

Antiviral Therapy and Liver Cancer

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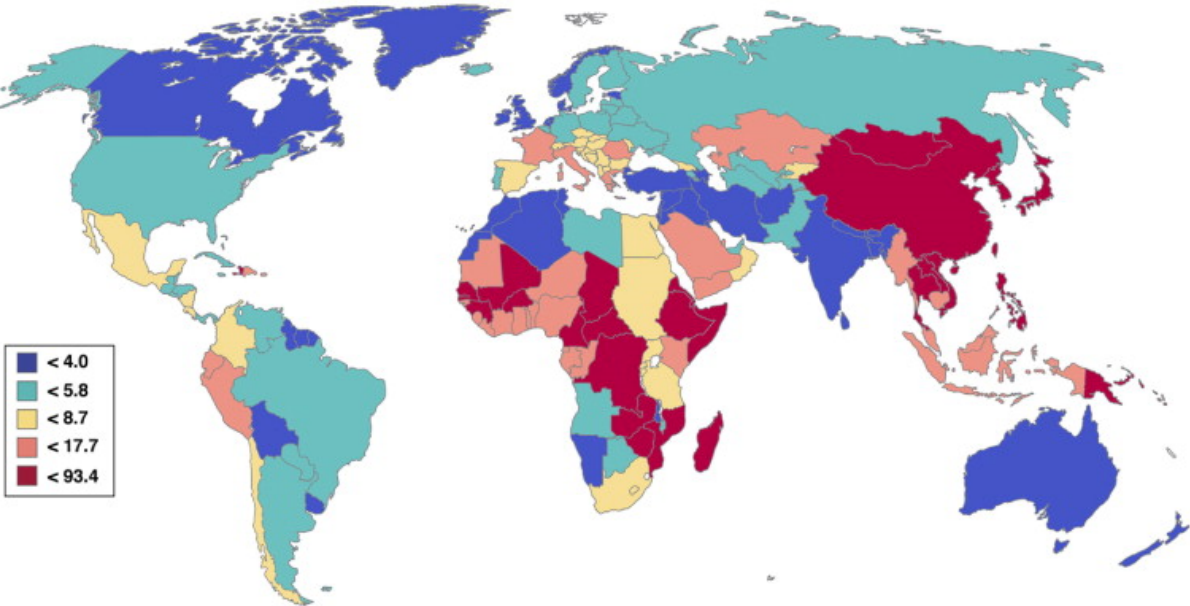
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Prevention through Antiviral Therapy

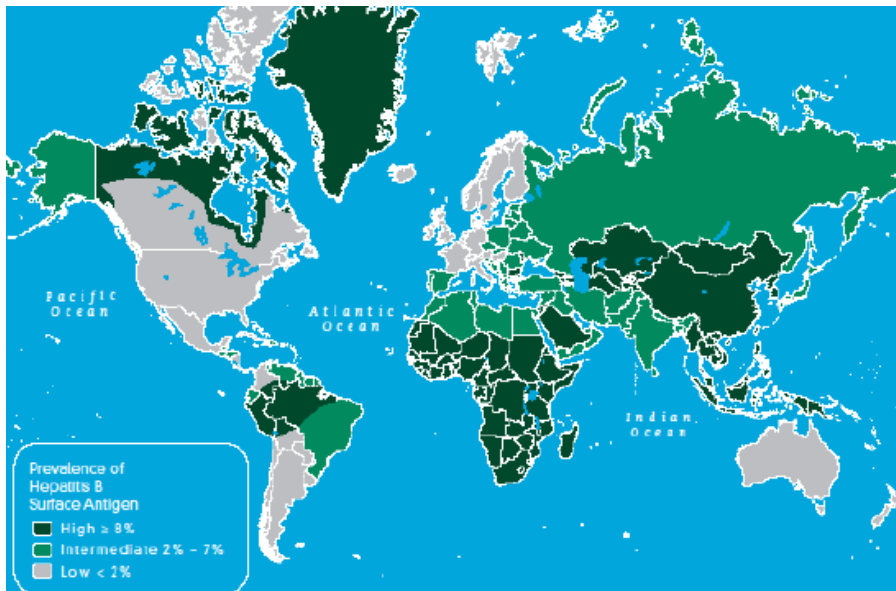
Mortality from HCC vs. HBV/HCV Epidemiology

El-Sareg, Rudolph; GE 2007: 132: 2557 Ioannou, Hepatology 2013, epub Hanafiah *et al.*, Hepatology 2013; 57: 1333

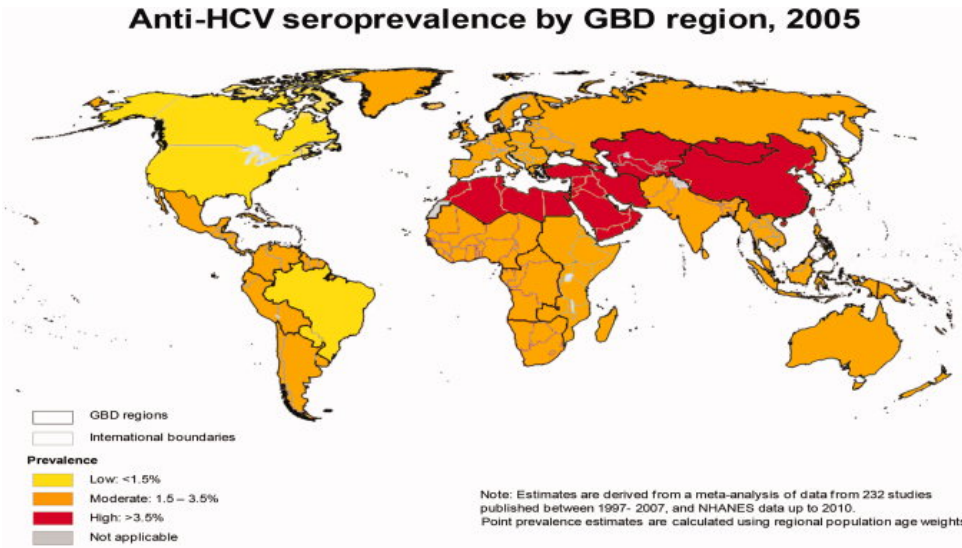
HCC



HBV

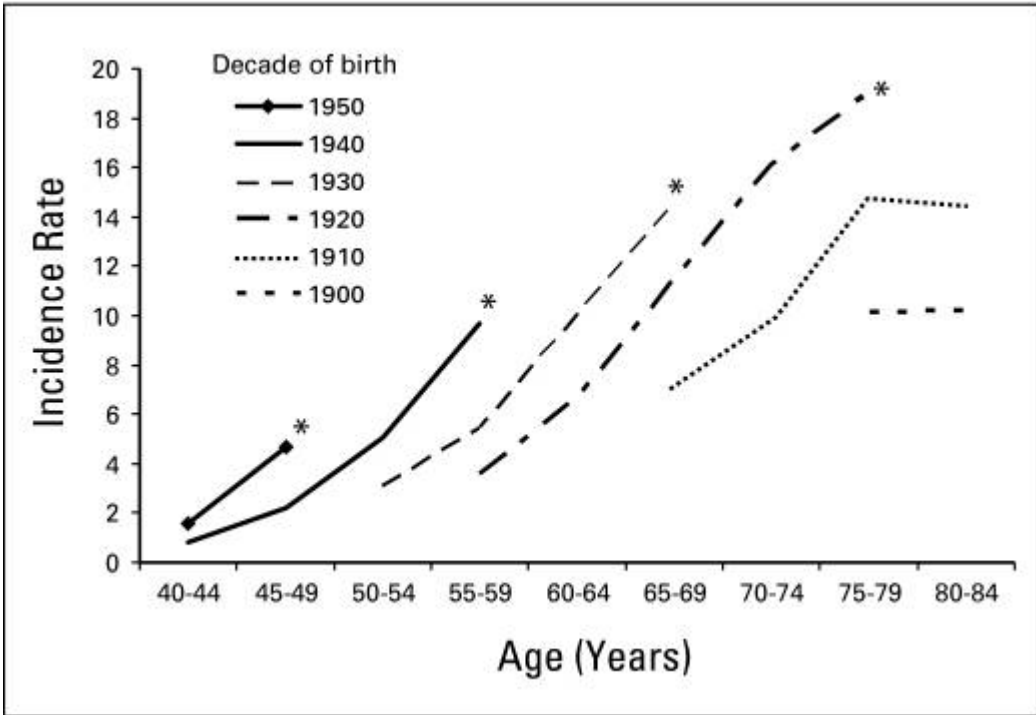
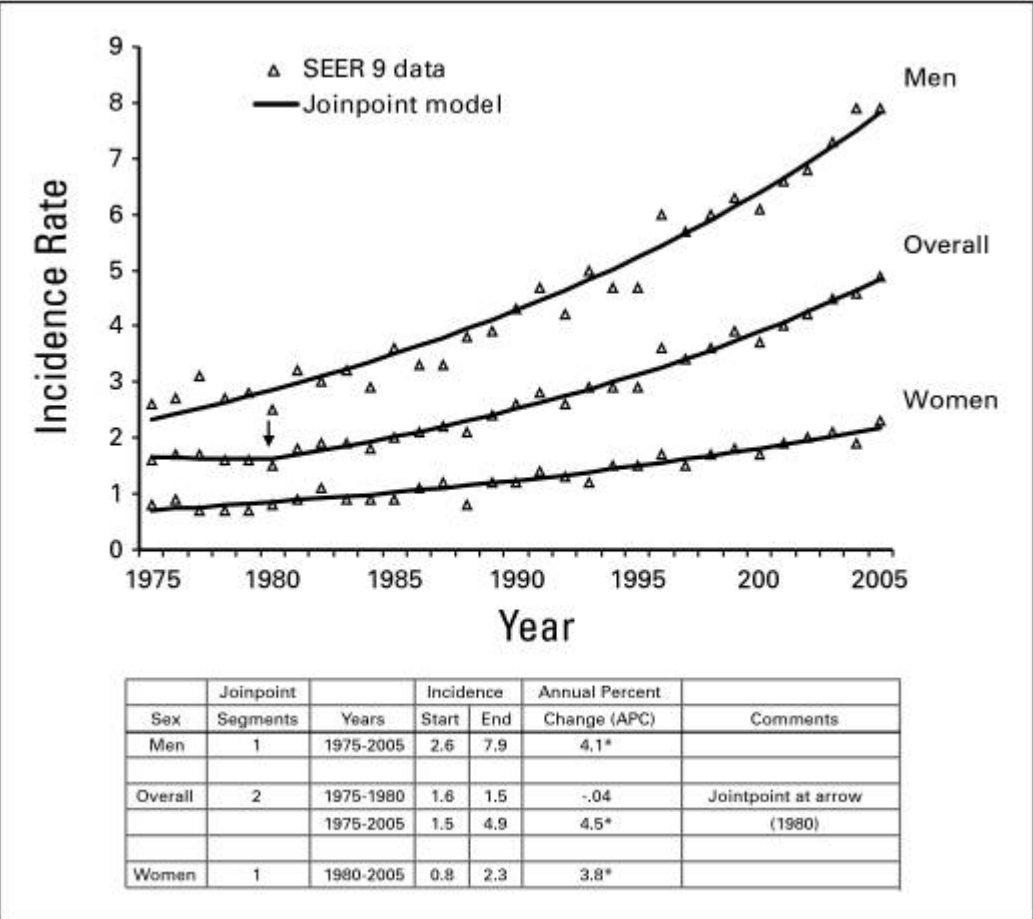


HCV



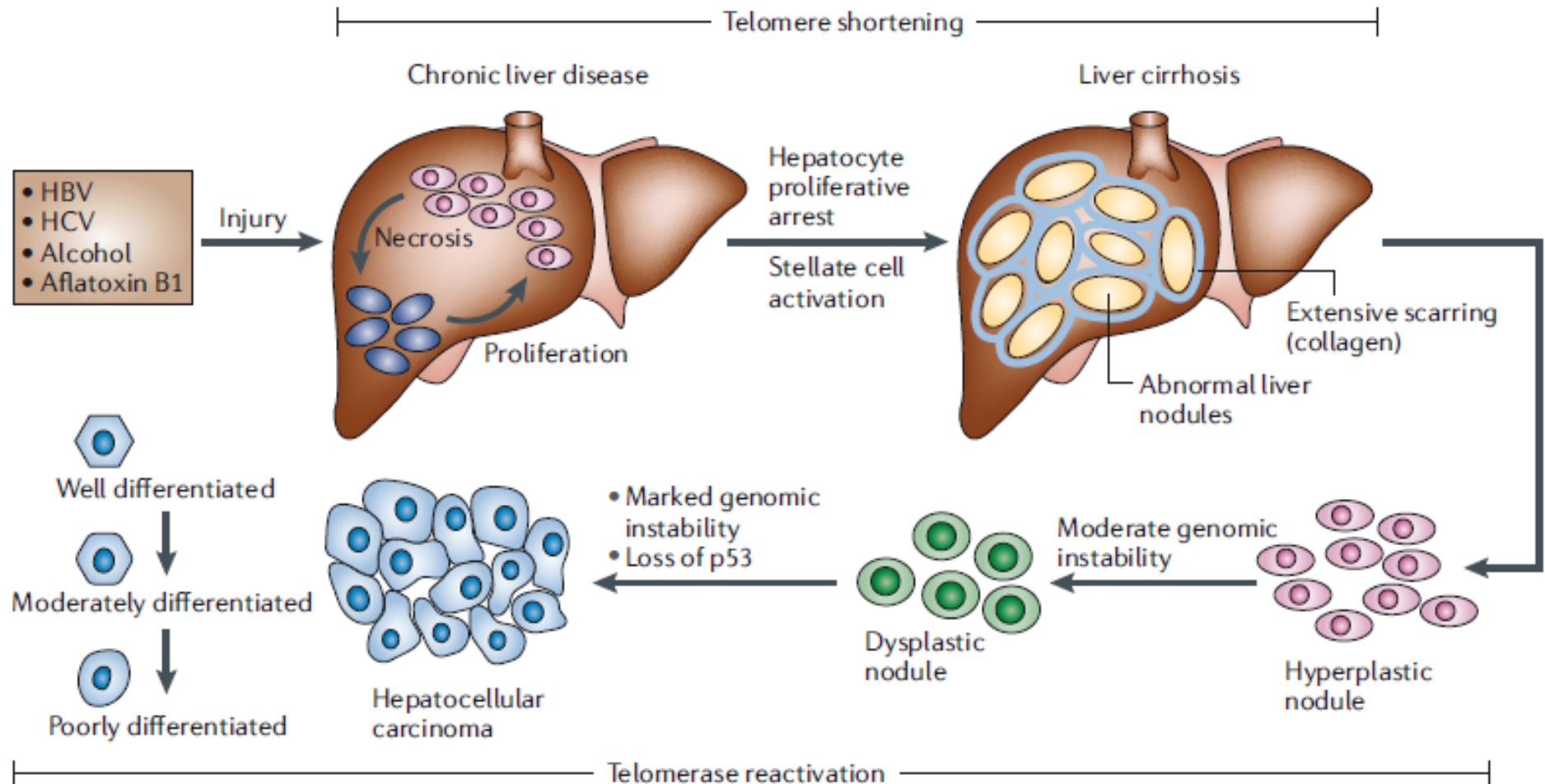
Incidence of HCC: US-Data 1975 - 2005

Altekruse *et al.*, JCO 2009; 27: 1485



Hepatocarcinogenesis

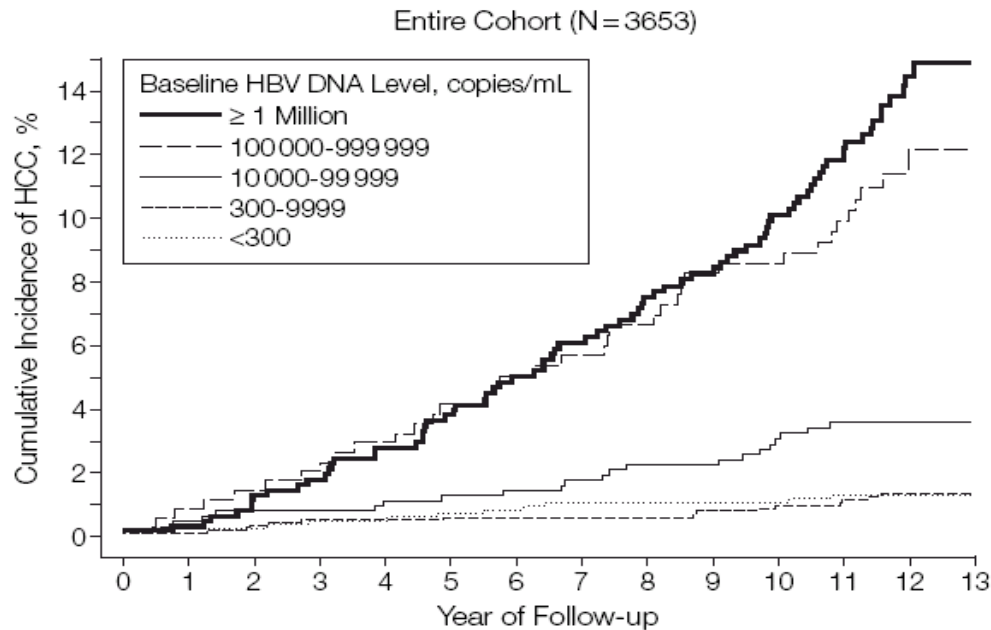
Farazi *et al.*, Nature Rev. Cancer 2006; 6: 674



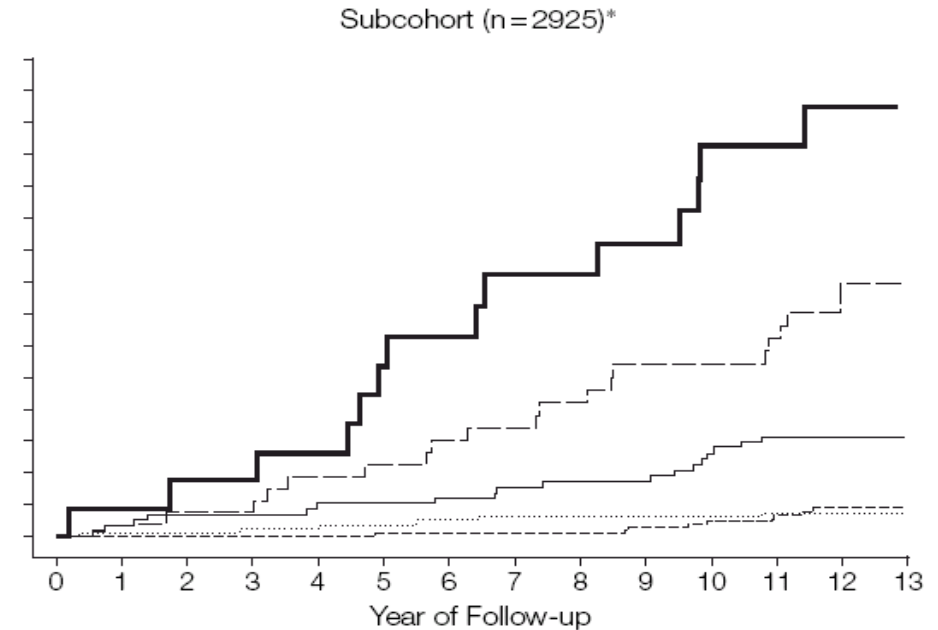
Viral Load and HCC-Risk

Chen *et al.*, JAMA 2006; 295: 65

Cumulative HCC-incidence dependent on HBV-DNA at baseline



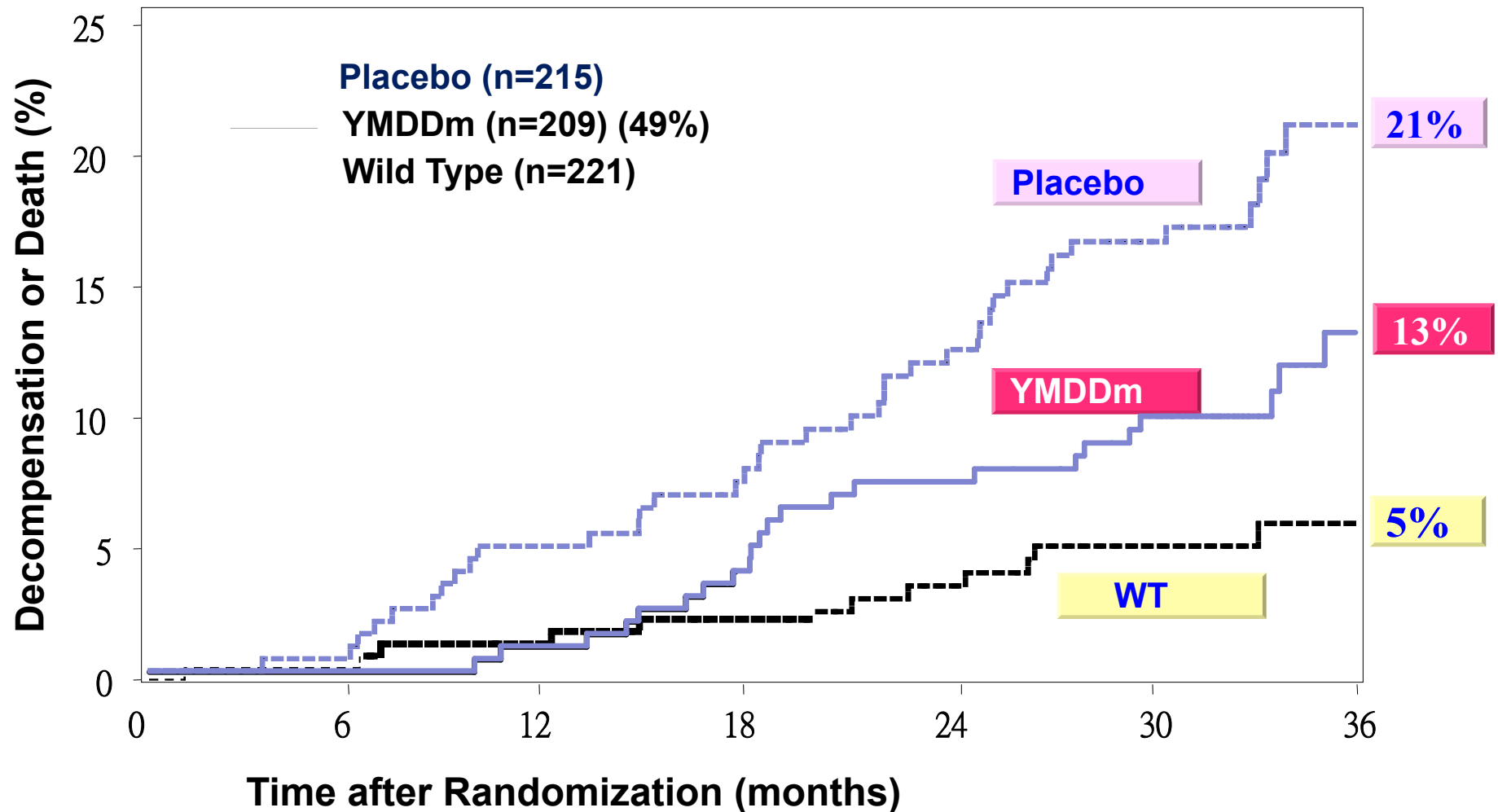
Patients total
(N=3653)



Patients with normal transaminases
(N=2925)

Lamivudine in HBV-associated Cirrhosis

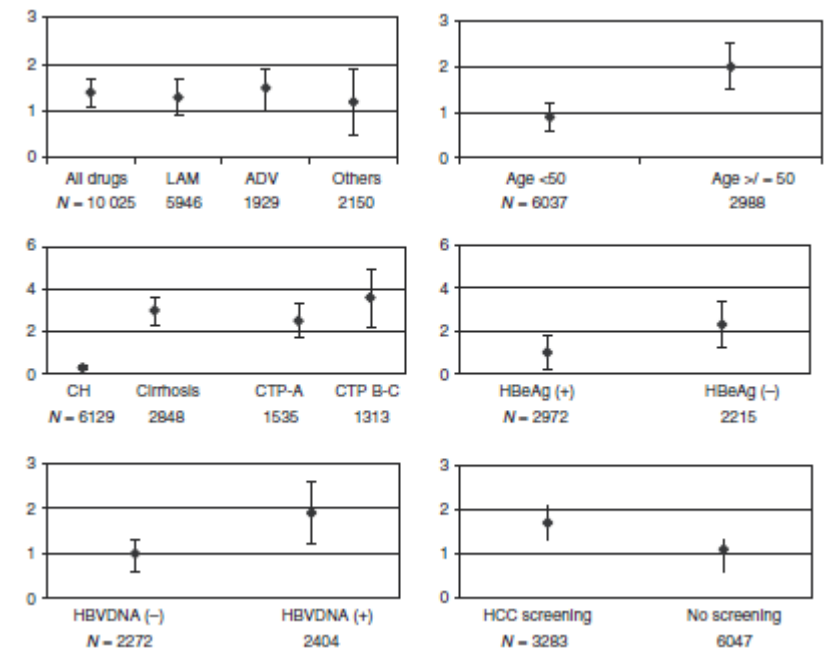
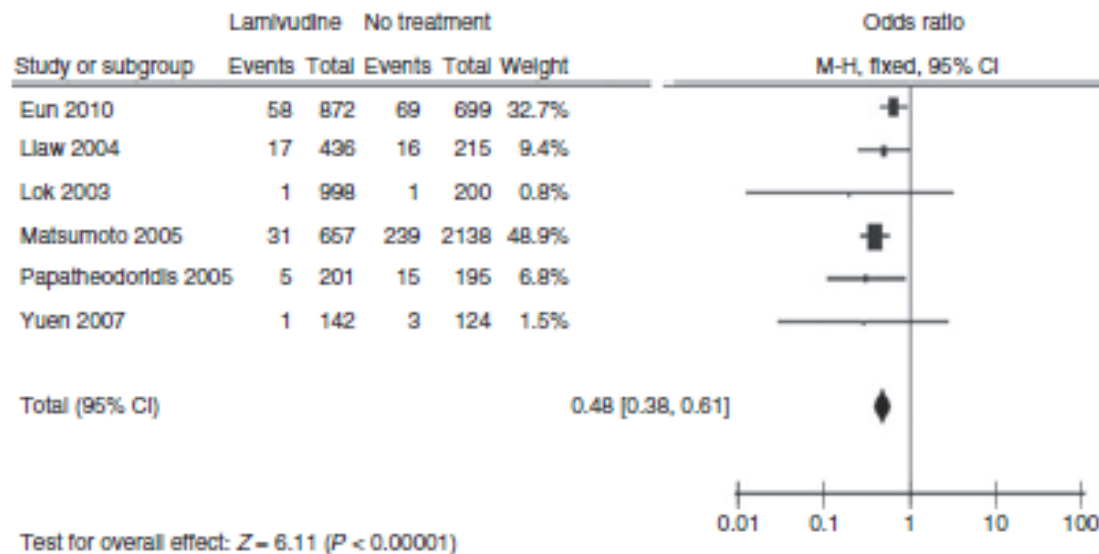
Liaw *et al.*, NEJM 2004; 351: 1521



Impact Oral HBV-Agents on HCC-MA

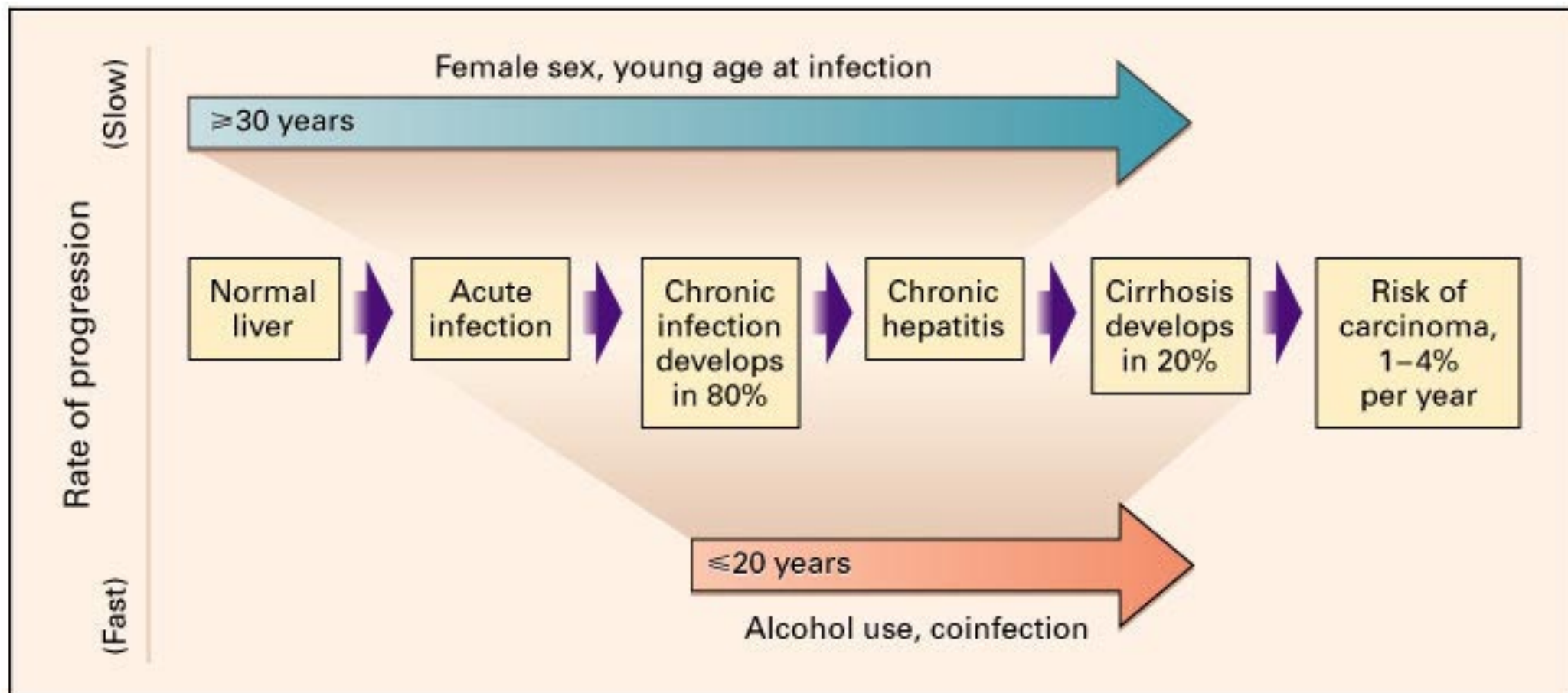
Singal *et al.*, APT 2013, epub

- 49 studies (out of 2562 screened), open-label to RCT's
- >20 patients, >2 years follow-up, adult HBV, no HIV, no OLT
- 23 LAM, 16 ADV, 6 ETV, 2 TBV, 2 TDF



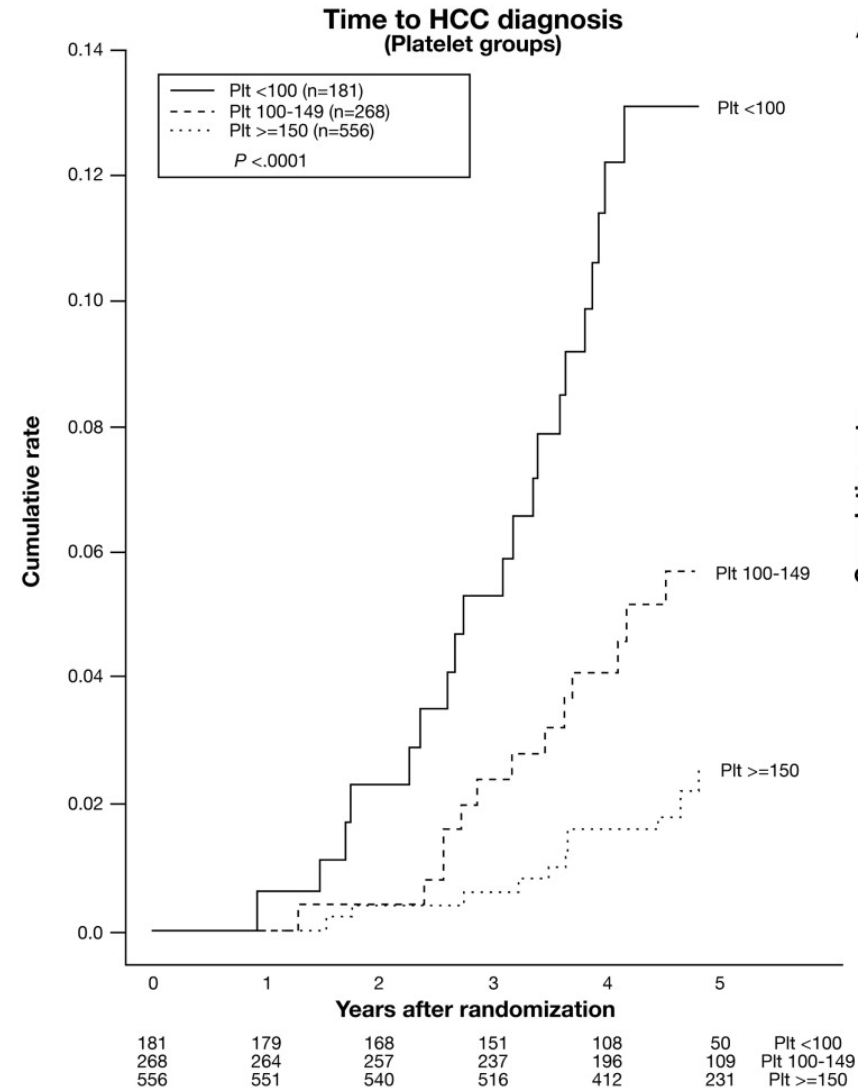
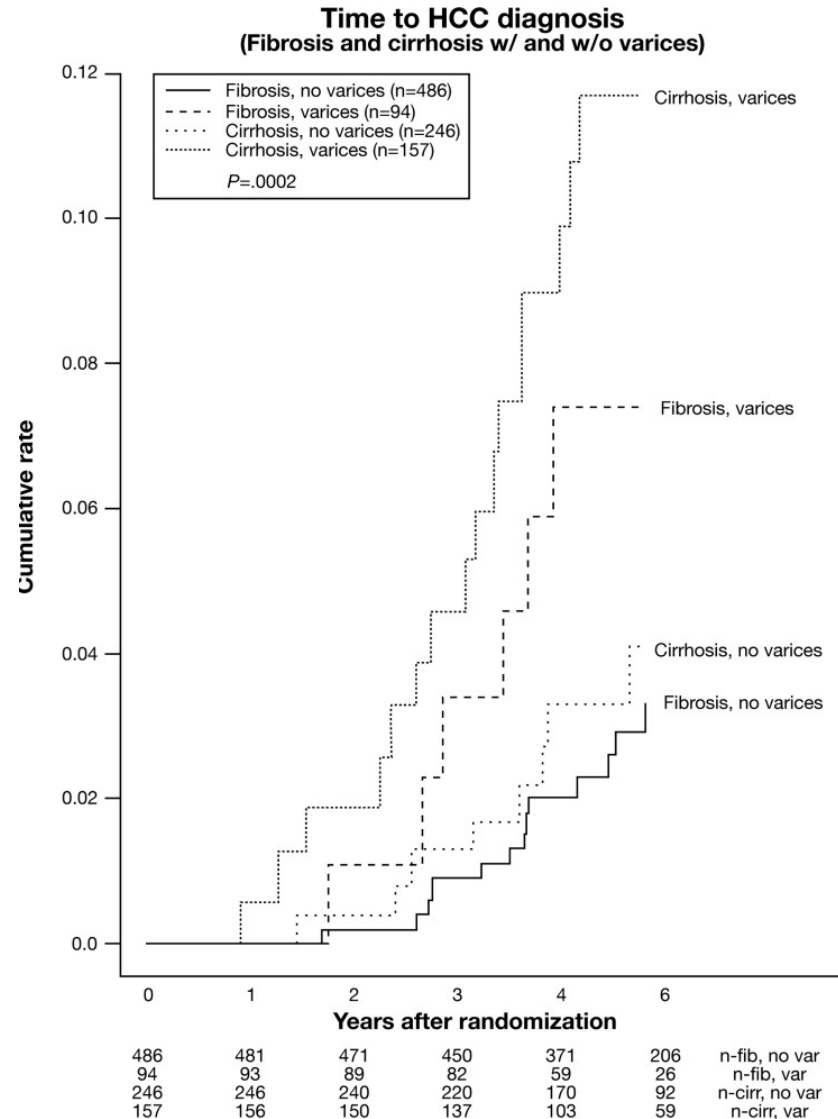
Natural Course HCV-Infection

Lauer & Walker, NEJM 2001; 365: 1425



HALT-C: Simple Predictors for HCC

Lok *et al.*, GE 2009; 136: 138



Therapy blocks Cirrhosis Progression

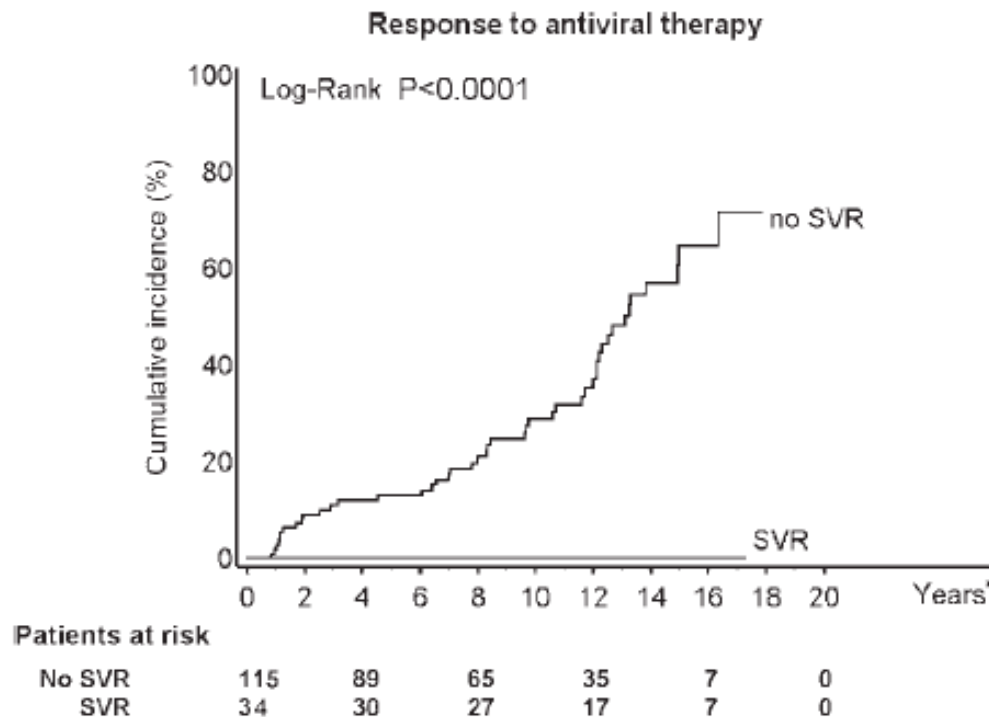
Bruno *et al.*, Hepatology 2010; 51: 2069

Iacobellis *et al.*, CGH 2011; 9: 249

- 218 HCV-cirrhotics Child A,
- 12 years prospective FU

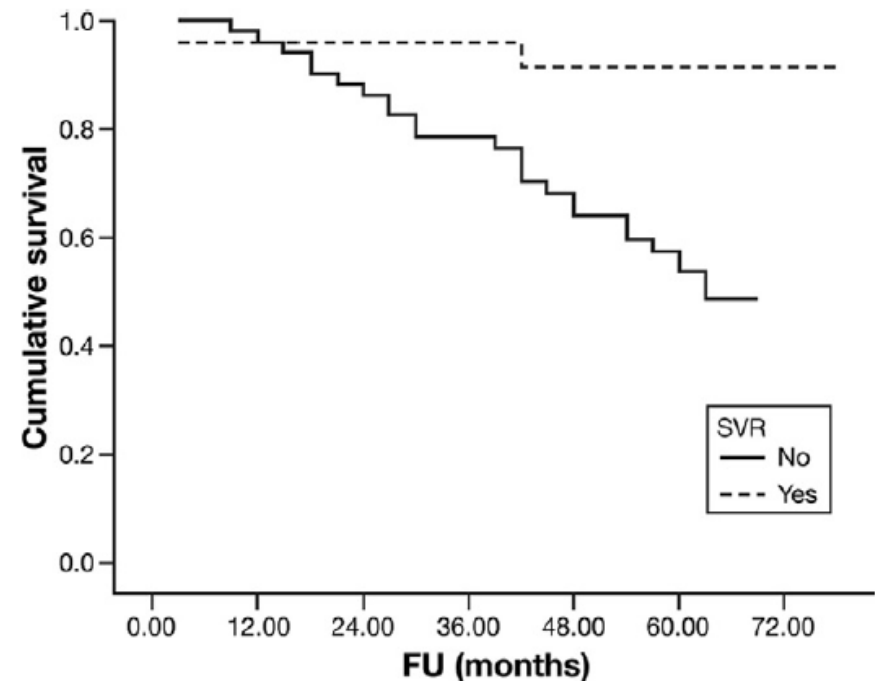
- 75 decompensated cirrhotics
- SVR vs. non-SVR

Development of varices



*since antiviral treatment initiation

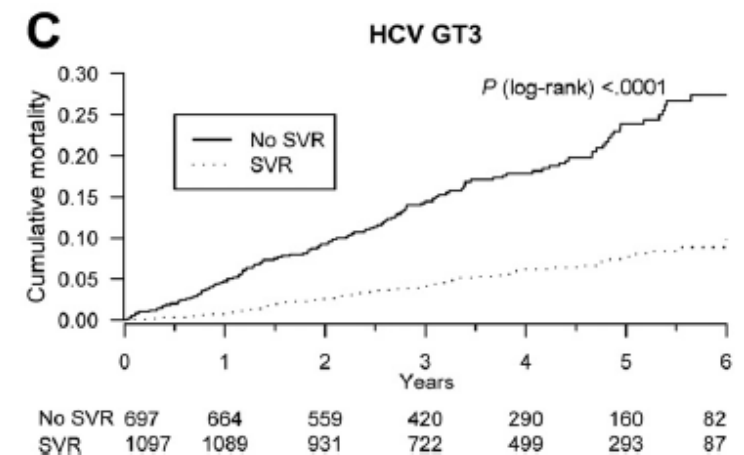
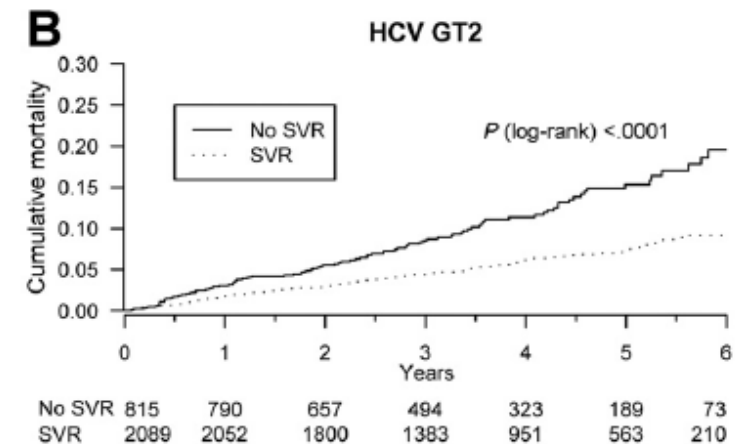
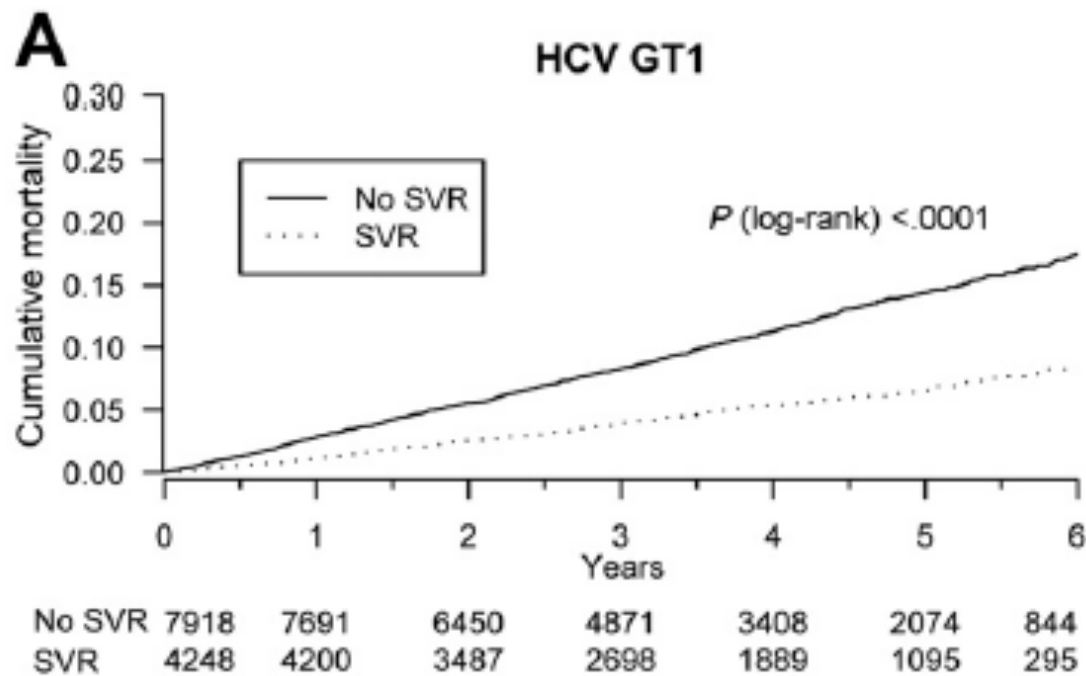
Survival



SVR reduces Mortality in HCV-Patients

Bachus *et al.*, CGH 2011; 9: 509

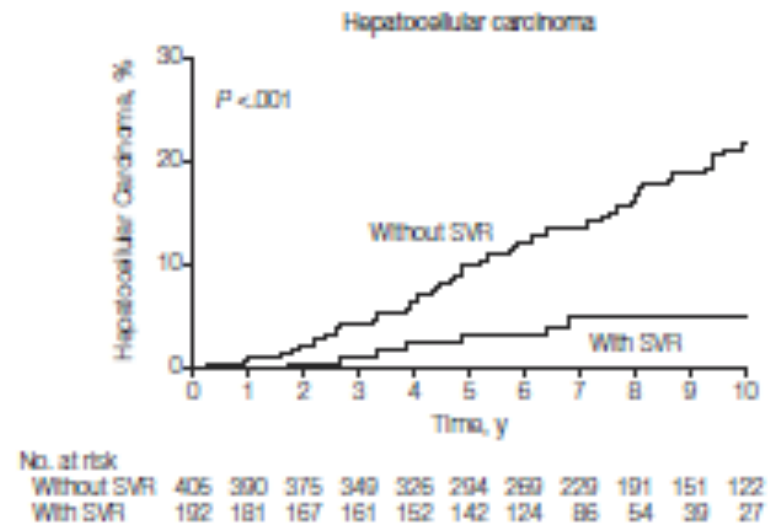
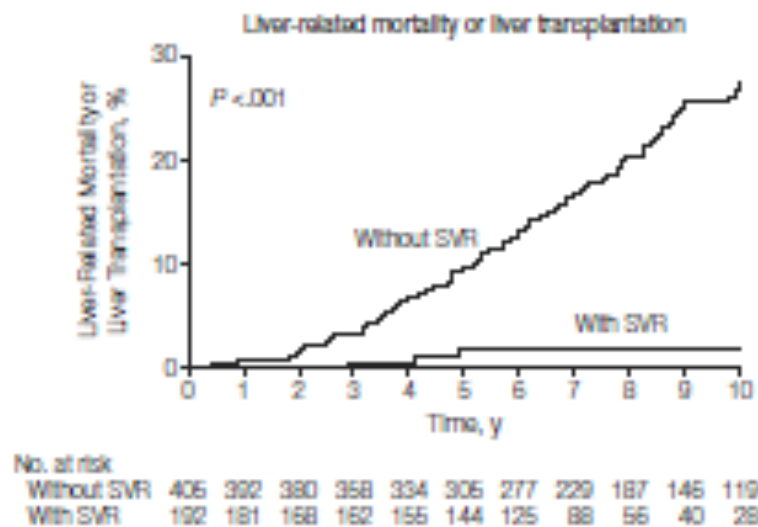
- 16864 patients, VA, 2001- 2009



SVR reduces HCC, Mortality, OLT

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

- 530 patients, advanced fibrosis (Ishak 4-6)
- IFN-based regimen 1990-2003, FU until 2010-2011

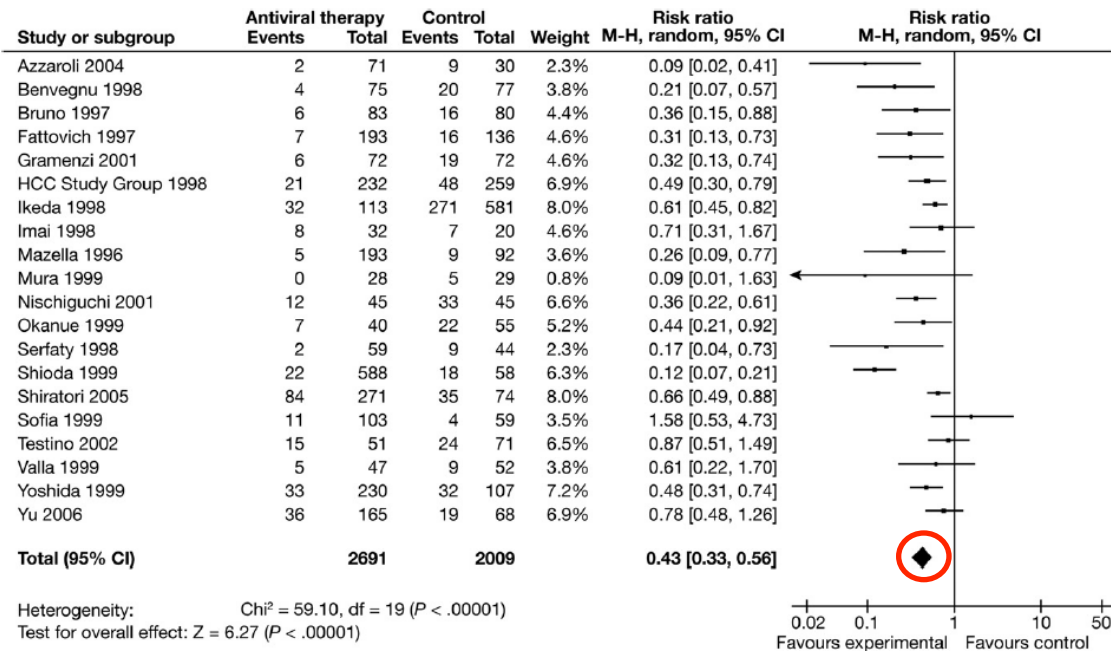


Antiviral HCV-Therapy prevents HCC

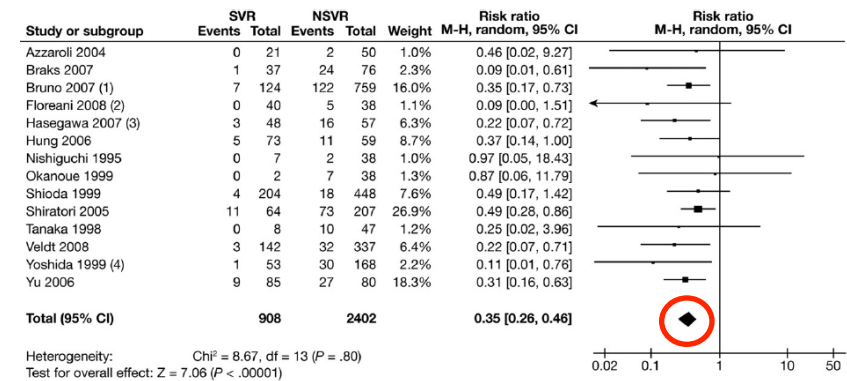
Singal *et al.*, CGH 2010; 8: 192

- Meta-analysis, 20 studies, 4700 patients

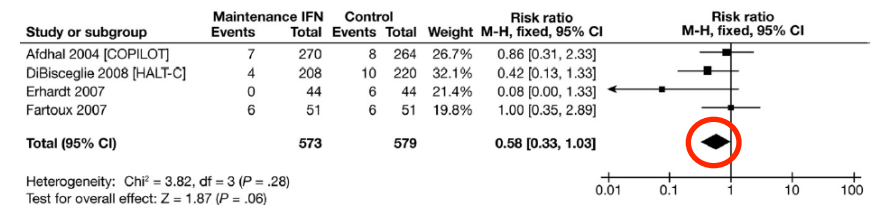
Therapy vs. no Therapy



SVR vs. no SVR



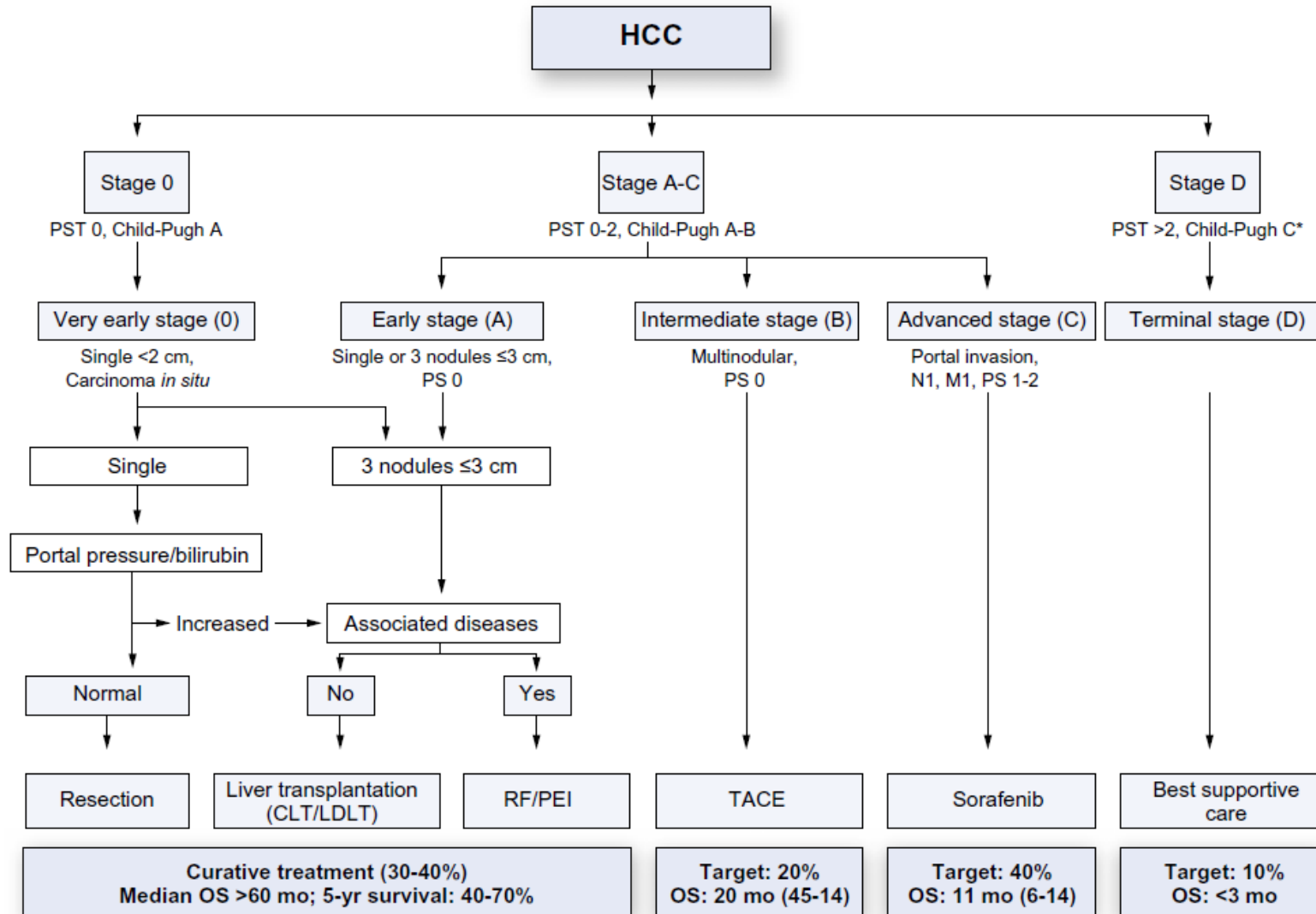
no SVR: continuous Tx vs. no TX



Antiviral Therapy during HCC-Therapy

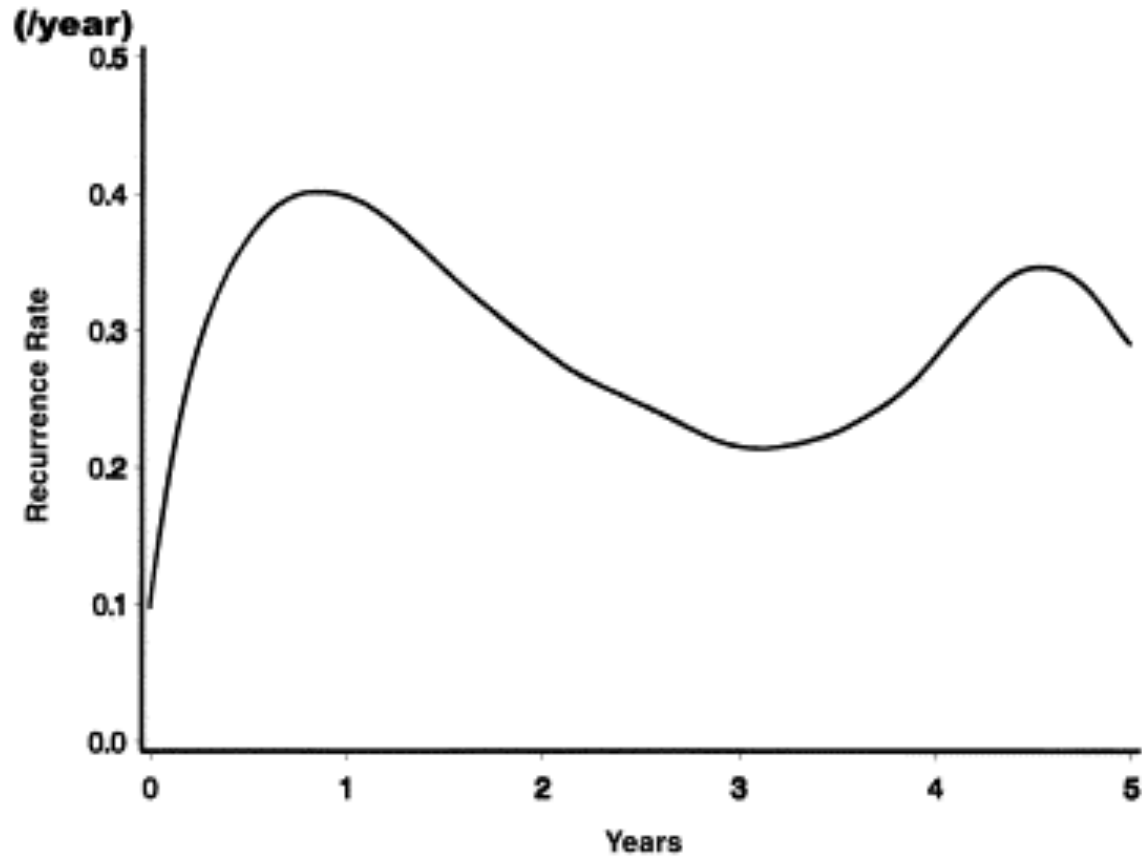
Guidelines: Recommendations HCC-Therapy

EASL-EORTC Guidelines, JHEP 2012; 56: 908



Recurrence of HCC after Curative Treatment

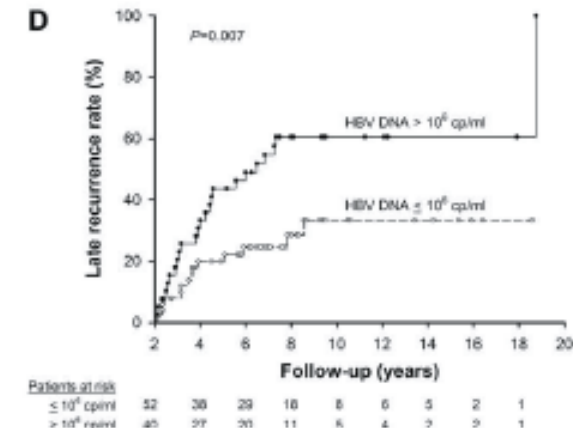
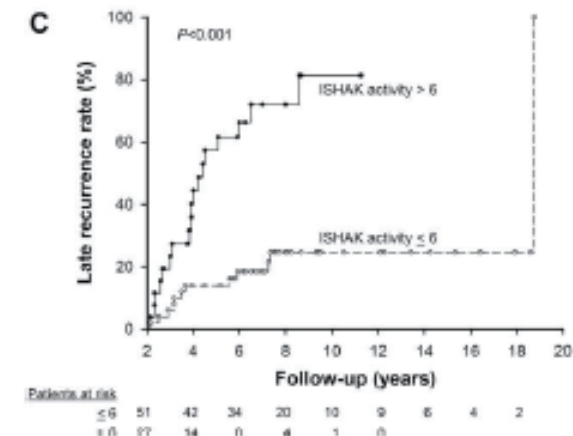
Imamura *et al.*, JHEP 2003; 38: 200



Recurrence HBV-related HCC

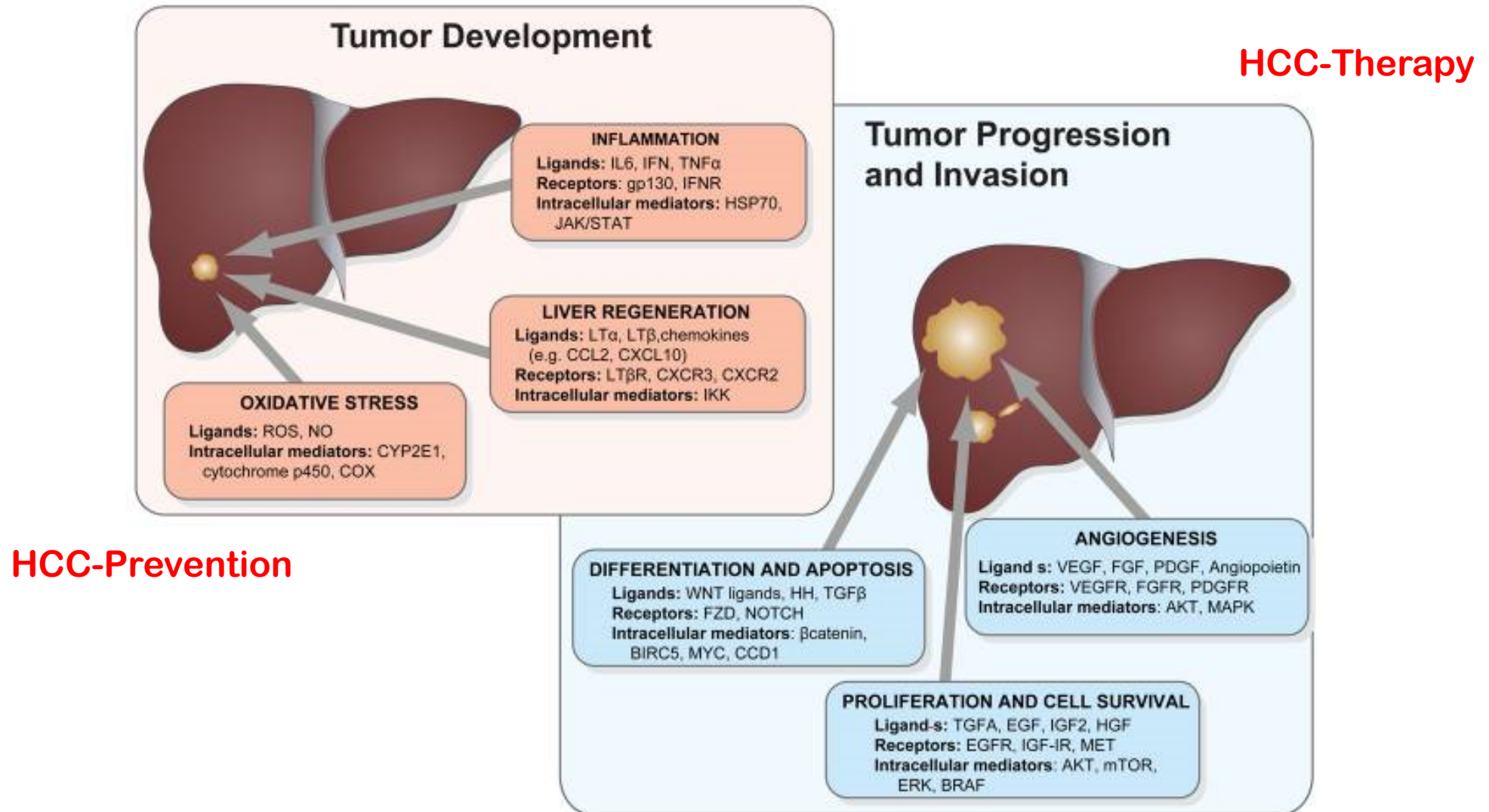
Wu *et al.*, JHEP 2009; 51: 890

- 193 HBV-associated HCC-patients, Taipeh
- Resection 1990-2002, FU 58 + 44 months: 134 recurrences
- Multivariate analysis
- Early recurrence (≤ 2 years)
 - multinodular HCC
 - vascular invasion
 - AFP >20 ng/mL
 - cut margin ≤ 1 cm
- Late recurrence (>2 years)
 - Ishak inflammatory activity >6
 - Multinodular HCC
 - HBV-DNA $>2 \times 10^5$ IU/mL



Dysregulated Signaling Pathways in HCC

Zender *et al.*, JHEP 2010; 52: 291

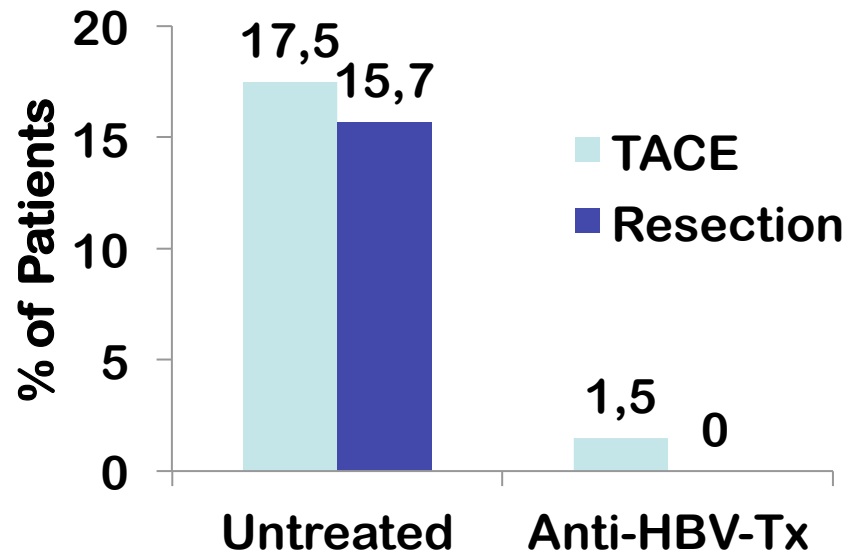


Anti-HBV-Therapy post TACE / Resection

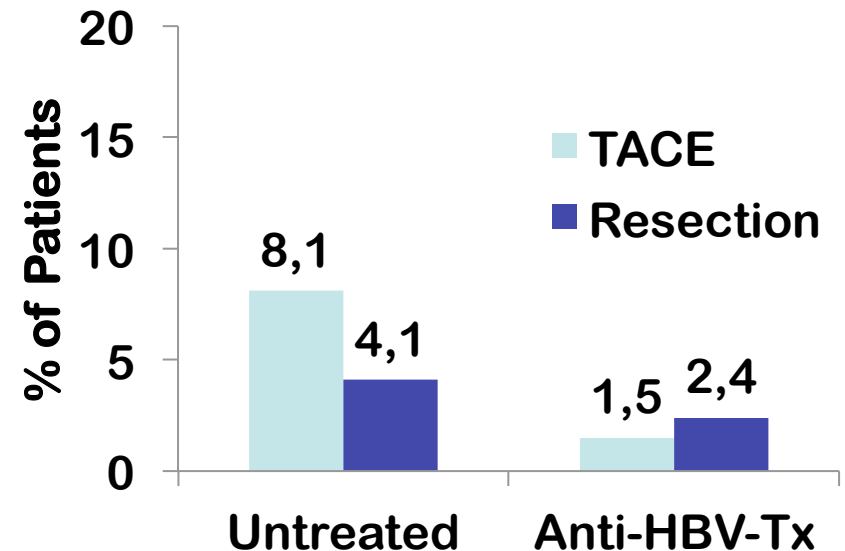
Lao *et al.*, Liver Int. 2013; 33: 595

- 590 HbsAg⁺ HCC-patients, Sun Yat-sen Center, Guangzhou
- 386 TACE (2007-2010), 204 Resection (2009-2010)
- Drugs: LAM, ADV, ETV, TBV
- Liver Deterioration: ALT↑ >3xULN, Bili↑ >2xULN, Child-Pugh ↑
- **Multivariate: anti-HBV tx independent predictor post TACE/resection deterior.**

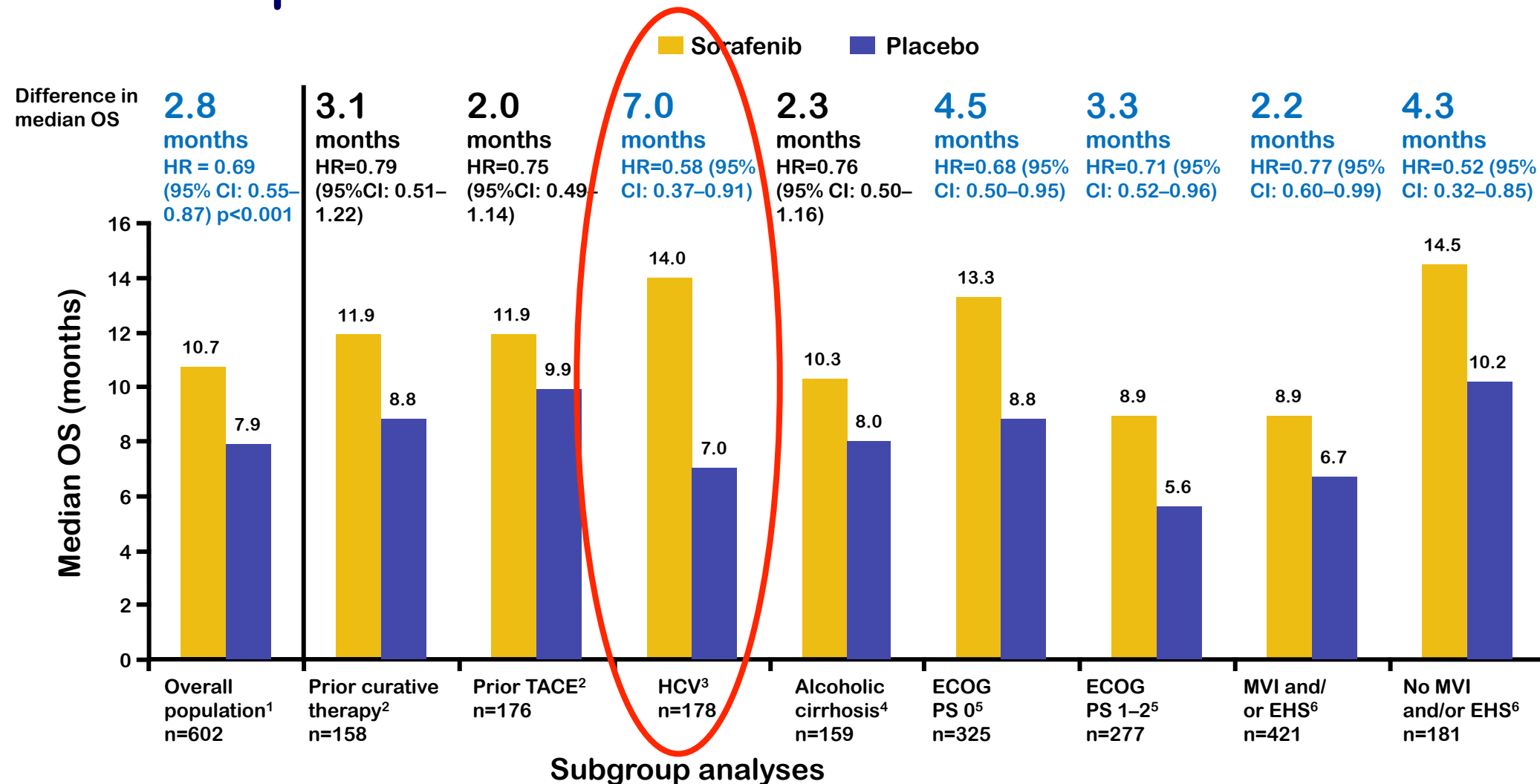
HBV-Reactivation (HBV-DNA ↑ 10x)



Liver Deterioration (ALT, Bilirubin, CP-Score)



Sorafenib: consistent survival advantage regardless of patient characteristics and disease extent

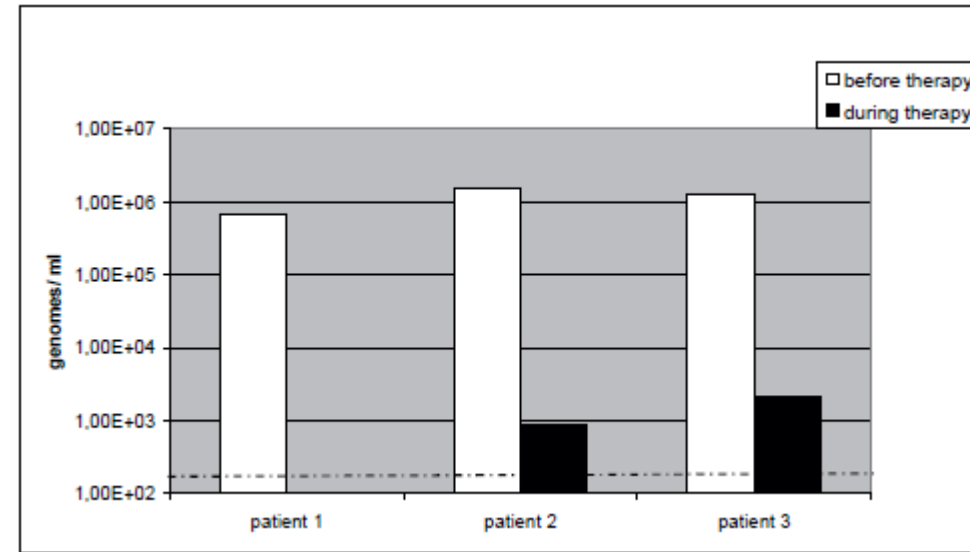
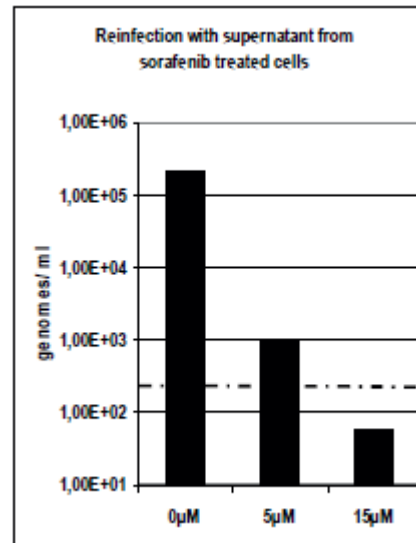
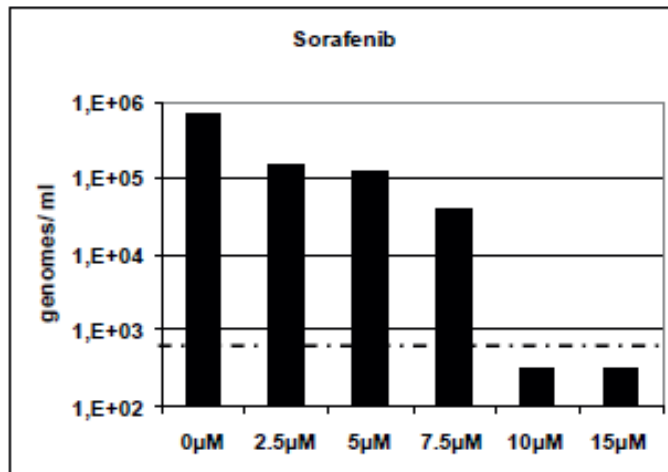


1. Llovet JM, et al. N Engl J Med 2008;359:378–90; 2. Galle P, et al. EASL 2008, Milan, Italy; 3. Bolondi L, et al. ASCO GI 2008, Orlando, FL, USA
4. Craxi A, et al. ASCO 2008, Chicago, IL, USA; 5. Raoul J, et al. ASCO 2008, Chicago, IL, USA; 6. Sherman M, et al. ASCO 2008, Chicago, IL, USA

Sorafenib: anti-HCV activity

Himmelsbach *et al.*, Gut 2009; 58: 1644

- HCV-NS5a interacts with c-RAF
- Sorafenib: RAF-inhibitor
- Blocks HCV-replication, gene expression, NS5a hyperphosphorylation
- other MKI's don't (like Sunitinib), downstream target inhibitors don't



Summary

- Antiviral therapy for both HBV and HCV can prevent progression of liver disease
- Antiviral therapy for both HBV and HCV can prevent HCC-development and survival
- Antiviral HBV-therapy improves survival post curative therapy for HCC
- Antiviral HBV-therapy reduces liver deterioration after resection / TACE for HCC
- IFN-based HCV therapies do not play a role in palliative treatments for HCC; HCV-treatment after curative treatments might be reasonable
- With new DAA-only based regimens, there might be an increasing role for HCV-treatment not only in curative but also in palliative situations with reasonable survival expectancy



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