

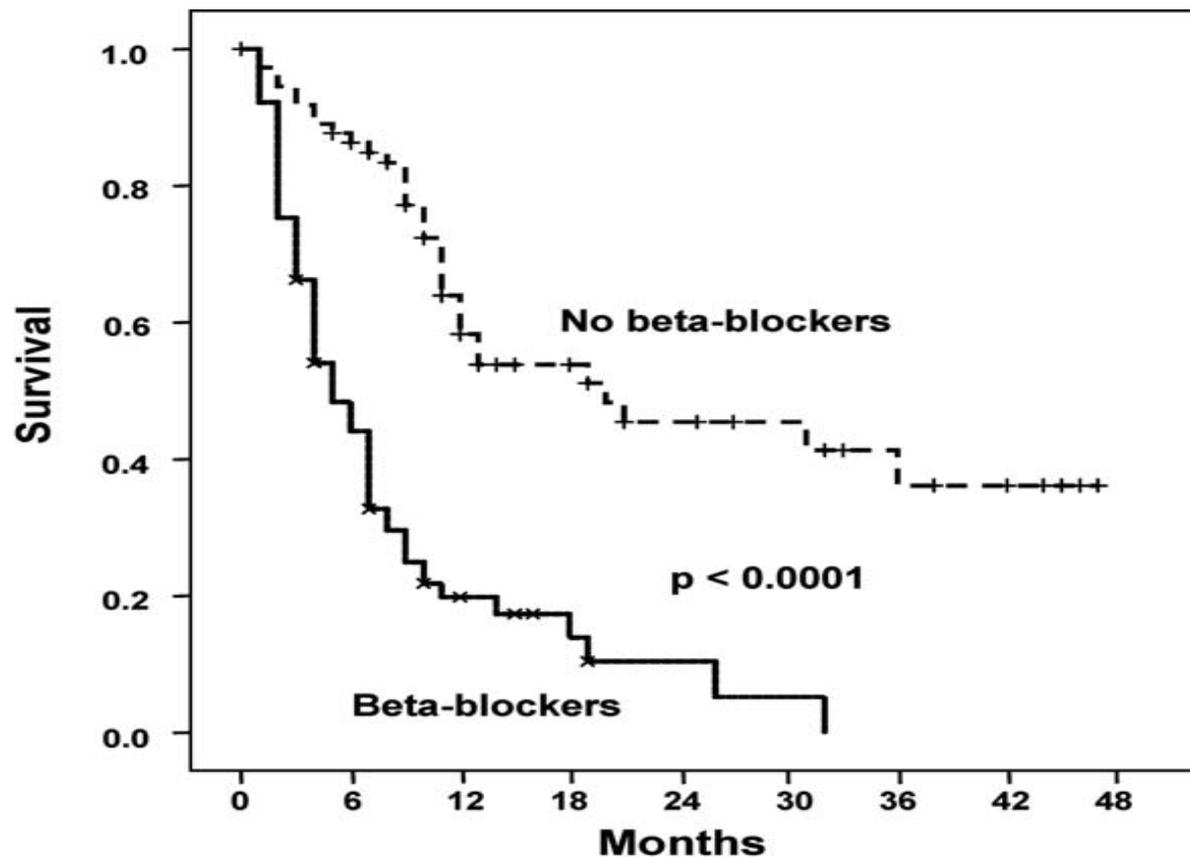


Carvedilol's role in portal hypertension:
likely much more than lowering vascular
resistance...impact on inflammation?

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Beta blockers may be C/I in patients presenting with refractory ascites and renal dysfunction?



β -Blocker treatment may increase paracentesis induced circulatory dysfunction and potentially decrease survival

Sersté et al Hepatology 2010 and J Hepatol 2011

There is a need to preserve organ blood flow whilst lowering portal pressure

Serste, et al; Hepatology 2010

BASL

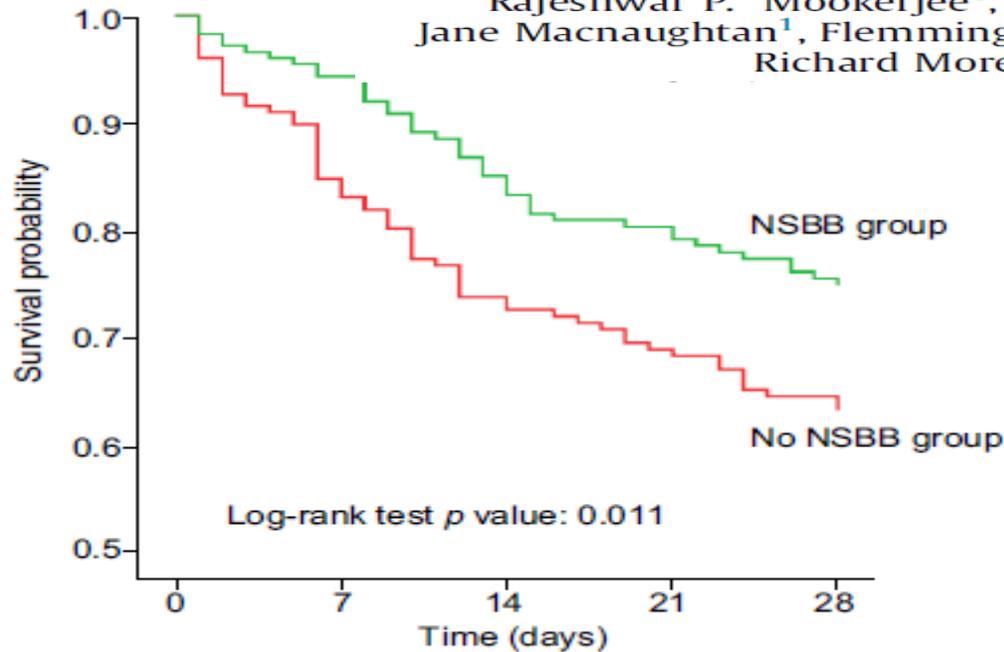
British Association for the Study of the Liver

But....Beta blockers in ACLF associated with reduced WBC and improved outcomes at low doses

Treatment with non-selective beta blockers is associated with reduced severity of systemic inflammation and improved survival of patients with acute-on-chronic liver failure[☆]

Rajeshwar P. Mookerjee¹, Marco Pavesi², Karen Louise Thomsen¹, Gautam Mehta¹, Jane Macnaughtan¹, Flemming Bendtsen³, Minneke Coenraad⁴, Jan Sperl⁵, Pere Gines^{6,7,8,9}, Richard Moreau^{10,11,12,13}, Vicente Arroyo², Rajiv Jalan^{1,*},

Journal of Hepatology 2016 vol. 64 | 574–582



Importantly, the 2 groups show no significant difference in MAP i.e likely non-haemodynamic mechanisms of BB

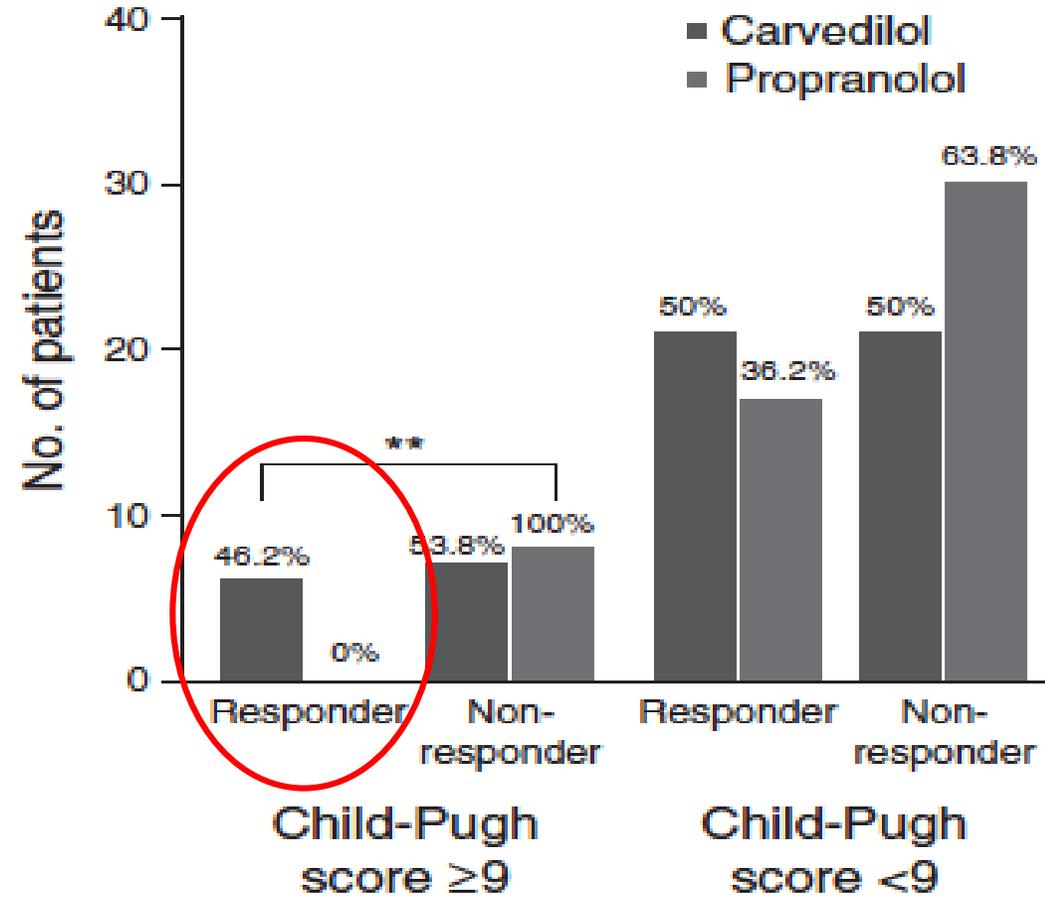
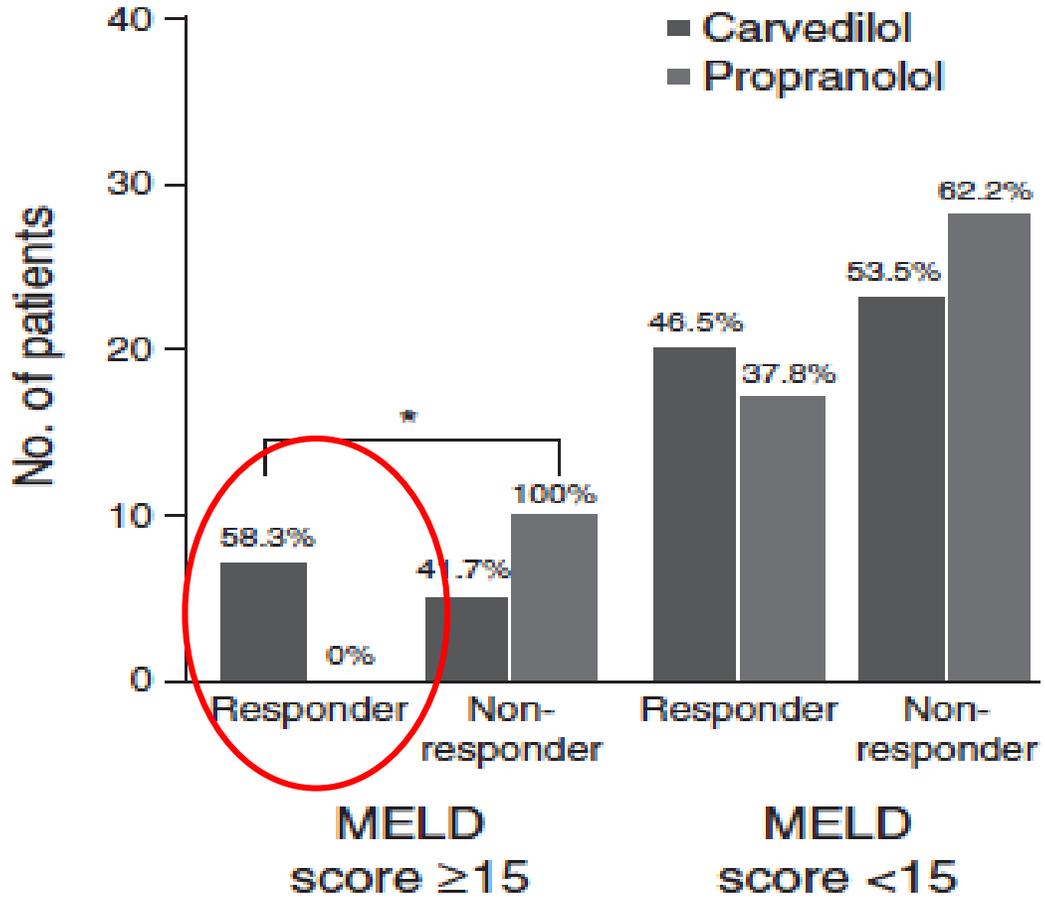
Effects on gut barrier function, immune cells and inflammatory response through modulating SNS?

NSBB are safe and may be beneficial to patients with refractory ascites awaiting OLT
Leithead et al Gut 2015

Carvedilol is associated with improved survival in cirrhosis with ascites

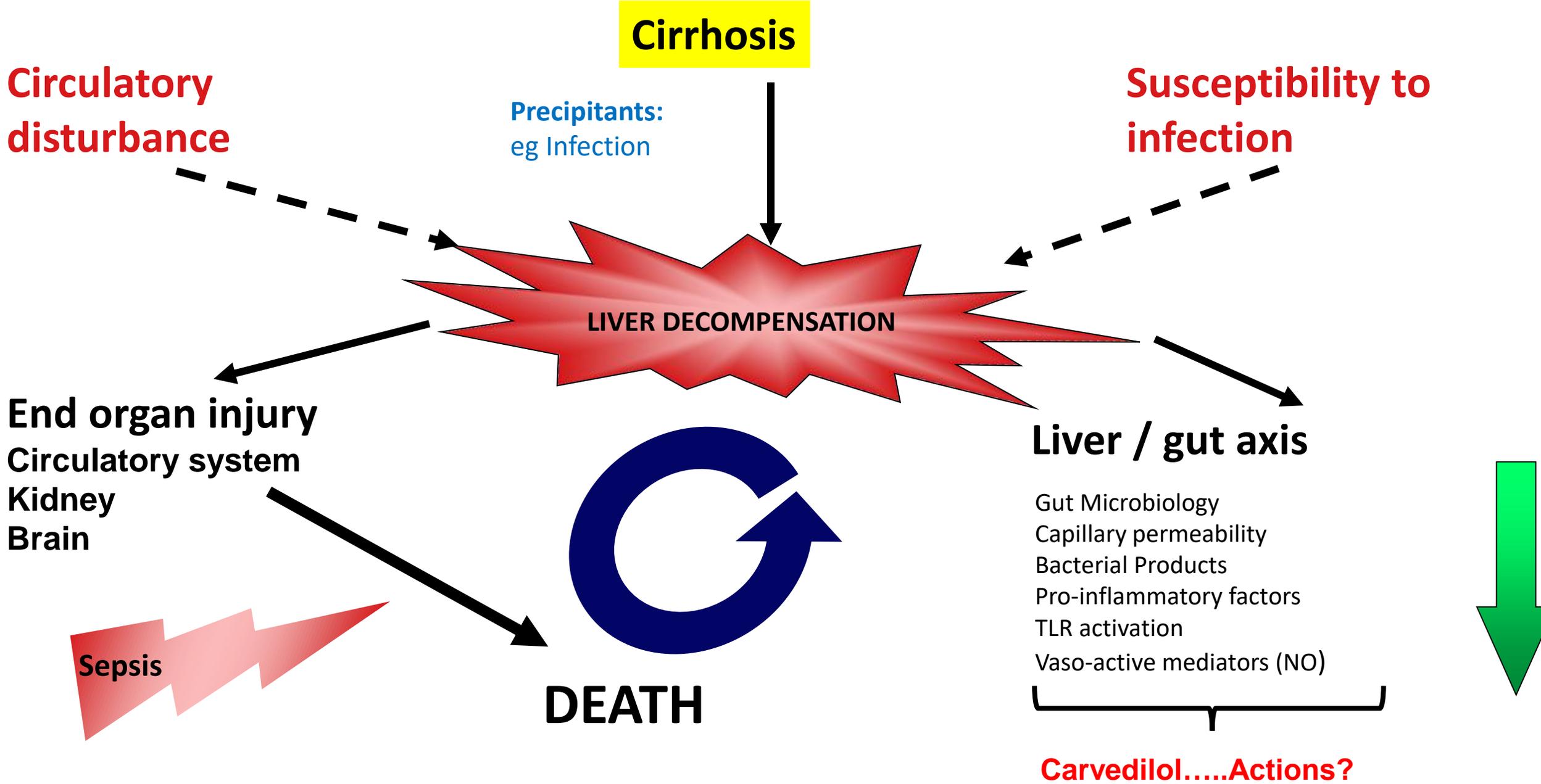
Sinha et al , J Hepatol 17

Carvedilol is more effective at lowering HVPG in advanced disease



Kim et al, Am J Gastro 2016

Impact of acute Decompensation of cirrhosis



EME- NIHR Application Nov'18:

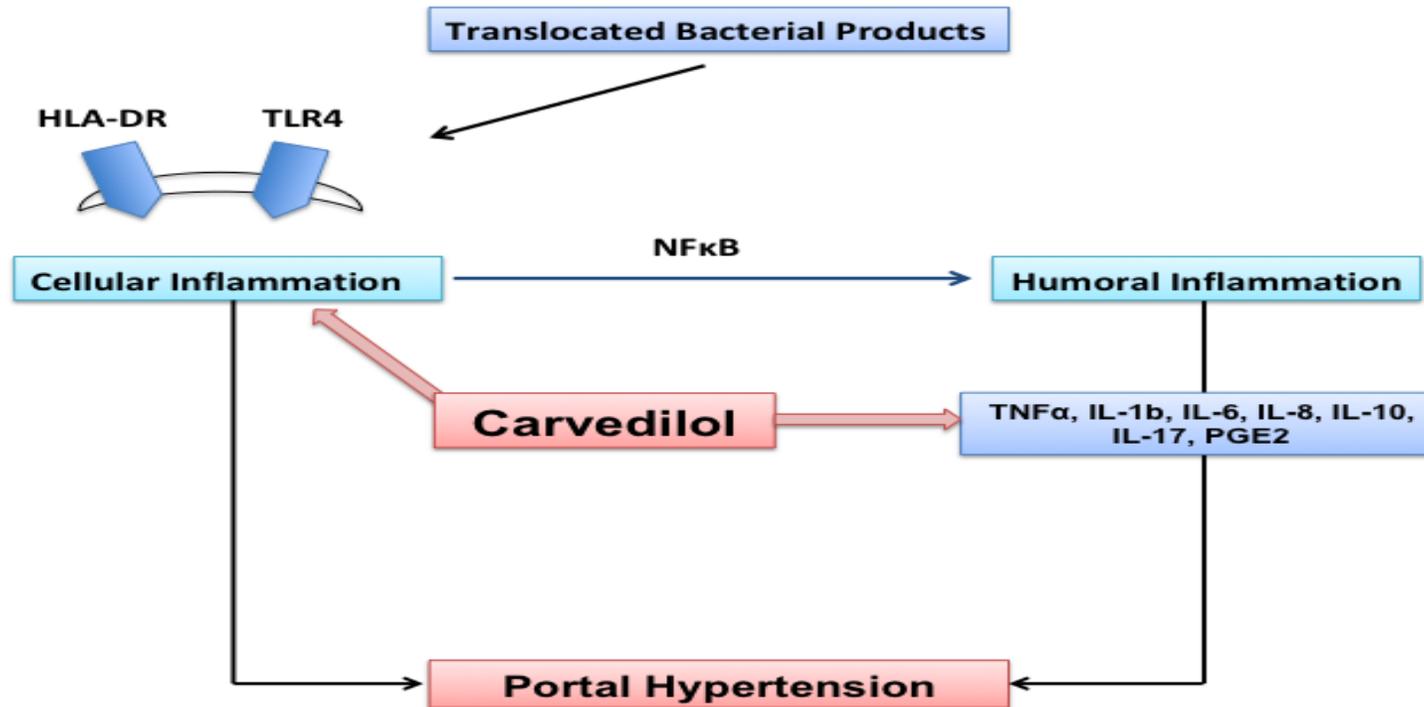
Mechanistic evaluation of changes in inflammatory responses with carvedilol therapy compared to non-pharmacological intervention for portal hypertension, and the relation to changes in bleeding and cirrhosis complication risks, for patients enrolled into the CALIBRE study

Research questions: [L] [SEP]

- Does carvedilol therapy reduce inflammation in cirrhosis patients with medium-large varices that have not bled and through which mechanisms?
- Do these mechanistic factors impact on development of cirrhosis complications and bleeding?

Hypothesis:

Carvedilol reduces systemic and cellular pro-inflammatory responses. This would lower risk of variceal bleeding and improve outcome from other complications of cirrhosis such as infections, with restoration of immune function towards normal levels



Primary Objective:

Assessment of effects of carvedilol vs. VBL on inflammation evidenced by:

- a) *Reduction in redox status*
- b) *Reduction in pro-inflammatory cytokines/chemokines*
- c) *Reduction in activation status of monocytes*
- d) *Reduced endothelial dysfunction*



Secondary Objective:

Assessment of effects of carvedilol vs. VBL on markers of bacterial translocation

EME submission- feedback, that this was out of call remit as not hypothesis driven but hypothesis generating?!

Way Forward....

- Consider re-submission to EME in Aug for the same stage 2 call with a re-worked study focusing on patients with high decompensation risk (CLIF-C AD score >50), in whom SIRS is a key pathophysiological driver. MRC an alternative strategy...

Q: Does carvedilol decrease onset of ACLF through reduction of systemic inflammation

Advantages: Many events over short time (<6 months)

Hard endpoints (25% likely development of ACLF at 90d;
30% hosp re-admission)

Easy to show difference between EVL vs Car groups

Disadvantages: Fewer de novo patients

Limited centers?