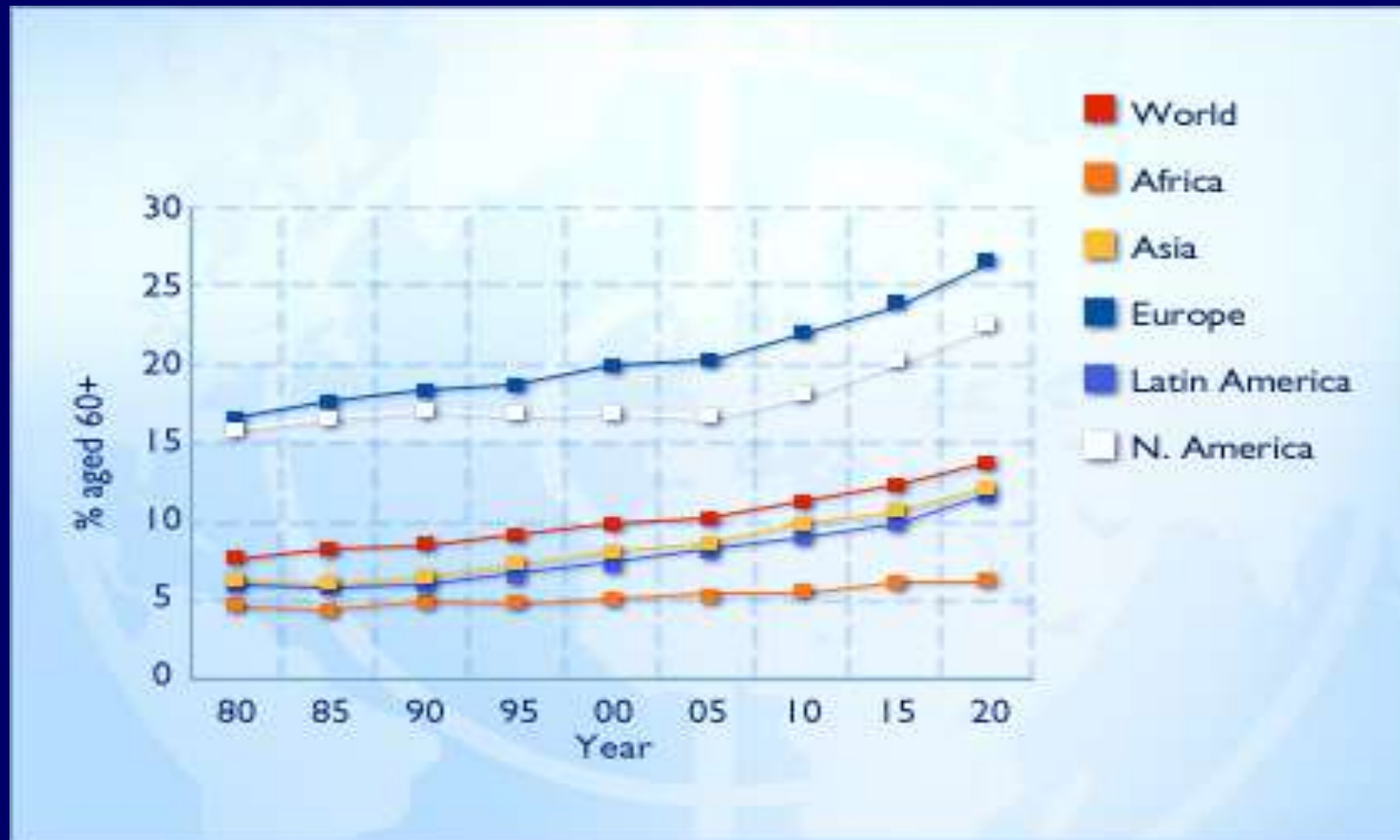# Should Elderly CHC Patients (>70 years old) be Treated?

Deepak Amarapurkar

Consultant Gastroenterologist & Hepatologist
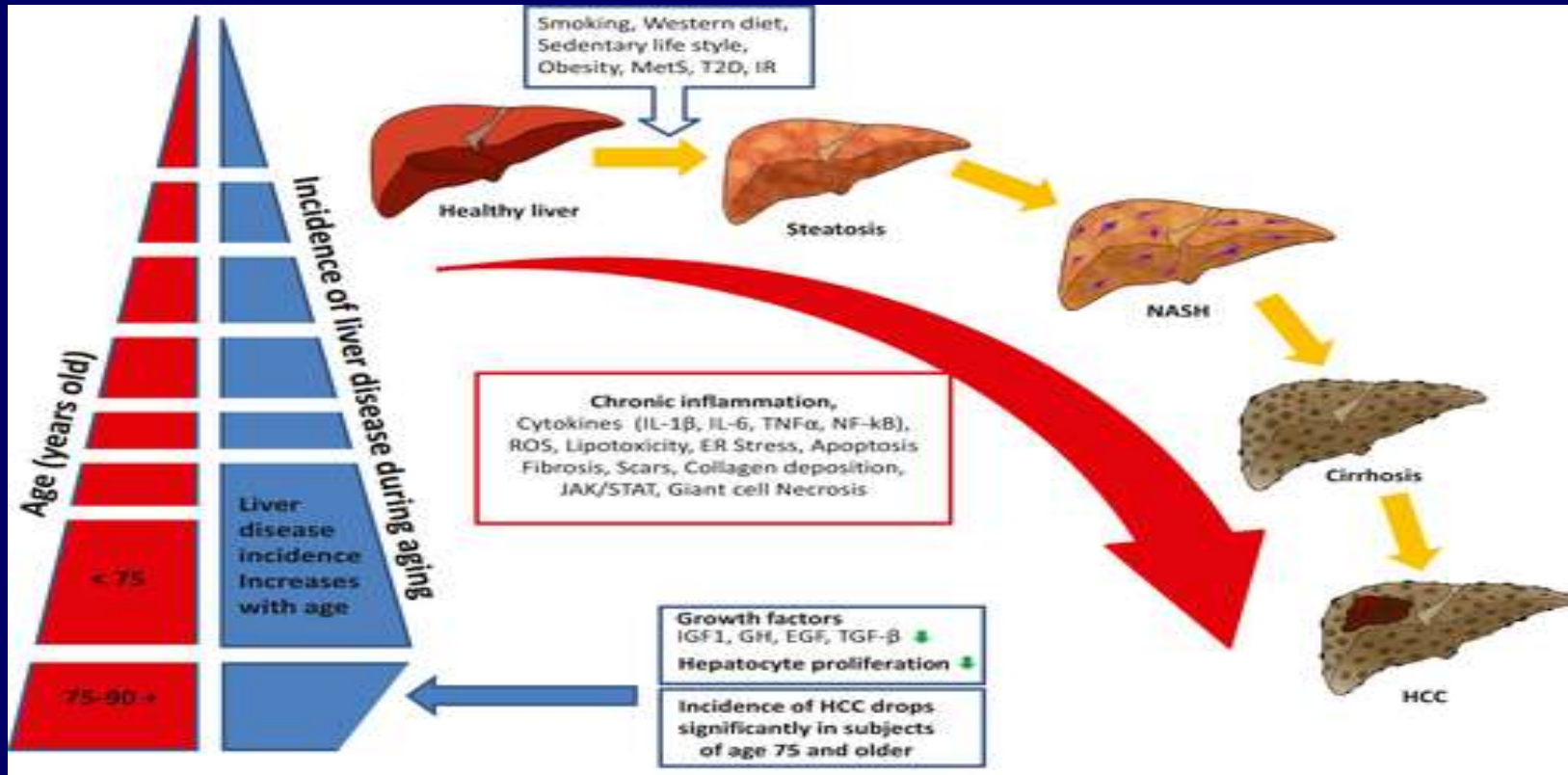
Bombay Hospital & Medical Research Center, Mumbai & Jagjivanram Western Railway Hospital, Mumbai

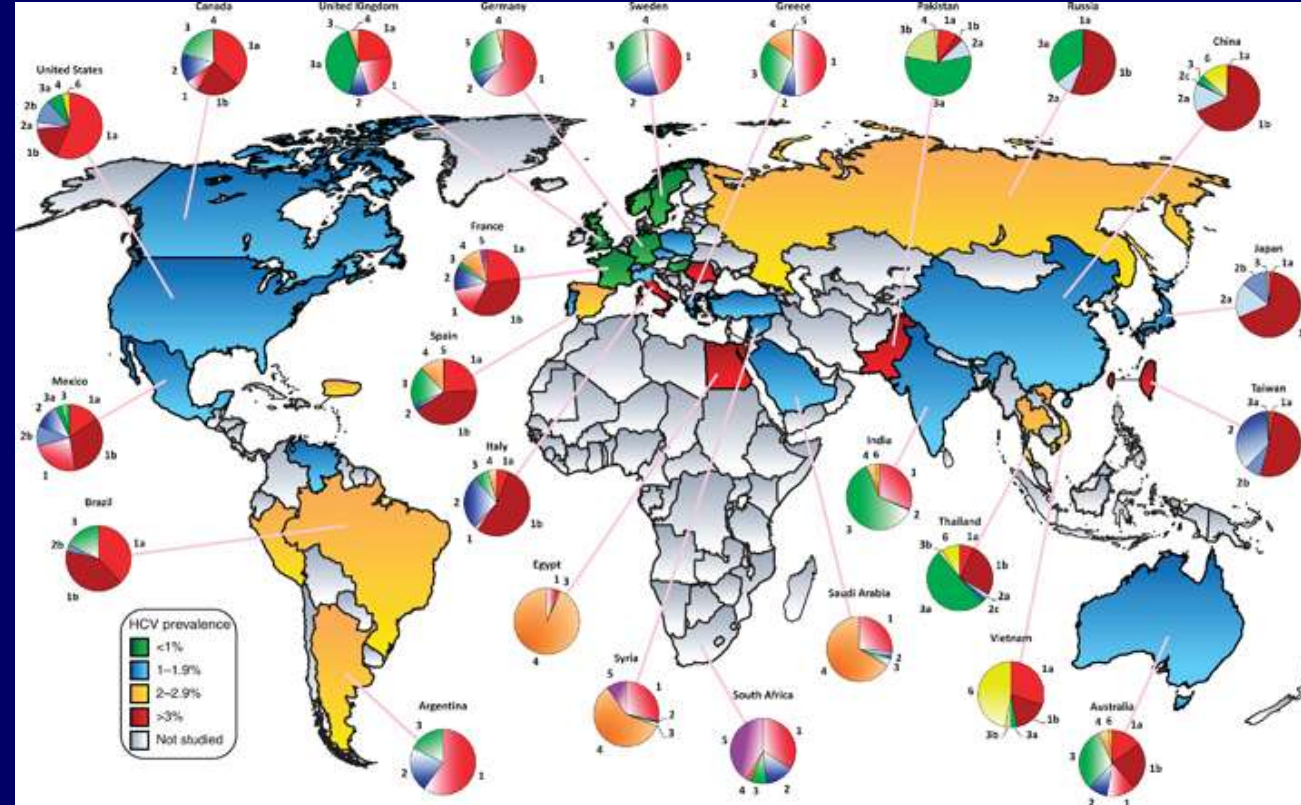# Worldwide prevalence of Aging population

2002 World Assembly on Ageing and its follow-up.

Impact on aging of liver disease

The Global Health Burden Of Hepatitis C Virus Infection

Age-specific Prevalence Of Hcv Infection And Incidence Of HCV-related Advanced Liver Disease In Four Representative Countries

Hajarizadeh, B. et al. Nat. Rev. Gastroenterol. Hepatol. 2013;10, 553–562
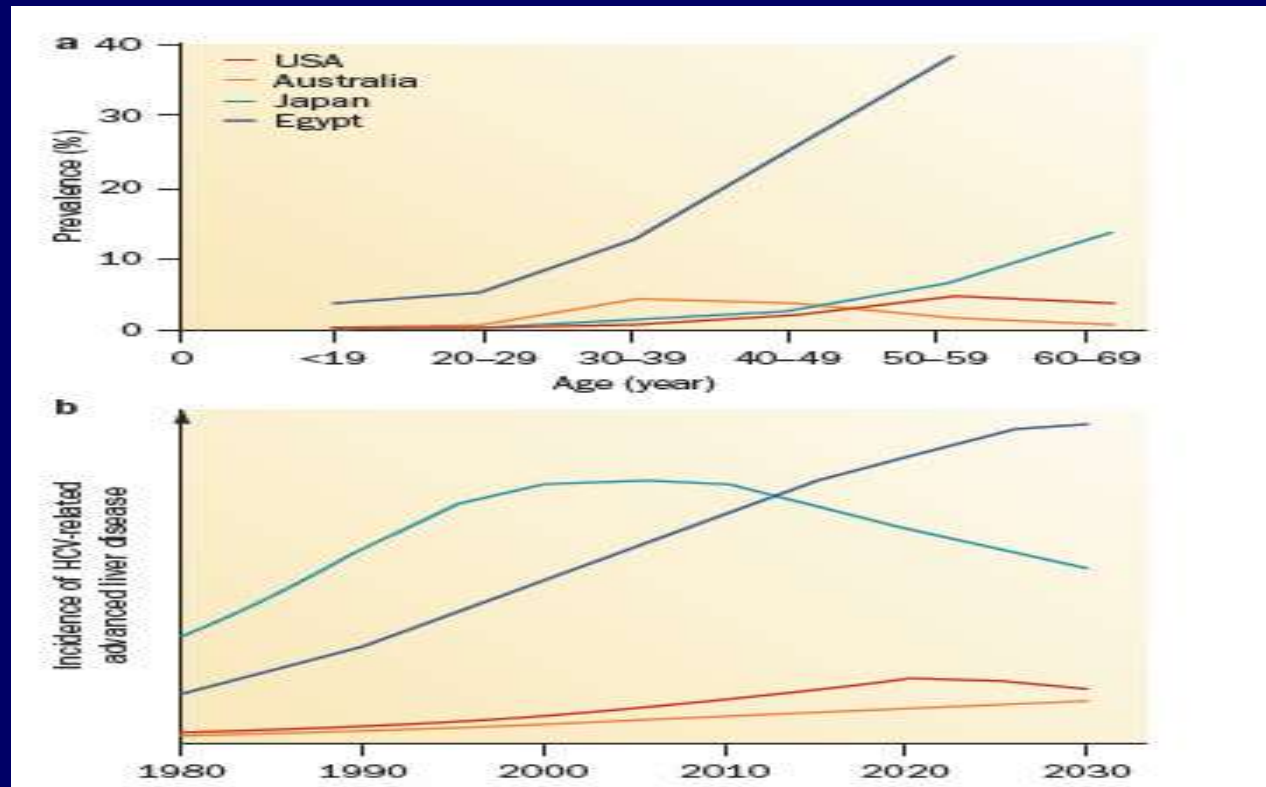
Japan has the oldest HCV prevalent population while India and China prevalent population is younger

2008 HCV Prevalent Population (000)
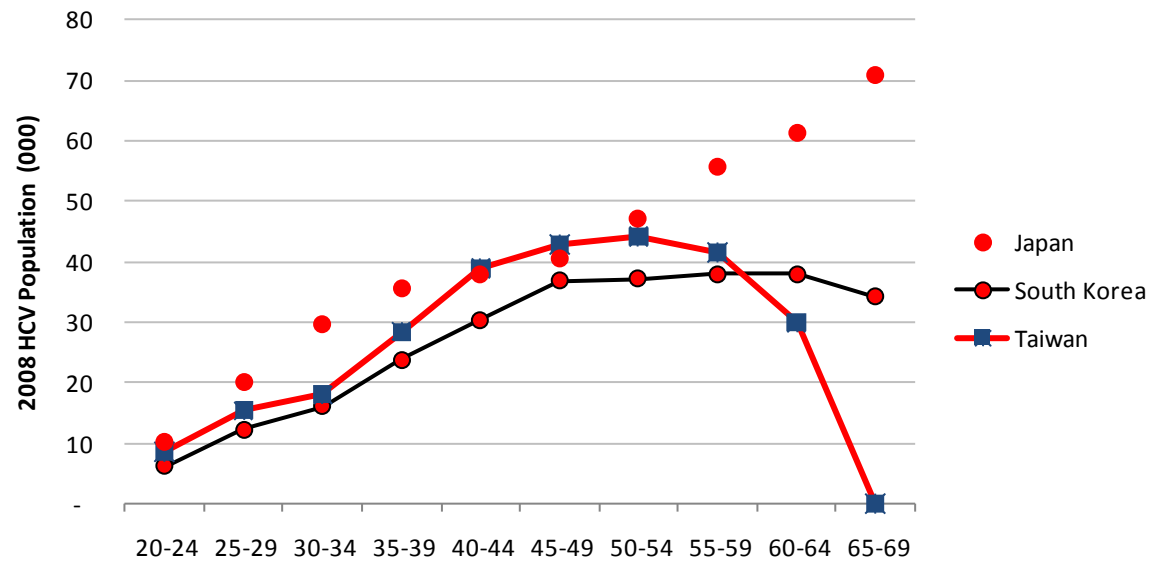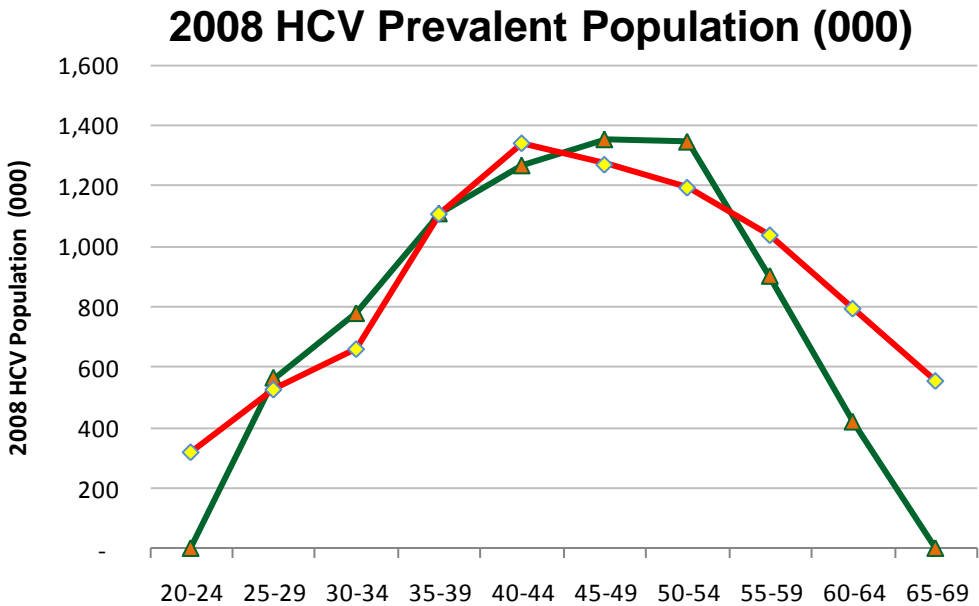
In Japan, South Korea, and Taiwan, the prevalence is expected to decline

Prevalent HCV Population
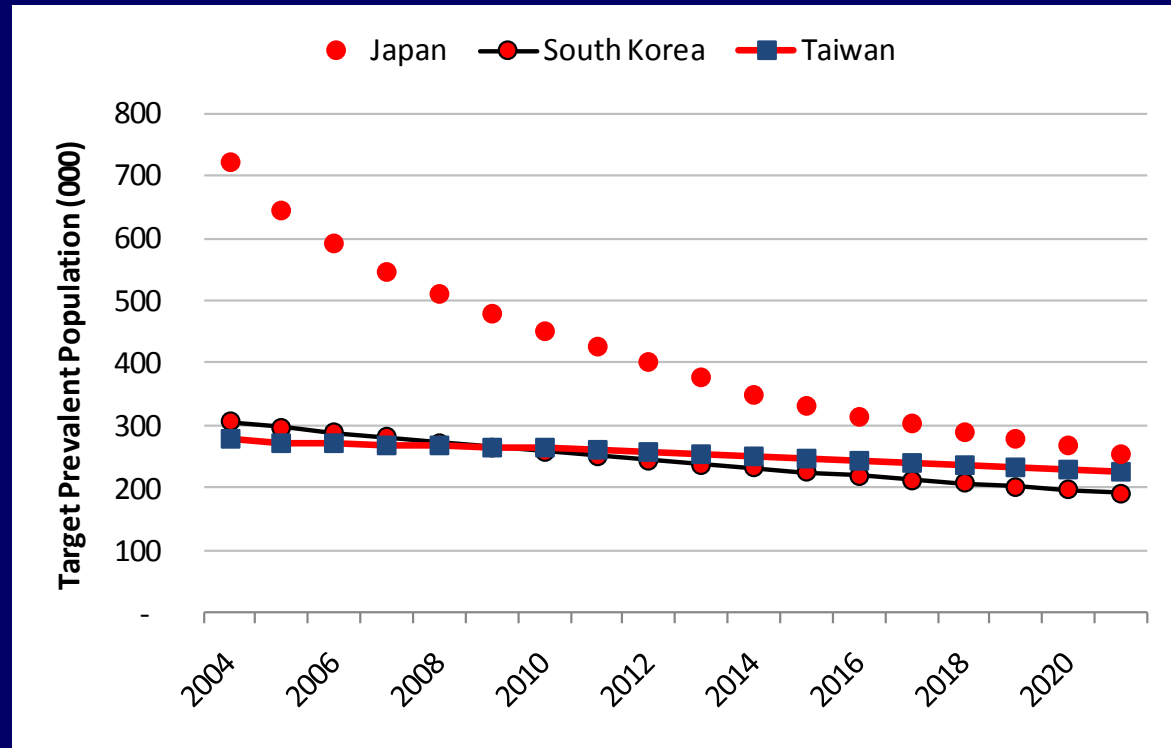
The disease burden, however, is expected to grow as the disease progresses.

In India And China, The Overall Prevalence Is Expected To Continue To Increase

Prevalent HCV Population

Incidence

Cured

Mortality
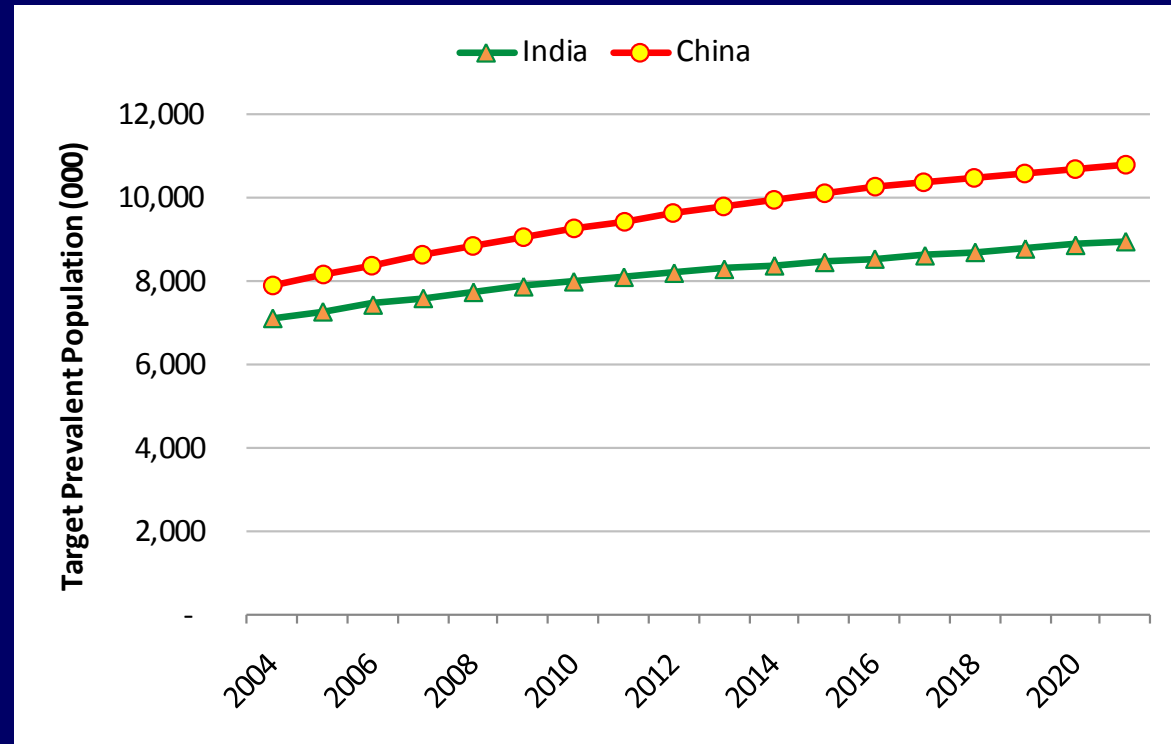
Diagnosis and treatment have to increase in order to manage Hepatitis C in these countries.
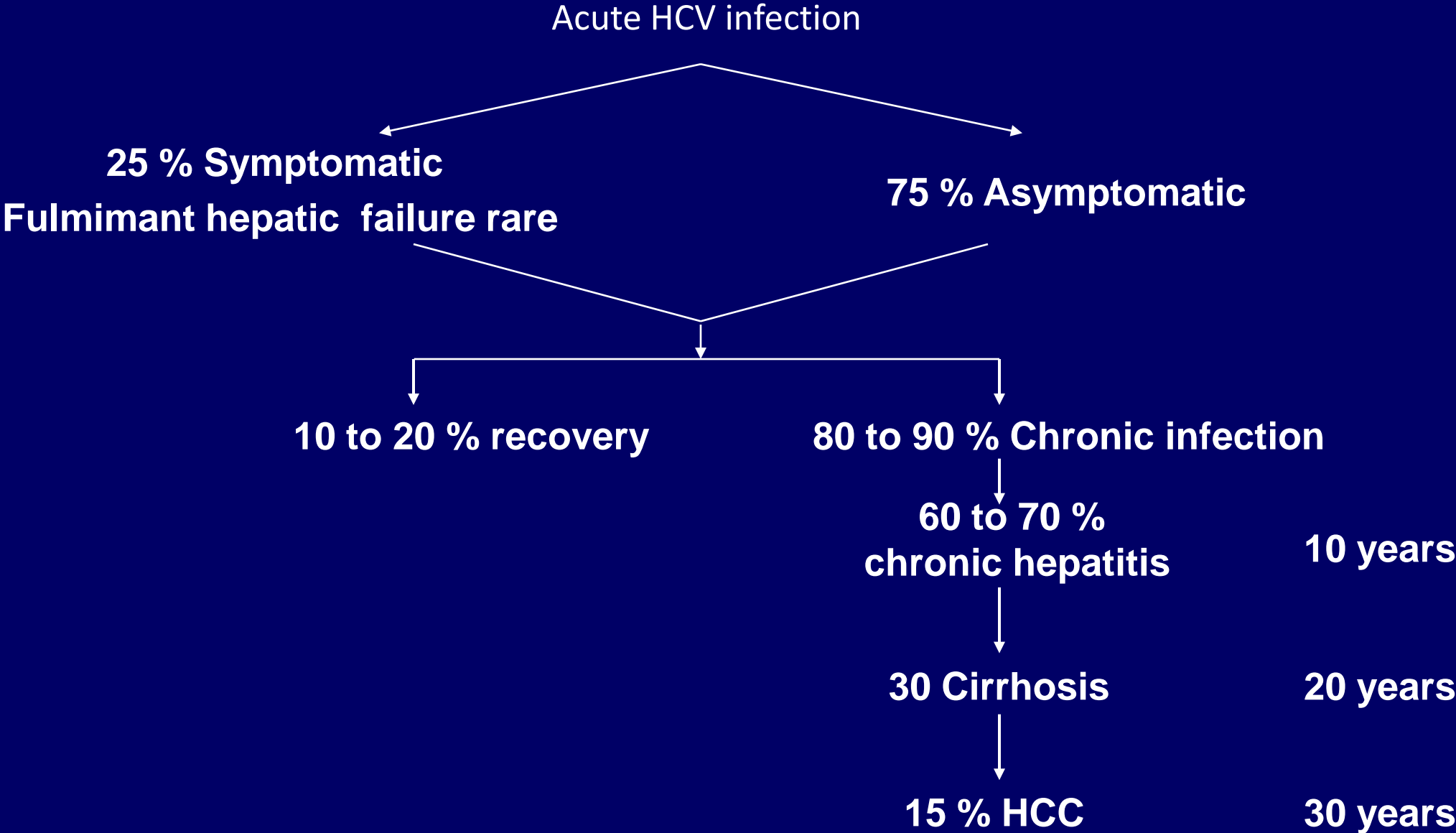
Impact Of Age At The Time Of Acquisition Of HCV Infection On Progression Of Disease
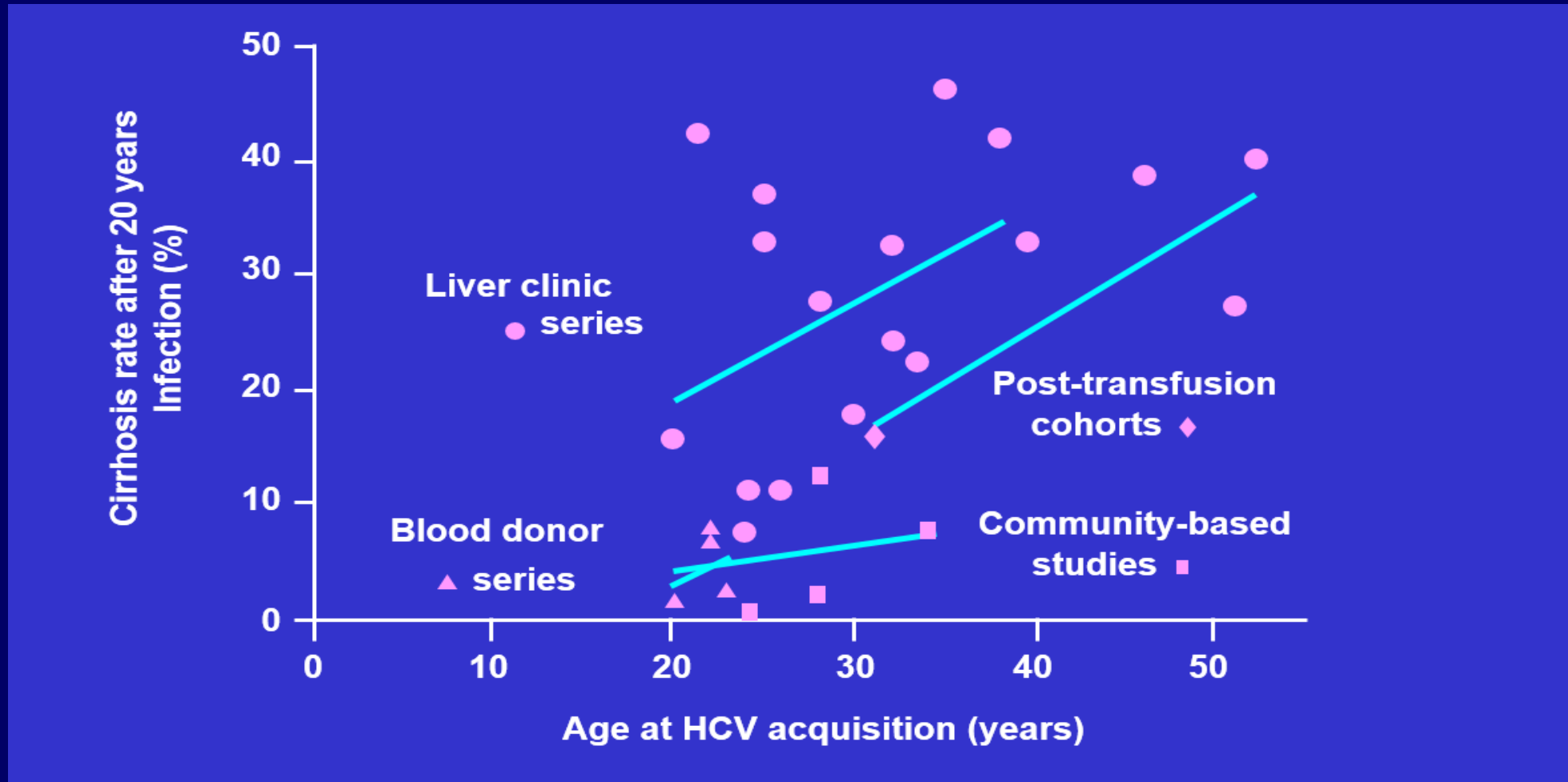
Spontaneous Viral Clearance According To Age Of Acquirance Of HCV Infection
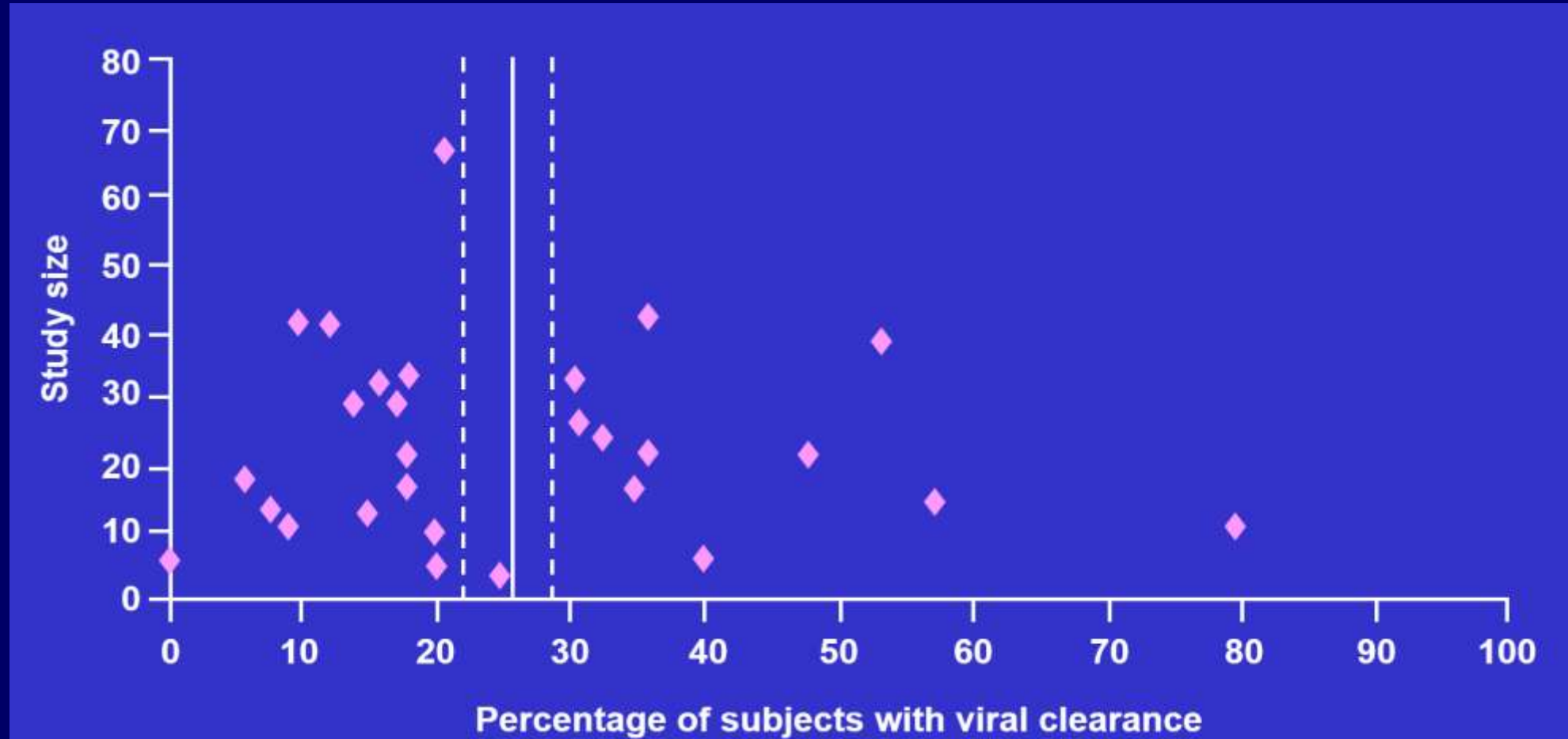
Prevalence Of Hepatitis C-related Cirrhosis In Elderly Asian Patients Infected In Childhood
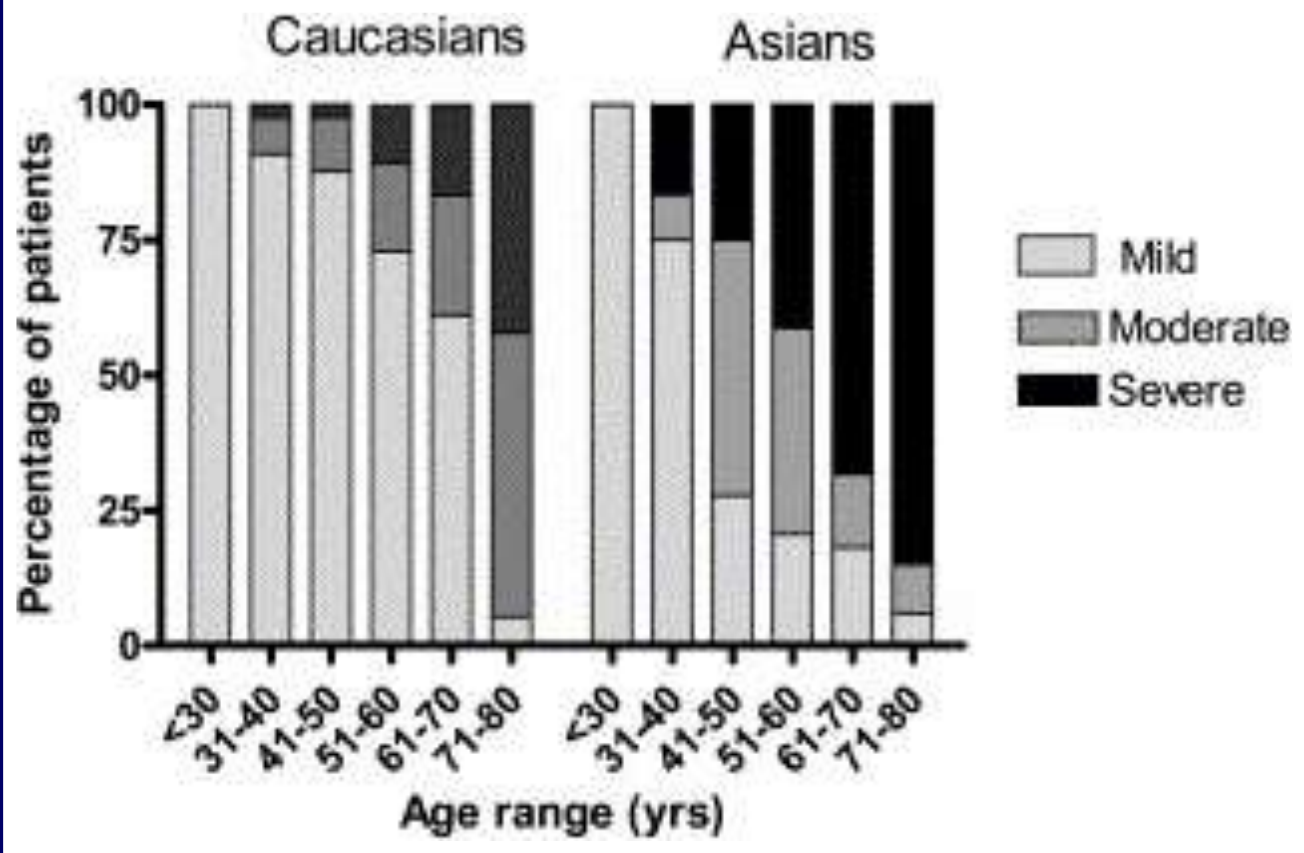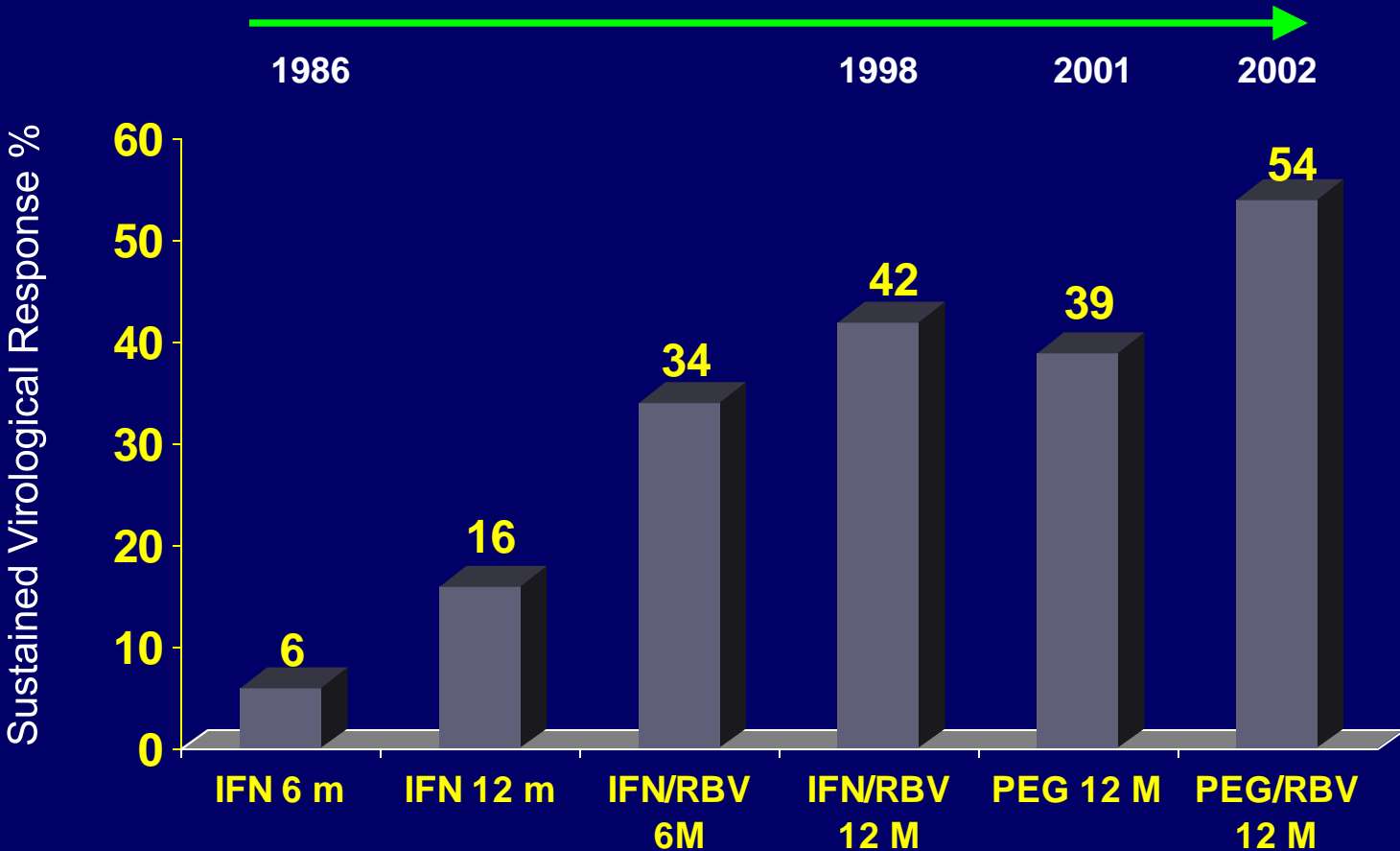
HCV Treatment 2013

Genotype	PegIFN-a	Ribavirin	Boceprevir or Telaprevir	Duration (Weeks)
1	√	√	√	24-48
2	√	√	No	24
3	√	√	No	24
4	√	√	No	48
5	√	√	No	48
6	√	√	No	24-48

Clinical Endpoints Stratified According To Response To Treatment

Outcome	Events (n)	Observation Period (Person-years)	Rate/100 person-years (95% CI)	pValue
Hepatocellular Carcinoma				
All patients	46	1164.7	3.94 (2.89–4.99)	
SVRs	6	481.1	1.24 (0.28–2.20)	<0.001
Non-SVRs	40	683.5	5.85 (4.23–7.47)	
Liver-Related Complications				
All patients	31	1150.4	2.69 (1.80–3.58)	
SVRs	3	477.9	0.62 (0.00–1.28)	<0.001
Non-SVRs	28	672.5	4.16 (2.73–5.59)	
Liver-Related Death				
All patients	31	1230.7	2.51 (1.68–3.34)	
SVRs	3	486.0	0.61 (0.00–1.29)	<0.001
Non-SVRs	28	744.7	3.76 (2.47–5.05)	
J Hepatol. 2010;52:652-7.				

Cumulative Incidence Of Hepatocellular Carcinoma Stratified According To Response To Treatment (P<0.001, By Log-rank Test). SVR, Sustained Virological Response..

J Hepatol. 2010;52:652-7.
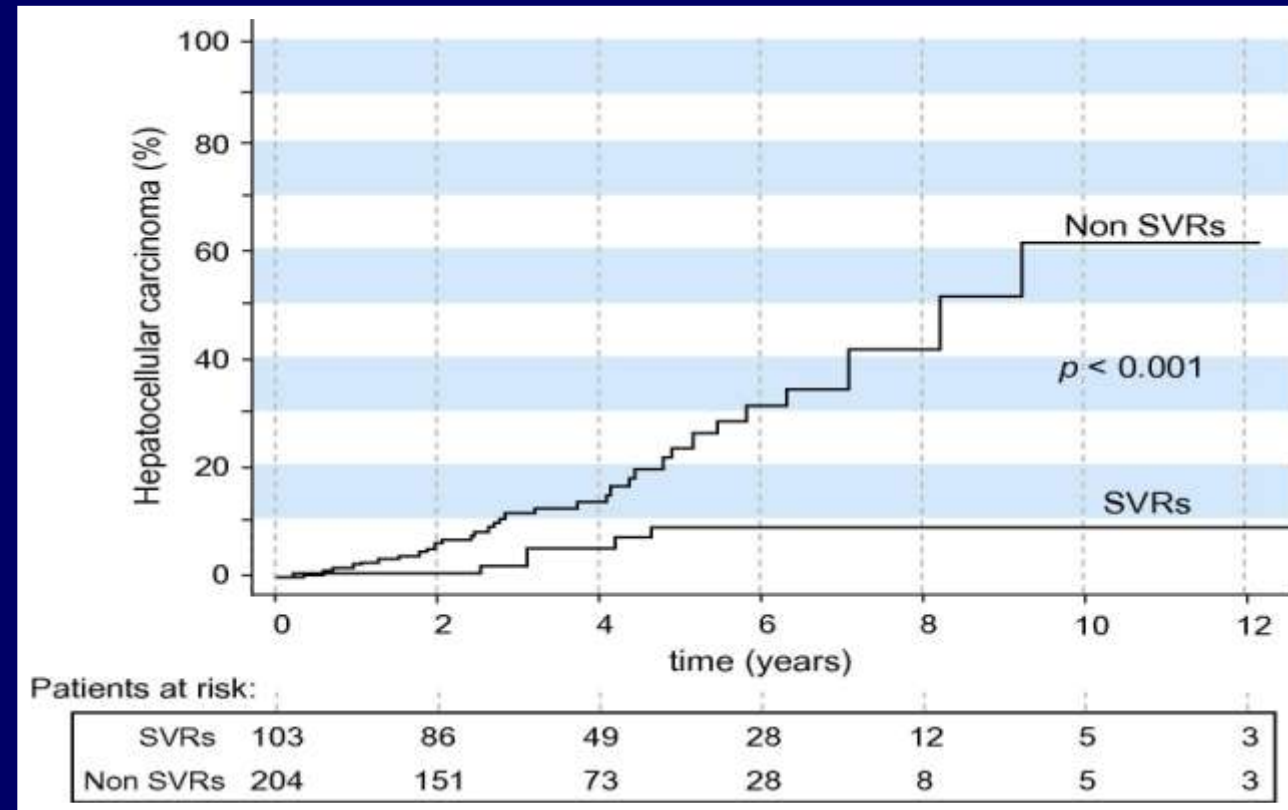
Factors Associated With Sustained Virological Response

- **Clinical Factors**

  - Body mass index, body weight
  - Age
  - Gender
  - Insulin resistance
  - Coinfection with HBV or HIV
  - Biochemical and pathological factors
  - ALT
  - GGT
  - Staging of liver fibrosis
  - Genetic factors
  - Race: Asian
  - IL28B (interferon lambda 3)-associated SNPs: favorable genotype
  - APASL CONSENSUS 2013

Treatment of chronic hepatitis C in Asia: When East meets West
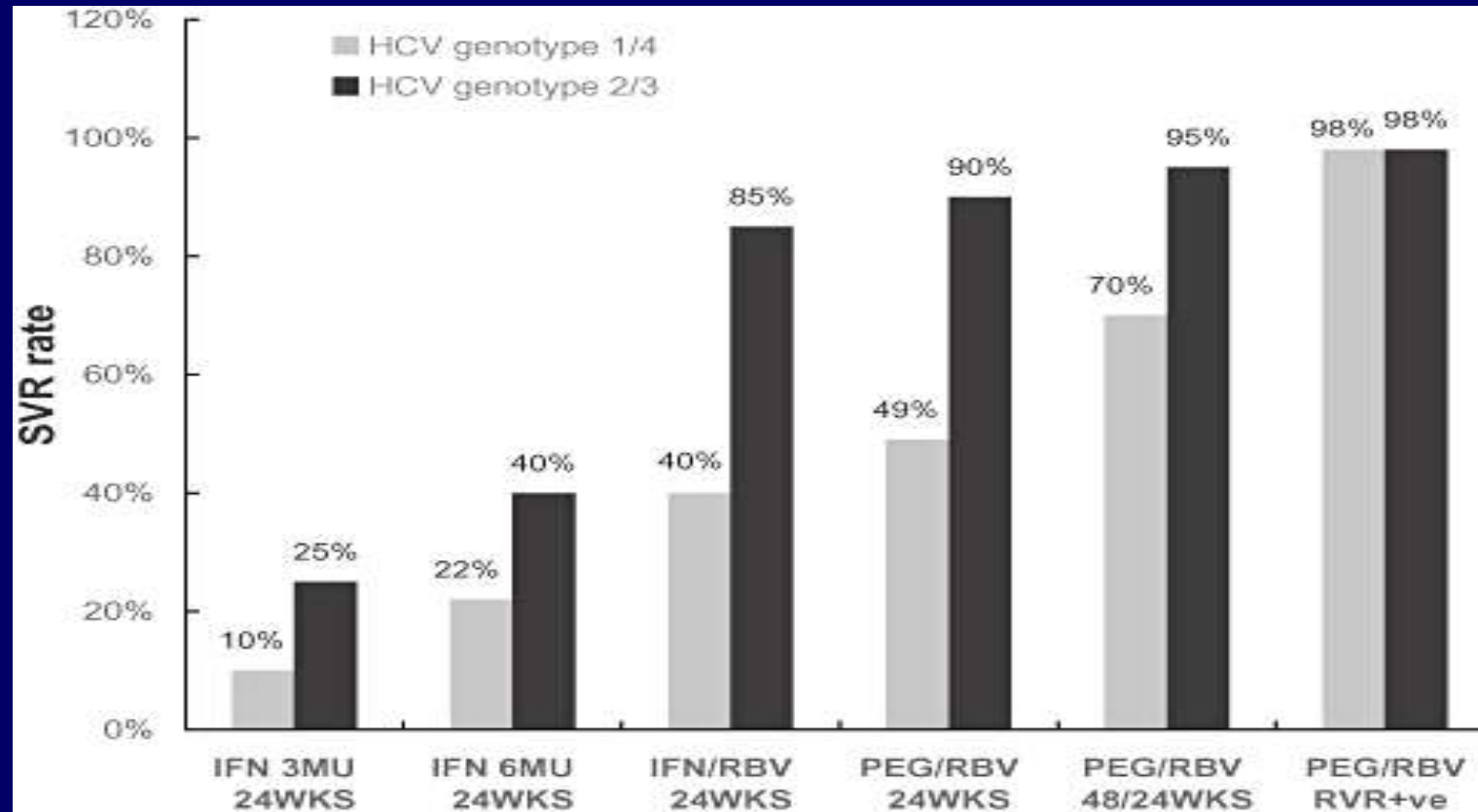
Regional Distribution of *IL28B* rs12979860 CC Genotype

Thomas DL, et al. *Nature*. 2009;461:798-801.

Contraindications For The Use Of Peginterferon Alfa And Ribavirin

- Absolute contraindications

- Present or past psychosis or severe depression

- Uncontrolled seizures

- Hepatic decompensation

- Pregnancy (ribavirin)

- Renal failure (ribavirin)

- Severe heart disease (ribavirin)

- Relative contraindications

- History of depression

- Uncontrolled diabetes mellitus

- Uncontrolled hypertension

Contraindications For The Use Of Peginterferon Alfa And Ribavirin

- Retinopathy

- Psoriasis

- Autoimmune thyroiditis or other active autoimmune disorders

- including autoimmune hepatitis

- Symptomatic heart disease or severe vascular disease (ribavirin)

- Anemia/ischemic vascular disease (ribavirin)

- Conditions requiring special caution for interferon administration

- Neutropenia (neutrophil count <1,500 cells/lL)

- Thrombocytopenia (platelet count <85,000/lL)

- Organ transplantation

- History of autoimmune disease

- Presence of thyroid autoantibodies

- __Age > 70 years__

- APASL CONSENSUS 2013

The Effect of Age on Response to Therapy With Peginterferon Plus Ribavirin in a Cohort of Patients With Chronic HCV Hepatitis Including Subjects Older Than 65 Yr

- **What Is Current Knowledge**

    – Treatment of hepatitis C virus (HCV) chronic hepatitis is provided by a combination of peginterferon plus ribavirin.

    – Age older than 40 yr is an independent predictor of reduced sustained virologic response.

    – Efficacy of peginterferon with ribavirin in chronic HCV patients older than 65 yr is not well established.

    - **Am J Gastroenterol. 2007;102:1383-91**

(A) End Of Treatment And Sustained Virologic Response In 74 Patients With Genotype 1 Or 4 Chronic Hepatitis C. (B) End Of Treatment And Sustained Virologic Response In 79 Patients With Genotype 2 Or 3 Chronic Hepatitis C
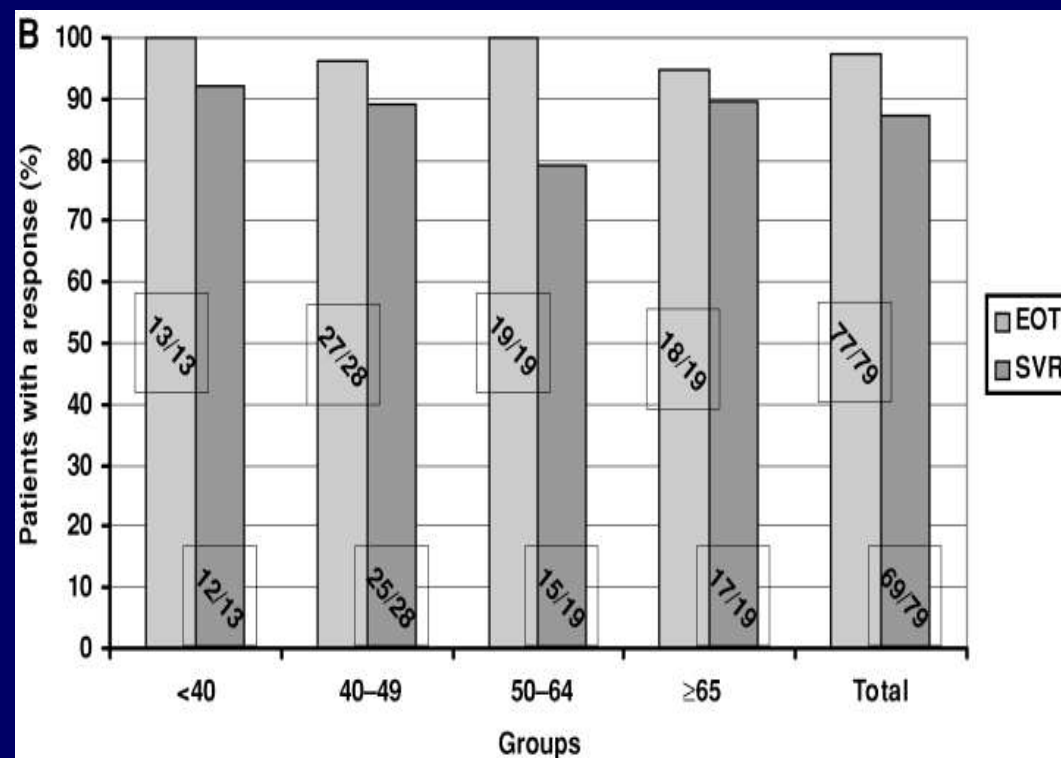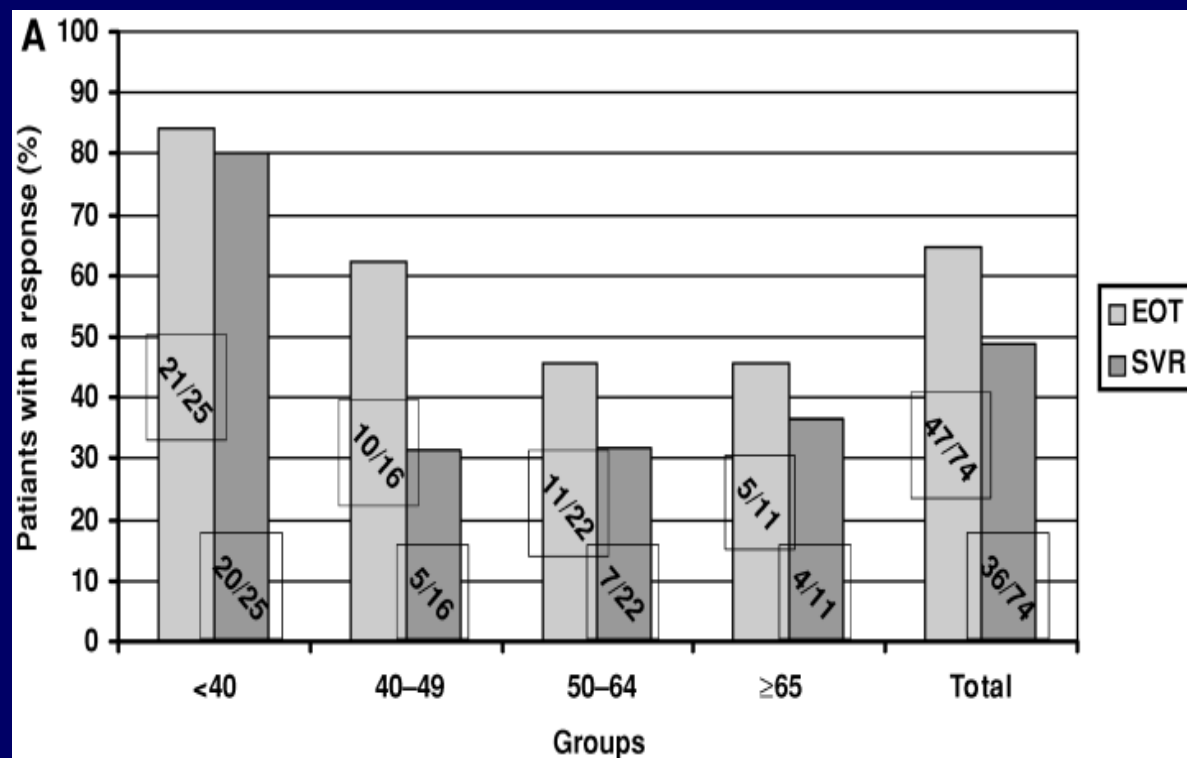
EOT = end of treatment response; SVR = sustained virologic response.

Proportions Of Side Effects And Discontinuation According To Age Group

Side Effects	Age Group (yr)				
	<40 N = 38	40–49 N = 44	50–64 N = 41	65 N = 30	Total N = 153
	N (%)				
Discontinuation					
Laboratory abnormalities	2 (5.3)	2 (4.6)	0 (0.0)	0 (0.0)	4 (2.6)
Adverse events	1 (2.6)	1 (2.3)	4 (9.8)	3 (10.0)	9 (5.9)
No response	3 (7.9)	2 (4.6)	4 (9.8)	2 (6.7)	11 (7.2)
Total	6 (15.8)	5 (11.4)	8 (19.5)	5 (16.7)	24 (15.7)

Am J Gastroenterol. 2007;102:1383-91

Study Highlights

- **What Is New Here**
  - – In patients infected with HCV genotypes 2 or 3, rates of sustained response were not related to different age groups.
  - – Patients older than 40 yr including those 65 yr showed similar reduced rates of sustained response.
  - – In patients infected with HCV genotypes 1 or 4, combination treatment may be safely extended to elderly patients with no major contraindications.

    - Am J Gastroenterol. 2007;102:1383-91

Synopsis Of Published Studies Evaluating The Effect Of Age On Sustained Virologic Response Rates

Ref	Study Design	No. of Patients	Drugs	Duration, wk	Age, yr	Total SVR, %	Effect of Age on SVR
Manns, 2001	RCT	1,530	IFN -2b + RBV	48	43 (21–68)[†]	49.2	Younger age, non-1 genotypes associated with SVR at multivariable analysis
			peg-IFN -2b + RBV				
Fried 2002	RCT	1,121	peg-IFN -2a + RBV	48	42.8 10.1[‡]	45.9	Age 40 yr (OR 2.60, 95% CI 1.60–3.95), non-1 genotypes (OR 3.25, 95% CI 2.09–5.12) associated with SVR at multivariable analysis
			peg-IFN -2a				
			IFN -2b + RBV				
Poynard 2000	Metanalysis	1,744	IFN -2b + RBV	24/48	NA	29.8	Age 40 yr (OR 1.4, 95% CI 1.1–1.9), genotype 2 or 3 (OR 6.0, 95% CI 4.6–7.8) associated with SVR at multivariable analysis
Alessi 2003	Retrospective	154	IFN			19.0	Two patient groups: <60, 60 yr Rates of SVR similar in the two groups A trend to more frequent major side effects in patients 60 ($P = 0.07$)
Bacosi 2002	RCT	119	AH	48	65	26.1	Comparison with patients <65 yr: NA
			IFN -n$_3$				
			IFN -n$_3$ + AH				

Synopsis Of Published Studies Evaluating The Effect Of Age On Sustained Virologic Response Rates

Ref	Study Design	No. of Patients	Drugs	Duration, wk	Age, yr	Total SVR, %	Effect of Age on SVR
Dalgard 2004	Non-RCT	122	peg-IFN -2b + RBV	14/24	37 (20–56)[†]	80.3	Age not associated with SVR at univariable and multivariable analysis
von Wagner 2005	RCT	153	peg-IFN -2a + RBV	16/24	40 11[‡]	77.1	Age not associated with SVR at univariable and multivariable analysis
Mangia 2005	RCT	283	peg-IFN -2b + RBV	12/24	46.6 12.2[‡]	76.7	Age not associated with SVR at univariable and multivariable analysis
Iwasaki 2006	Prospective	208	IFN -2b + RBV	24	54.5 10.4[‡]	37.0	Three patient groups: <50, 50–59, 60 yr A trend to a lower SVR in patients 60 (P = 0.078) and in patients 60 with genotype 1 (P = 0.094) Discontinuation or dose reduction more frequent in patients 60 (P < 0.001) Age <60 associated with adherence at multivariable analysis
Kumada 2006	Observational	288	IFN + RBV	30/40	53.8 11.1[‡]	36.5	Two patient groups: <65, 65 yr A trend to a lower SVR in patients 65 (P = 0.08) non-1 genotypes (OR 21.24, 95% CI 6.54 − 82.78) associated with SVR at multivariable analysis Dose reduction (P = 0.045) and discontinuation (P = 0.041) more frequent in patients 65 yr

Synopsis Of Published Studies Evaluating The Effect Of Age On Sustained Virologic Response Rates

Ref	Study Design	No. of Patients	Drugs	Duration, wk	Age, yr	Total SVR, %	Effect of Age on SVR
Thabut 2006	Retrospective	165	IFN	NA	NA	18.8	Two patient groups: 65–80, >80 yr.
			IFN + RBV				Comparison with patients <65 yr: ND
			peg-IFN				Dose reduction in 7% and discontinuation in 20% of treated patients
			peg-IFN + RBV				
Antonucci 2007	Retrospective	153	peg-IFN + RBV	24/48	48.0 25.0–75.0†	68.6	Four patient groups: <40, 40–49, 50–64, 65 yr Age 40–49 (OR 0.16, 95% CI 0.05–0.59), age 50–64 (OR 0.13, 95% CI 0.03–0.49), age 65 (OR 0.21, 95% CI 0.05–0.91), genotypes 2 or 3 (OR 10.99, 95% CI 4.26–28.63) associated with SVR at multivariable analysis Age groups 40 had similar odds of achieving SVR (P = 0.71) The effect of age on SVR was maintained only in the 74 patients infected with genotype 1 or 4 (P = 0.046)

SVR = sustained virological response; RCT = randomized clinical trial; peg-IFN = peginterferon; RBV = ribavirin; AH = amantadine; ND = not done; NA = not available.

* Only patients with HCV genotypes 2 or 3 were enrolled.

† Mean (range); ‡ Mean SD.

Am J Gastroenterol. 2007;102:1383-91

Efficacy Of Peginterferon-alpha-2b Plus Ribavirin In Patients Aged 65 Years And Older With Chronic Hepatitis C

Flow Chart For Patient Selection

658 patients screened for eligibility

64 patients not enrolled
56 did not meet entry protocol criteria
 8 met exclusion criteria

3 patients with indeterminate genotype

591 patients included in efficacy analysis

118 patients discontinued treatment
 73 For adverse events
  1 Unknown
44 Non eradication of HCV

473 patients completed treatment

473 patients completed follow up period
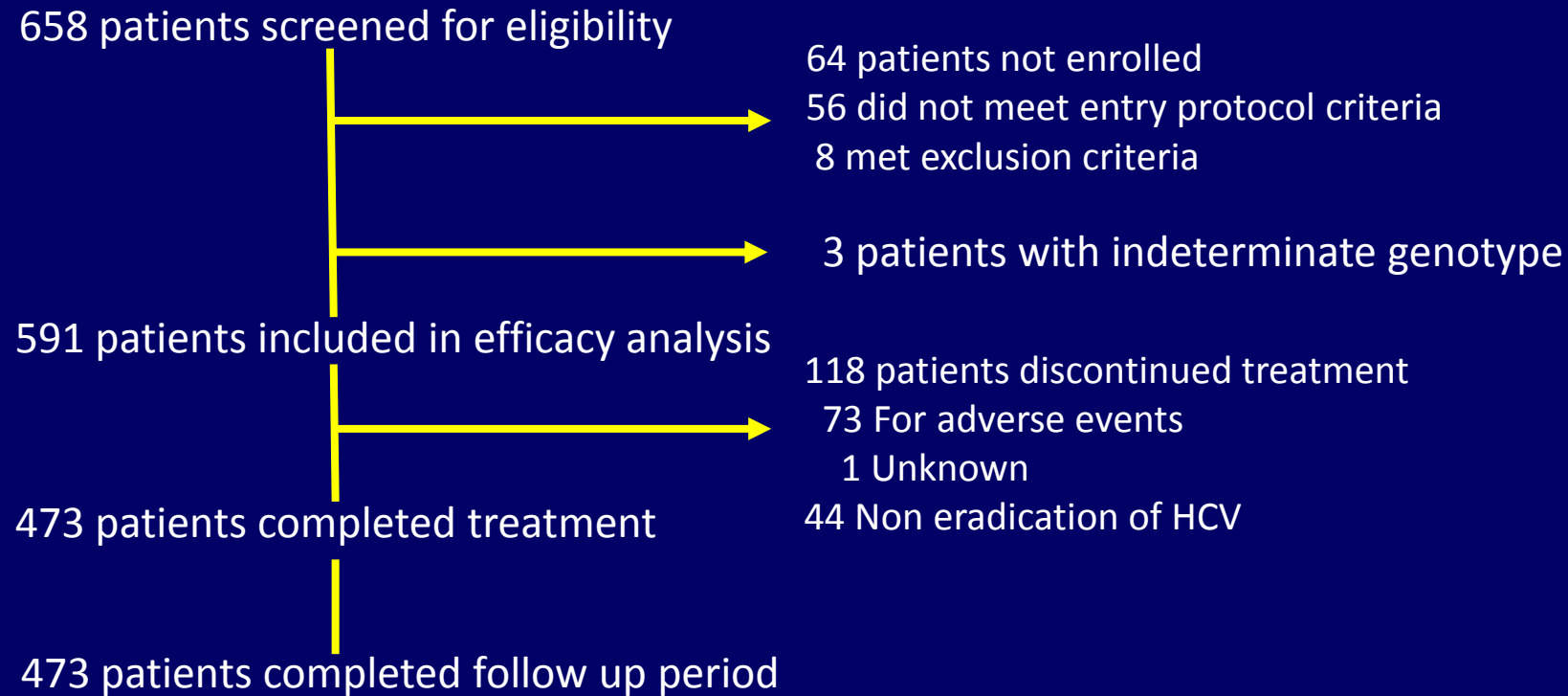
Baseline Clinical Characteristics Of Patients Treated With Combination Therapy

	Total patients (*n*=591)	Patients aged <65 years (*n*=476)	Patients aged ≥65 years (*n*=115)	*P* value
Sex ratio (male/female)	327/264	270/206	57/58	0.1659
Age (years)	**54.7 ± 11.6**	**51.5 ± 10.6**	**67.9 ± 2.2**	**<0.0001**
Body weight (kg)	60.1 ± 11.3	60.9 ± 11.4	56.7 ± 10.1	0.0006
Body mass index	22.9 ± 3.2	22.9 ± 3.2	22.9 ± 3.2	0.9221
Baseline serum ALT (IU/L)	64.8 ± 57.3	66.5 ± 60.6	57.7 ± 40.4	0.1425
GGT (IU/L)	57.8 ± 76.7	58.9 ± 78.9	53.3 ± 67.3	0.4880
Haemoglobin (g/dl)	**14.1 ± 1.3**	**14.2 ± 1.4**	**13.7 ± 1.2**	**<0.0001**
Platelets (× 10^4/µl)	17.7 ± 5.7	18.0 ± 5.9	16.1 ± 4.3	0.0013
Genotype (1/2)	467/124	374/102	93/22	0.5870
HCV RNA (kIU/ml)	1863.3 ± 1456.3	1896.4 ± 1454.9	1726.2 ± 1460.5	0.2611
Activity (A0/A1/A2/A3)	16/255/141/19	13/202/115/13	3/53/26/6	0.6053
Fibrosis (F0/F1/F2/F3/F4)	37/228/107/56/5	31/191/83/37/3	6/37/24/19/2	0.0310

Efficacy of combination therapy

|	Total patients (*n*=591)	Patients aged <65 years (*n*=476)	Patients aged ≥65 years (*n*=115)	*P* value
SVR rate (intention-to-treat)	**48.7 (288/591)**	**51.5 (245/476)**	**37.4 (43/115)**	**0.0067**
RVR rate (intention-to-treat)	20.0 (118/591)	21.2 (101/476)	14.8 (17/115)	0.1213
EVR rate (intention-to-treat)	62.6 (370/591)	64.5 (307/476)	54.8 (63/115)	0.0534
EVR rate (per-protocol)	71.0 (336/473)	71.1 (281/395)	70.5 (55/78)	0.9113
ETR rate (intention-to-treat)	81.0 (479/591)	83.2 (396/476)	72.2 (83/115)	0.00
Combination therapy discontinuation rate *	**12.5 (74/591)**	**9.9 (47/476)**	**23.5 (27/115)**	**<0.0001**

Liver International 2010; 30,527-37

Univariate Analysis Of Factors Associated With Sustained Virological Response In Patients Aged ≥65 Years Treated With Combination Therapy

	Total patients (n=115)	Patients who achieved a SVR (n=43)	Patients who did not achieved a SVR (n=72)	P value
Sex ratio (male/female)	57/58	27/16	30/42	0.0284
Age (years)	67.9 ± 2.2	67.9 ± 2.3	67.8 ± 2.1	0.7666
Body weight (kg)	56.7 ± 10.1	56.9 ± 7.1	56.5 ± 11.4	0.8417
Body mass index	22.9 ± 3.2	22.8 ± 1.9	23.0 ± 3.7	0.6980
Baseline serum ALT (IU/L)	57.7 ± 40.4	57.2 ± 41.3	58.0 ± 40.2	0.9178
GGT (IU/L)	53.3 ± 67.3	61.2 ± 98.3	48.8 ± 40.4	0.3471
Haemoglobin (g/dl)	13.7 ± 1.2	13.8 ± 1.2	13.6 ± 1.3	0.3341
Platelets (× 10^4/μl)	16.1 ± 4.3	16.3 ± 4.7	16.0 ± 4.1	0.7412
Genotype (1/2)	93/22	29/14	64/8	0.0047
HCV RNA (kIU/ml)	1726.2 ± 1460.5	1383.6 ± 1247.0	1930.9 ± 1546.4	0.0514
Activity (A0/A1/A2/A3)	3/53/26/6	1/17/10/4	2/36/16/2	0.4132
Fibrosis (F0/F1/F2/F3/F4)	6/37/24/19/2	0/16/9/7/0	6/21/15/12	
ALT, alanine aminotransferase; GGT, γ-glutamyl transpeptidase; HCV RNA, hepatitis C virus RNA; kIU, kilo international units; SVR, sustained virological response.				

A Virological Response To Combination Therapy According To The Age And Gender Of Patients With Genotype 1. ITT, Intention-to-treat; NR, Nonresponder; SVR, Sustained Virological Response
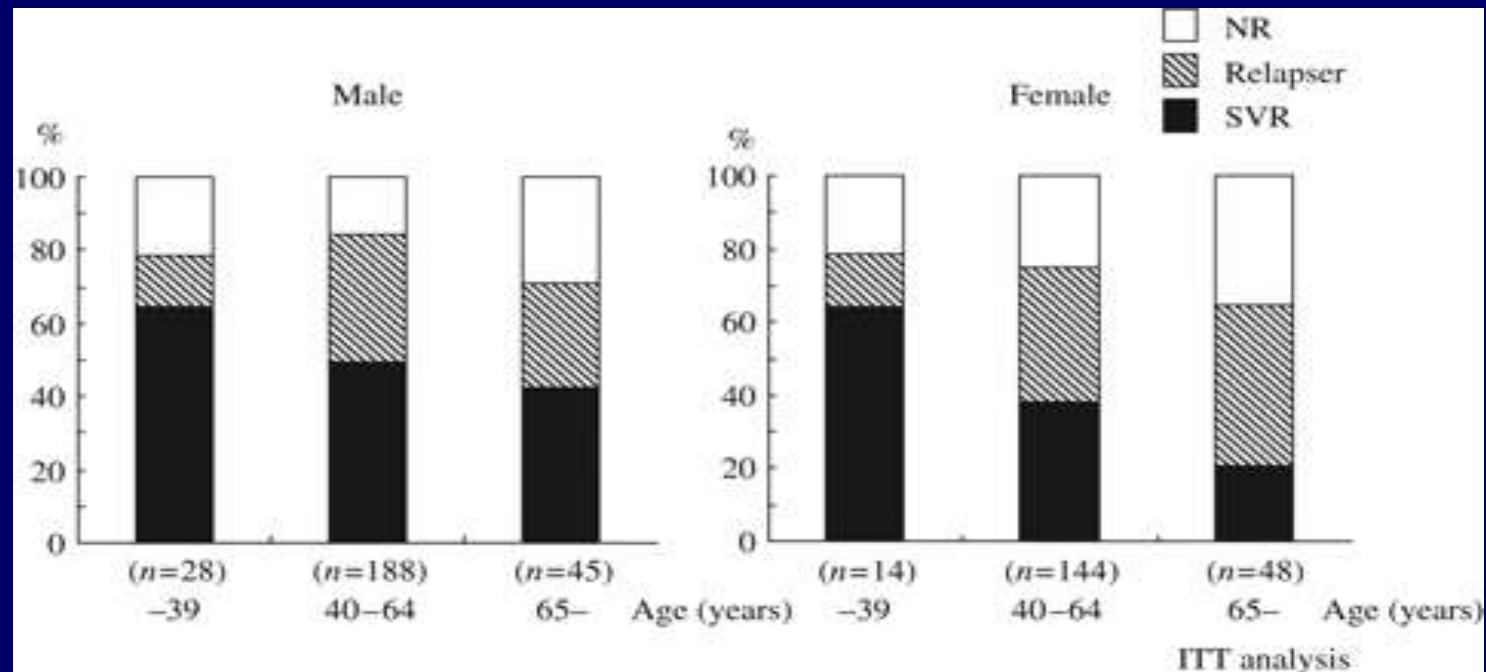
A Virological Response To Combination Therapy According To The Age And Gender Of Patients With Genotype 2. ITT, Intention-to-treat; NR, Nonresponder; SVR, Sustained Virological Response.
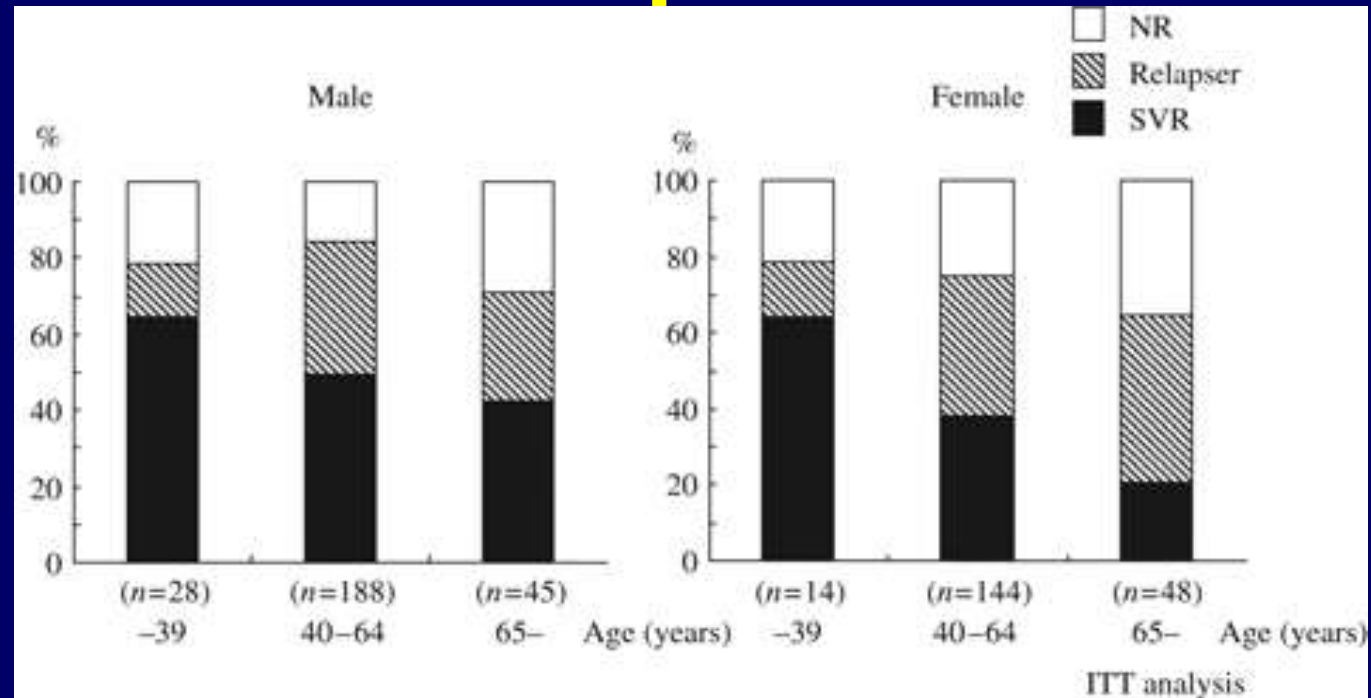
Multivariate Analysis Of Factors Associated With A Sustained Virological Response In Combination Therapy

	Variable	Odds ratio (95% CI)	*P* value
Age		0.959 (0.942–0.975)	<0.0001
Genotype	1 vs. 2	0.415 (0.255–0.676)	<0.0001
CI, confidence interval.			
Liver International 2010; 30,527-37			

Sustained Virological Response (SVR) In Young And Elderly Patients And Relation To Genotype

	All therapies (*n* = 545)	Therapies in patients <60 years (*n* = 474)	Therapies in patients ≥60 years (*n* = 71)*	Therapies in patients ≥65 years (*n* = 27) (subgroup)**
SVR	304 (55.8%)	271 (57.2%)	33 (46.5%)	11 (41%)
Genotype 1/4/6	123 (40.3%)	111 (42.9%)	12 (26.1%)	5 (26.3%)
Genotype 2/3	181 (75.4%)	160 (74.4%)	21 (84%)	6 (75%)

**(therapies in patients ≥65 years) is a subgroup of * (therapies in patients ≥60 years).

Liver Int. 2013 Jul 24. doi: 10.1111/liv.12279. [Epub ahead of print]

Feasibility Of Antiviral Therapy In Young And Elderly Patients

	All therapies (n = 545)	Therapies in patients <60 years (n = 474)	Therapies in patients ≥60 years (n = 71)*	Therapies in patients ≥65 years (n = 27)**
Dose reduction of PEG-IFN-α	91 (16.7%)	76 (16%)	15 (21.1%)	4 (14.8%)
Dose reduction of ribavirin	87 (16%)	57 (12%)	30 (42.3%)	13 (48.1%)
Dose increase of ribavirin	20 (3.7%)	20 (4.2%)	0 (0%)	0 (0%)
Early stop of antiviral therapy	102 (18.7%)	87 (18.4%)	15 (21.1%)	6 (22.2%)
Genotype 1/4/6 (305 therapies)	84 (27.5%)	70 (27%)	14 (30.4%)	6 (22.2%)
Genotype 2/3 (240 therapies)	18 (7.5%)	17 (7.9%)	1 (4%)	0 (0%)
1.**(therapies in patients ≥65 years) is a subgroup of * (therapies in patients ≥60 years).				
Liver Int. 2013 in press				

Results Of The Multiple Regression Analysis, Dependent Variable Sustained Virological Response, Generalized Estimating Equations Model

	Odds ratio	95% CI	*P*-value
Age ≥60 years	0.909	(0.423–1.953)	0.81
Gender male	1.254	(0.802–1.975)	0.32
Cirrhosis	0.405	(0.22–0.746)	0.003
Genotype 2/3	4.204	(2.690–6.625)	<0.001
Earlier treatment	0.347	(0.113–1.059)	0.06
High viral load (>600 000 IU/ml)	0.469	(0.275–0.794)	0.01
Liver Int. 2013 in press			

Subgroup Analysis Of Cirrhotic Patients, Dependent Variable Sustained Virological Response, Results Of Logistic Regression Analysis

	Odds ratio	95% CI	*P*-value
Age ≥60 years	0.957	(0.339–2.705)	0.935
Dose reduction PEG-INF-α	1.411	(0.530–3.760)	0.489
Dose reduction ribavirin	0.631	(0.195–2.045)	0.442
Liver Int. 2013 in press			

Interferon Free Regimens For Elderly Patients

Sofosbuvir For Hepatitis C Genotype 2 Or 3 In Patients Without Treatment Options

Characteristic	Interferon Treatment Not An Option		Prior Interferon Treatment	
	Placebo (N = 71)	12 Wk of Sofosbuvir Ribavirin (N = 207)	12 Wk of Sofosbuvir Ribavirin (N = 103)	16 Wk of Sofosbuvir Ribavirin (N = 987)
Age – Yrs	52	52	54	54
Range	28-67	21-75	30-69	24-70

In patients with HCV genotype 2 or 3 infection for whom treatment with peginterferon and ribavirin was not an option, 12 or 16 weeks of treatment with sofosbuvir and ribavirin was effective. Efficacy was increased among patients with HCV genotype 2 infection and those without cirrhosis. In previously treated patients with genotype 3 infection, 16 weeks of therapy was significantly more effective than 12 weeks.

N Engl J Med 2013; 368:1867-1877

Sofosbuvir for Previously Untreated Chronic Hepatitis C Infection

Characteristic	NEUTRINO Study	FISSON Study	
	SOF + PEG + RBV For 12 Wk (N = 327)	SOF + RBV For 12 Wk (N = 256)	PEG + RBV For 24 Wk (N = 243)
Mean Age – Yrs (Range)	52 (19-70)	48 (20-77)	48 (19-77)
Treatment discontinuation rates	2%	1%	11%
Any serious Adverse Events	1%	3%	1%
In a single-group study of sofosbuvir combined with peginterferon–ribavirin, patients with predominantly genotype 1 or 4 HCV infection had a rate of sustained virologic response of 90% at 12 weeks. N Engl J Med 2013; 368:1878-1887			

Is There Anything New For Elderly Patients Without Interferon & Ribavirin ?

All-Oral Combination of Faldaprevir, Deleobuvir, and PPI-668 With and Without RBV Effective in Treatment-Naive HCV Genotype 1a–Infected Patients

Characteristic	Faldaprevir + Deleobuvir 600 mg + PPI-668 + RBV (n = 12)	Faldaprevir + Deleobuvir 400 mg + PPI-668 + RBV (n = 12)	Faldaprevir + Deleobuvir 600 mg + PPI-668 (n = 13)	*All Patients (N = 37)*
Median age, yrs (range)	**57 (30-65)**	**55 (42-62)**	**55 (22-71)**	**55 (22-71)**

In a small, ongoing phase II study, 81% of patients achieved undetectable HCV RNA by Week 4, and 100% of evaluable patients had SVR4.

AASLD - 2013

AI443-014: High SVR12 Rates With All-Oral Regimen of Daclatasvir, Asunaprevir, and BMS-791325 for 12 Weeks in Treatment-Naive Patients With Genotype 1 HCV

Characteristic	Daclatasvir + Asunaprevir + BMS-791325 75 mg BID (n = 80)	Daclatasvir + Asunaprevir + BMS-791325 150 mg BID (n = 86)	Total (N = 166)
Median age, yrs (range)	54 (23-68)	54 (23-69)	54 (23-69)

Expansion of the AI443-014 phase II trial demonstrated that the all-oral regimen of daclatasvir, asunaprevir, and BMS-791325 produced SVR12 rates in > 90% of patients while being generally well tolerated

AASLD 2013

C-WORTHY: High Virologic Efficacy and Favorable Safety of 12-Week, All-Oral Regimens of MK-5172/MK-8742 With and Without Ribavirin in Previously Untreated Genotype 1 HCV

Characteristic	MK-5172 100 mg + MK-8742 20 mg + Ribavirin (n = 25)	MK-5172 100 mg + MK-8742 50 mg + Ribavirin (n = 27)	MK-5172 100 mg + MK-8742 50 mg (n = 13)
Mean age, yrs (range)	48.7 (26-70)	43.9 (20-62)	43.3 (24-73)
In pilot study, high SVR12 response rates observed regardless of HCV subtype or inclusion of ribavirin AASLD 2013			

Conclusion

- CHC patients beyond the age of 70 years should be treated with peginterferon and ribavirin on case to case basis evaluating the risk benefit ratio, expected longevity of the person and associated comorbidities

- New interferon and ribavirin free oral DAAs may change the landscape of treatment of CHC patients beyond the age of 70 years

Efficacy Of Peginterferon-alpha-2b Plus Ribavirin In Patients Aged 65 Years And Older With Chronic Hepatitis C

Flow Chart For Patient Selection