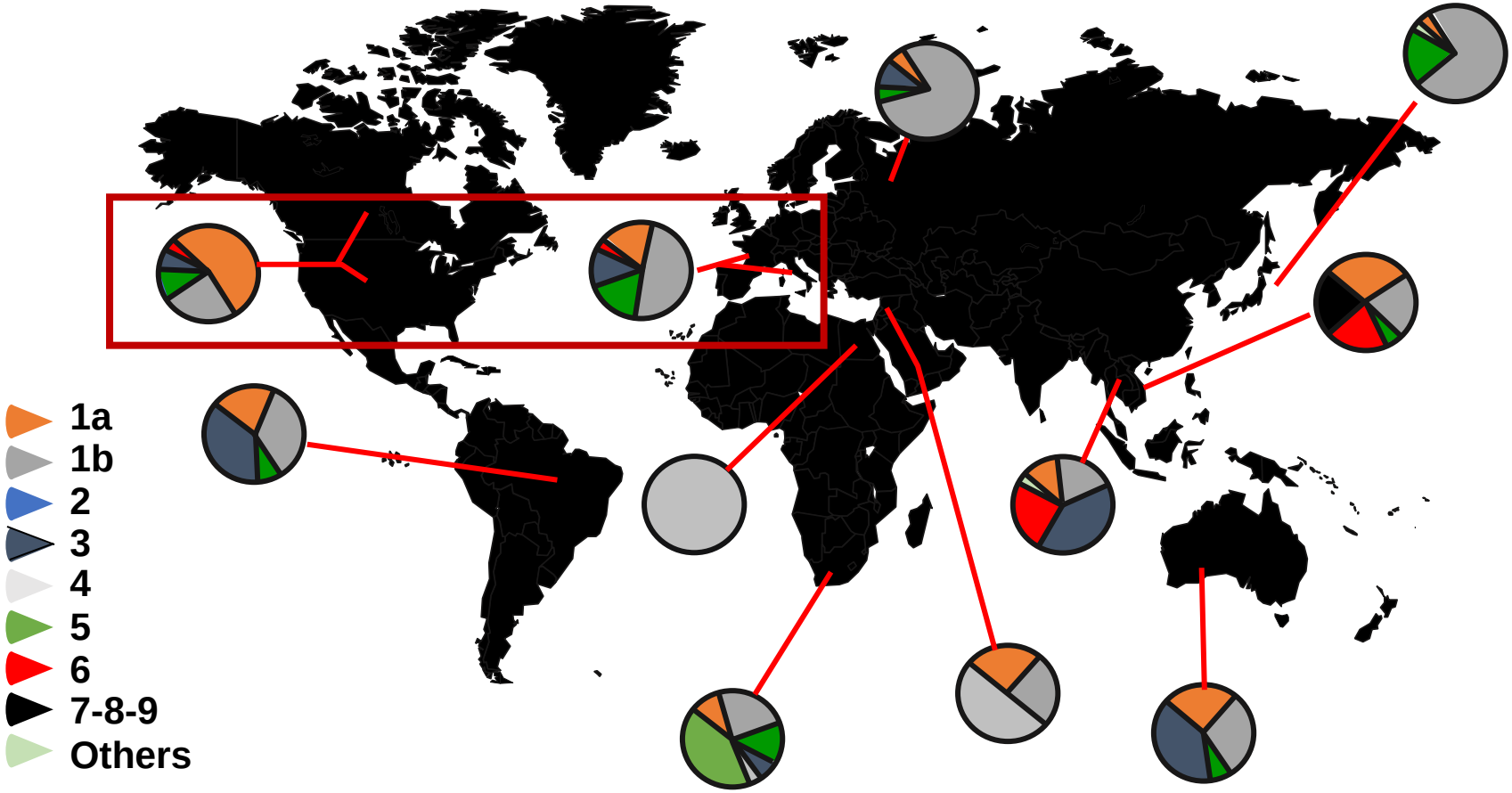


World Health Organization 2018

HCV in The Netherlands

- ~ 0,2% of the population
- ± 30,000 patients

Worldwide spread HCV Genotypes

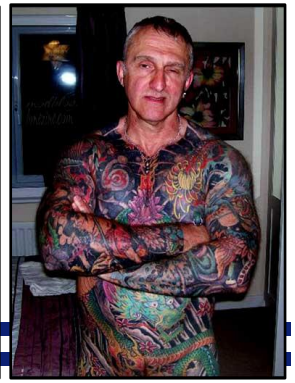


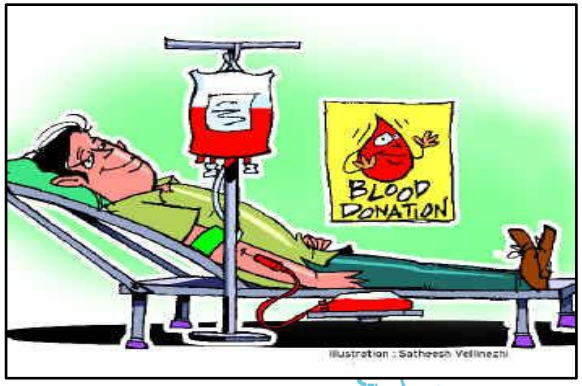
Zein N. Clin Microbiol Rev. 2000;13:223-235.

Etiology = Blood to Blood contact

- Injecting drug use (IDU)
- Blood product transfusion (Before 1992)
- Needle accident
- Tattoo's
- Vertical transmission (~4%)
- Sexual transmission (< 1%)

Rapid viral replication (10^{12}), mainly in hepatocytes





Laboratory Diagnostics

ALT & AST	Indicate hepatitis	→ Non-specific
Anti-HCV IgG	Antibodies against HCV	→ Lifetime! (na ± 8 weken)
HCV RNA	Indicates active infection	
HCV genotype		

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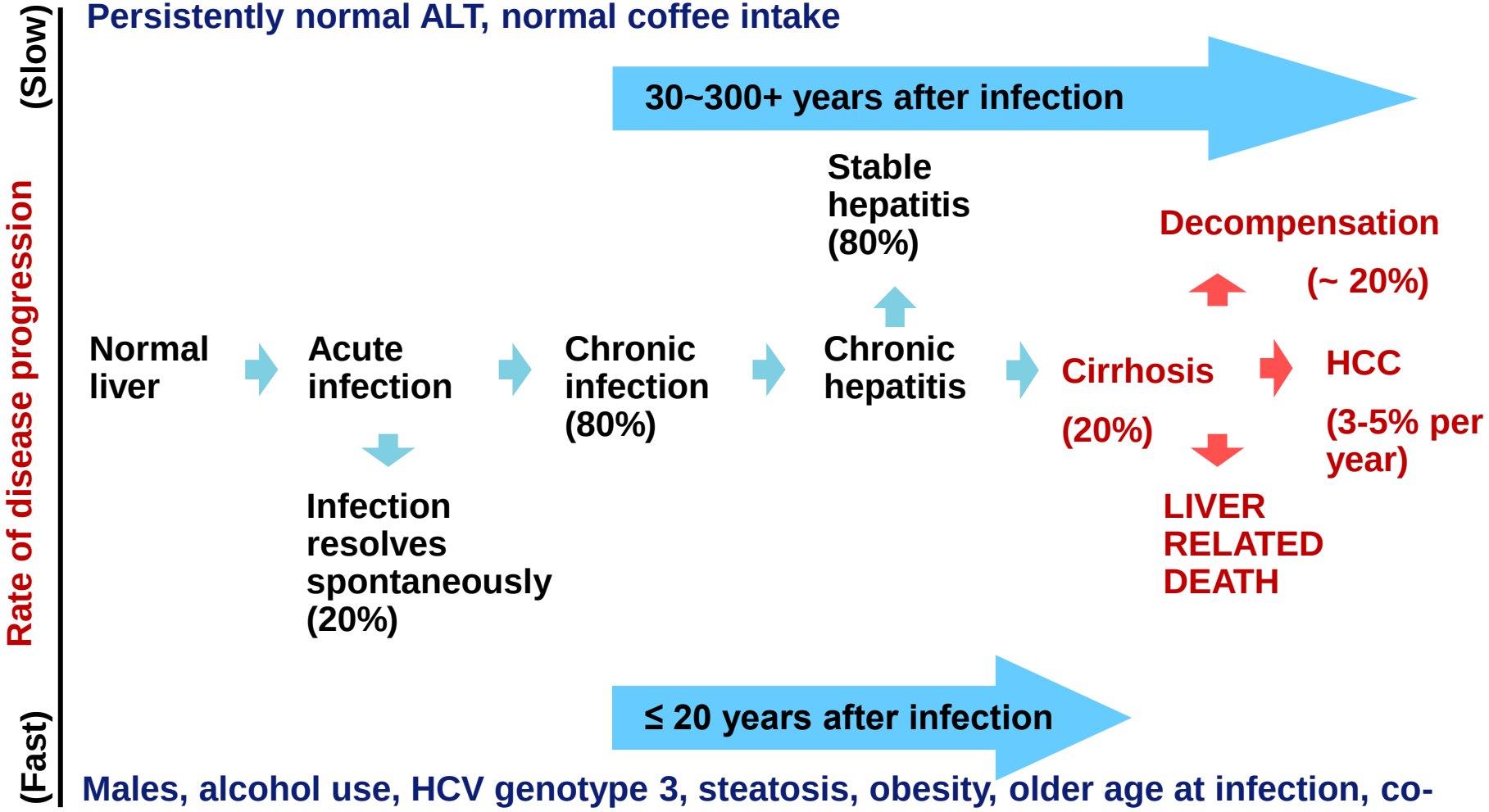
Natural History



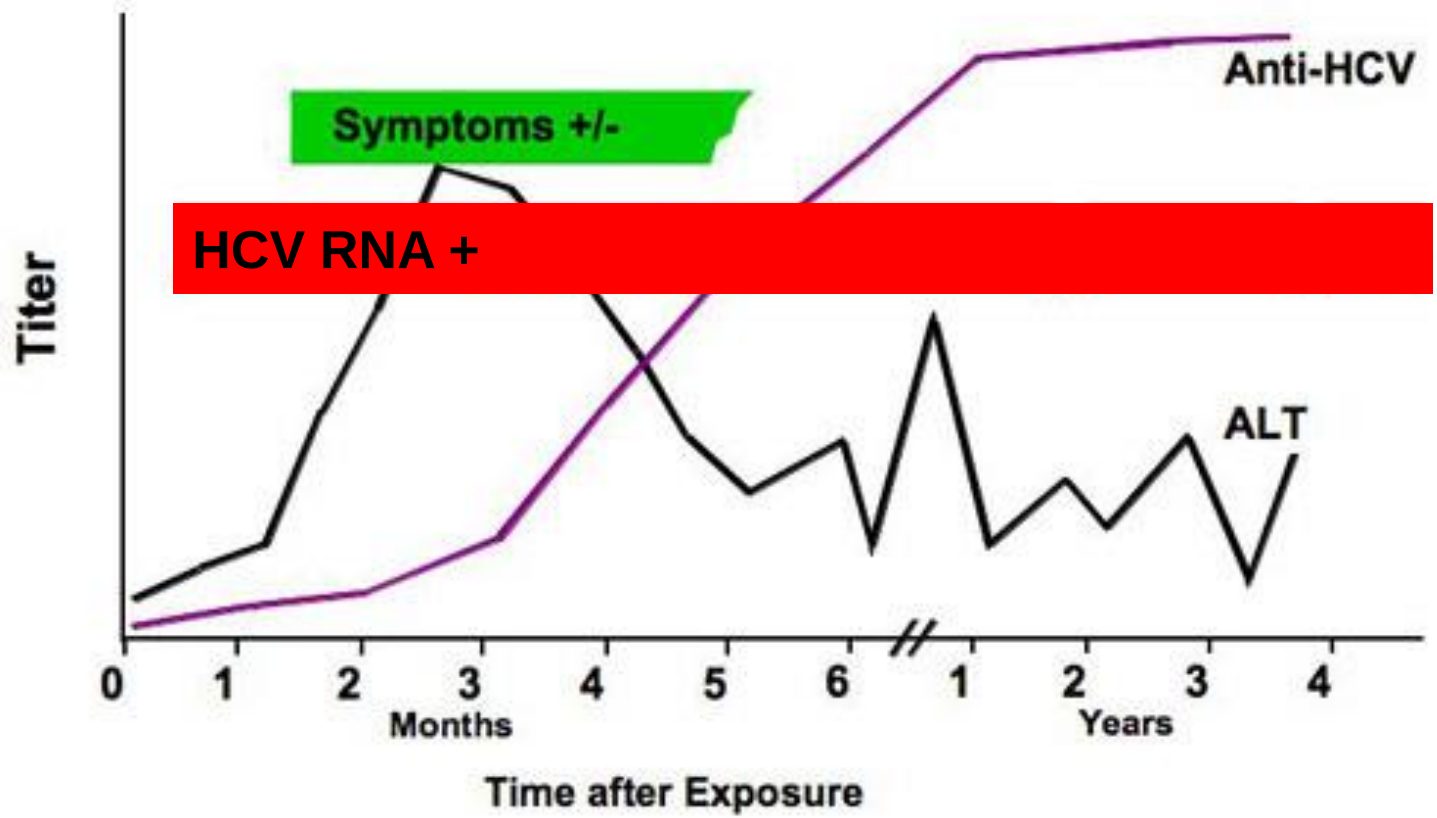
Acute HCV Infection

Normal liver → **Acute infection** → **Infection resolves spontaneously**

- If symptoms → non-specific
  - Flu-like episode / Malaise
  - Jaundice
- HCV RNA may be negative
- Lifelong anti-HCV IgG positive…
- Mostly unaware!

From Acute to Chronic

Chronic Hepatitis C = detectable HCV RNA for > 6 months



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Chronic HCV infection

Normal liver → **Acute infection** → **Chronic infection (80%)** → **Chronic hepatitis**

- Mostly non-specific extra-hepatic symptoms

- Most chronic hepatitis C patients show only mild ALT elevation
  - 30 % have persistently normal ALT levels

→ Diagnostic Challenge

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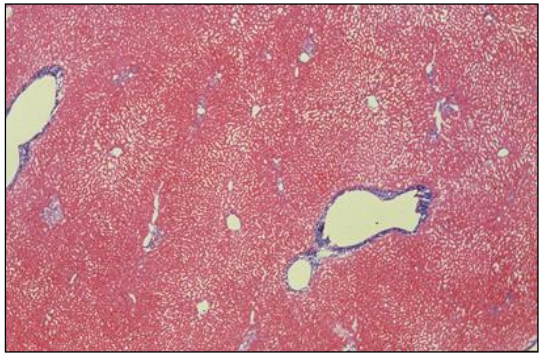
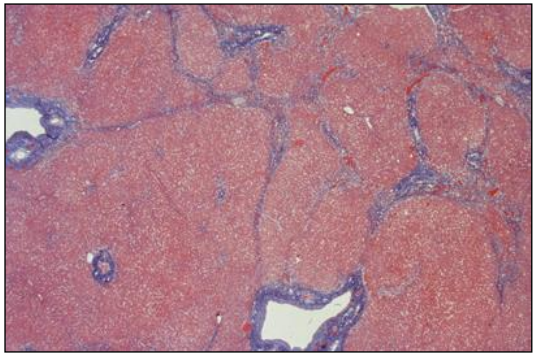
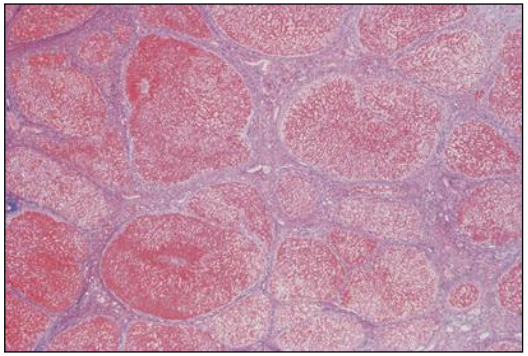
Chronic HCV Infection

Chronic hepatitis → Cirrhosis

Healthy liver	Liver fibrosis	Cirrhosis
		

External sign of cirrhosis

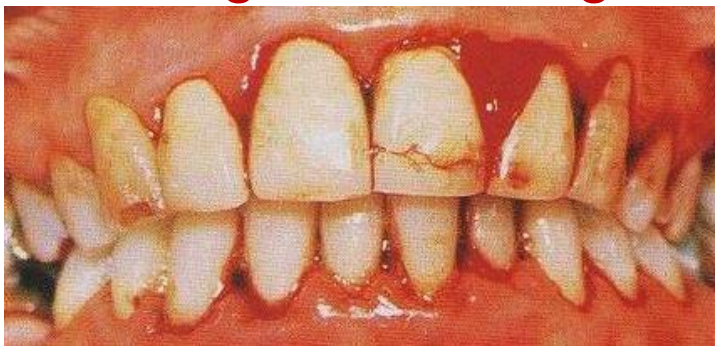
Gynaecomastie

Erythema palmare

Caput medusae

Spider naevi

Gingival bleeding



Cirrhosis-related Complications

Risk of severe complications

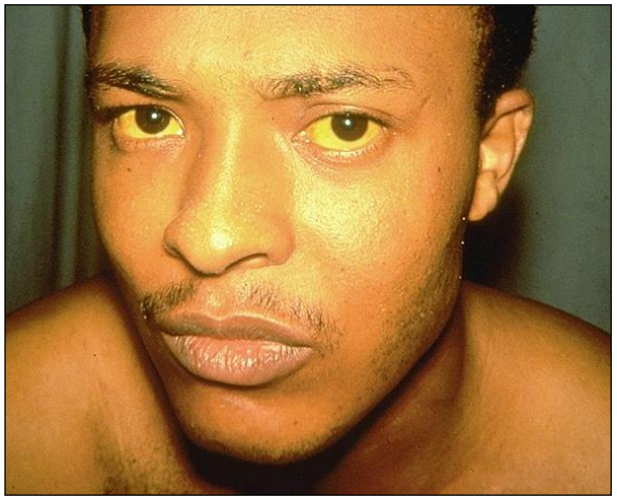
Decompensation

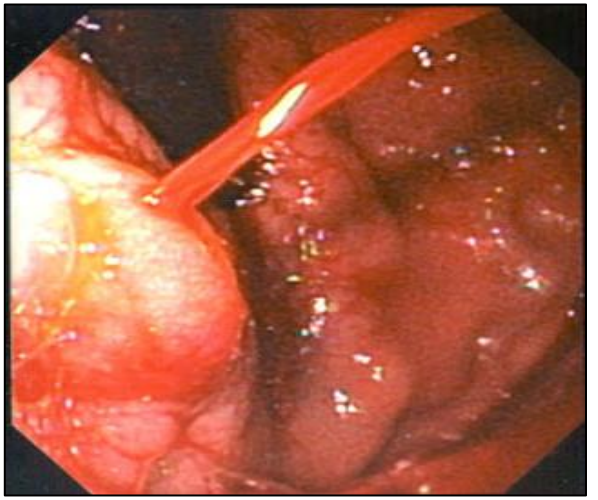
Cirrhosis → **HCC**

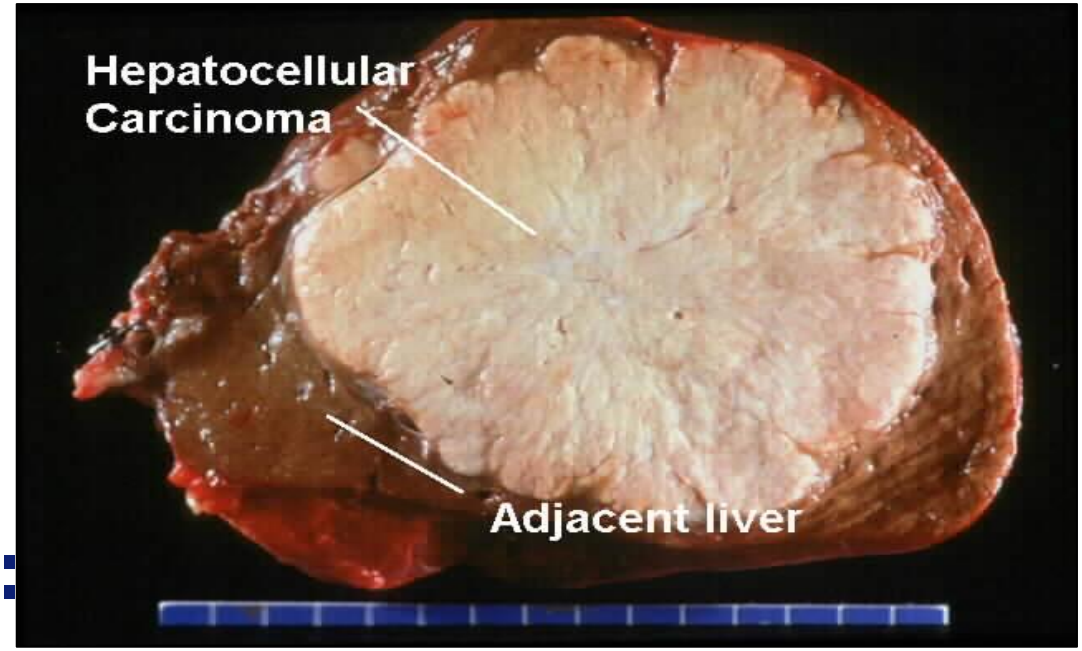
LIVER RELATED DEATH

LTx

Liver Failure and HCC

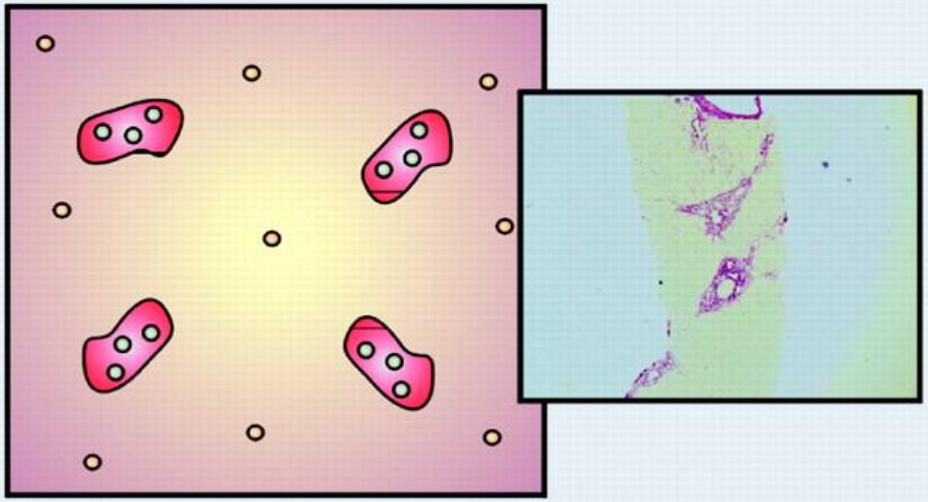






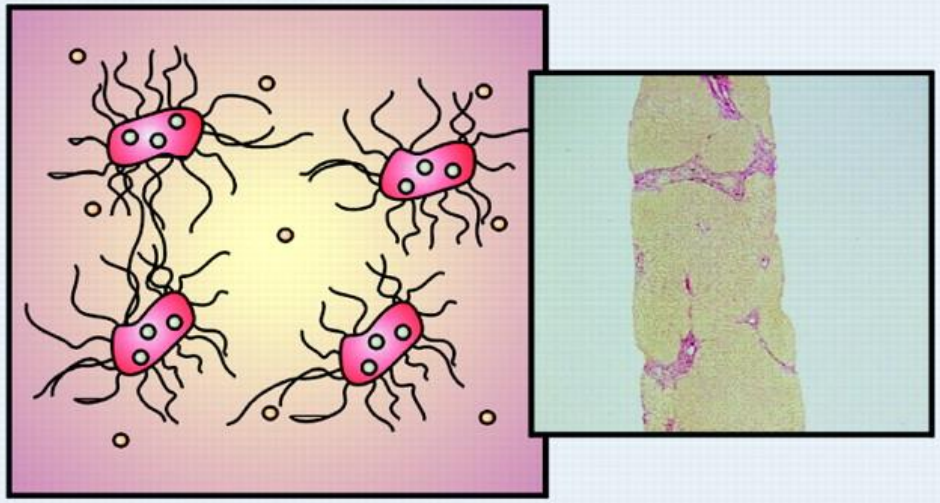
Staging according to Metavir Score

F1



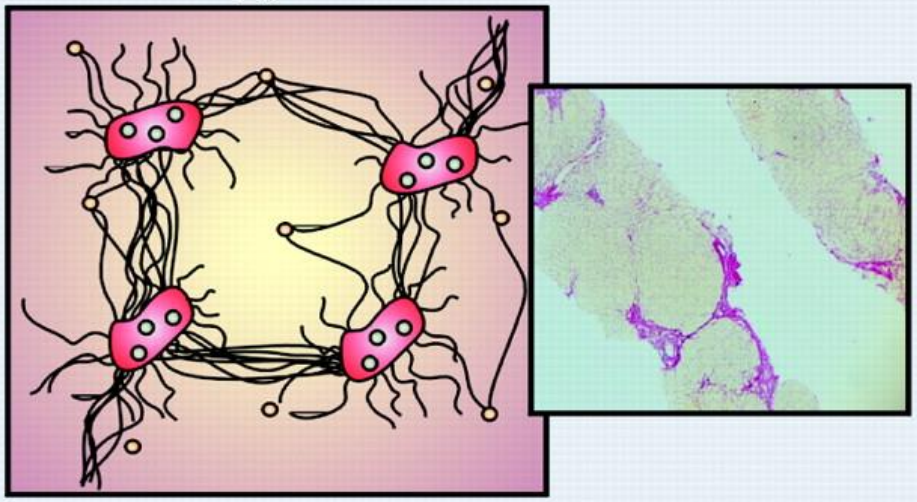
Portal fibrosis

F2



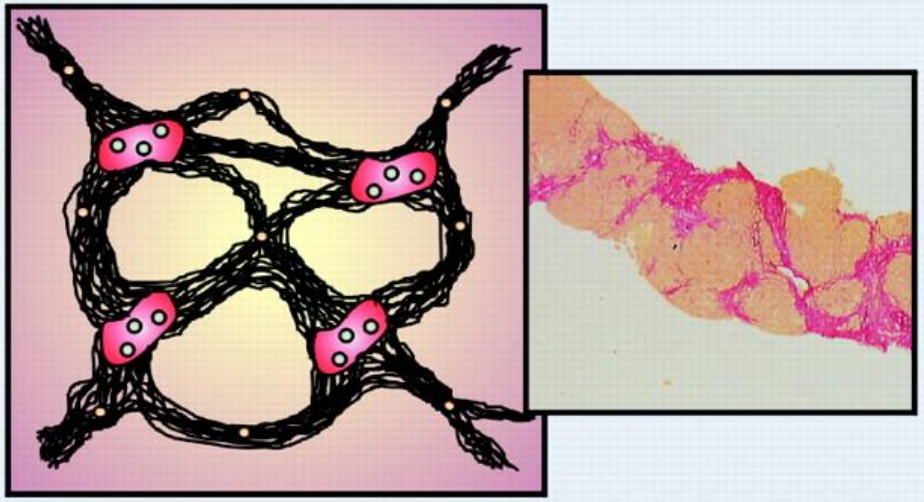
Portal fibrosis
with few septa

F3

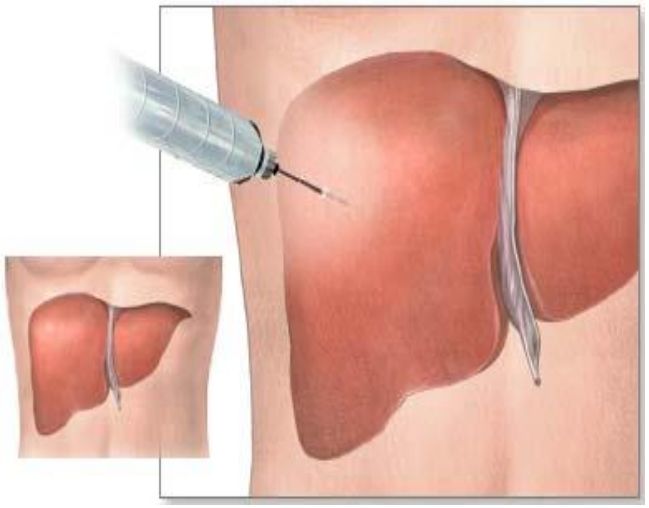


Septal fibrosis

F4



Cirrhosis



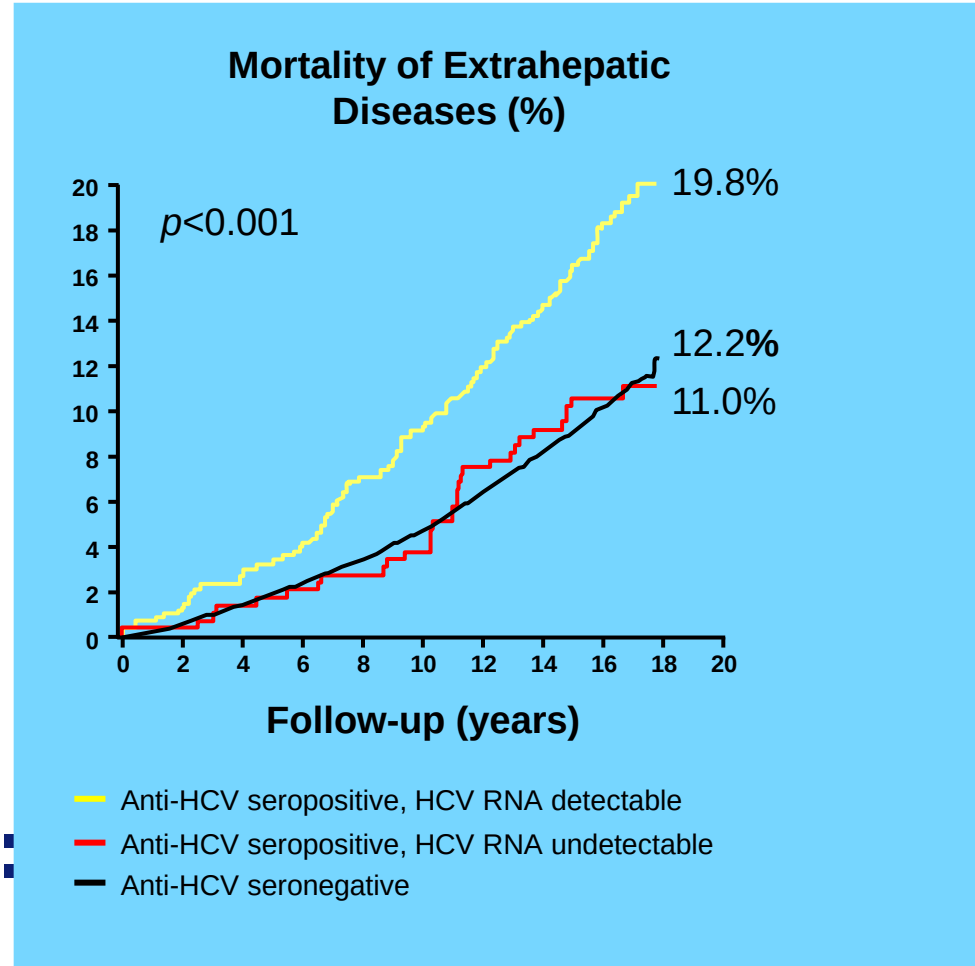
Liver biopsy

Transient Elastography (Fibroscan)

HCV infection and Extrahepatic Disease

- Extrahepatic manifestations are reported in up to 74%
  - Negatively impacts the HRqOL

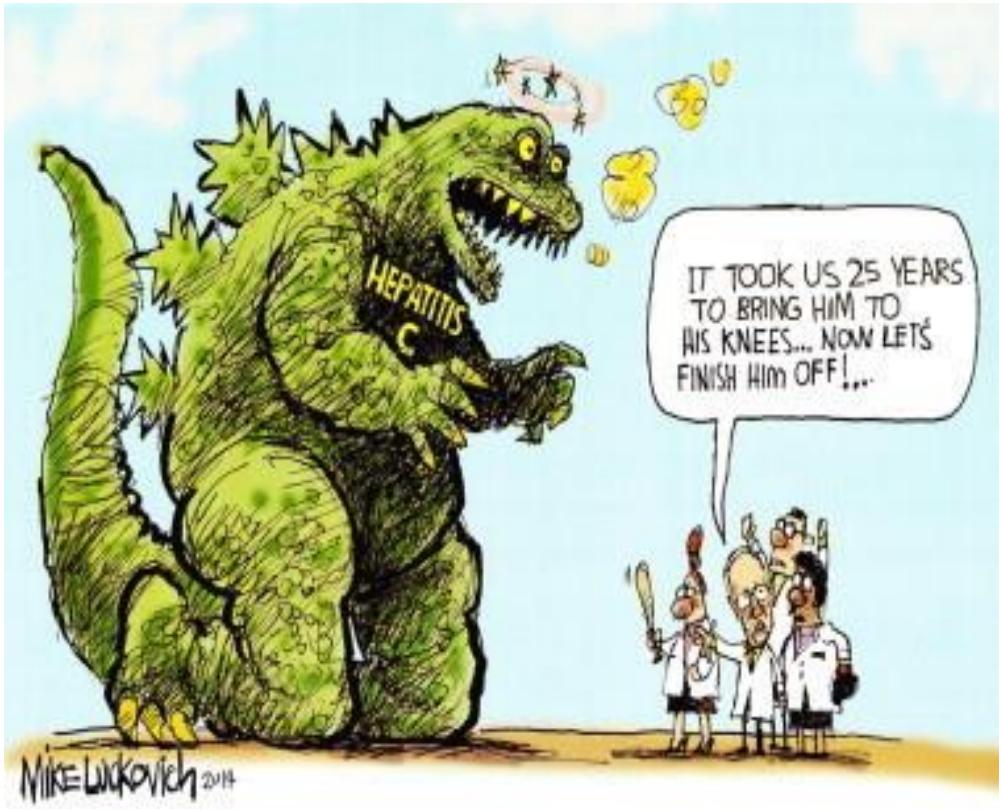
- For example:
  - Depression
  - Vasculitis
  - Renal impairment
  - Diabetes mellitus
  - Cardiovascular events
  - Malignant lymphoma



Lee *J Infect Dis* 2012

Burden of Disease

Chronische Hepatitis C
Een Behandelbare Infectieziekte?



There's a lot you should know about Hepatitis C.

Like the fact it can be treated.

Clearance of Chronic HCV Infection

- Antiviral therapy has the potential to result in a sustained virological response (SVR) = viral eradication
  - HCV RNA negativity in the circulation 12-24 weeks following antiviral therapy
  - Long-term durability[1]
- SVR is the marker of successful antiviral therapy!

[1]Swain *Gastroenterology* 2010

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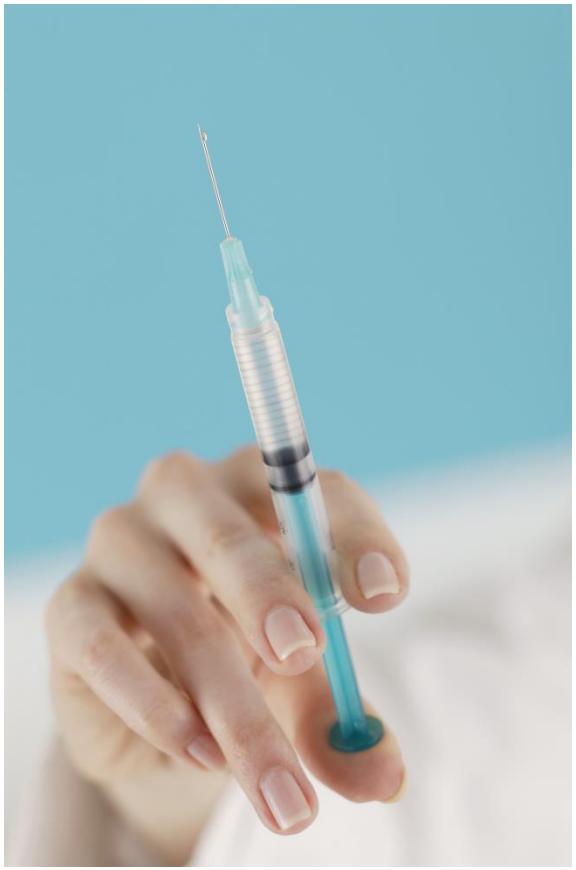
Anti-viral Therapy

Peginterferon

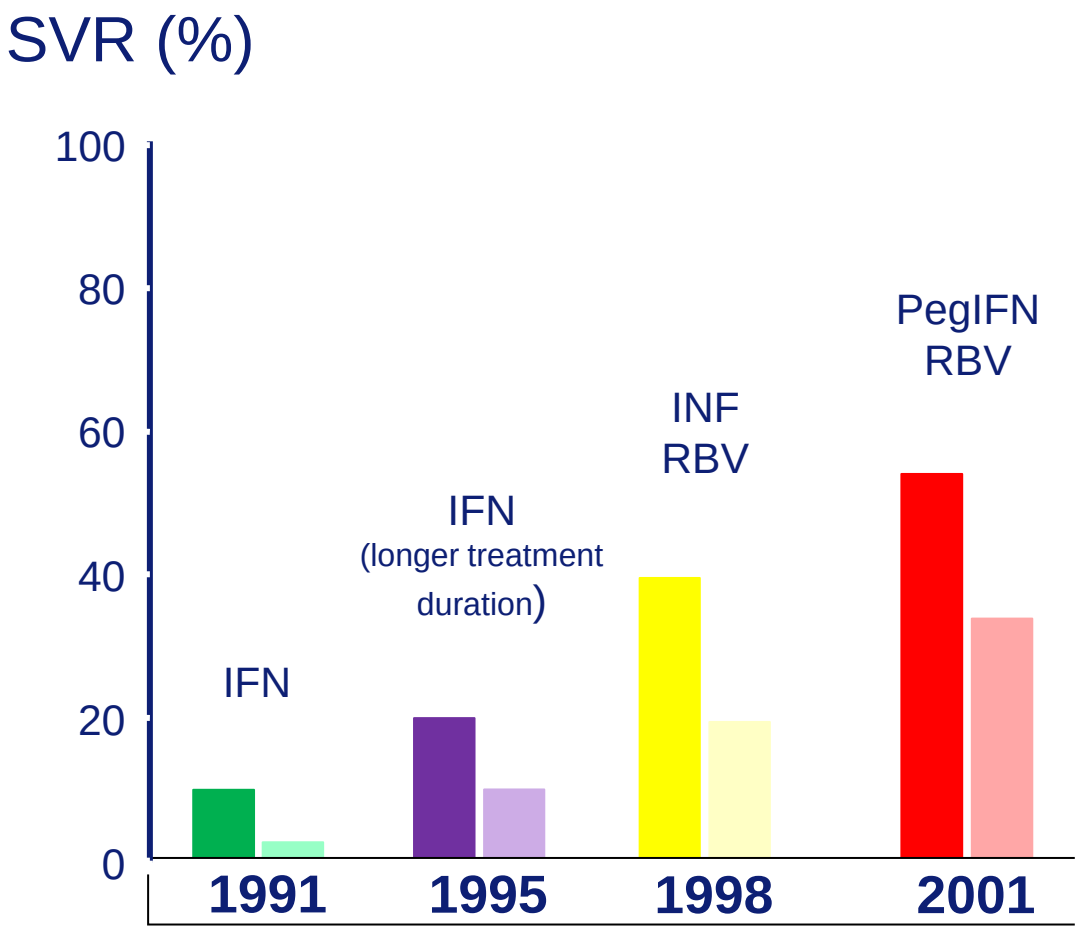


Ribavirin

Side effects!

SVR in a limited number of patients

All patients
Cirrhosis

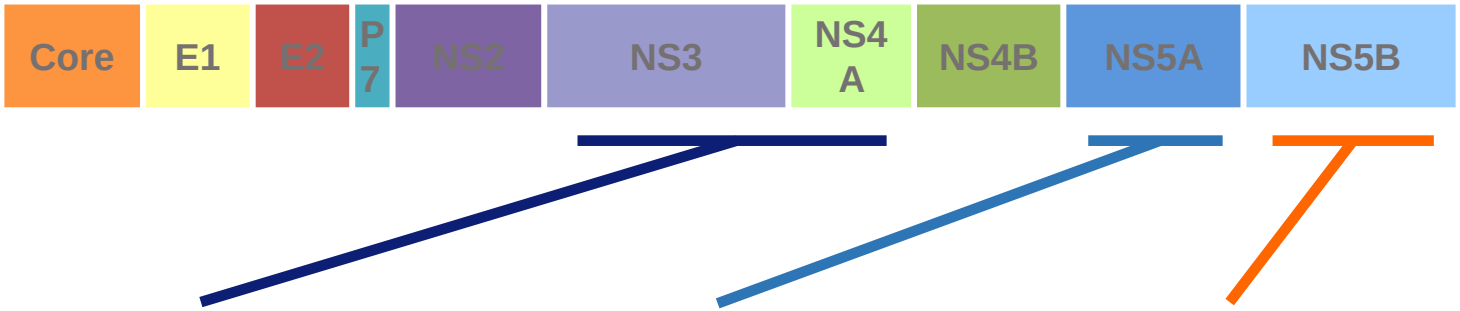


Anti-viral Therapy

Direct-Acting Antivirals (DAA's)

No side effects

Direct Acting Antivirals (DAAs)



NS3-4A protease Inhibitors	NS5A Inhibitors	NS5B polymerase Inhibitors
~previr	**~asvir**	**~buvir**
Telaprevir	Daclatasvir	Sofosbuvir
Boceprevir	Ledipasvir	Dasabuvir
Simeprevir	Ombitasvir	
Paritaprevir		

2013-2015: >20 clinical trials on HCV in NEJM only…!

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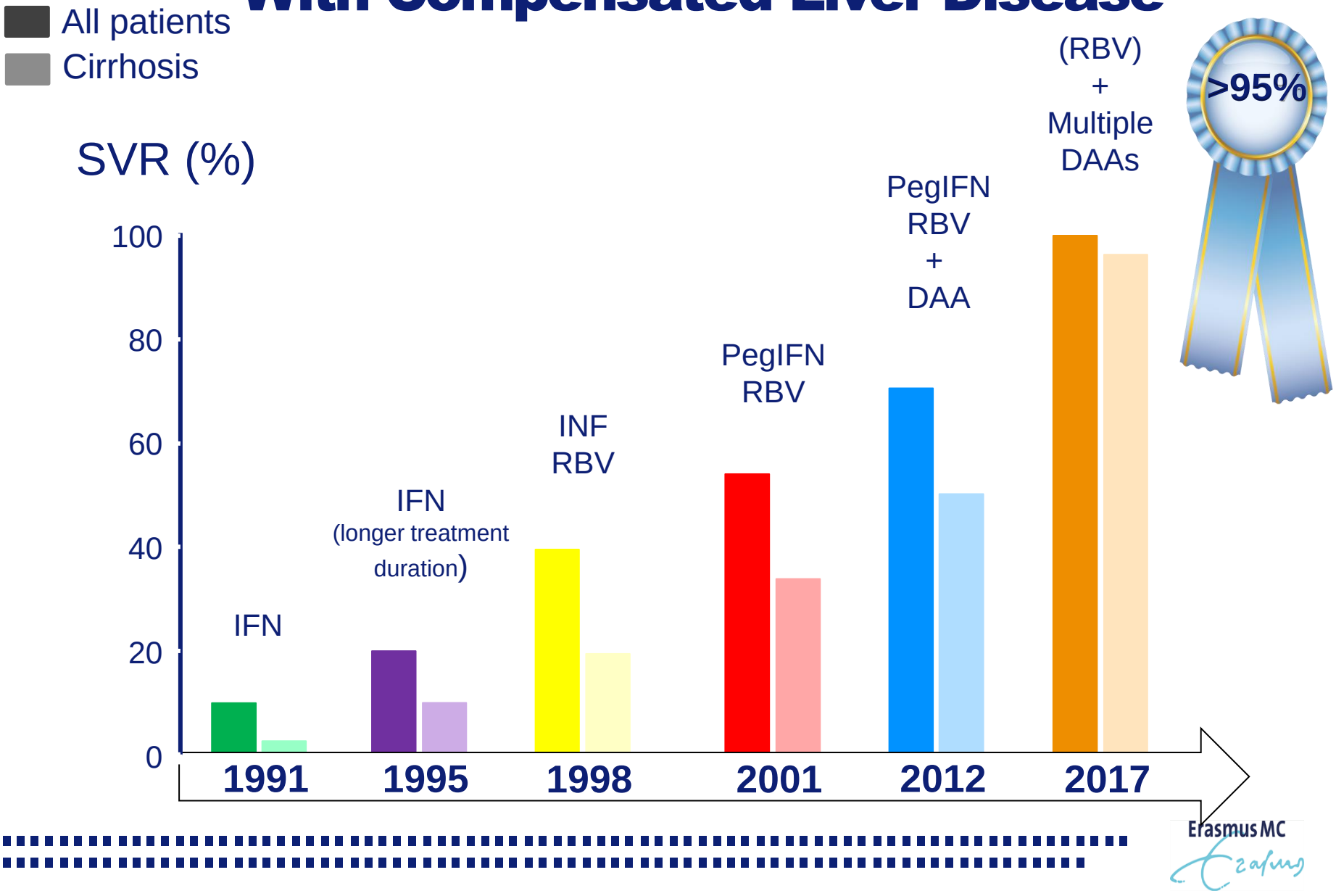
SVR in Almost All Patients With Compensated Liver Disease



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SVR in Almost All Patients With Compensated Liver Disease

All patients
Cirrhosis

SVR

100

80

60

40

20

0

PegIFN
RBV
+
DAA

(RBV)
+
Multiple
DAAs

>95%

2012

2017

A true revolution!

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High costs

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Therapeutic Options in The Netherlands

- Different DAA treatment strategies available <u>for all patients</u>
  - Sofosbuvir
  - Ledipasvir/Sofosbuvir
  - Grazoprevir/Elbasvir
  - Velpatasvir/Sofosbuvir
  - Voxilaprevir/Velpatasvir/Sofosbuvir
  - Glecaprevir/Pibrentasvir

  } pangenotypisch

- Treatment duration of 8-12 weeks
- No/minimal side effects

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What is the Clinical Relevance of SVR?

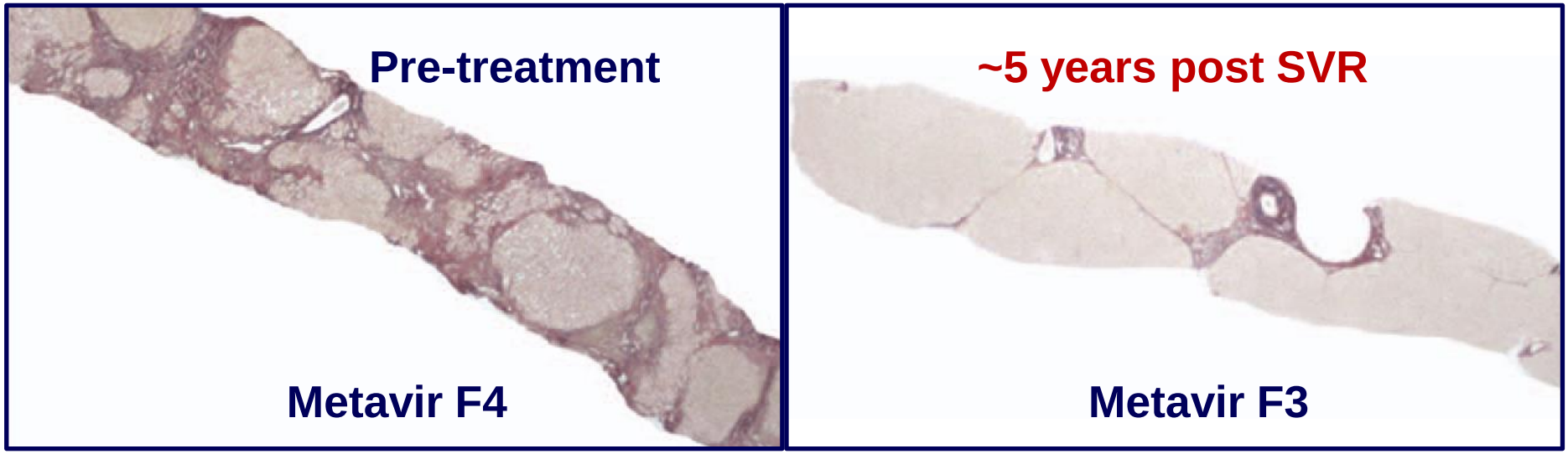
Goal of anti-viral therapy

Sustained Virological Response (SVR) is NOT the goal of antiviral therapy

We treat patients in order to:

- Improve life expectancy
- Reduce liver-related morbidity (HCC)
- Increase health-related quality of life

Regression of Hepatic Fibrosis



Paired liver biopsies of a single patient with HCV-induced cirrhosis

D'Ambrosio *Hepatology* 2012

Regression of Hepatic Fibrosis

- Largest histological study:
  - n=679 with ≥METAVIR F2
  - 2nd liver biopsy 24 weeks after treatment

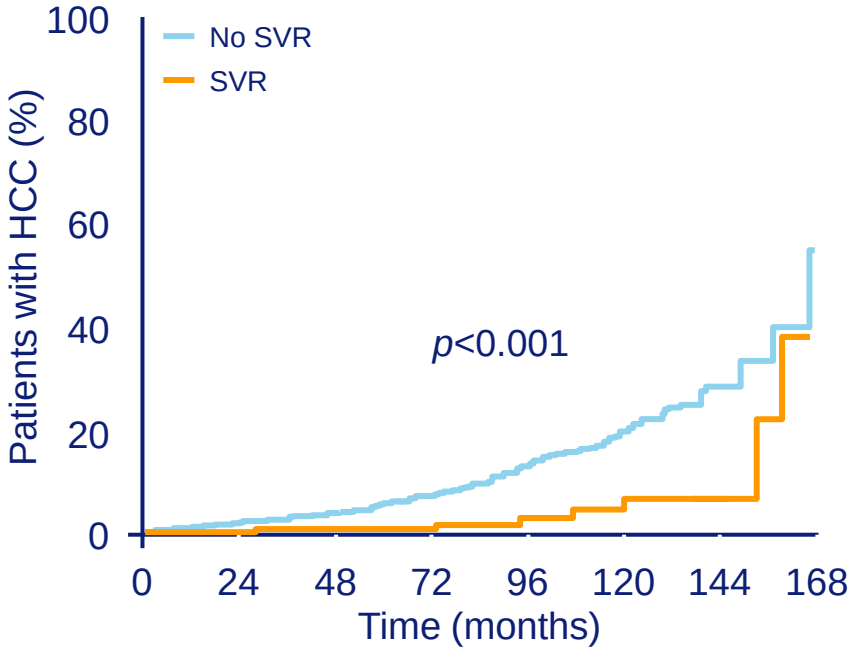
	Estimated fibrosis progression rate per year	
		During and after treatment
Groups	Number	Median (95% CI)
All patients	2579	0.0 (0;0)
F0/F1	1900	0.0 (0;0)
Sustained responders	771	0.0 (0;0)
Non-responders	1129	0.0 (0;0)
F2/F3/F4	679	–0.488 (–0.522;–0.491)
Sustained responders	210	–0.591 (–0.627;–0.550)
Non-responders	469	0 (–0.443;0)

- Regression of fibrosis in 75 of 153 (49%) patients with cirrhosis

CI: confidence interval; F: METAVIR fibrosis stage

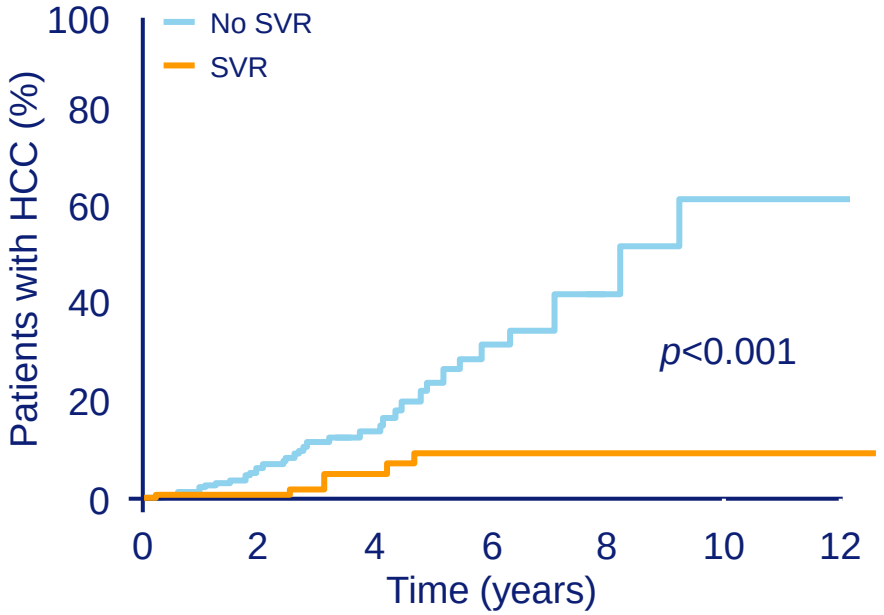
Poynard T, et al. Gastroenterology 2002;122:1303–13.

Reduced Incidence of HCC in case of SVR



No. at risk:

SVR	124	119	115	108	69	40	11
No SVR	759	699	640	541	359	221	41



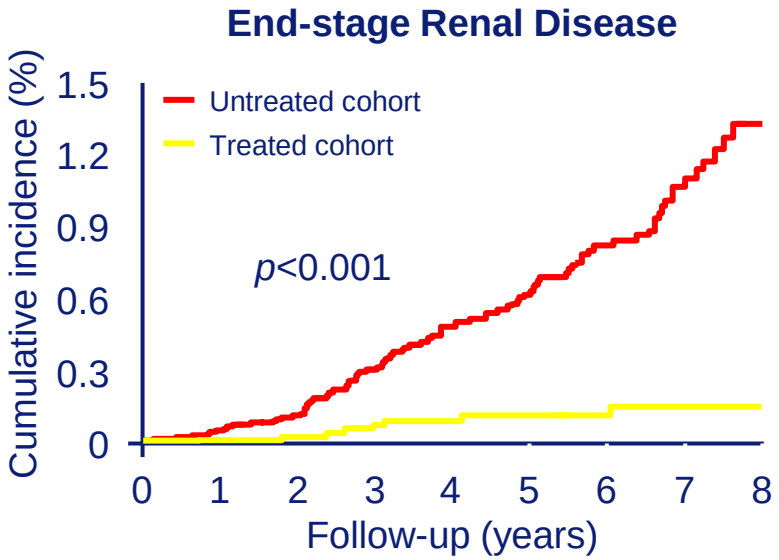
No. at risk:

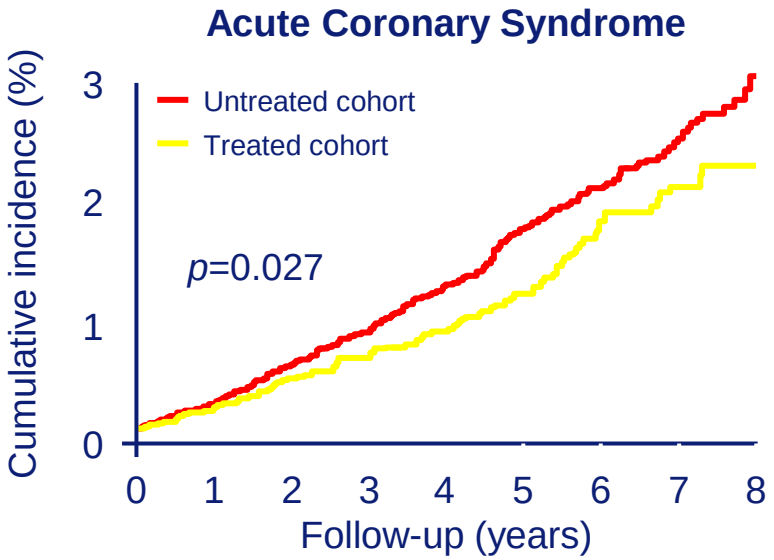
SVR	103	86	49	28	12	5	3
No SVR	204	151	73	28	8	5	3

- Bruno *Hepatology* 2007
  - 883 cirrhotic patients from Italy
  - Median follow-up 8.0 years
- Cardoso *J Hepatol* 2010
  - 307 cirrhotic patients from France
  - Median follow-up 3.5 years

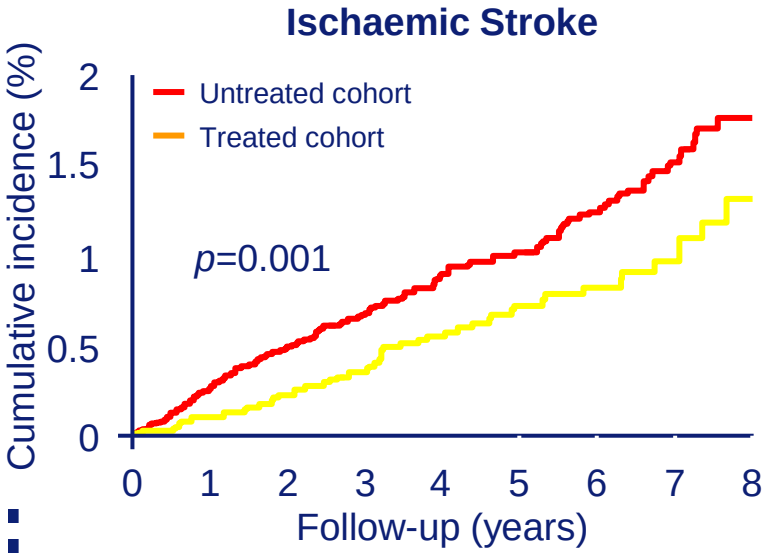
Bruno S, et al. Hepatology 2007;45:579–87;
Cardoso AC, et al. J Hepatol 2010;52:652–7.

Clinical Benefit Beyond the Liver





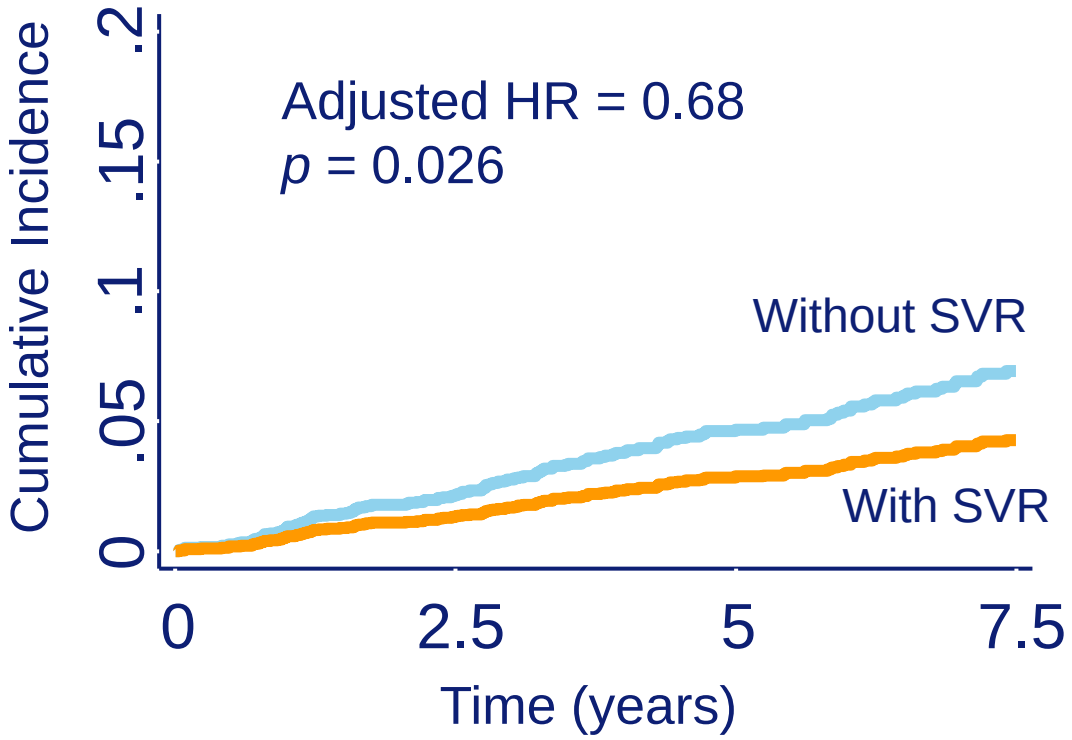
- Nationwide Taiwanese cohort study
  - 12,384 treated patients
  - 24,768 propensity score-matched untreated controls
  - Median follow-up: 3.3 years



Hsu YC, et al. Gut 2015;64:495–503.

Extrahepatic Mortality

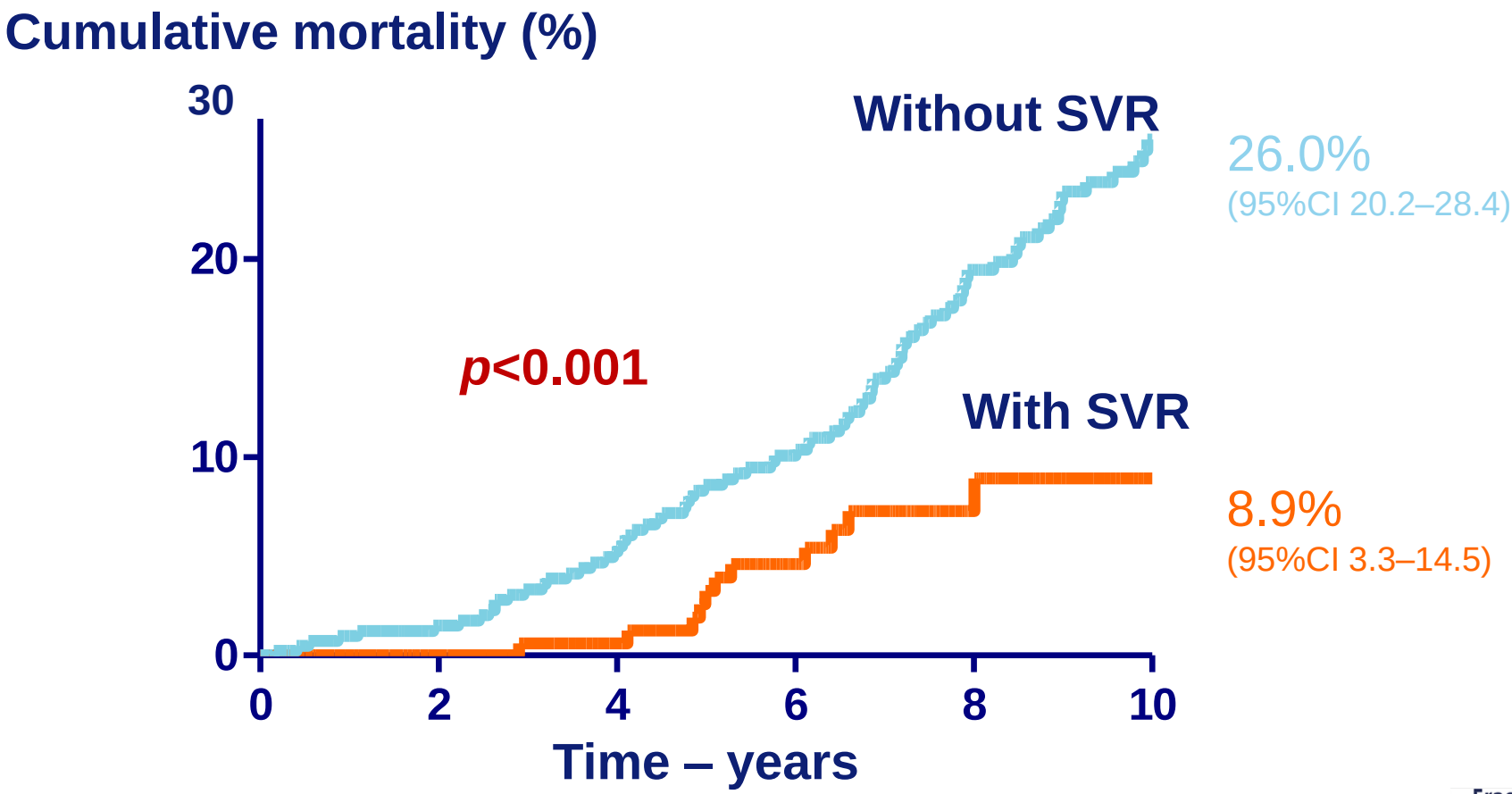
- Nationwide cohort study
- n = 3,385
  - *Expected to include over 80% of the HCV-infected population in Scotland*
- Various stages of fibrosis
- Median follow-up: 5.3 years



Innes *Hepatology* 2015

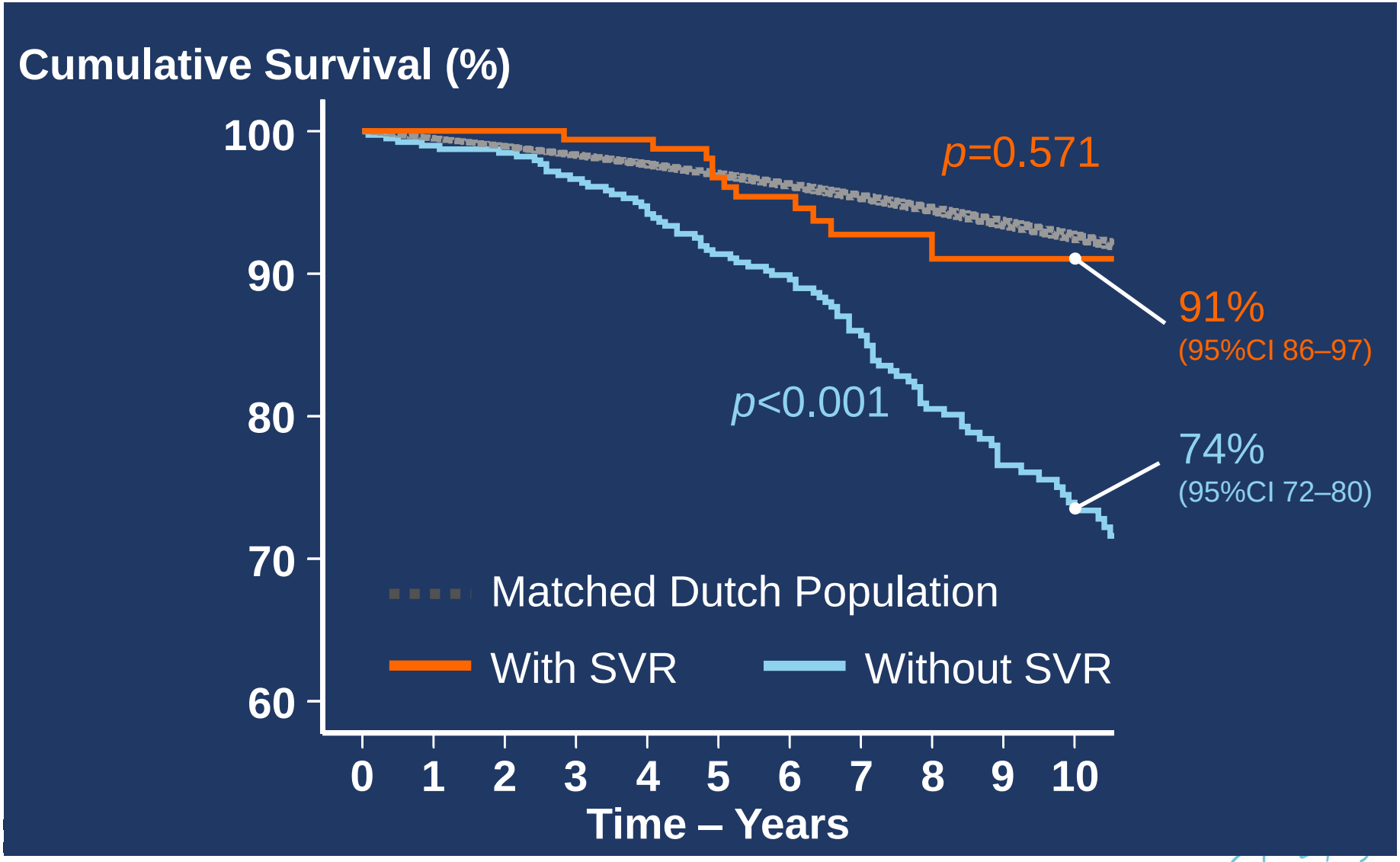
All-Cause Mortality According to Response in HCV Patients with Compensated Cirrhosis

- 530 patients with Ishak F4–6
- Median follow-up: 8.4 years



Van der Meer AJ, et al. JAMA 2012;308:2584–93.

Compared with the General Population



Van der Meer AJ, et al. JAMA 2014;312:1927–8.

Multivariate Cox Analysis

ALL-CAUSE MORTALITY	HR (95% CI)	*p*-value
SVR	**0.26** (0.14–0.49)	**<0.001**
Age (per year)	**1.09** (1.05–1.10)	**<0.001**
Male gender	**1.52** (0.93–2.48)	**0.09**
HCV genotype 3	**2.08** (1.18–3.66)	**0.01**
Fibrosis score		**0.020**
4	**ref.**	
5	**1.29** (0.60–2.77)	**0.52**
6	**1.87** (1.02–3.45)	**0.04**
Diabetes mellitus	**1.76** (1.02–3.01)	**0.04**
History of severe alcohol use	**2.20** (1.32–3.67)	**0.002**

SVR is included as a time-dependent covariate. The model is stratified for treatment centre and corrected for year treatment started.

Van der Meer AJ, et al. JAMA 2012;308:2584–93.

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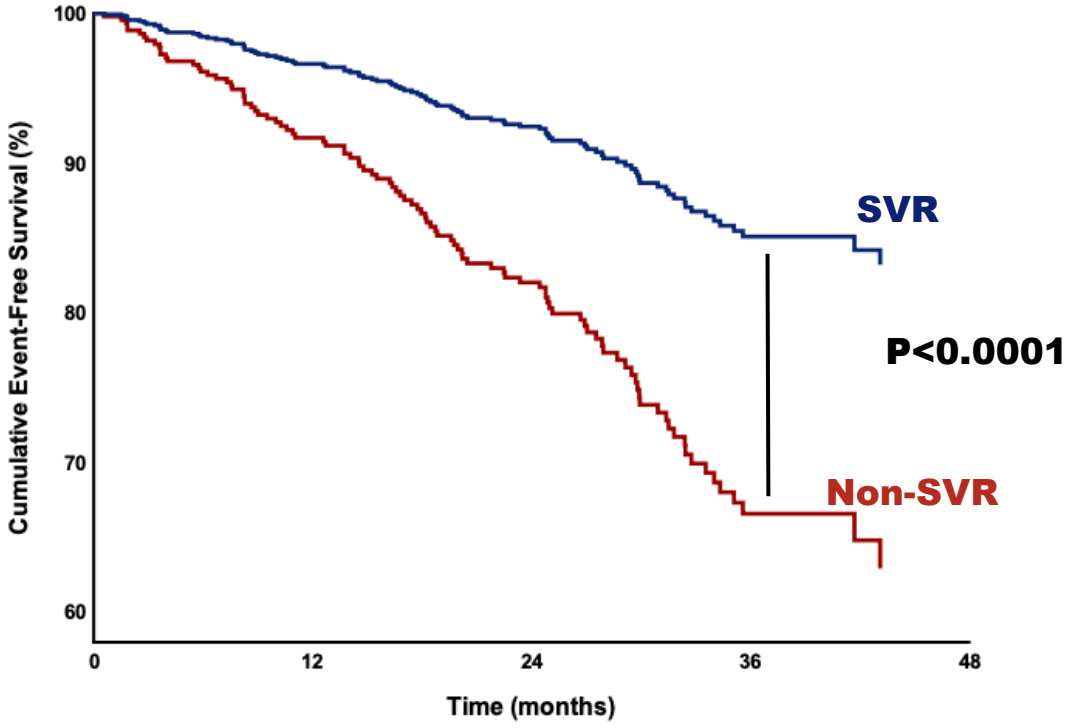
DAA era Event-Free Survival in Patients with CP-A Cirrhosis



	aHR (95% CI)	P-value
Age	1.05 (1.02-1.07)	0.0001
Male sex	1.43 (0.92-2.22)	0.11
Genotype 3	2.30 (1.41-3.76)	0.001
History of alcohol abuse	1.61 (1.00-2.59)	0.05
Albumin, g/L	0.94 (0.89-0.98)	0.003
Total Bilirubin, µmol/L	1.00 (0.98-1.03)	0.87
Platelet count, $10*10^9$/L	0.99 (0.95-1.03)	0.50
SVR	**0.40 (0.25-0.63)**	**0.0001**

Krassenburg et al. AASLD 2019.

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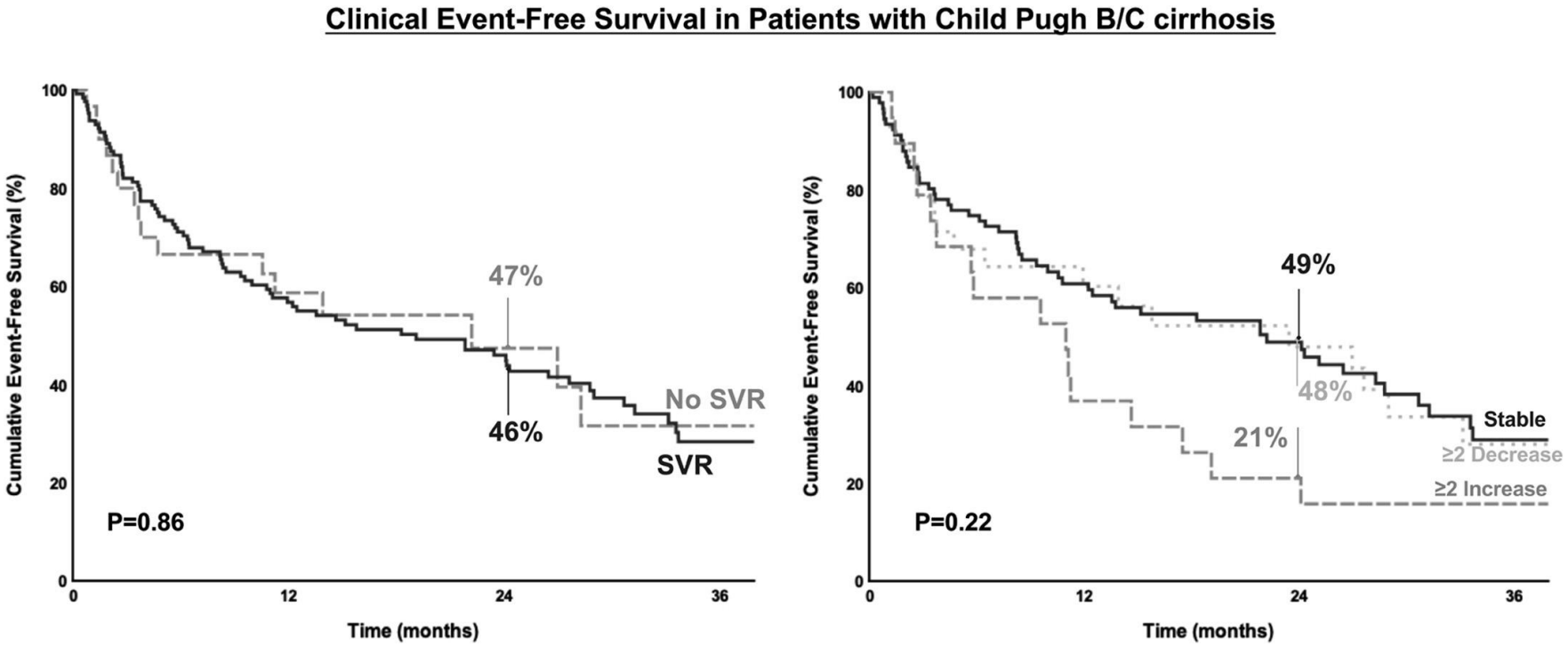
SVR is Not Associated with an Improved Event-Free Survival in Patients with CP-B/C Cirrhosis



Krassenburg et al. Journal of Hepatology. 2020

Treatment of HCV patients with decompensated cirrhosis

Advantages

- Improvement of biochemistry
- Reduction of mortality on LTx-waiting list
- Possibility of concomitant HCC treatment

Disadvantages

- Less urgent of LTx waiting list as MELD score goes down
- Lower SVR compared to Tx after LTx
- More side-effects

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Chronische Hepatitis C
Een Behandelbare Infectieziekte?

Ja!

What's next?

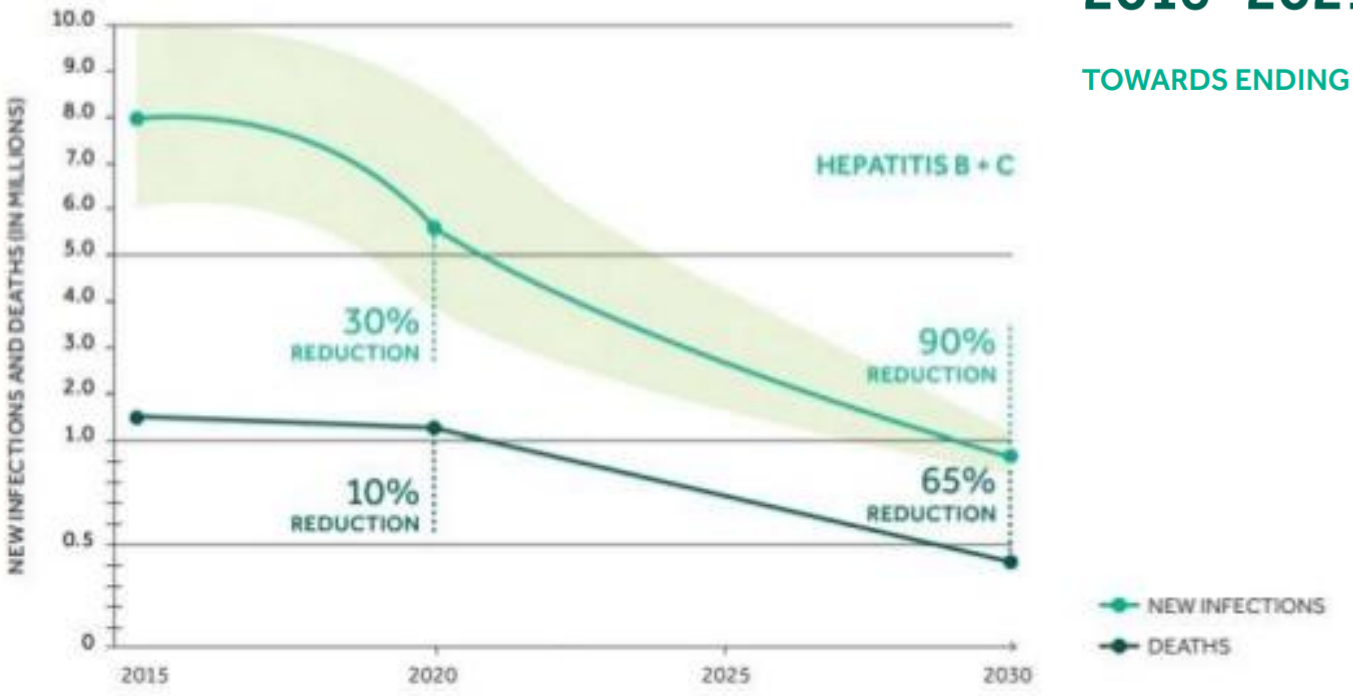
World Health Organization

GLOBAL HEALTH SECTOR STRATEGY ON
VIRAL HEPATITIS 2016–2021

TOWARDS ENDING VIRAL HEPATITIS

WHO target

Elimination of viral hepatitis by 2030



Erasmus MC

National hepatitis plan

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Heropsporing HCV: CELINE

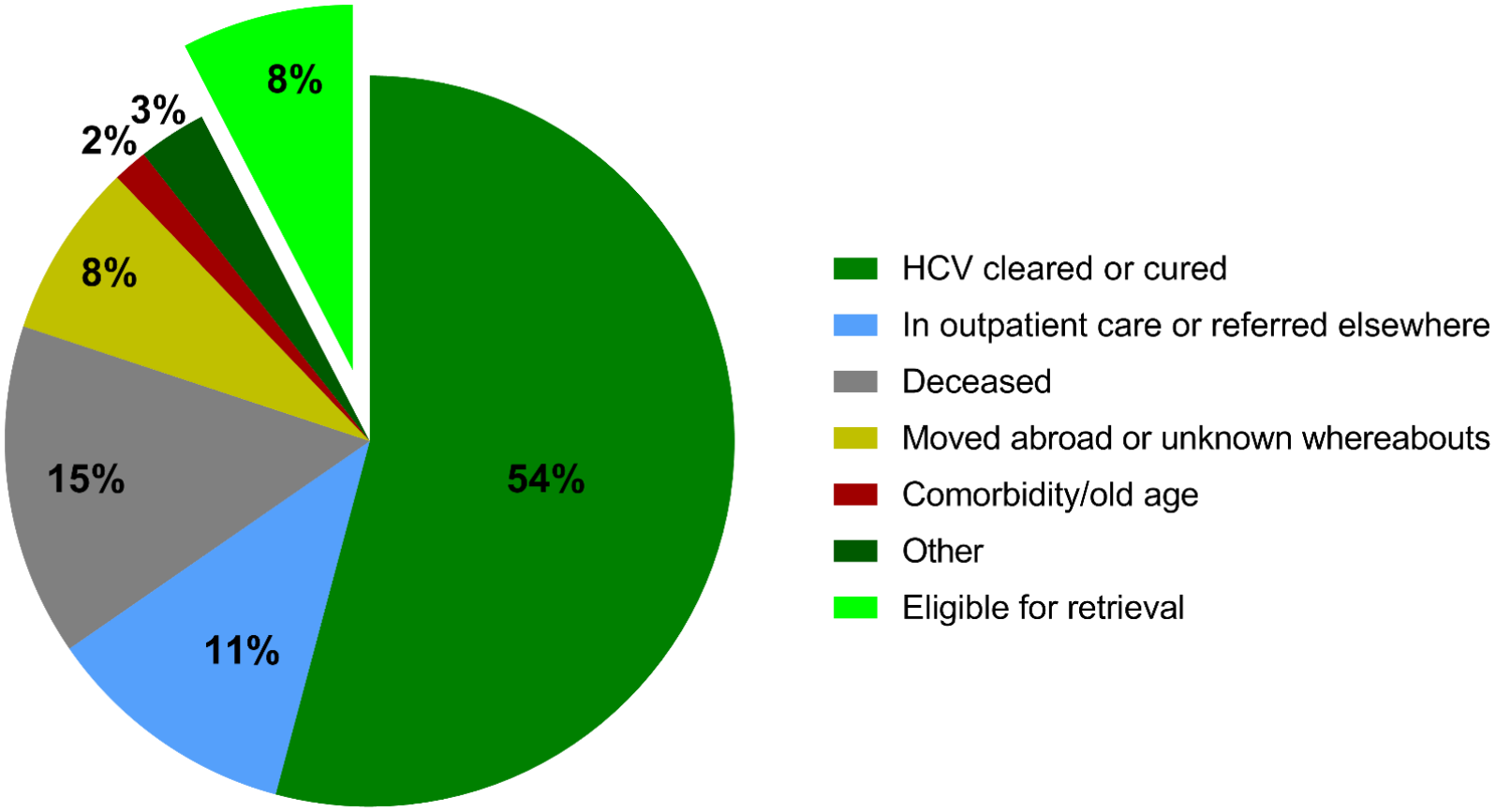
(Hepatitis C Elimination in the NEtherlands)

CELINE

2018 – 2022

Gecoördineerd vanuit 3 UMC regio's

Outcome of 20.183 anti-HCV positive patients, identified in 45 centers



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HCV behandeling anno 2022

Antivirale middelen:

Glecaprevir/pibrentasvir

Sofosbuvir/velpatasvir

Sofosbuvir/velpatasvir/voxilaprevir

Hulpmiddelen:

HCV-Richtsnoer

HCV TherapySelector

Liverpool HEP Drug interactions

(Lever-elastografie/Fibroscan)

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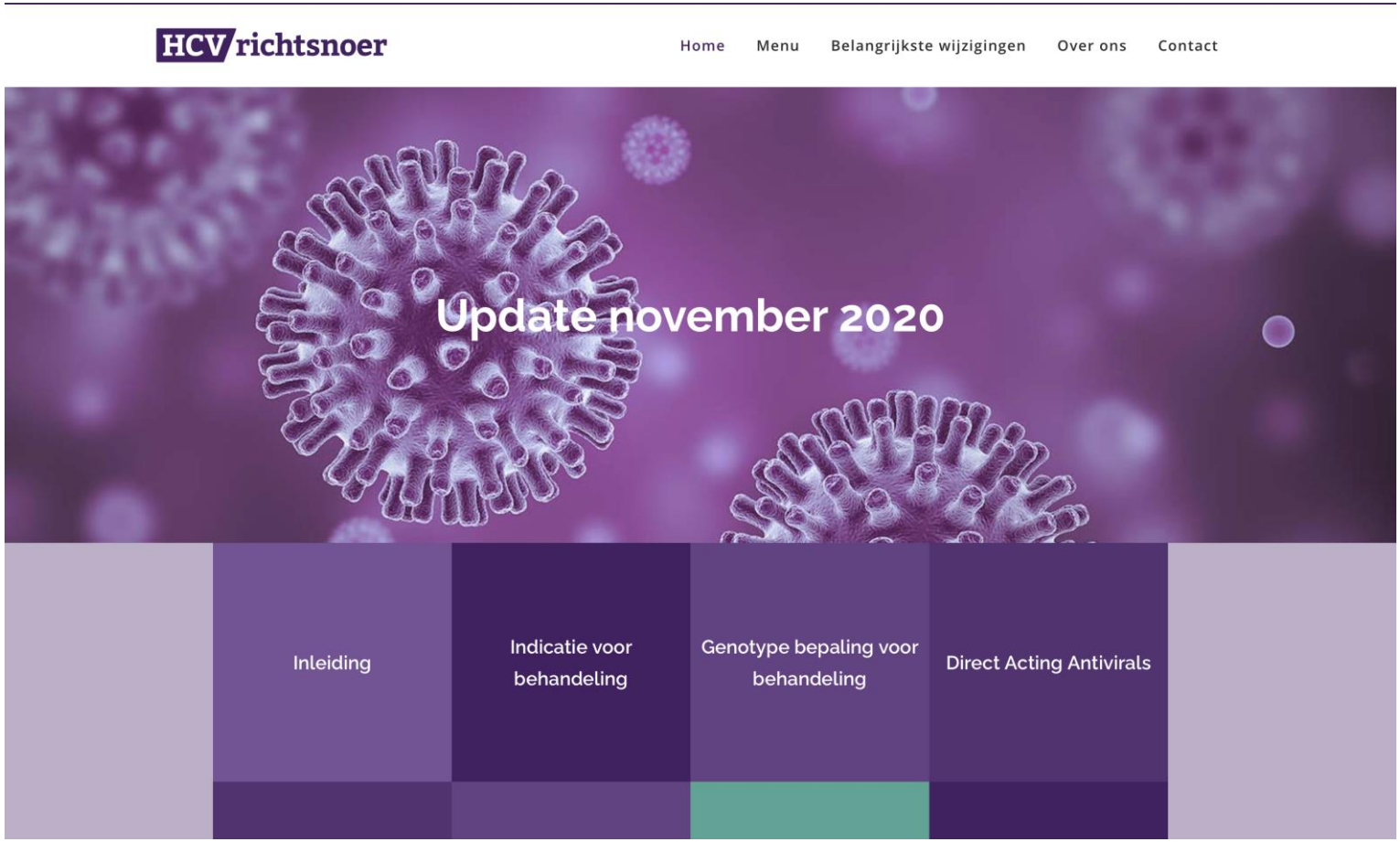
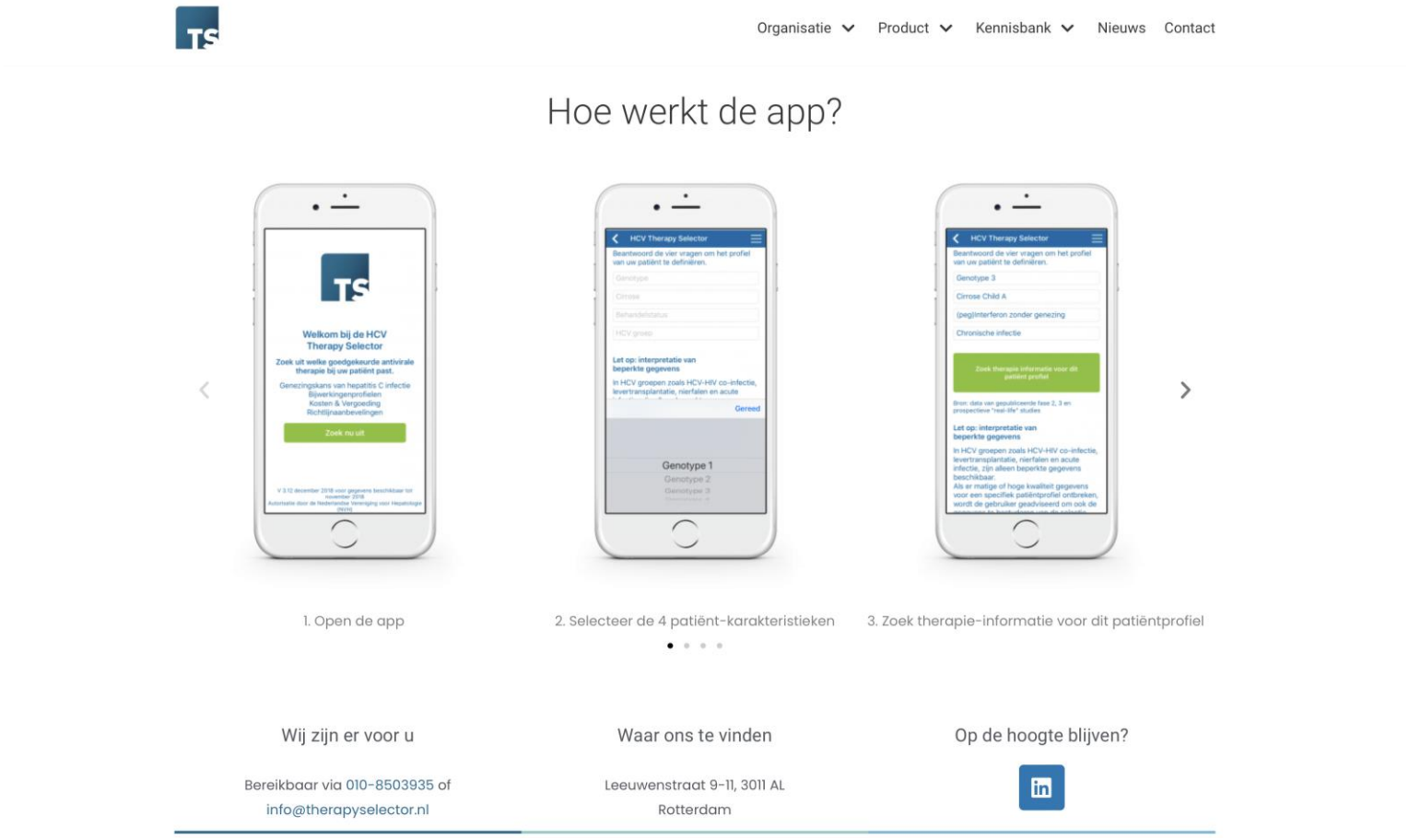
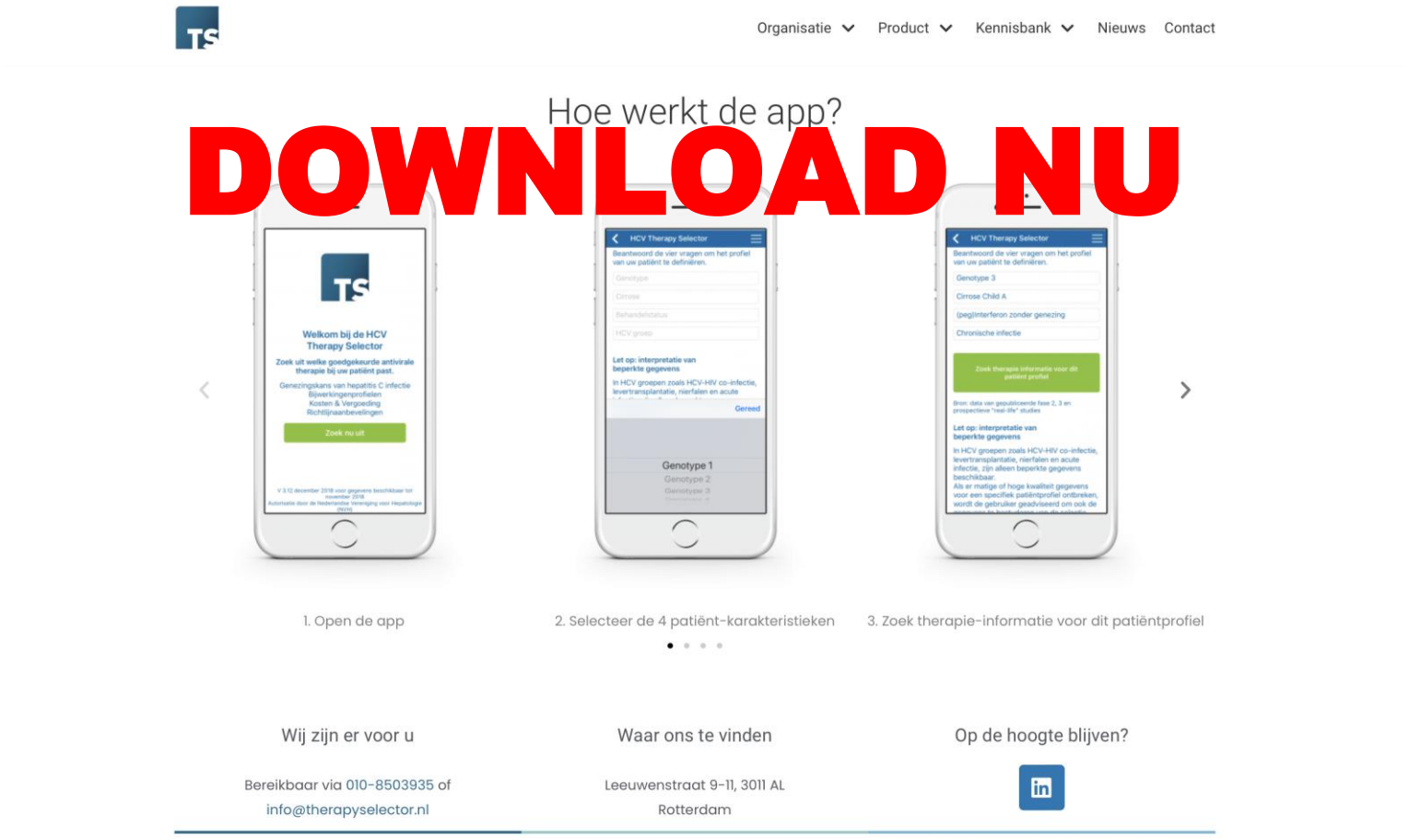
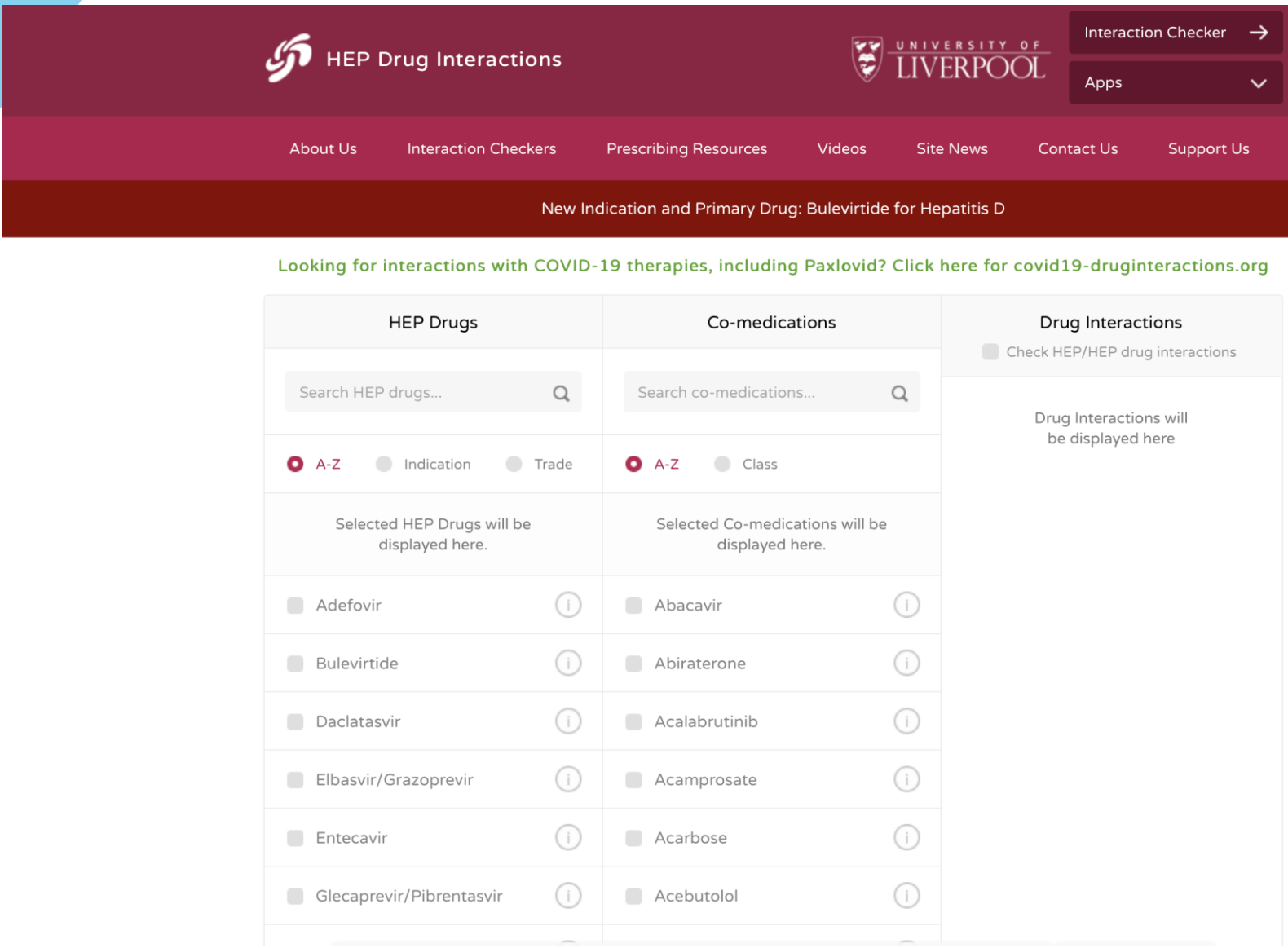

HCV richtsnoer
Home
Menu
Belangrijkste wijzigingen
Over ons
Contact
Update november 2020
Inleiding
Indicatie voor behandeling
Genotype bepaling voor behandeling
Direct Acting Antivirals

App store: Therapyselector



App store: Therapyselector




HEP Drug Interactions
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Interaction Checker
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New Indication and Primary Drug: Bulevirtide for Hepatitis D
Looking for interactions with COVID-19 therapies, including Paxlovid? Click here for covid19-druginteractions.org
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Co-medications
Drug Interactions
Check HEP/HEP drug interactions
Search HEP drugs...
Search co-medications...
Drug Interactions will be displayed here
A-Z
Indication
Trade
A-Z
Class
Selected HEP Drugs will be displayed here.
Selected Co-medications will be displayed here.
Adefovir
Bulevirtide
Daclatasvir
Elbasvir/Grazoprevir
Entecavir
Glecaprevir/Pibrentasvir
Abacavir
Abiraterone
Acalabrutinib
Acamprosate
Acarbose
Acebutolol

HBV-HCV coinfection

Recommendations	Grade of evidence	Grade of recommendation
Treat with the same anti-HCV regimens, following the same rules as HCV monoinfected patients	B	1
Patients fulfilling the standard criteria for HBV treatment should receive NA treatment according to EASL 2017 CPG on the management of HBV infection	A	1
Patients who are HBsAg+ should receive NA prophylaxis at least until Week 12 post anti-HCV therapy and be monitored monthly if HBV treatment is stopped	B	1
In patients who are HBsAg–, anti-HBc Ab+ on anti-HCV therapy • Monitor serum ALT levels monthly • Test HBsAg and HBV DNA if ALT levels do not normalise or rise • Initiate NA therapy if HBsAg and/or HBV DNA are present	B	1

EASL CPG HCV. J Hepatol 2018;69:461–511.

Immune-complex mediated manifestations of CHC

Recommendations	Grade of evidence	Grade of recommendation
Mixed cryoglobulinaemia and renal disease associated with CHC must be treated with IFN-free, RBV-free DAA-based anti-HCV combinations, according to the above recommendations	B	1
Careful monitoring for adverse events is mandatory	B	1
The indication for RTX in HCV-related renal disease must be discussed by a MDT	B	1
HCV-associated lymphoma should be treated with IFN-free, RBV-free DAA regimens according to the above recommendations, in combination with specific chemotherapy, taking into account possible DDIs	B	1

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EASL CPG HCV. J Hepatol 2018;69:461–511.

Patients with renal impairment, including haemodialysis

Recommendations	Grade of evidence	Grade of recommendation
Mild to moderate renal impairment (eGFR ≥30 mL/min/1.73 m²)		
• Treat according to the general recommendations • No dose adjustments are needed • Patients should be carefully monitored	A	1
Severe renal impairment (eGFR <30 mL/min/1.73 m² or ESRD*)		
• Treat in expert centres with close monitoring by a MDT	B	1
• GLE/PIB for 8 or 12 weeks (all GT)	A	1
• GZR/EBR for 12 weeks (GT 1a, 1b and 4)†	A	1
• OBV/PTV/r + DSV for 12 weeks (GT 1b)	A	1
• Use SOF with caution, only if an alternative treatment is not available	B	1
• Risk/benefit of treating patients with ESRD and an indication for kidney transplant before or after renal transplantation require individual assessment	B	1

*ESRD on haemodialysis (CKD stage 4/5) without an indication for liver transplant; †With HCV RNA level ≤800,000 IU/mL (GT 1a/4)

EASL CPG HCV. J Hepatol 2018;69:461–511.

Non-hepatic solid organ transplant recipients*

Recommendations	Grade of evidence	Grade of recommendation
Treat HCV infection before or after transplantation, provided that life expectancy exceeds 1 year	A	1
Before transplantation, while on waiting list, patients can receive HCV treatment according to general recommendations for GT, liver disease severity and prior anti-HCV treatment	A	1
After transplantation, • Treat with fixed-dose SOF/LDV (GT 1, 4, 5 and 6) or SOF/VEL (all GT) according to the general recommendations† • Treat patients with an eGFR <30 mL/min/1.73 m^2 with GLE/PIB for 12 weeks‡	A B	1 1

*Including kidney, heart, lung, pancreas or small bowel recipients;
†Without the need for immunosuppressant drug dose adjustments;
‡Immunosuppressant drug levels need to be monitored and adjusted as needed during and after EOT
EASL CPG HCV. J Hepatol 2018;69:461–511.

Recipients of an HCV+ organ transplant

Recommendations	Grade of evidence	Grade of recommendation
Organs from anti-HCV Ab+, HCV RNA+ donors can be transplanted to HCV RNA+ recipients	B	1
Use of anti-HCV Ab+, HCV RNA+ organs for HCV RNA– recipients is possible, provided that: • It is allowed by local regulations • Rigorous informed consent is obtained • Rapid post-transplant DAA therapy is guaranteed	C	2
Use of liver grafts with moderate (F2) or advanced (F3) fibrosis is not recommended	B	2

EASL CPG HCV. J Hepatol 2018;69:461–511.

Take home messages

Chronic HCV infection may lead to cirrhosis, at which stage patients are at risk of hepatic decompensation and HCC

Patients with chronic HCV infection have an impaired overall survival due to an increase in liver-related as well as liver-unrelated mortality

Diagnosing chronic HCV infection can be challenging as symptoms are lacking and liver enzymes may be normal

In HCV-infected patients with compensated liver disease:

- The rate of SVR with DAAs is almost 100%
- SVR is associated with an improved survival

In HCV-infected patients with decompensated liver disease

- The rate of SVR with DAAs is approximately 80%
- The clinical benefit of SVR in this population remains to be determined..

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Chronische Hepatitis C
Een Behandelbare Infectieziekte?

JA !