

Primary Prevention of Variceal Bleeding

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 - MBBCH, Cairo university , June 1987.
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 - Resident of internal medicine , Cairo university, 1979 to 1982.
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 - Chairman of hepatology department, NLI since 2008



Diagnosis Of Cirrhosis

Screening & Frequency of Surveillance

- As patients with risky varices can be offered prophylactic therapy so, screening by upper endoscopy is mandatory for all cirrhotic patients.
- Frequency of Surveillance
 - Compensated cirrhosis
 - No varices, rescreen in 2-3 years
 - Small varices, rescreen in 1-2 years
 - Decompensated cirrhosis, rescreen yearly

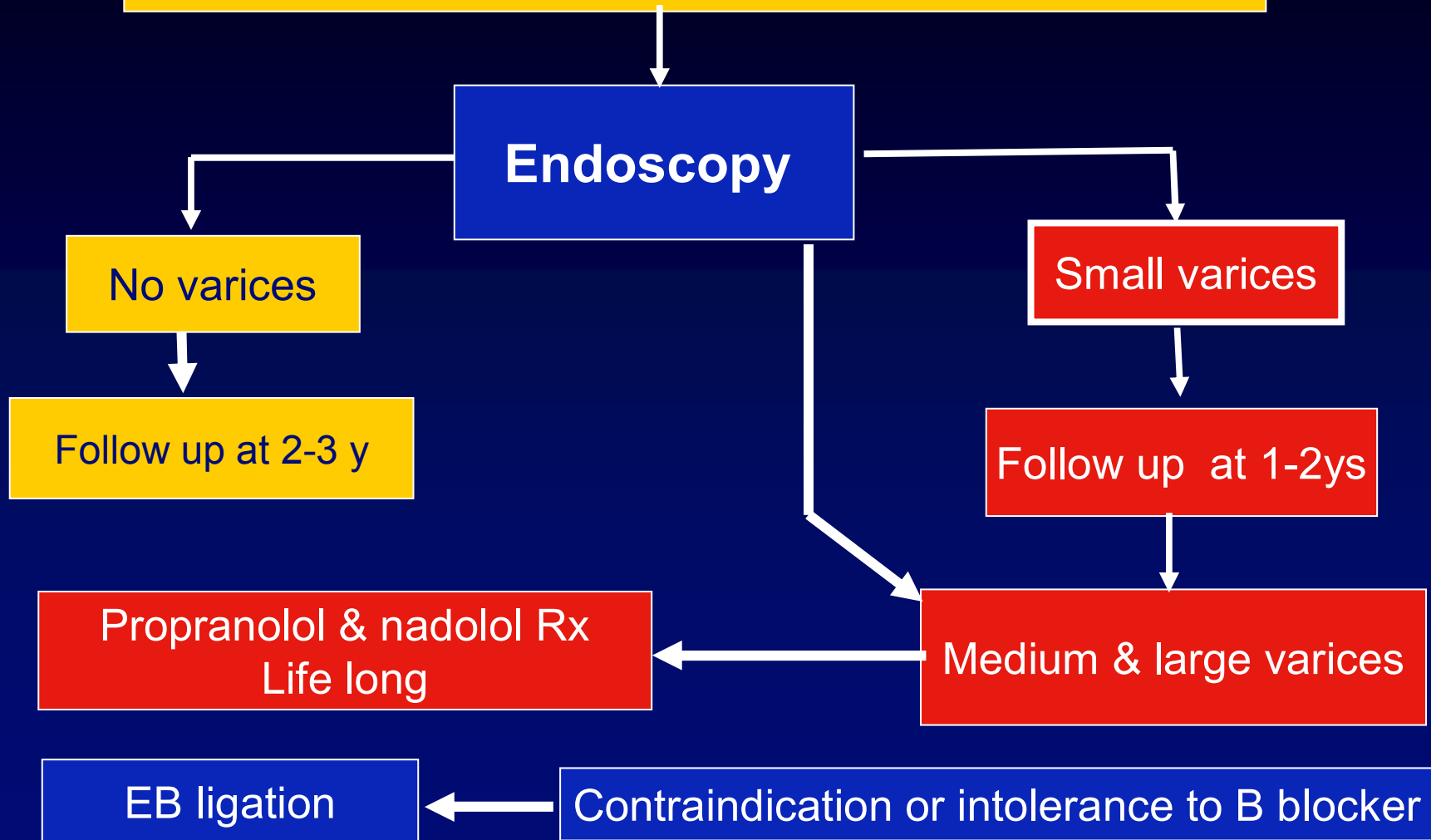
De Franchis R. J Hepatol 2005;43:167-76.

Lebrec D, et al. a French consensus. Eur J Gastroenterol Hepatol 2005;17:

Merli M, et al. J Hepatol 2003; 38:266-272

de Franchis R. J Hepatol 2000;33:846-852.

Diagnosis of Cirrohsis

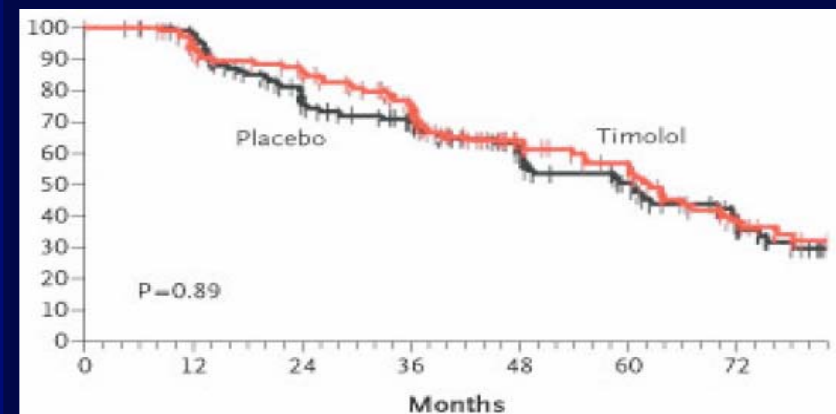


Is There Any Pre-primary Prophylaxis

I. No varices: Can we prevent its formation?

- Cirrhotic patients without varices having HVPG of > 6 mmHg were enrolled In RCT
- No statistically significant differences were found between studied groups in the development of varices or variceal hemorrhage.
- Patients in whom HVPG was below 10 mm Hg or in whom HVPG decreased by greater than 10% had a significantly lower risk of developing varices.

	Timolol n=108	Placebo n=105
Varices	39	39
V bleeding	3	3
Ascites/ Encph	32	24
AEs	20	6
Mortality	10	15



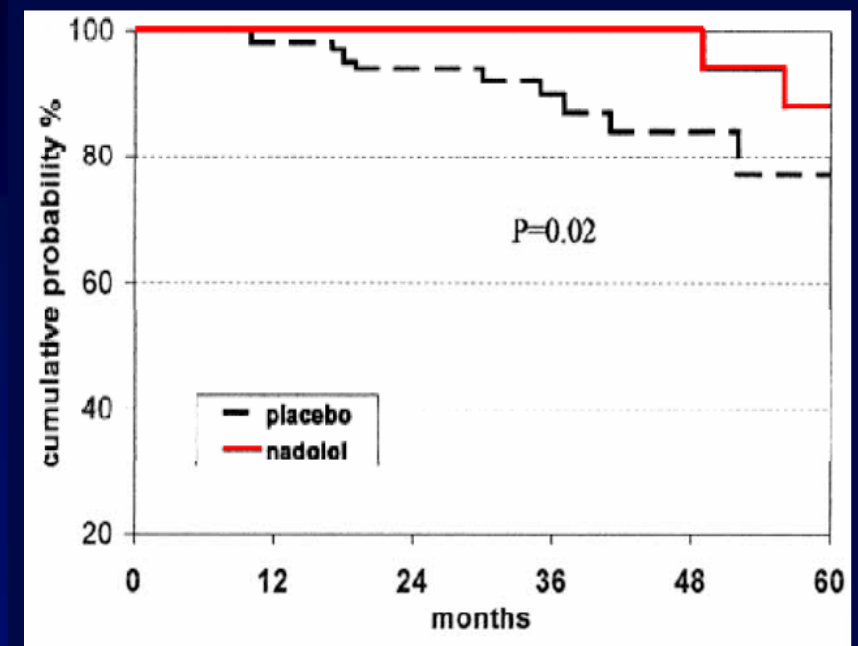
No Varices: Can we prevent its formation?

In Conclusion:

- No benefit form using NSBB (timolol) for prevention of variceal formation.
- Complications were more with NSBB
- These results do not support the use of NSBB in cirrhosis without varices

Small Varices: Can we prevent size increase?

- RCS including 158 cirrhotic patients who had small varices were enrolled (83 patients received nadolol and 78 received placebo) . After a mean follow-up of 36 mo
- Nadolol significantly slowed enlargement of small varices (11%) than placebo (37%) at 3 years
- In patients with non-risky small varices, the use of NSBB to prevent further increase in size are optional



Small Varices: Can we prevent bleeding?

- Incidence of first bleeding from small varices was low over 2 years (7% with placebo). Decreased further with NSBB (2%) (NS) in a meta-analysis
- High-risk small varices (red wale signs or in Child C) bled at a similar rate to large varices
- In these patients NSBB must be used to prevent bleeding

Is There Any Pre-primary Prophylaxis

In conclusion for preprimary prophylaxis:

- No indication to treat patients without varices for the prevention of the formation of varices
- Patients with small varices could be treated with a nonselective B-blocker.

Primary Prophylaxis

High Risk Varices

- Prophylaxis for large varices decreases the relative risk of first variceal bleeding by ~60% and mortality by ~45% vs no therapy
- Both NSBB and EVL are effective in prevention of first variceal bleed



Primary Prophylaxis

Pharmacologic Treatment & EVBL

- The risk of bleeding is virtually abolished when HVPG or the variceal pressure is reduced by as much as or more than 20% of baseline values or HVPG is reduced below 12 mm Hg

I: Pharmacologic treatment: Aims:

- Prevent the first bleeding episode
- Improve survival by reducing bleeding-related mortality
- Drugs available : Nonselective B-blockers (NSBB), nitrates, and spironolactone.

Drugs for Primary Prophylaxis: NSBB

- NSBB should be titrated empirically to decrease the resting heart rate by 25% of baseline value or <55 b/m.
- Advantages of NSBB:
 - prevention of bleeding from other portal hypertension sources (PHG and gastric varices)
 - possible reduction in incidence of SBP
- Starting dose: Propranolol 20 mg BID, Nadolol 40 mg QD
- Dose adjusted to maximal tolerated doses. Median dose of PP 80 mg BID & Nadolol 80 mg OD
- Risk of bleeding recurs when treatment is stopped, and therapy should be continued indefinitely

Nitrates

- IMN compared with propranolol in three RCTs studies showed a nonsignificant increase in bleeding rate and mortality with IMN*.
- IMN versus placebo in patients with contraindications or intolerance to B-blockers failed to show any benefit from IMN in the prevention of first bleeding**.
- One study reported an increased mortality with IMN among patients older than 50. This suggests that IMN should not be used as single agent.**

D'Amico et al., Semin Liver Dis 1999;19(4):475–505.*

Garcia-Pagan Gastroenterology 2001;121(4):908–914.**

Nitrates

- The combination of IMN and B-blockers has been compared with B-blockers alone in three RCTs.
- No significant advantage was detected between the two treatment groups in bleeding or mortality rates.
- Bleeding rate was 15% in the B-blocker–treated patients vs 10% in the combination therapy patients; the 5% bleeding risk reduction with the combination therapy was not significant (95% CI -16% to 6%).
- These results do not support the use of combination therapy for the prevention of first variceal bleeding.

Merkel et al., *Lancet* 1996;348(9043):1677–1681.

D'Amico Get al., *Gastroenterol Int* 2002;15:40–50.

Garcia-Paganet al., *Hepatology* 2003;37:1260–1266.

Diuretics

- Spironolactone counteract the increase in plasma volume that sustains the hyperdynamic circulation in portal hypertension, so can lowers HVPG in patients with cirrhosis.

Garcia-Pagan et al., Hepatology 1994;19(5):1095–1099.

- RCT compared its combination with nadolol vs nadolol alone for the prevention of first variceal bleeding and ascites in compensated cirrhotic patients
- They showed similar results in HVPG reductions, bleeding rates, and 2-year mortality rates

Abecasis et al., Hepatology 2003;37(2):359–365.

- Thus once large varices have been identified should be treated empirically with BB. NSBB can reduce risk of bleeding by nearly 50% over 2ys
- Overall, NSBB are more beneficial in patients with medium or large varices without ascites than in those with ascites.
- This effect is small and nonsignificant in patients with small varices.
- EVBL be an acceptable alternative to beta blockade in patient intolerant or contraindicated to BB , as shown in RCT examine VBL versus beta blockade

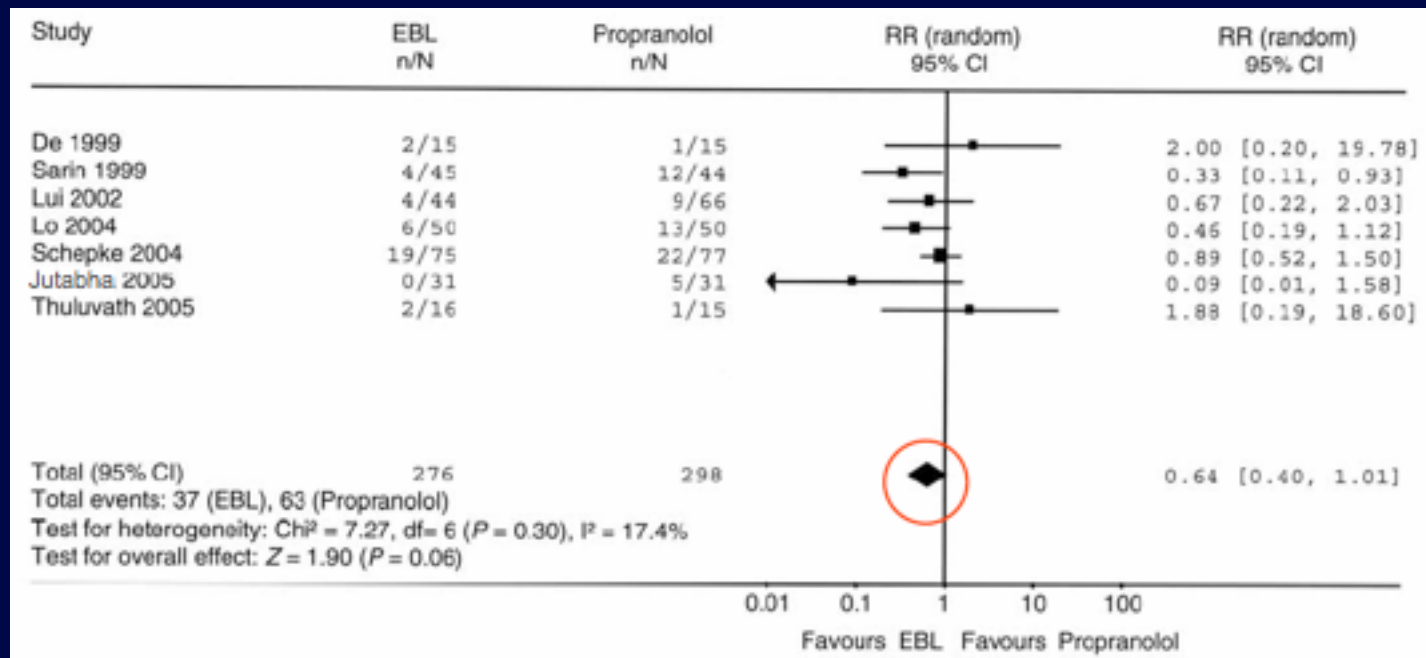
Khuroo et al. Aliment Pharmacol Ther 2005;21:347-361

Garcia-Pagan JC, Bosch J. Nat.Clin Pract.Gastroenterol Hepatol 2005;2:526-535.

Primary Prophylaxis

High Risk Varices: EVL or NSBB

- In 2 meta-analyses including 1,435 patients EVL was associated with slightly but significantly lower first variceal bleeding rate



Khuroo et al. Aliment Pharmacol Ther 2005;21:347-361

Garcia-Pagan JC, Bosch J. Nat.Clin Pract.Gastroenterol Hepatol 2005;2:526-535.

This meta analysis concluded that in cirrhotic patients with moderate to large varices (who have not bled) EVL compared with B blockers significantly reduced bleeding episodes and adverse events. However, it had no effect on mortality.

Adverse event	Total	Severe	Fatal
Ligation related			
Oesophageal ulcers	47	8*	2
Oesophageal perforation	1	1	–
Dysphagia	23	–	–
Chest pain	11	–	–
Fever	03	–	–
Others/not defined	18	–	–
Total (six trials/241 patients)	103 (42.7%)	9 (3.7%)	2 (1.9%)
β -Blockers related			
Hypotension	39	12	–
Breathlessness	25	20	–
Bradycardia	16	1	–
Psychiatric manifestations	13	1	–
Bronchospasm	6	–	–
Impotence	6	1	–
Raynaud's	3	1	–
Others/not defined	40	3	–
Total (six trials/ 264 patients)	148 (56.1%)	39 (14.8%) [†]	2 (1.4) [‡]

Khuroo et al. Aliment Pharmacol Ther 2005 ;21:347-361
 Garcia-Pagan JC, Bosch J. Nat.Clin Pract.Gastroenterol Hepatol 2005;2:526-535.

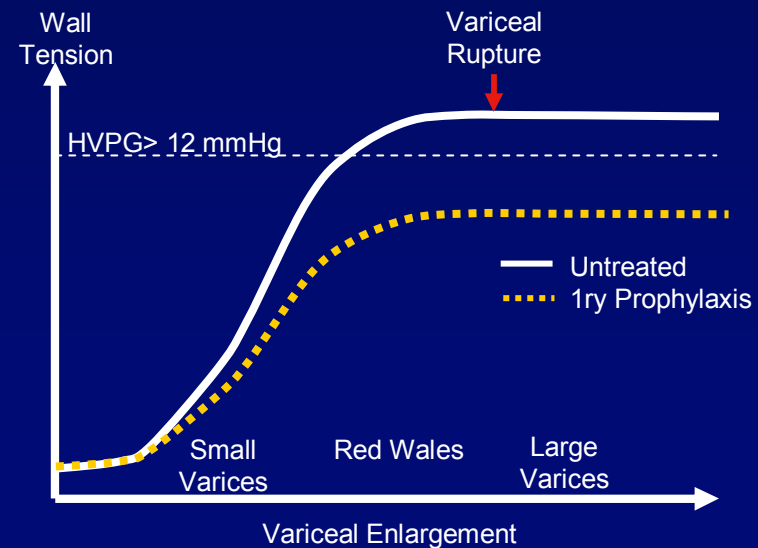
- Another meta analysis about EVL for prophylaxis of OVB showed that, EVL compared with beta blocker significantly reduce rates of first gastrointestinal bleeding by 31% and first variceal bleeding by 43%
- Severe adverse effect were less with EVL compared with beta blockers

Primary Prophylaxis

HVPG measurements & NSBB

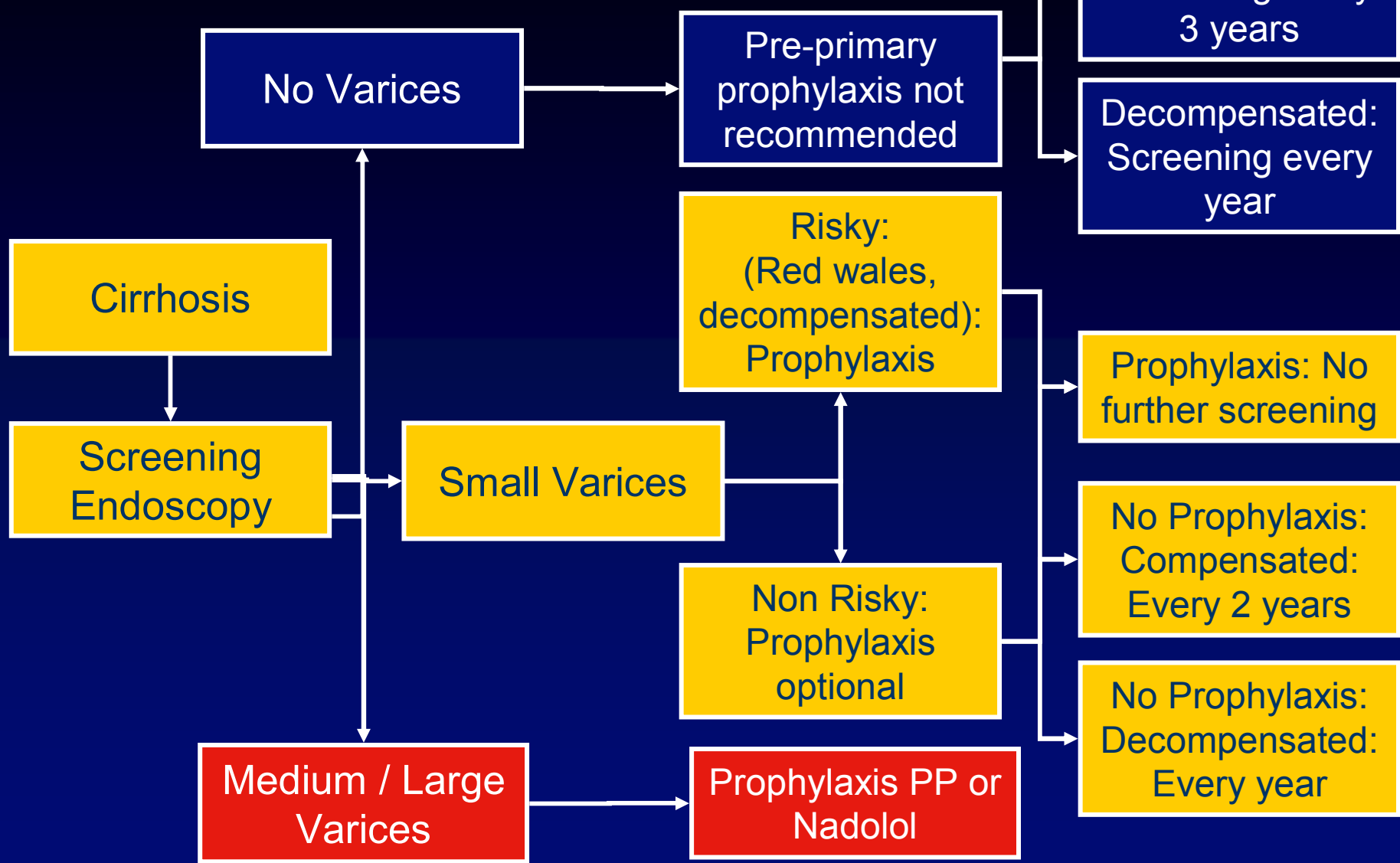
- 40% are hemodynamic non-responders
- HVPG monitoring identifies patients who will benefit from NSBB therapy in primary prophylaxis
- 'a la carte' treatment using HVPG response needs to be evaluated

N=396		
Reduction vs baseline	<20%	>20%
Reduction to	>12 mmHg	<12 mmHg
Rebleeding	48%	16%



Albillos A, et al. Am J Gastroenterol 2007;102:1116-1126.
 Bureau C, et al. Hepatology 2002; 36:1361-1366.

In Conclusion



Contraindication or intolerance to B blocker

EB ligation

Recommendations for clinical practice

- Patients without varices should be screened for the appearance of varices every 2 to 3 years (endoscopically). No treatment is recommended for prevention of the development of varices.
- Patients **with small varices** should be screened for enlargement of varices every 1 - 2 years. At present, there is no evidence to recommend treatment for the prevention of variceal bleeding in these patients because of their low risk of bleeding.

Recommendations for clinical practice

- Patients with medium or large varices should be treated with a nonselective B-blocker. The dose should be titrated individually.
- IMN alone or in combination with nonselective B-blockers, are not recommended for primary prophylaxis
- EBL is an alternative to NSBB in patients with medium or large varices with contraindications or who are intolerant to BB.

Thank You