

The Natural History of HCV Infection

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Disclosures

- K.B. Kielland has given sponsored lectures for MSD and AbbVie

The natural history of hepatitis C

- Spontaneous clearance
- Progression of liver fibrosis
- All-cause and liver-related mortality
- Extrahepatic manifestations
- Disease progression in the era of direct-acting antivirals (DAA)

- Main focus will be on people who inject drugs (PWID)

Spontaneous clearance

- Spontaneous clearance is found between 15% and 40%, significant difference between studies
- A meta-analysis of 31 studies with a total of 675 subjects with acute hepatitis C concluded with a weighted mean of 26% spontaneous clearance
- Spontaneous clearance usually occurs the first 6 months, but retarded clearance may happen during some few years

Micallef JM, Kaldor JM, Dore GJ. J
Viral Hepat 2006; 13(1):34-41

Spontaneous clearance

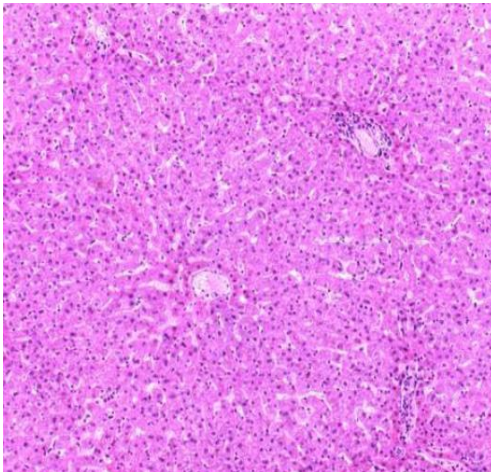
Increased clearance	Reduced clearance
Female gender	Male gender
Age < 35 years	Age >35 years
Symptomatic acute HCV infection	No acute symptoms
HBV co-infection	HIV co-infection
Complicated interaction between a long list of genetic factors	

Micallef JM, Kaldor JM, Dore GJ.. J Viral
Hepat 2006; 13(1):34-41

Classification of the progression of liver fibrosis in hepatitis C

Biopsies: Metavir stages F0–F4

Normal liver
F0



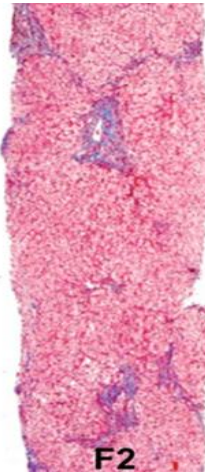
Amar Paul Dhillon, UCL Medical School Royal Free Campus, London

F1



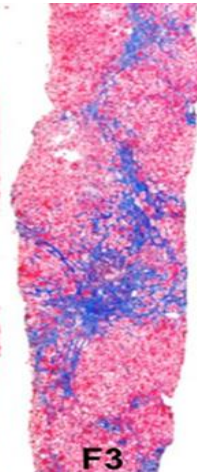
F1

F2



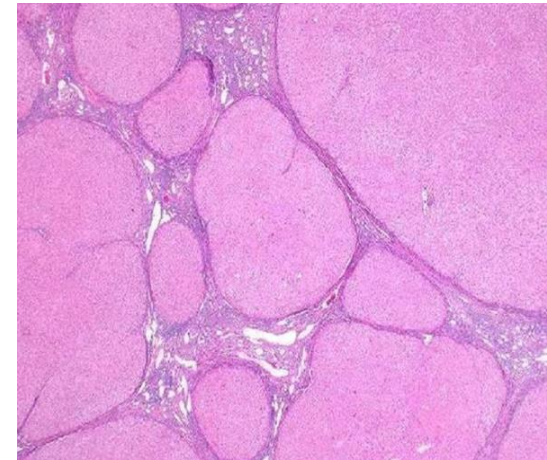
F2

F3



F3

Cirrhosis
F4



Shashidhar Venkatesh Murthy,

F1 = portal fibrosis without septa
F2 = portal fibrosis with few septa
F3 = numerous septa without cirrhosis
(septal or bridging fibrosis)

Elastography

Mean duration of Metavir stages

A meta-analysis concluded with the following mean progression time through the Metavir stages

- F0–F1: 9 years
- F1–F2: 12 years
- F2–F3: 12 years
- F3–F4: 8 years
- F0–F4: 40 years

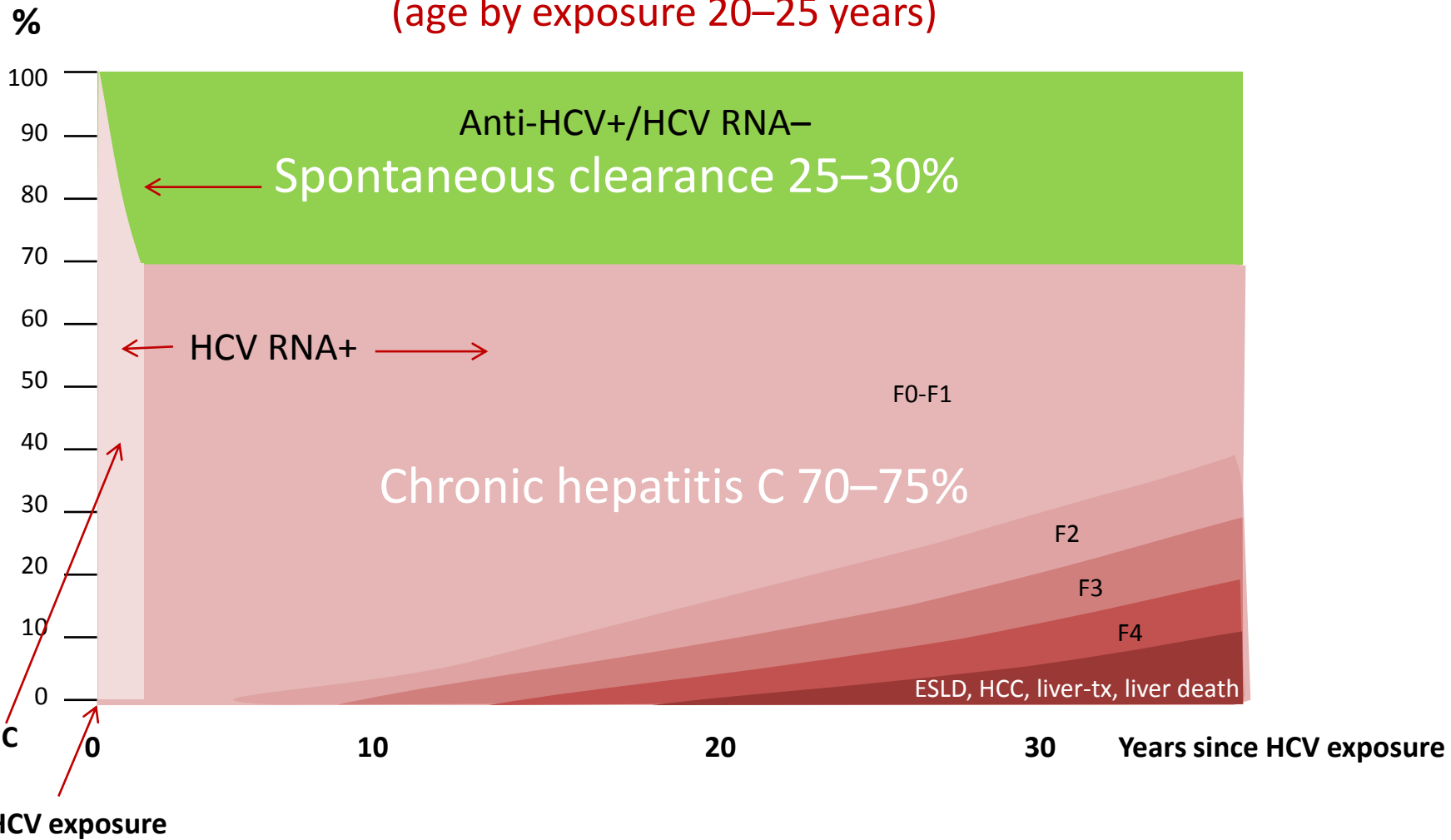
Conclusions:

- For probable more than half the patients the progression is very slow (“non-fibrosing”)
- For at least 1/3 it is much more rapid.

Thein HH, Yi Q, Dore GJ, Krahn MD. *Hepatology* 2008; 48(2):418-431.

The natural course of liver disease in chronic hepatitis C

(age by exposure 20–25 years)



Factors which may increase or reduce fibrosis progression

Host factors

Male gender

High age at exposure

Untreated co-infection HIV

Untreated co-infection HBV

Overweight/steatosis/NASH

Insulin resistance/
metabolic syndrome/DM2

Genetic and other factors

External factors

Alcohol

(Tobacco)

(Cannabis)

Coffee (reduced fibrosis?)

Chocolate (reduced fibrosis?)

Viral factors

Genotype 3

Genetic variability

HCV RNA quantity

Cirrhosis

- Cirrhosis:
 - Annual risk of liver cancer (HCC): 1–5%
 - Annual risk of hepatic failure (decompensation): 3–6% (variceal hemorrhage, ascites, encephalopathy)
- Decompensated cirrhosis:
 - Risk of death the following year 15–20%

Westbrook RH, Dusheiko G.. J Hepatol. 2014 Nov;61(1 Suppl):S58-68.

Thein HH, Yi Q, Dore GJ, Krahn MD. Hepatology 2008;48:418–431.

Natural course of injecting drug use

Meta-analyses of mortality:

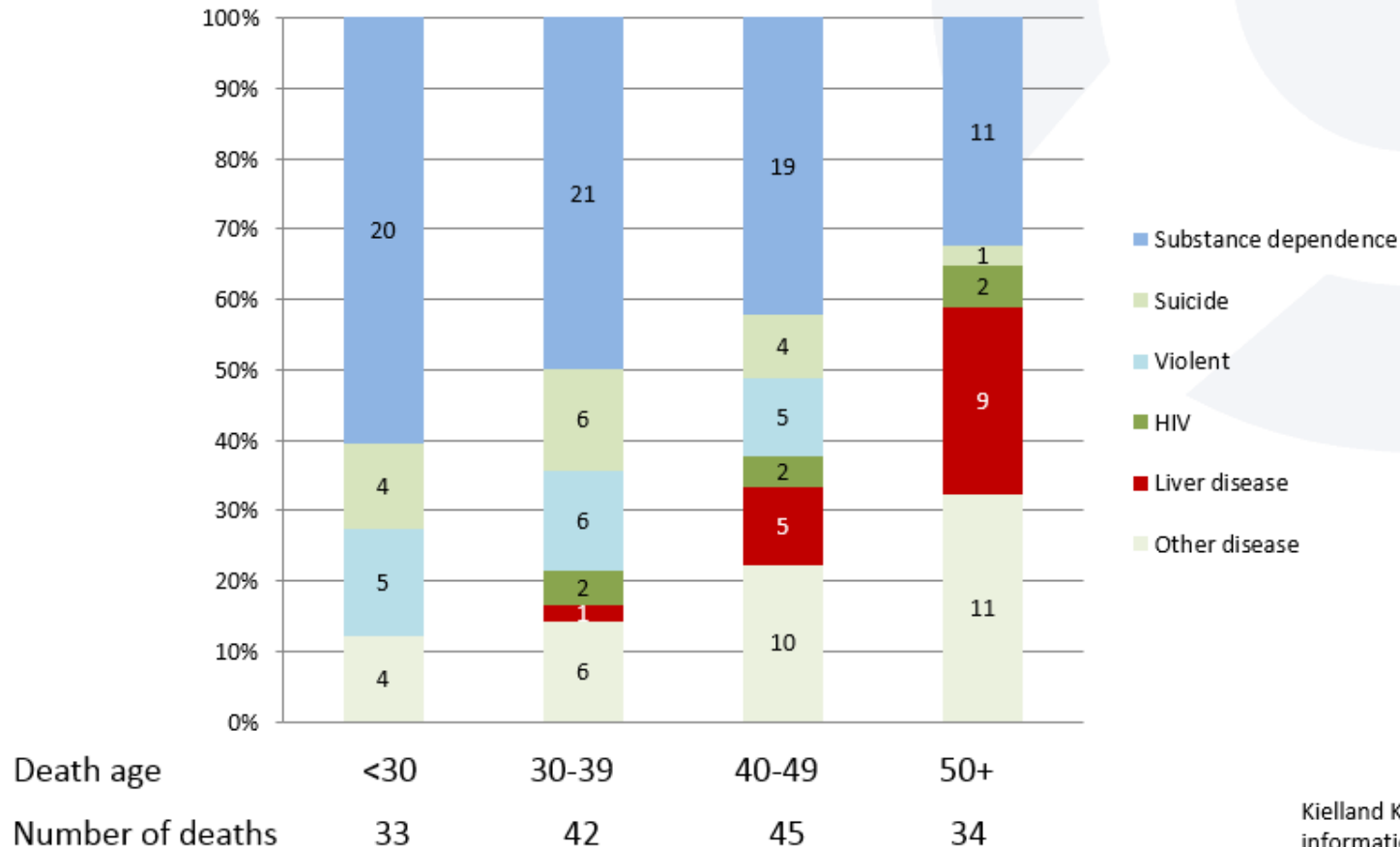
- People who inject drugs:
 - ✓ Mortality rate: **2.3**/100PY.
 - ✓ Standard mortality rate: **15**
 - ✓ Main causes of deaths: **Overdose and HIV**

Mathers. Bull World Health Organ 2013

- Dependent users of heroin/other opioids:
 - ✓ Mortality rate: **2.1**/100PY
 - ✓ Standard mortality rate: **15**
 - ✓ Main cause of death: **Overdose**

Degenhardt. Addiction 2011

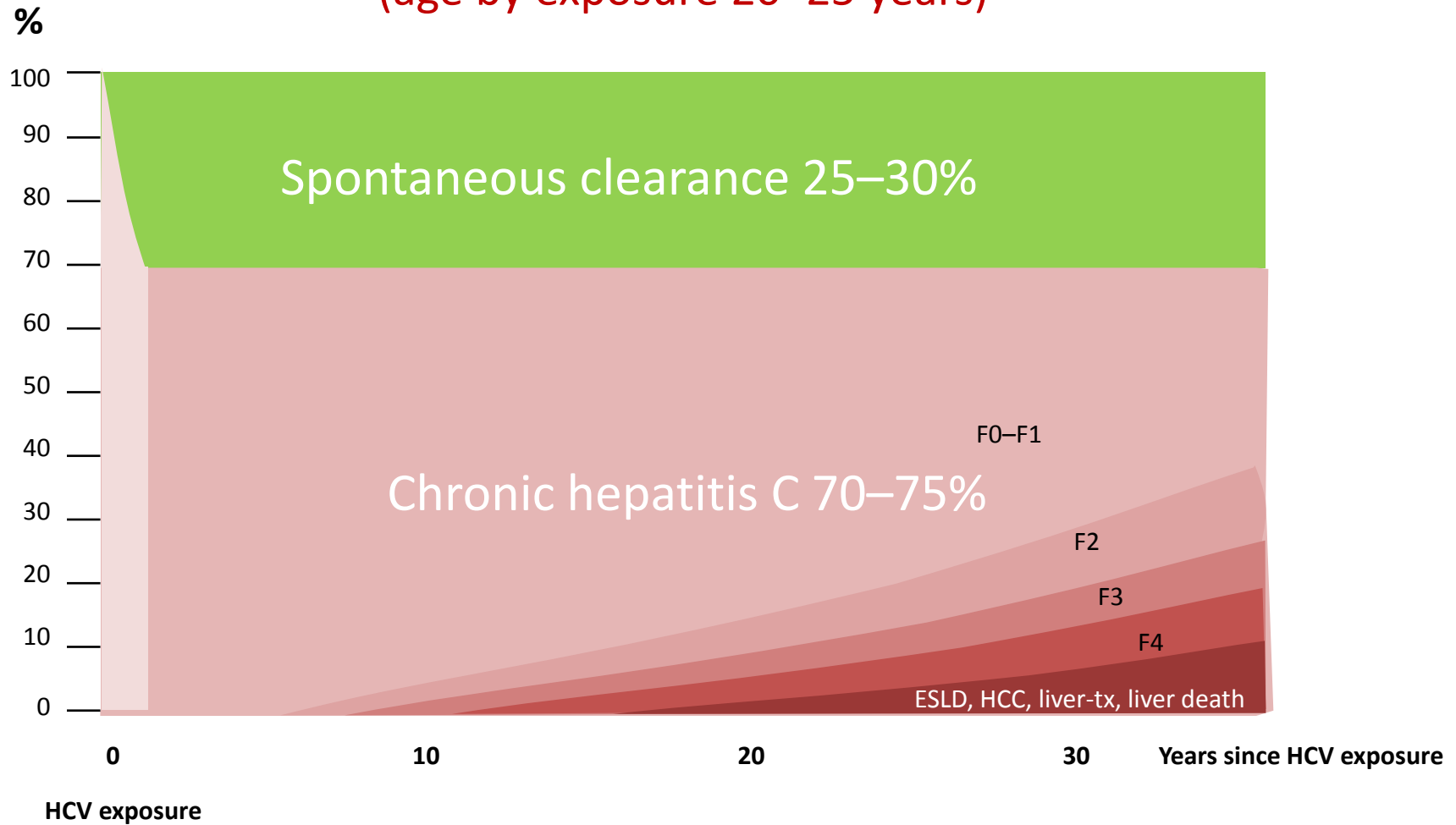
Causes of death among PWID with chronic hepatitis C according to death age



Kielland KB, unpublished information

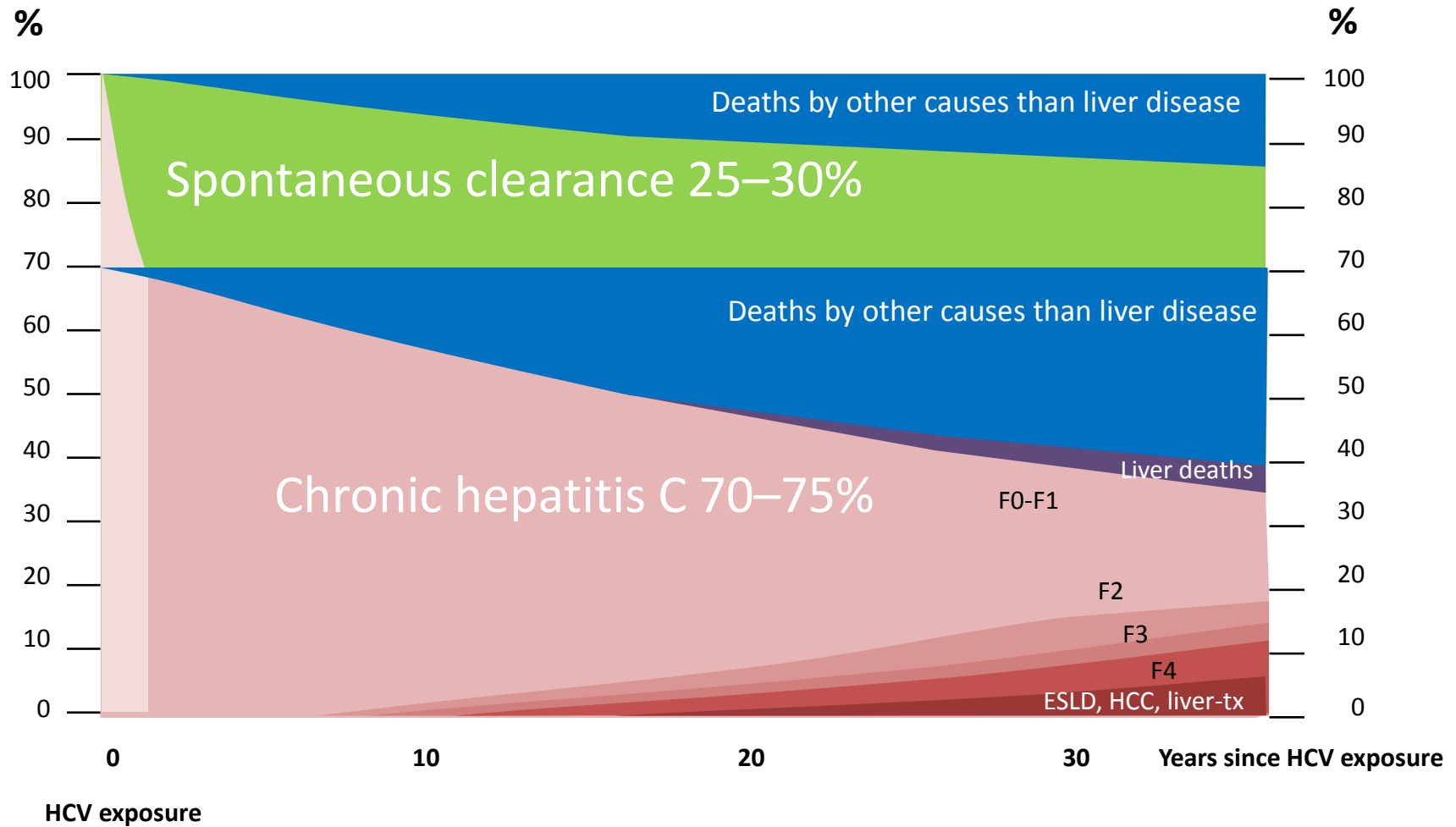
Natural course of chronic hepatitis C

(age by exposure 20–25 years)

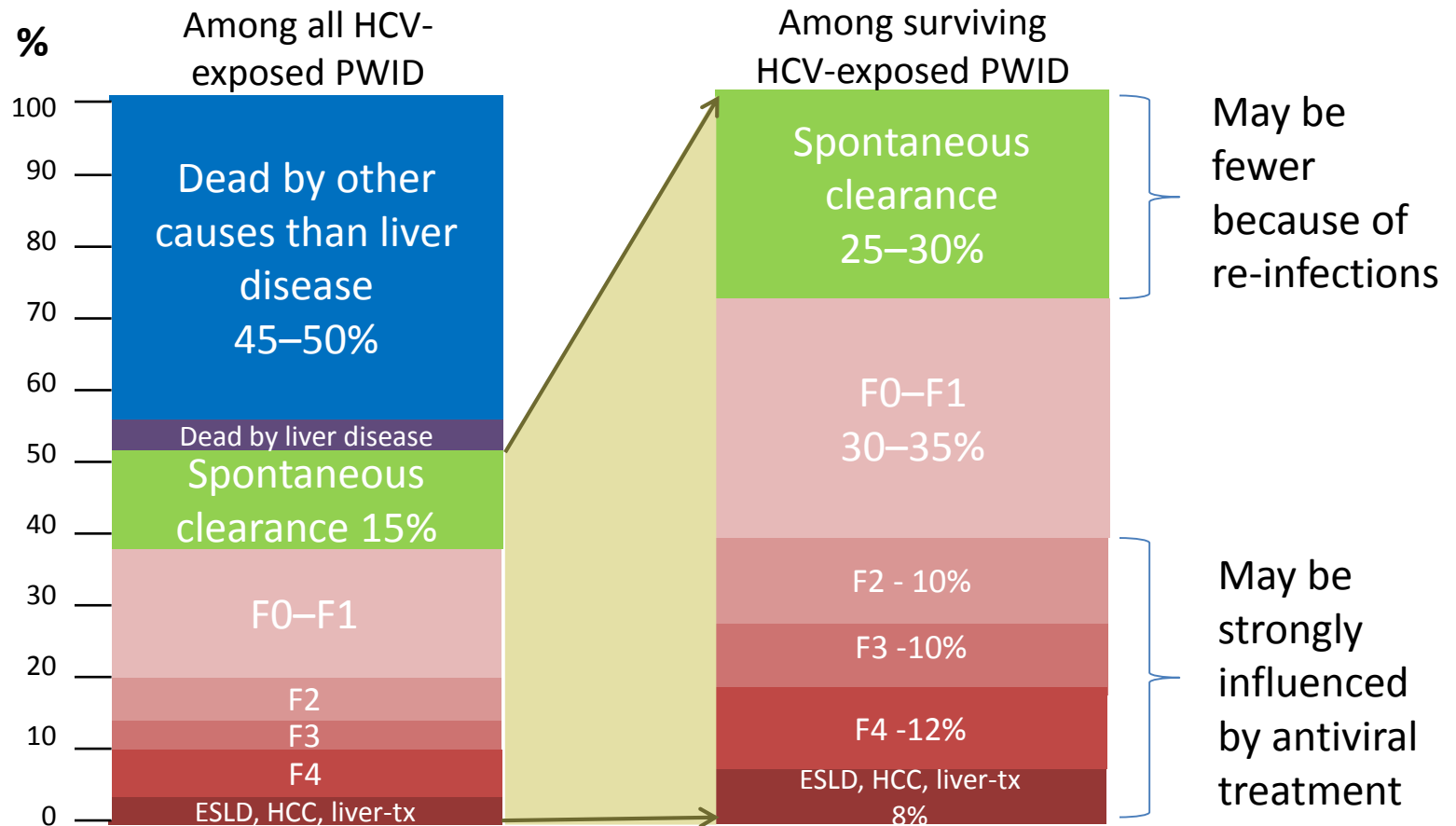


Natural course of chronic hepatitis C in PWID

(age by exposure 20–25 years)



Estimated situation for anti-HCV positive PWID at age 50–60 years – about 30–35 years after HCV exposure



Extrahepatic manifestations

Certain associations with HCV:

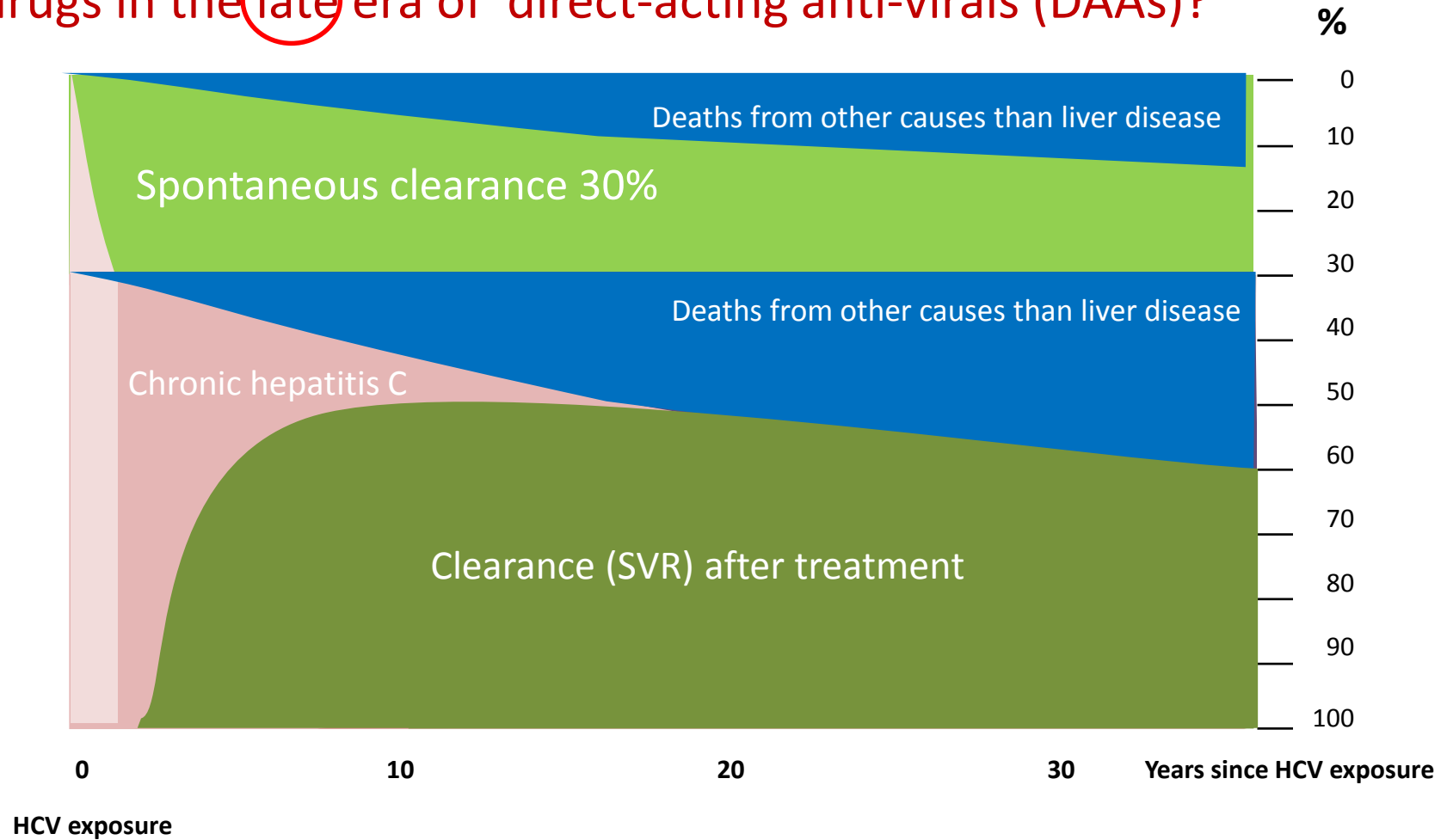
- Cryoglobulinemia
 - >50% (mostly low levels without clinical consequences)
 - Prevalence increases with age, and in Europe higher in the south than in the north
 - Skin disease (<5%)
 - Kidney disease (glomerulonephritis)
 - Peripheral neuropathy
- Non-Hodgkin lymphoma, relative risk 2.0-2.5

Extrahepatic manifestations

Possibly or probably associated with HCV:

- Diabetes mellitus type 2
- Some autoimmune diseases
- Fatigue, depression secondary to the chronic inflammation
- Vascular disease?
- Brain affection directly associated with virus replication in the brain?
 - Impaired cognitive function? Depression? Fatigue?

Natural course of chronic hepatitis C in people who inject drugs in the late era of direct-acting anti-virals (DAAs)?



Conclusions

- 30–40% of PWID with CHC will develop advanced liver fibrosis/cirrhosis within 25–40 years
- After age 40–50 years, liver disease becomes an increasingly important cause of death
- Among PWID under 40–50 years of age, other causes of death dominate
- Direct-acting antivirals may eliminate both the burden of liver disease and liver-related mortality