BASL Portal Hypertension SIG Meeting
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CALIBRE Trial.

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NHS University Hospitals Birmingham NHS Foundation Trust

NHS National Institute for Health Research

BASL British Association for the Study of the Liver

CALIBRE

Disclosures

- None

Background

- Variceal bleeding accounts for 11% admissions with a GI Bleed in the UK with 4 week mortality 15%
- 50% of all cirrhotic patients have varices
- Prevention of variceal bleeding is an important clinical goal
- Recent UK guidelines have fuelled the debate about optimal therapy for primary prevention

Jairath et al, 2014, Tripathi 2015, NICE 2016

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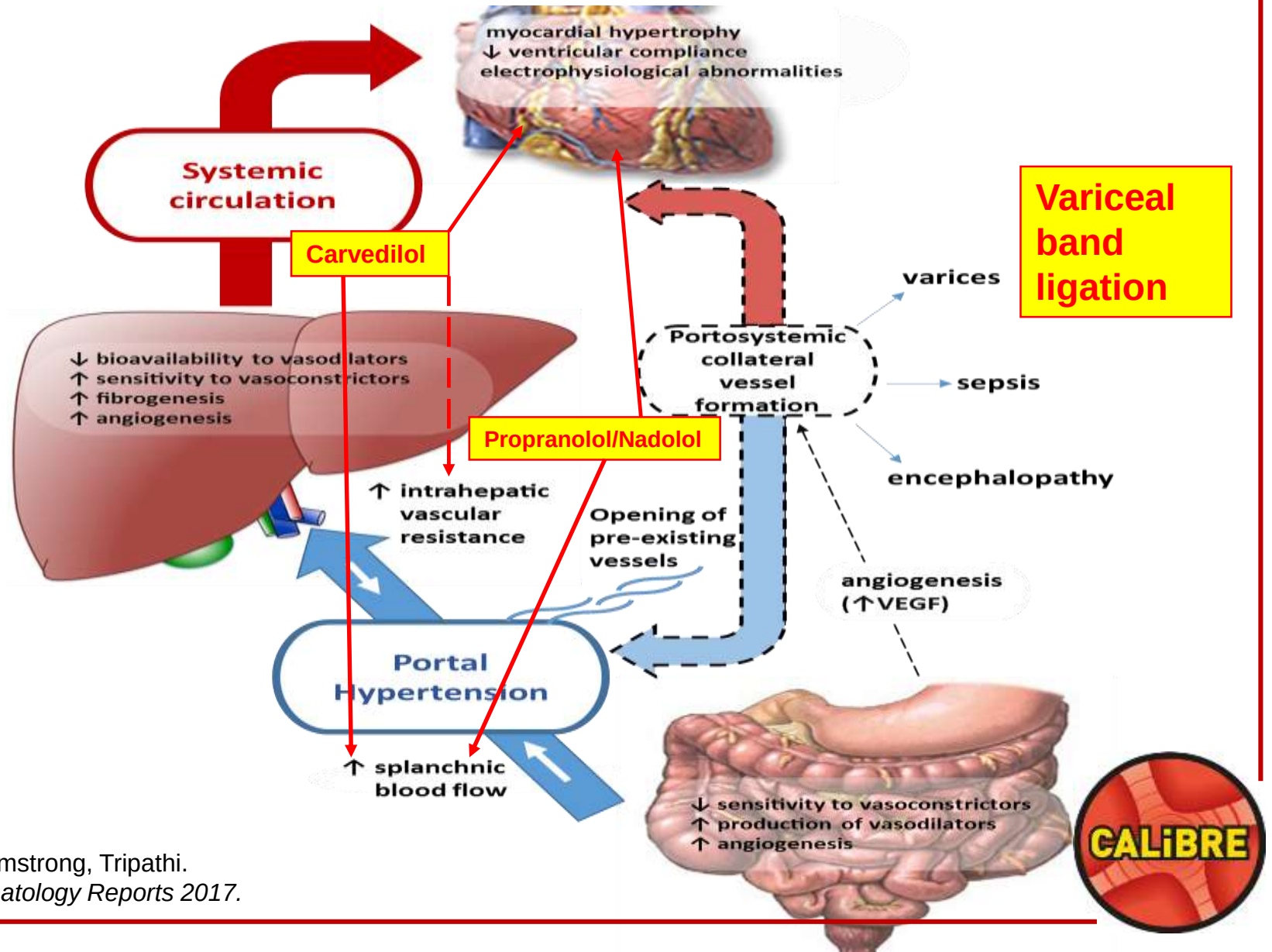
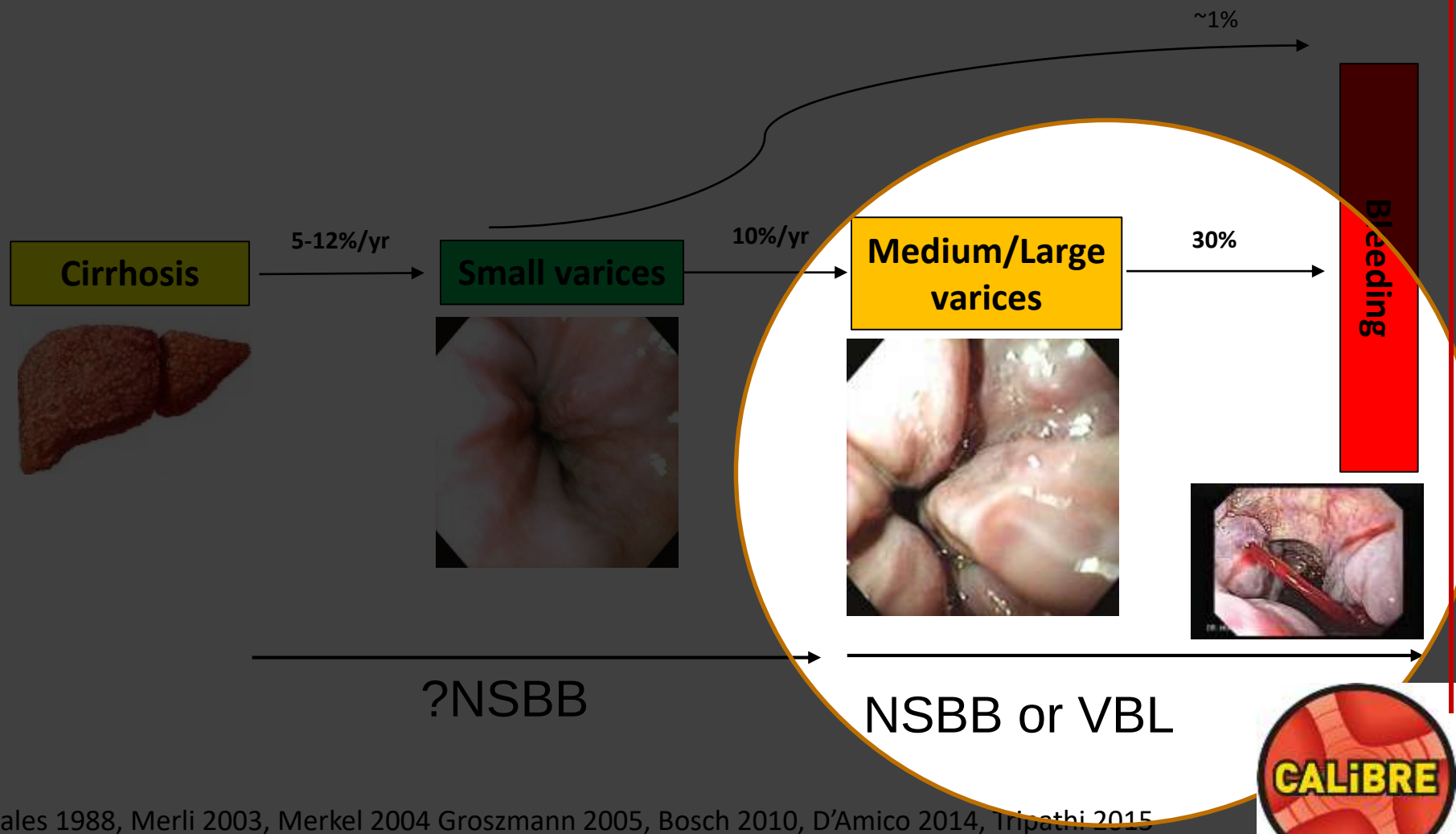
Pathogenesis of portal hypertension



Dhaliwal, Armstrong, Tripathi.
Current Hepatology Reports 2017.

Natural history of varices



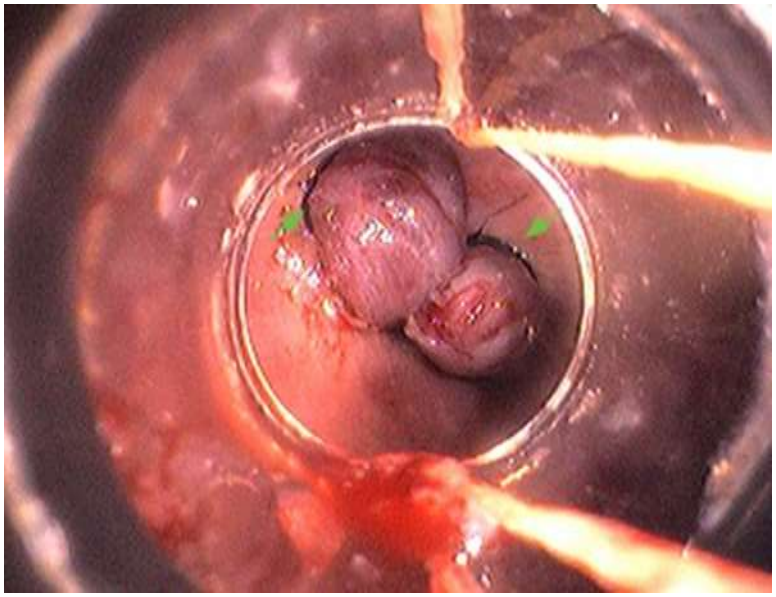
Cales 1988, Merli 2003, Merkel 2004 Groszmann 2005, Bosch 2010, D'Amico 2014, Tripathi 2015

Non-selective beta-blockers

	PROPANOLOL, NADOLOL	CARVEDILOL
PROPOSED MECHANISM OF ACTION	β-1 activity to reduce cardiac output and reduce portal blood flow through splanchnic vasoconstriction via β-2 blockade. 1/3 respond haemodynamically	x2-4 greater beta-blocking action of propranolol Additional intrinsic α1-adrenergic activity. Greater portal hypotensive effect than propranolol (Banares, Hepatol 2002; Sinagra APT 2014) 2/3 respond haemodynamically. Effective in propranolol non-responders
SIDE EFFFECTS/ CAUTIONS	Hypotension, bradycardia, caution in peripheral vascular disease/asthma **To be discontinued at time of SBP, renal impairment and hypotension?**	
INDICATIONS	1^{y} prophylaxis in grade II or larger varices. With VBL for 2^{y} prevention.	
DOSE	Propranolol: 40mg BD, titrated up if tolerated or once HR < 50-55bpm Nadolol: 40mg OD (maximum dose 240mg) or once HR < 50-55bpm	12.5mg OD if tolerated (HR < 50-55bpm, SBP < 90 mmHg)

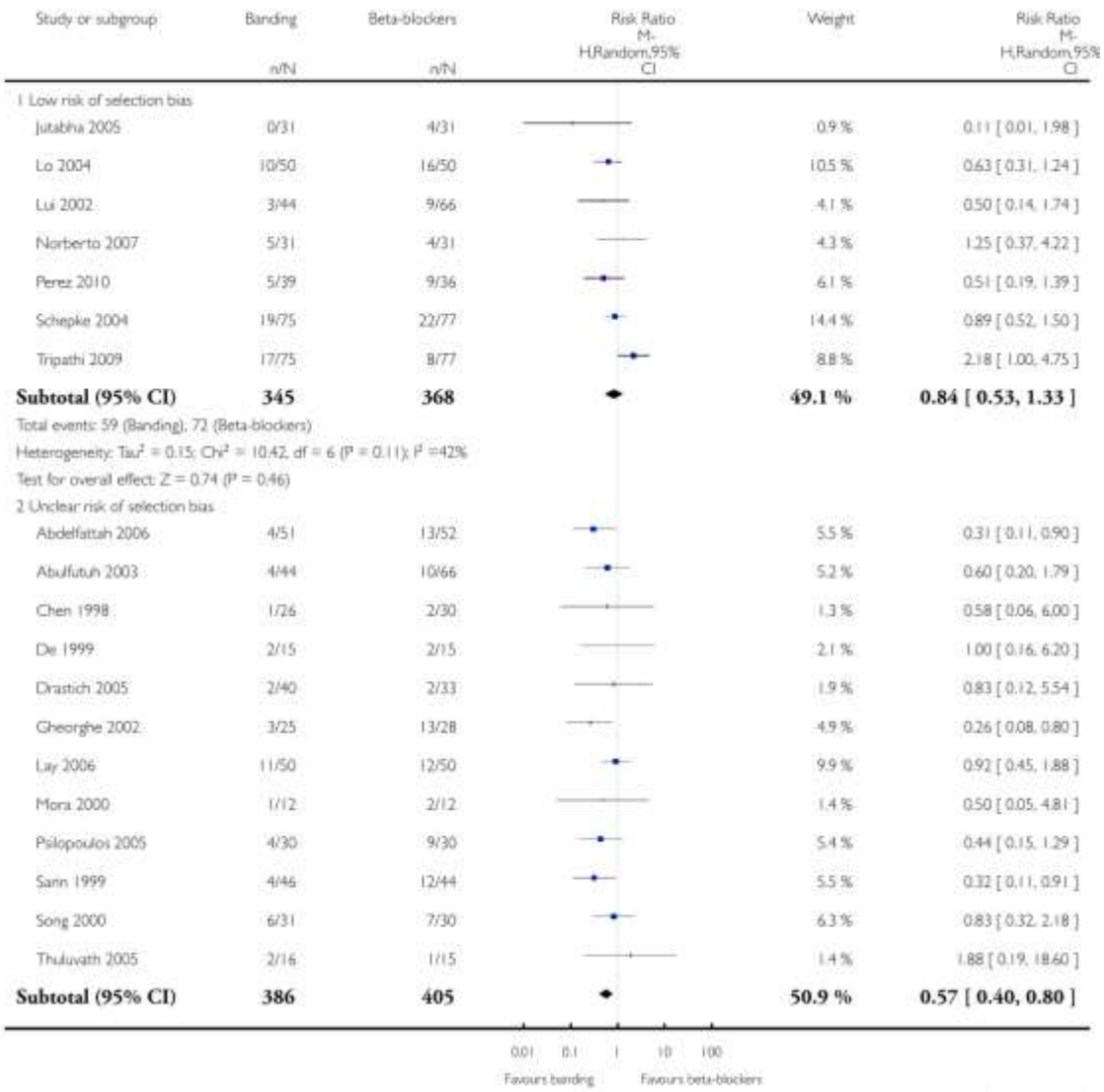
Reiberger, Gut 2012, Rajoriya, Tripathi, WJP 2016

Variceal band ligation (VBL)



- VBL: reduced local complication over sclerotherapy and better outcomes
- Compared with placebo 64% reduction in variceal bleeding and 45% reduction in mortality (Imperiale, Hepatol 2001)
- Technique very important with multibanders.
- Not for small varices

VBL vs NSBB – Variceal bleeding



Gluud, Cochrane 2012

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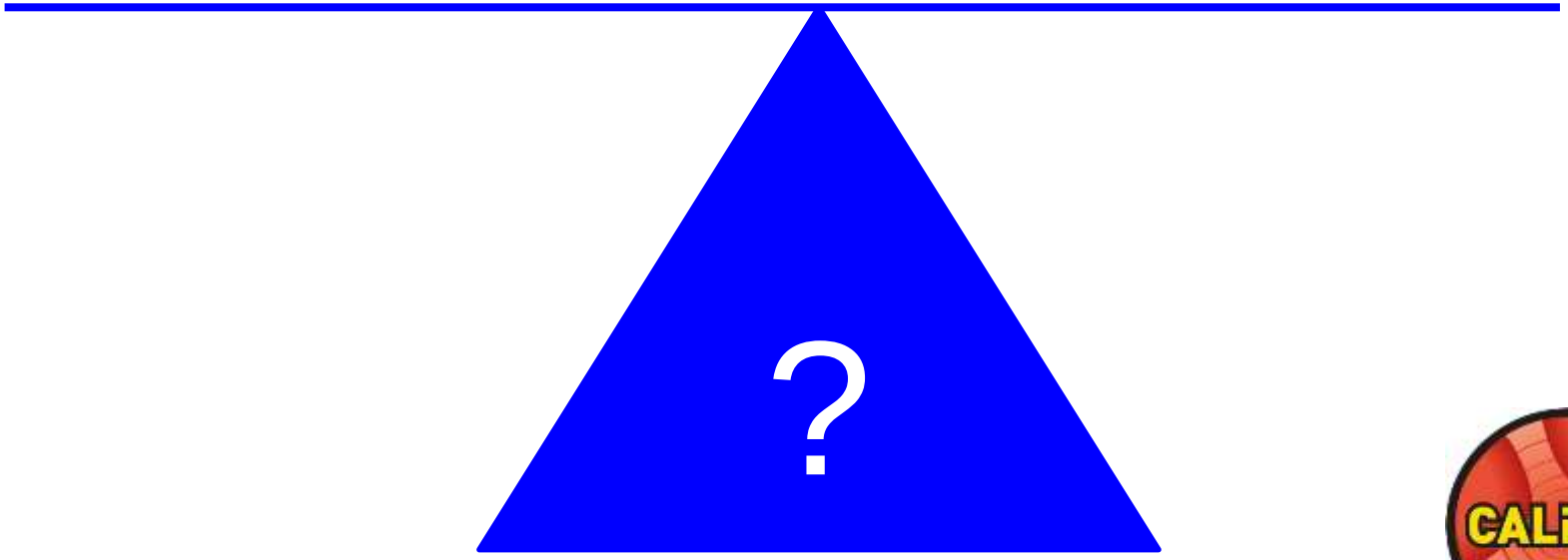
Primary prevention in medium/large varices - UK Guidelines Conundrum

NICE 2016:
Use VBL as first line

BSG 2015:
Recommends VBL and NSBB (propranolol (nadolol/carvedilol)) and suggests NSBB as first line. VBL if contraindications of NSBB



NICE 2016, Tripathi 2015

Health Technology Assessment Programme

NHS National Institute for Health Research

HTA no 16/99

Primary prevention of variceal bleeding in patients with liver cirrhosis

Introduction

The aim of the HTA Programme is to ensure that high quality research information on the effectiveness, costs and broader impact of health technology is produced in the most efficient way for those who use, manage, provide care in or develop policy for the NHS. Topics for research are identified and prioritised to meet the needs of the NHS. Health technology assessment forms a substantial portfolio of work within the National Institute for Health Research and each year about fifty new studies are commissioned to help answer questions of direct importance to the NHS. The studies include both primary research and evidence synthesis.

Research Question:

What is the clinical and cost effectiveness of non-selective beta-blockers compared to endoscopic variceal band ligation for primary prevention of variceal bleeding?

1. **Intervention:** Oral non-selective beta-blockers (NSBB), choice to be justified by applicants.
2. **Patient group:** Adults with cirrhosis and medium or large oesophageal varices, no history of variceal haemorrhage and no contraindications to beta blocker use.
3. **Setting:** Secondary care.
4. **Control:** Endoscopic variceal band ligation (VBL).
5. **Study design:** A randomised non inferiority trial to compare NSBB against VBL. When appropriate subgroup analyses should be performed. The trial data should also be incorporated into a new or updated systematic review with meta-analyses. A model of cost effectiveness is required.
6. **Important outcomes:** Time to first variceal bleeding event; overall mortality.
   Other outcomes: Adverse effects; an updated meta-analysis; patient preference; QoL; cost effectiveness.
7. **Minimum duration of follow-up:** Duration of study sufficient to accumulate enough events to inform the model.

Trial Design	• A multicentre randomised controlled, open-label, self-evident two-arm trial with internal pilot.
Aim	• To investigate the clinical and cost-effectiveness of carvedilol versus variceal band ligation in patients with cirrhosis and medium to large oesophageal varices that have not bled
Sample size 2630 - CALIBRE largest ever Phase III trial in cirrhosis	• Based on superiority hypothesis – 33% proportional difference in 1 year bleeding with carvedilol (absolute 12% (VBL), 8% (carvedilol))
NIHR HTA funded - £2.3m	• Sponsor University of Birmingham • Over 75 months
Recruitment over 4 years nationally	• All acute NHS trusts and health boards in UK potentially eligible
Primary end point	• Any variceal bleeding within 1 year of randomisation

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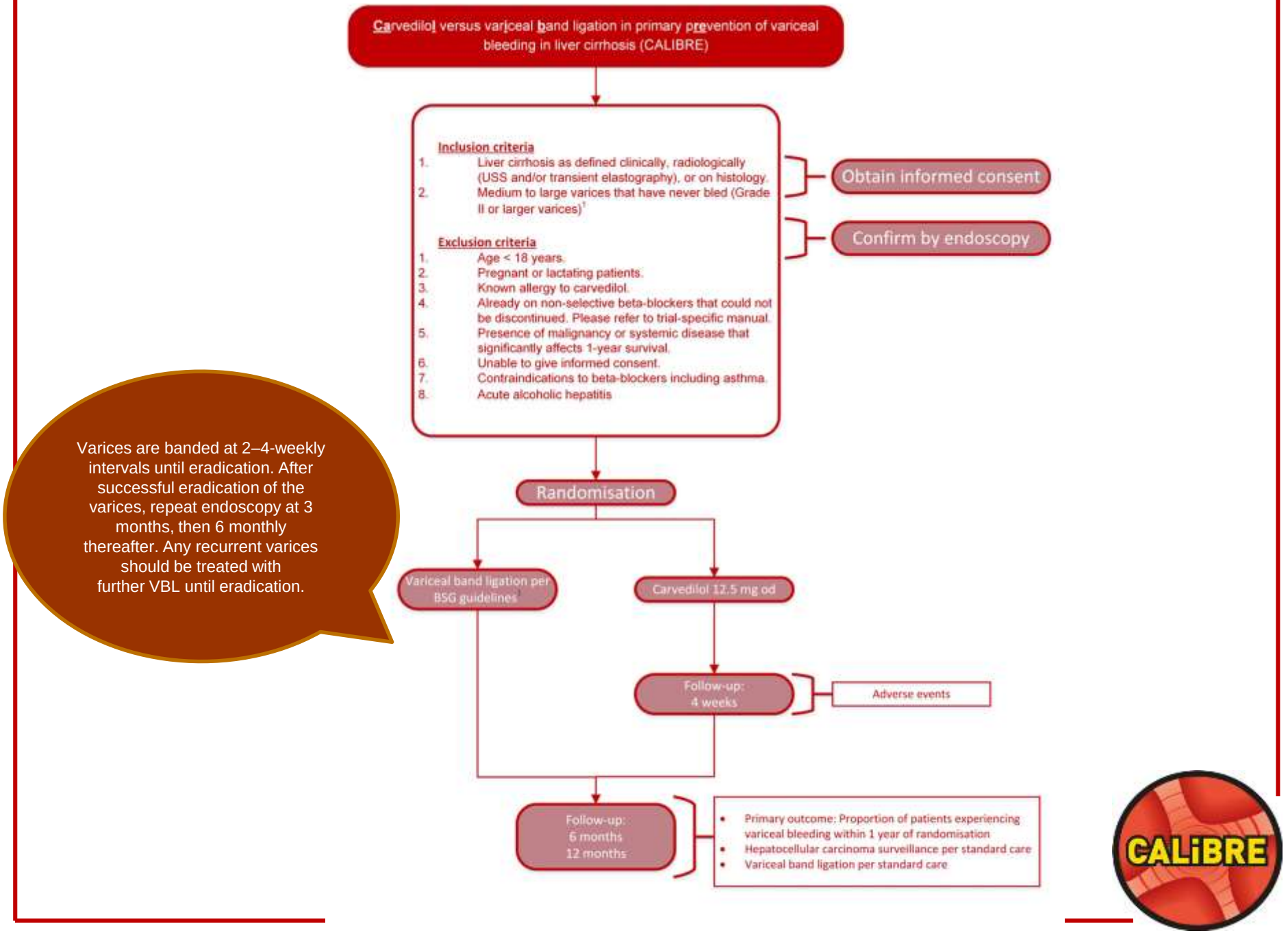
Carvedilol versus variceal band ligation in primary prevention of variceal bleeding in liver cirrhosis (CALIBRE)
Inclusion criteria
1. Liver cirrhosis as defined clinically, radiologically (USS and/or transient elastography), or on histology.
2. Medium to large varices that have never bled (Grade II or larger varices)[1]
Obtain informed consent
Confirm by endoscopy
Exclusion criteria
1. Age < 18 years.
2. Pregnant or lactating patients.
3. Known allergy to carvedilol.
4. Already on non-selective beta-blockers that could not be discontinued. Please refer to trial-specific manual.
5. Presence of malignancy or systemic disease that significantly affects 1-year survival.
6. Unable to give informed consent.
7. Contraindications to beta-blockers including asthma.
8. Acute alcoholic hepatitis
Randomisation
Variceal band ligation per BSG guidelines[2]
Carvedilol 12.5 mg od
Follow-up: 4 weeks
Adverse events
Follow-up: 6 months 12 months
Primary outcome: Proportion of patients experiencing variceal bleeding within 1 year of randomisation
Hepatocellular carcinoma surveillance per standard care
Variceal band ligation per standard care
Varices are banded at 2–4-weekly intervals until eradication. After successful eradication of the varices, repeat endoscopy at 3 months, then 6 monthly thereafter. Any recurrent varices should be treated with further VBL until eradication.
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BMJ Open Gastroenterology

Study protocol for a randomised controlled trial of carvedilol versus variceal band ligation in primary prevention of variceal bleeding in liver cirrhosis (CALIBRE trial)

Dhiraj Tripathi,[1,2] Peter Hayes,[3] Paul Richardson,[4] Ian Rowe,[5] James Walter Fersuon,[1,2] Peter Devine,[6] Jonathan Mathers,[7] Christopher Poyner,[7] Sue Jowett,[7] Kelly Handley,[8] Margaret Grant,[8] Gemma Slinn,[8] Peter Brocklehurst,[8] Khaled Ahmed,[8] on behalf of CALIBRE trial collaborative group

To cite: Tripathi D, Hayes P, Richardson P, *et al*. Study protocol for a randomised controlled trial of carvedilol versus variceal band ligation in primary prevention of variceal bleeding in

ABSTRACT

Introduction Liver cirrhosis is the fifth largest cause of adult deaths, and a major complication, variceal bleeding is associated with a 1-year mortality of 40%. There is uncertainty on the first-line therapy for prevention of variceal bleeding owing to a lack of adequately powered

hypertension and variceal bleeding. In patients with cirrhosis, varices develop at a rate of 5% per year with 10 year cumulative incidence of 44%.[3] At least 3000 patients are admitted to hospital in England per year with variceal bleeding with inpatient mortality

Grant activation: March 2018

0 - 6 months:

- Application for ethical and governance approval through REC and MHRA with appropriate documents. For sites outside of England the appropriate processes will be followed.
- Ethical approval obtained.
- Trial included on the NIHR portfolio study.
- Sites identified for pilot phase of study with site-specific documentation completed by nominated PIs.
- Trial steering committee (TSC) and Data Monitoring Committee (DMC) formed.
- Randomisation methods finalised.
- Trials registered with ISRCTN and Eudra-CT.

6-18 months:

- Pilot sites begin screening and recruitment with aim of 20 sites over 12 months..
- Once recruitment target of at least 240 patients is met trial to be rolled out nationally through CRN network leads for Gastroenterology & Hepatology.

19-54 months:

- National recruitment commenced January 2019.
- This will be assessed by the trial management group and TSC.

55-66 months:

- Follow up of patients recruited.

67-75 months:

- Analysis of data and dissemination.

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CALIBRE - Carvedilol versus variceal band ligation in primary prevention of variceal bleeding in liver cirrhosis

In 'calibre'
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Setting

Target population

Intervention

Measurement of outcomes and costs

NHS National Institute for Health Research

Conclusions

- Prevention of variceal bleeding is an important clinical goal
- Controversy regarding efficacy of banding vs NSBB in primary prevention of medium/large varices.
- CALIBRE aims to provide conclusive evidence in primary prevention.

THANK YOU!

CALIBRE TRIAL MANAGEMENT GROUP

Clinical

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