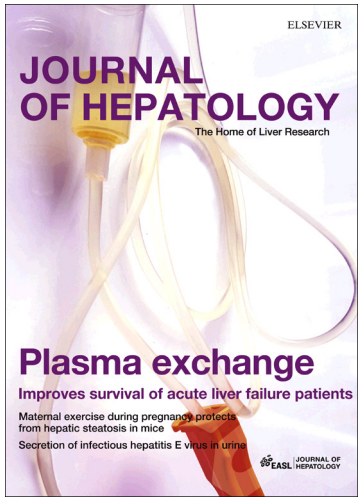

Grand Rounds

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Grand Round: Anticoagulation in Chronic Liver Disease

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Abstract:

In this Grand Round, we first present a case of a man with decompensated liver disease who subsequently developed a fatal pulmonary embolism, having not been prescribed prophylactic anticoagulation to prevent venous thromboembolic disease. We go on to discuss the burden of thrombotic disease in those with chronic liver disease, before a more detailed discussion regarding the current evidence, safety data, and clinical dilemmas regarding the use of anticoagulation in patients with chronic liver disease, as well as discussing potential future directions within this field.

Clinical case:

A 59-year-old man, with a history of cirrhosis related to chronic hepatitis C virus infection, was admitted to hospital through the emergency department complaining of a painful swollen left leg. He had experienced several hospital admissions over the previous few months due to recurrent diuretic-resistant ascites and worsening hepatic encephalopathy. His problems with ascites and encephalopathy had resulted in reduced mobility, worsening nutrition and sarcopenia. Despite achieving a sustained virological response following antiviral treatment, his MELD score had continued to increase and he had been listed for orthotopic liver transplantation.

Following admission, Doppler ultrasonography confirmed a large thrombus within the left common femoral vein. Laboratory tests at this time demonstrated haemoglobin of 12.8 g/dl, platelet count 114 x 10^9/l, and international normalised ratio of 1.3; a thrombophilia screen was negative. A CT of his chest, abdomen and pelvis revealed cirrhosis, splenomegaly and ascites, but no evidence of malignancy. Gastroscopy three months earlier had shown grade 2 oesophageal varices but no red signs, and he had been started on carvedilol at this point. He underwent a repeat endoscopy following this admission which demonstrated grade 2 varices with red signs, and it was decided that his varices should be eradicated by band ligation prior to commencing anticoagulation. During his previous hospital admissions, his physicians had decided not to administer pharmacological prophylaxis against venous thromboembolism due to concerns regarding bleeding risk related to his cirrhosis, and because of the need for repeated large volume paracentesis.

Following endoscopy, the patient complained of chest pain and dyspnoea. He suffered a cardiac arrest from which he could not be resuscitated. A post-mortem examination revealed a large pulmonary embolus as the cause of death.

Clinical questions that are prompted by this case include:

(1) What is the burden of thrombotic disease (venous thromboembolism and splanchnic vein thrombosis) in those with chronic liver disease?

(2) Which patients with cirrhosis should be given prophyalxis against venous thromboembolic disease?

(3) What are the treatment options for thrombotic disease in those with chronic liver disease?

(4) How safe is anticoagulation therapy to use in those with chronic liver disease?

(5) What emerging therapies are there in the field, and what are the likely future directions for the treatment of thromboembolic disease in those with chronic liver disease?

(6) Are there potential benefits for the use of anticoagulant drugs beyond the prophylaxis and treatment of thrombosis in those with chronic liver disease?

1. What is the burden of thrombotic disease (venous thromboembolism and splanchnic vein thrombosis) in those with chronic liver disease?

The interaction between liver injury and the coagulation cascade is multi-faceted and complex (Borensztajn *et al*., 2010). On the one hand, coagulopathy is a well-documented sequel of chronic liver failure; conversely, evidence is increasingly emerging which supports pro-fibrotic states as being prothrombotic, and that activation of the coagulation cascade has a role in the generation of chronic liver injury.

Advanced fibrosis is associated with impaired synthesis of all clotting factors, except Factor VIII and von Willebrand factor (Tripodi *et al,* 2005; Tripodi *et al*, 2006). This defect is demonstrated by prolongation of the prothrombin time (PT) and the activated partial thromboplastin time (APTT), tests which both represent the status of procoagulant proteins synthesised by the liver. However, the use of these conventional tests of haemostasis on peripheral blood correlates poorly with the risk of bleeding in chronic liver disease (Tripodi *et al,* 2010), reflecting the inability of these tests to take into account an imbalance in endogenous anticoagulants and procoagulants. Patients with advanced fibrosis have significantly lower levels of protein C and

antithrombin (Tripodi *et al*, 2005). Furthermore, this partial deficiency of anticoagulant proteins in those with advanced chronic liver disease is accompanied by enhanced thrombin generation within these patients (Gatt *et al,* 2010), together resulting in a procoagulant state. This could in part explain why the historical assumption that cirrhotics are 'auto-anticoagulated' and therefore protected against developing peripheral thromboembolic disease has now been demonstrated to be untrue.

Studies have demonstrated an incidence of between 0.5-6.3% of newly-diagnosed pulmonary thromboembolism (PE) or deep vein thrombosis (DVT) amongst hospitalised cirrhotics, and cirrhotic patients do not demonstrate a reduced risk of PE/ DVT compared to non-cirrhotic patients (Northup *et al,* 2006, Gulley *et al,* 2008). Furthermore, a prolonged international normalised ratio (INR) does not negate a risk of venous thromboembolism (VTE) in this setting (Dabbagh *et al*, 2010). Risk stratification scores that have been validated to predict VTE within a general population of hospitalised patients also appear to accurately predict VTE specifically amongst hospitalised patients with chronic liver disease, i.e. Padua Predictor Score (Bogari *et al,* 2014). More surprisingly, an increased relative risk of VTE has been observed amongst those with chronic liver disease in a case control population based study (Søgaard *et al,* 2009). In this Danish study of 99,444 patients with thromboembolic disease, cirrhotics had a 1.7-fold increased relative risk of venous thrombosis compared to the general population. This increased relative risk of VTE was confirmed in cirrhotic patients under the age of 45 years in a large US-based population study of hospitalised patients (Wu *et al,* 2010). However, interestingly, in patients over 45 years old, there was no significant increased VTE risk observed in cirrhotics compared to matched non-cirrhotic controls; however, this may have solely reflected age-related risk factors for VTE outweighing that of cirrhosis itself beyond this age (Wu *et al,* 2010). As well as cirrhosis possibly increasingly the risk of VTE, further recent data suggests that cirrhotics with VTE may have an increased mortality over a short period (30 days) compared to those with VTE but without cirrhosis (Søgaard *et al,* 2015).

Aside from VTE, one other major category of thrombotic disorders found in people with chronic liver disease is splanchnic vein thrombosis, a category that includes mesenteric, portal and hepatic vein thromboses. Portal vein thrombosis (PVT) may occur both in those with and without chronic liver disease, but this is the commonest thrombotic complication in cirrhotic patients. It is more commonly found in those with decompensated cirrhosis, with prevalence in those with decompensated cirrhosis ranging from 8-25% (Francoz *et al*, 2005), compared to ~1% in compensated cirrhosis (Okuda *et al,* 1985). The incidence of PVT occurring over a 12-month period in cirrhotic patients awaiting orthotopic liver transplantation (OLT) has been reported as 7% (Francoz *et al,* 2005). Mechanistic factors involved in the development of PVT in cirrhotic patients are likely multifactorial. Thrombophilic genetic defects within these patients have also been extensively investigated; the *G20210A* prothrombin gene mutation is the genetic variant most consistently identified as being associated with PVT in cirrhotic patients (Amitrano *et al,* 2004; Erkan *et al,* 2005), although the Factor V Leiden *G1691A* mutation (Erkan *et al,* 2005) may also be a risk factor. There is no current supportive evidence

for the JAK2 *V617F* mutation being associated with PVT within cirrhotic patients (Saugal *et al,* 2015). Whilst non-selective beta-blockade could theoretically precipitate PVT by decreasing portal venous blood flow, a large longitudinal study found no evidence that use of these medications was an independent risk factor for occurrence of PVT (Nery *et al,* 2015). Whilst local factors (including intra-abdominal surgery, infections and/ or inflammatory conditions of the abdomen) are well-established as risk factors for PVT in general (EASL, 2016), the specific degree of risk that they present for the development of PVT in those with chronic liver disease is undefined.

2. Which patients with cirrhosis should be given prophyalxis against venous thromboembolic disease?

Studies have looked at the role of anticoagulation in both preventing and treating thromboembolic disease in people with chronic liver disease. Current guidelines do not recognise the thromboembolic risk associated with chronic liver disease and do not make specific recommendations for the prophylaxis or treatment of thromboembolic disease (NICE, 2015).

The reported use of prophylactic anticoagulation for VTE in patients with chronic liver disease (21-25%) remains significant lower than in other inpatient groups (30-70%) (Cohen *et al*, 2008). Studies investigating the relationship between the use of prophylactic anticoagulation in patients with cirrhosis and the risk of VTE have given contradictory results, perhaps reflecting the fact that these are predominantly retrospective studies with differences in coding and/ or means of defining cases of chronic liver disease, More specifically, some studies have failed to demonstrate a significant difference in the incidence of venous thromboembolic events in people with chronic liver disease given prophylactic anticoagulation compared to those who were not (Dabbagh *et al,* 2010), or observed no significant difference between incidence of VTE in those treated with pharmacological, mechanical or no prophylaxis (Smith *et al,* 2013). In contrast, other studies have shown a decreased incidence of VTE in patients with chronic liver disease given pharmacological prophylaxis (Barclay *et al,* 2013). In this latter study, multivariate logistic regression analysis identified risk factors for VTE amongst hospitalised cirrhotics as being active malignancy, trauma or surgery during hospitalization, or previous history of VTE (Barclay *et al*, 2013). This is in keeping with VTE studies from other hospitalised patient populations, and suggests that patients with cirrhosis with risk factors should not be precluded from receiving VTE prophylaxis. Further prospective studies are required not only to fully determine if cirrhotic patients benefit from receiving prophylactic doses of anticoagulation in preventing VTE, but which prophylactic regimen is most appropriate. In the interim, it has been suggested that VTE prophylaxis is considered on a case-by-case basis in hospitalised cirrhotic patients, based on risk factor assessment for VTE (in particular, the likelihood of prolonged immobilisation). If anticoagulation is contraindicated (e.g. because of the potential risk of bleeding), then mechanical prophylaxis should be considered (Pincus *et al,* 2012).

3. What are the treatment options for thrombotic disease in those with chronic liver disease?

Therapeutic anticoagulation of venous thromboembolism (Table 1): Data regarding the efficacy and monitoring of full dose anticoagulation in treating VTE in patients with cirrhosis are currently limited. Any recommendations that are made at present for are principally based on extrapolation of data from studies evaluating anticoagulation in treating splanchnic vein thrombosis. Particular concerns in this area at present relate to the lack of data addressing optimal anticoagulation dosing regimens in cirrhotics, as well as recognition that the conventional means of monitoring anticoagulation effect may be inadequate in those with chronic liver disease (Lisman *et al,* 2013). For instance, use of warfarin (or other vitamin K antagonists (VKAs)) in those with chronic liver disease and a baseline prolonged INR presents a difficult scenario, both because of the potential to underdose patients in reaching a perceived target INR range (given that their INR is already prolonged), as well as given the limitations of INR as a measure of coagulation status in these patients as already described (EASL, 2016; Tripodi *et al,* 2010). Whilst many centres aim for a target INR of 2.0-3.0 in this scenario (an approach supported by guidelines (EASL, 2016)), there have been almost no studies assessing the safety and efficacy of this approach in cirrhotic patients, and particularly in those with decompensated disease. However, a recent study of 23 cirrhotic patients has demonstrated that a target INR of 2.0-3.0 can be reached with VKA doses similar to those in non-cirrhotics; endogenous-thrombin-potential reduction mirrored the effect of low molecular weight heparin (LMWH) and VKAs, and has been suggested as a candidate for monitoring the anticoagulant in cirrhotics since its activity reflects both the pro- and anticoagulants targeted by these drugs (Tripodi *et al,* 2016). EASL guidelines recommend that further studies – including randomised trials – are required to better understand the impact of current anticoagulation dosing regimens on coagulation parameters in cirrhotics, and to identify more targeted means of monitoring anticoagulation effect.

Anticoagulation in cirrhotic patients with non-malignant portal vein thrombosis: Whilst the natural history of non-malignant PVT in cirrhosis is variable (Luca *et al,* 2012) – with it now being clear that some such patients experience spontaneous complete recanalisation (particularly those in whom thrombosis is partial) (Nery *et al,* 2015) - the major clinical concern is of the potential for progression of thrombosis without further intervention. A number of studies have consistently shown much higher rates of portal vein recanalisation in patients treated with LMWH or VKAs than those without therapy (with assessment for recanalisation typically occurring by six months post-initiation of anticoagulation) (Table 2). Having a time interval between appearance of thrombosis and instigation of anticoagulation of less than six months appears to predict recanalisation (Senzolo *et al,* 2012). Re-thrombosis after complete recanalisation occurred in 38.5% of patients after anticoagulation was stopped in one study (Delgado *et al,* 2012), suggesting that anticoagulation should be continued after the immediate recanalisation of the portal vein (i.e. continued for at least several months longer than the typical six month course, and/ or up to OLT). A small rate (<5%) of bleeding complications

were observed, with some of these representing variceal bleeding events); however, this is counterbalanced by a trend towards decreased liver-related events (including ascites, hepatic encephalopathy and complications of portal hypertension) in patients in whom complete recanalisation occurred (Delgado *et al,* 2012). Bleeding complications appeared to be highest in those with platelet counts < 50 x 10^9/l (Delgado *et al,* 2012), with a 40% reduction in LMWH dosing being an adaptation that has been suggested as suitable for such patients (Senzolo *et al,* 2012). The evidence regarding the possible role of thrombolysis in such patients is extremely scarce (EASL, 2016). TIPSS has a potential role for patients with ongoing portal hypertensive complications despite anticoagulation.

4. How safe is anticoagulation therapy to use in those with chronic liver disease?

Anticoagulation is widely-used in medicine as a treatment for deep vein thrombosis and pulmonary embolus, and prophylactically in particular settings, e.g. reduction of the risk of stroke in patients with atrial fibrillation. Despite these established benefits, a number of clinicians have reservations about the use of these drugs - particularly if they have witnessed a significant adverse event - and this may account for the under use of anticoagulation where clinically indicated (Rashid *et al,* 2006). It is therefore natural for hepatologists to have safety concerns regarding the risk of bleeding related to these drugs when used in people with advanced liver disease, especially if there is significant thrombocytopenia, and/ or the presence of varices. In addition to this, there are additional concerns regarding the safe and effective monitoring of the anticoagulation effect when treating these patients, as already discussed in Section 3.

Despite this, several recent studies of anticoagulation in those with advanced fibrosis or cirrhosis appear to demonstrate acceptable safety profiles. Studies of VTE prophylaxis in cirrhotics patients have demonstrated no significantly increased risk of bleeding with anticoagulation (Intagliata *et al*, 2014; Smith *et al*, 2013, Barclay *et al*, 2013). Reichert and colleagues did demonstrate that if the INR was greater than 1.5, then the risk of bleeding was increased, but this was only for bleeding classified as of minor severity (Reichert *et al*, 2014) and stratification by type of anticoagulation has demonstrated that unfractionated heparin results in a higher bleeding risk than low molecular weight heparin in cirrhotic patients (Intagliata *et al,* 2014). Consistent with this, evaluation of a prophylactic dose of enoxaparin (4000 IU daily) to prevent PVT in patients with Child B/ C cirrhosis resulted in no increased risk of bleeding events in these patients when heparin was given for a period of 48 weeks when compared to a matched control group patients treated with placebo alone (Villa *et al*, 2012). It is probable that cirrhotics are more sensitive to unfractioned heparin (Potze *et al,* 2013), and therapeutic doses of this type of heparin also resulted in a significant drop in haemoglobin and platelet counts in cirrhotic patients (Fuentes *et al*, 2015); the authors of this study conclude that the drop in haemoglobin likely reflected

bleeding events during therapy, whilst the drop in platelet count could have represented heparin-induced thrombocytopenia. In contrast, administration of therapeutic doses of LMWH given over prolonged periods (mainly in the context of treating extrahepatic portal vein thrombosis) appears to be safe, with no significantly increased risk of bleeding (even in the presence of advanced fibrosis) when given alone (Amitrano *et al.,* 2010; Francoz *et al,* 2005, Delagado et al 2012, Maruyama *et al*, 2012, Werner *et al*, 2013) or in conjunction with transjugular intrahepatic portosytemic shunt insertion (Senzolo *et al*, 2012). It is important to note that in the majority of these studies, a clear protocol for assessment and eradication of varices prior to commencement of anticoagulation was described (see Table 2). One anticoagulated patient experienced a significant bleed from an ulcer occurring after sloughing off of a variceal ligation band (Francoz *et al,* 2005); recent guidelines have stated that either beta-blockade or band ligation are acceptable to use as variceal bleeding prophylaxis in this scenario before starting anticoagulation (EASL, 2016). Cerini and colleagues evaluated the impact of anticoagulation therapy on upper GI bleeding, predominantly due to portal hypertension in cirrhotics, and found it did not influence outcome measured by mortality, use of rescue therapy, intensive care admission, transfusion requirement or length of hospital stay, when matched to cirrhotics of similar severity not on anticoagulation (Cerini *et al,* 2015). Finally, preliminary results from a UK-based multi-centred study evaluating the anti-fibrotic effects of warfarin anticoagulation in patients with chronic HCV infection post-OLT – reported in abstract form – have not reported an increased risk of bleeding (Dhar *et al*, 2015). Unsurprisingly, in keeping with this a small study of pre-cirrhotic patients, examination of the anti-fibrotic effect of anticoagulation has similarily demonstrated that there is no increased risk of bleeding with a short course of warfarin (Dhar *et al*, 2012). The safety profile of anticoagulation in pre-cirrhotic patients would be expected to be comparable to those without chronic liver disease.

As such, prolonged anticoagulation is not without precedent in the setting of patients with advanced fibrosis. In particular, with careful screening and management of varices, there does not seem to a significantly increased risk of bleeding, implying that patients may be safely anticoagulated either in the setting of prophylaxis or therapeutic treatment.

5. What emerging therapies are there in the field, and what are the likely future directions for the treatment of thromboembolic disease in those with chronic liver disease?

Until very recently, anticoagulants used in clinical practice have principally been limited to heparins and VKAs (such as warfarin) (Figure 1). Although these drugs are highly efficacious anticoagulants, they have drawbacks that limit their usage. Specifically, warfarin is administered orally, but has to be monitored regularly due to a narrow therapeutic window, marked inter- and intra-individual variability in metabolism, a slow onset of action, and food and drug interactions. Monitoring can be inconvenient to patients and has added cost

implications. Heparins have a more rapid onset of action, but have to be given parenterally, which is often performed by a healthcare professional if the patient is unwilling. Long term use of heparins can be associated with osteopenia, thrombocytopenia, or idiopathic hepatitis (Ansell & Askin, 2011), and care has to be taken if there is significant renal dysfunction; in addition, hypersensitivity reactions are recognised, which may necessitate a switch of heparin preparation and/ or change to an alternative anticoagulant (Schindewolf *et al,* 2012). The need to develop novel anticoagulants with better ease of use and safer side effect profiles has recently culminated in several new drugs arriving in clinical practice, which inhibit single coagulation proteins such as activated Factor X or thrombin (Yeh *et al,* 2015) (Table 1, Figure 1). These direct acting drugs have commonly been labeled as direct oral anticoagulants (DOACs). DOACs are now approved for use in a variety of traditional indications for anticoagulants. Although these are more expensive than conventional anticoagulants, this is offset by a quick onset of action and the lack of need for montoring (Yeh *et al,* 2015).

Clinical experience of DOACs in cirrhotics is limited since many of the initial clinical trials involving these novel anticoagulants excluded patients with advanced liver disease. Data is therefore limited to *in vitro* and pharmalogical studies, isolated case reports and a small retrospective cohort study (Intagliata *et al,* 2016b).

Dabigatran is an oral direct thrombin inhibitor; no differences in coagulation markers were observed after its administration between healthy controls and patients with Child-Pugh B cirrhosis (Stangier *et al*, 2008), but its *in vitro* anticoagulant effect has been demonstrated to increase with increasing severity of liver disease (Potze *et al*, 2014). No clinical trials to date have used it in chronic liver disease patients.

Rivaroxaban - a Factor Xa inhibitor - is also of interest. Kutibza and colleagues demonstrated increased drug levels and prolongation of prothrombin times in patients with Child-Pugh B cirrhosis after a single dose administration of rivaroxaban but no adverse events were reported (Kutibza *et al*, 2013). A case of acute PVT in a Child-Pugh A cirrhotic treated successfully with rivaroxaban has also been described (Martinez *et al*, 2014). Intagliata *et al* recently reported on 20 patients with Child-Pugh A/ B cirrhosis who had been treated with DOACs (Intagliata *et al,* 2016a). The main indication was PVT, and nearly half had been given rivaroxaban; the remainder had been prescribed apixaban, another Factor Xa inhibitor. They reported no significant increase in bleeding risk in those given DOACs when compared to cirrhotics who had been treated with traditional anticoagulants, and there was no observed hepatotoxicity.

Larger prospective studies are required to determine whether these drugs can be safety recommended for routine use in those with chronic liver disease. One significant outstanding concern regarding the DOACs is a lack of widely-available antidotes, but recent clinical trials suggest that the novel drug monoclonal antibody fragment idarucizumab is effective for reversal of dabigatran (Pollack *et al,* 2015), whilst the novel drug andexanet may soon fill this therapeutic gap for the direct Factor Xa inhibitors (Connolly *et al,* 2016). There is a need to not only examine the efficacy and safety of DOACs in treating thrombosis in patients with chronic liver

disease, but to examining the potential effect of these medications in pre-cirrhotic and Child-Pugh A patients in preventing progression to cirrhosis and decompensation respectively.

6. Are there potential benefits for the use of anticoagulant drugs beyond the prophylaxis and treatment of thrombosis in those with chronic liver disease?

In a single centered randomised controlled trial, the use of prophylactic enoxaparin, a LMWH, was evaluated in 70 patients with Child B or C cirrhosis to determine whether the incidence of PVT could be reduced (Villa *et al*, 2012). Patients were randomized to either treatment with 4000 IU of enoxaparin for 48 weeks, or the control group who received standard treatment (no anticoagulation). At 48 weeks, no patient randomized to the enoxaparin arm had developed a PVT, versus 16.6% of the control group. Furthermore, there was a significant reduction in the occurrence or recurrence of liver decompensation (defined as the development of ascites, encephalopathy, spontenous bacterial peritonitis or portal hypertensive bleeding) in the enoxaparin group versus the control group (11.7% versus 59.4%), as well as increased transplant-free survival. The improvement in liver decompensation and survival may have been related in part to the prevention of PVT, but this alone cannot explain the effect, and the authors had suggested a possible additional protective effect on the intestinal microcirculation (Villa *et al* 2012). This study was not designed to delineate the underlying mechanism by which survival benefit is conferred, and further work is required to clarify this. At present, there is a consensus that, whilst these results are provocative and interesting, further studies are required to validate these findings and identify any subgroups of patients who would benefit from this strategy – and any potential mechanisms of action - before it is routinely employed (EASL, 2016).

As well as growing recognition that cirrhosis may be a prothrombotic state, there is also increasing evidence supporting an association between prothrombotic conditions and advanced hepatic fibrosis. Several studies have confirmed that the presence of thrombophilia increases the risk of severe fibrosis in people with chronic viral hepatitis. Papatheodoridis and colleagues demonstrated that patients with either chronic hepatitis B or hepatitis C virus infection with advanced fibrosis (Ishak stage 4–6) were significantly more likely to have thrombophilia related to deficiencies of protein C, plasminogen and anti-thrombin III compared to patients with milder fibrosis (Papatheodoridis *et al,* 2003). Furthermore, Factor V Leiden (FVL) - a well-characterised mutation in the coagulation system, which causes activated protein C resistance and amplification of the coagulation cascade - conferred a near fourfold increase in the risk of rapidly-progressive fibrosis in a Caucasian population with chronic hepatitis C virus (HCV) infection (Wright *et al,* 2003). Protein C deficiency, increased expression of factor VIII and hyperhomocysteinemia have also been associated with accelerated fibrosis in patients with chronic HCV (Poujol-Robert *et al.,* 2004), whilst a Dutch population-based cohort study identified presence of FVL or prothrombin *G202010A* mutations as independent risk factors for a liver stiffness score of ≥ 8.0kPa on transient elastrography (Plompen *et al,* 2015). Animal studies have displayed similar

results; C57BL/6 mice treated with carbon tetrachloride to induce fibrosis developed significantly more fibrosis if carrying the FVL mutation than did wild type mice (Anstee *et al,* 2008).

There is now a well-established link between the activation of the coagulation cascade and the progresison of liver fibrosis, including a role for coagulation proteins (Anstee *et al,* 2011). Firstly, as described above, epidemiological studies have demonstrated an association between thrombophilic conditions and more advanced hepatic fibrosis (Wright *et al*, 2003; Papatheodoridis *et al*, 2003; Poujol-Robert *et al*, 2004; Plompen *et al*; 2015). Secondly, in addition to its role in activating fibrinogen, thrombin has been shown to promote fibrogenesis via protease-activated receptor (PAR)-mediated activation of hepatic stellate cells (HSC) (Anstee *et al,* 2011). Mouse models of chronic liver disease have demonstrated that hepatocyte tissue factor (TF) may be a key mediator underlying local initiation of the coagulation cascade in cirrhosis (Rautou *et al,* 2016). Factor Xa (FXa) - a protease activated upstream of thrombin in the coagulation cascade - has also been shown to promote fibrogenesis, both by thrombin generation and PAR-mediated HSC activation (Dhar *et al,* 2012), making it an attractive therapeutic target.

If prothrombotic states accelerate liver fibrosis, and coagulation proteins activate HSCs to promote fibrosis, then conversely it might also be expected that anticoagulation may reverse hepatic fibrosis. Data from several animal studies support this hypothesis. For example, warfarin and thrombin antagonists have been demonstrated to have anti-fibrotic properties in a carbon tetrachloride mouse model of liver fibrosis (Anstee *et al*; 2008). Rivaroxaban, an oral direct-acting FXa inhibitor, has proven to be more effective in suppressing fibrosis than direct thrombin inhibition in an abstract presenting data from a thioacetamide mouse model of liver fibrosis (Dhar *et al*, 2012). In keeping with this, prolonged administration of enoxaparin in a rat model of cirrhosis (induced using carbon tetrachloride or thioacetamide) resulted in an improvement in both portal hypertension and liver fibrosis, probably by potentiating fibrosis regression, and resulting in a reduction of portal pressures (Cerini *et al,* 2016). Interestingly, in contrast, in a single study of chronic cholestatic liver injury in mice (induced by alpha-naphthylisothiocyanate), an apparent interaction between fibrin and $\alpha_M\beta_2$ on leucoytes was identified that appeared to result in regression of hepatic fibrosis (Joshi *et al,* 2016). Collectively, these data therefore suggest that whilst anticoagulation could potentially have a role as an anti-fibrotic agent in non-biliary fibrosis, it may conversely accelerate fibrosis in chronic biliary disease.

A UK-based multi-centred phase II study evaluating the anti-fibrotic effect of warfarin anticoagulation in patients transplanted for HCV cirrhosis has recently reported interim results which potentially support these findings in humans, having demonstrated a reduction in fibrosis scores at one year post-OLT in warfarinised patients compared to those not taking anticoagulation; completion of this study is awaited to validate these findings (Dhar *et al*, 2015). As such, the beneficial effects on both fibrosis and portal pressures may in part

explain the apparent efficacy of anticoagulation in preventing decompensation in cirrhotics, and further studies exploring the benefits of anticoagulation in this setting are required.

Back to the clinical case:

In the context of the above evidence, the original clinical case may now be revisited.

This man was clearly at increased risk of VTE due to his reduced mobility, as well as because of his chronic liver disease *per se*. The reasons given by his physicians as contraindications for VTE prophylaxis previously are not strongly valid, i.e.:

- His INR was only modestly prolonged, and the current literature suggests that VTE prophlaxis within cirrhotics does not appear to be associated with a significantly increased risk of bleeding, at least with an INR below 1.5 (Reichert *et al*, 2014). Furthermore, the limitation of the use of a prolonged INR as a marker of bleeding risk in those with chronic liver disease is now increasingly-understood (Tripodi *et al,* 2010). He had had his varices appropriately treated, minimising the risk of bleeding from this route.
- Low molecular weight heparin is relatively short-acting, and may be stopped at least 12 hours before an invasive procedure, such as paracentesis.

Whilst prophylactic-dose low molecular weight heparin has been shown to be effective at preventing the occurrence of portal vein thrombosis in a randomised controlled trial setting (Villa *et al,* 2012), the literature regarding the efficacy of prophylactic dosing of anticoagulation in preventing VTE in cirrhotic patients is contradictory, and further prospective studies are required. Based on the current literature, the decision about use of VTE prophylaxis in patients with cirrhosis should be decided on a case-by-case basis. However, given this man's clear risk factors for VTE – coupled with this apparent low bleeding risk, following treatment of his varices - a compelling case might be made that the potential benefits of pharmacological VTE prophylaxis in this patient outweighed the possible risks during his previous hospital admissions. A proposed algorithm for the use of prophylaxis against venous thromboembolic disease in people with cirrhosis is provided in Figure 2.

With regards to treatment of pulmonary embolism in a patient with cirrhosis – whilst both heparin and vitamin K antagonists have consistently been demonstrated to be effective therapies for the treatment of splanchnic vein thrombosis, there are almost no studies that address the efficacy of these medications in the treatment of VTE in patients with chronic liver disease. Furthermore, considerable uncertainties exist regarding how to

optimally administer these anticoagulants and safely monitor their effects within these patients, and as such any recommendations are influenced by *in vitro* data and clinician experience rather than a specific evidence base (Table 1). However, based on extrapolation from studies in the treatment of splanchnic vein thrombosis, it might be argued that either of these classes of medication would be likely be effective treatments of a pulmonary embolism of this man. These same studies have demonstrated that as long as variceal screening/ treatment is appropriately instigated prior to commencement of anticoagulation, then these medications are generally associated with no significant additional bleeding risk compared to those without chronic liver disease (Table 2); this appears to be the case even when anticoagulation is started soon after endoscopic treatment of varices with red signs (Maruyama *et al,* 2012). Current guidelines recommend a target INR of 2.0 – 3.0 where vitamin K antagonists are used, a target APTT prolonged to 1.5-2.5 over the normal value where unfractionated heparin is administered, and recommend against routine laboratory monitoring of the anticoagulation effect of low molecular weight heparin; however, these guidelines similarly acknowledge the limited evidence on which these recommendations are made (EASL, 2016), and further randomised studies are needed to gather additional evidence and provide further guidance within this area. Unfractionated heparin may require closer monitoring than low molecular weight heparin within these patients; cirrhotic patients appear to have increased sensitivity to unfractionated heparin compared to non-cirrhotic patients (Potze *et al,* 2013), and the risk of heparin-induced thrombocytopenia may be higher with unfractionated heparin. Therefore, at this point in time, low molecular weight heparin or vitamin K antagonists are the major options available.

The current experience of the use of direct oral anticoagulants (DOACs) in treating thrombotic disease in those with chronic liver disease is limited. Whilst early data suggest that they may be safe and effective within this setting (Intagliata *et al,* 2016a; Intagliata *et al,* 2016b), further studies are required before they may be recommended for routine use.

Summary:

Challenges exist regarding the use of anticoagulants in patients with chronic liver disease, ranging from pre-existing ideas regarding safety, the absence of established detailed guidelines, and the lack of adequately powered prospective studies. There is unquestionably a rapidly-emerging understanding of the role for anticoagulation in those with chronic liver disease for a range of indications, both for their direct effect upon treating thrombosis and for the potential role that they may have in reducing decompensation events, and

their anti-fibrotic properties. DOACs offer distinct advantages over traditional anticoagulants, but further data regarding their safety and efficacy are required before these might be adopted in routine clinical practice.

Figure/ Table Legends:

Table 1: Summary of the use of anticoagulants in the treatment of thromboembolic disease in those with chronic liver disease.

Table 2: Clinical studies of prophylaxis and treatment of non-malignant portal vein thrombosis with anticoagulation in people with cirrhosis.

Figure 1: Mechanism of action of anticoagulants. Dabigatran: direct thrombin inhibitor. Rivaroxaban, apixaban: direct factor Xa inhibitors. Vitamin K antagonists (i.e. warfarin): inhibition of the synthesis of the vitamin K-dependent clotting factors II, VII, IX and X (as well as the anticoagulation proteins of protein C and protein S). Heparin: binds to the enzyme inhibitor antithrombin III, causing a conformational change that activates the protein; activated antithrombin III then inactivates several serine proteases, in particular thrombin and Factor Xa. TFPI: tissue factor pathway inhibitor.

Figure 2: Proposed algorithm for the use of prophylaxis against venous thromboembolic disease in people with cirrhosis.
***We have not stated a threshold INR to define high risk of bleeding in cirrhotics, given the limitations of INR in assessing bleeding risk within these patients. This should be assessed on a case-by-case basis.**
****Affected patients will require band ligation/ beta-blockade prior to consideration of pharmacological VTE prophylaxis (Villa *et al,* 2012; EASL, 2016).**

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N.B. Author names in bold designate shared co-first authorship.

Fig.1

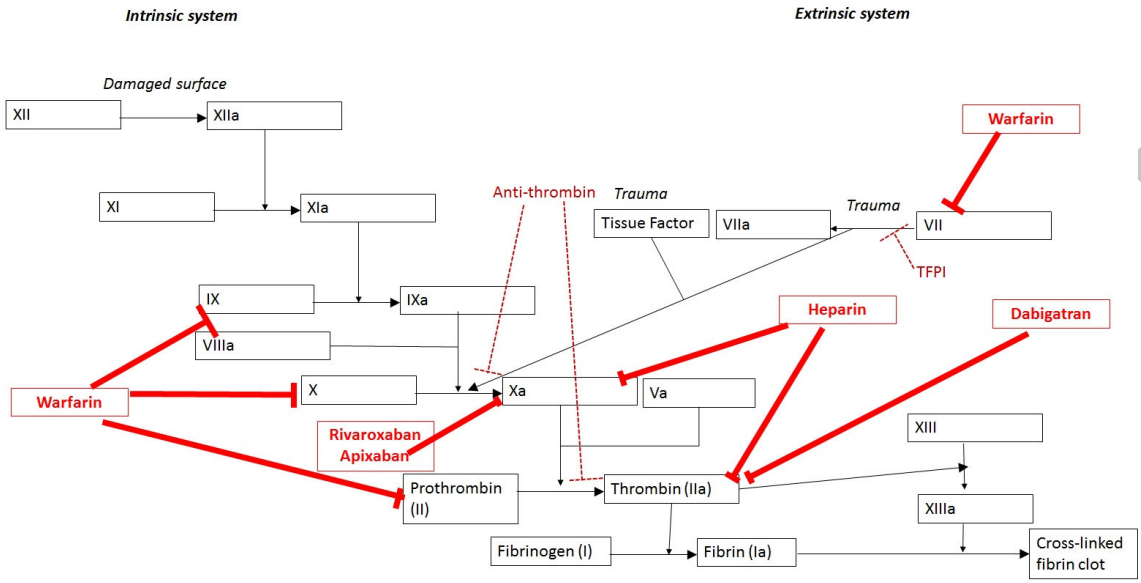
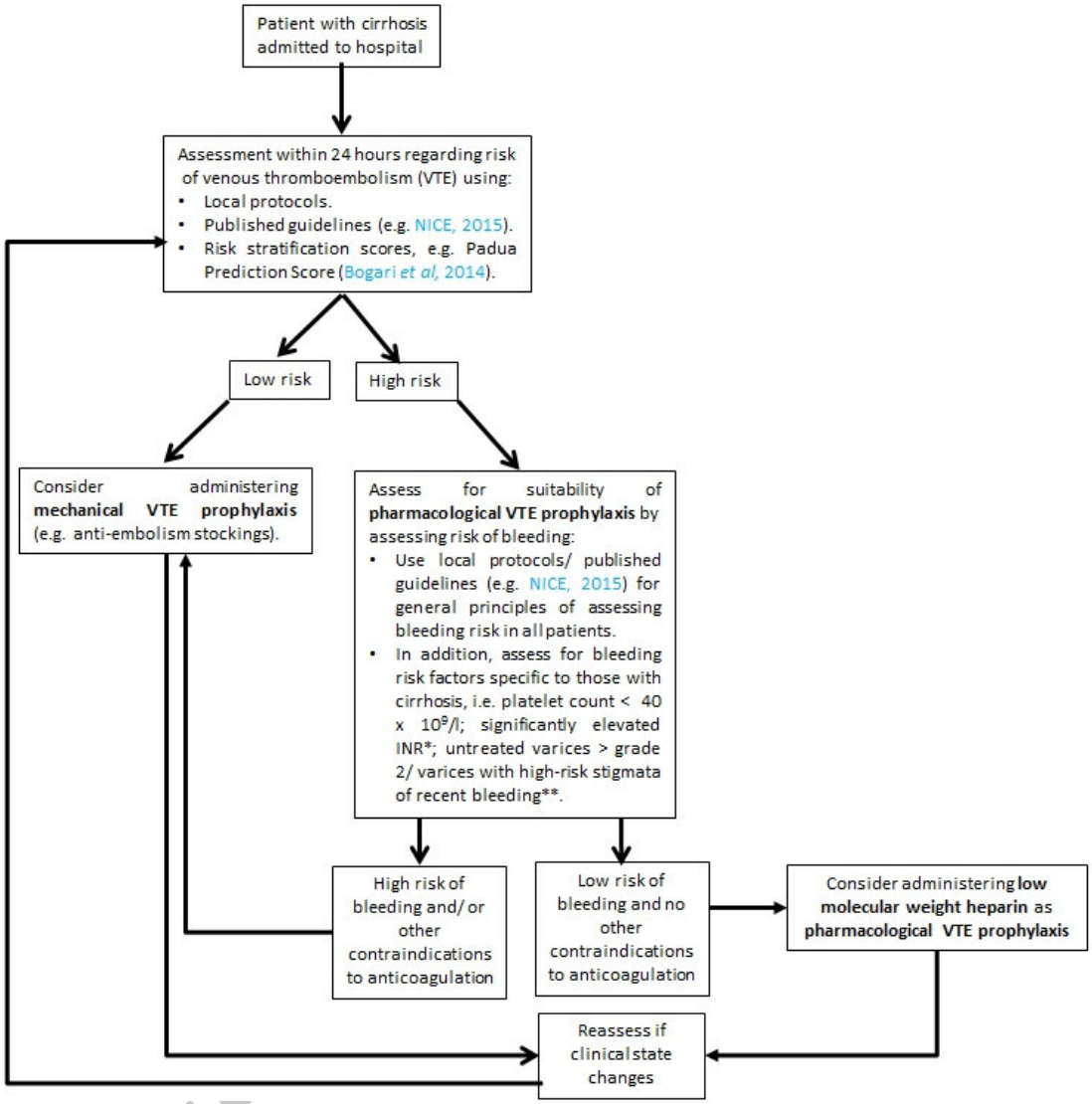


Fig. 2



Class of anticoagulation		Examples	Mode of action	Monitoring in patients with chronic liver disease*	Potential complications specific to those with chronic liver disease	Reversal agents	Peri-procedural management of anticoagulant**
Heparins	Unfractionated heparin		Binds to antithrombin III; activated antithrombin III then inactivates several serial proteases, in particular thrombin and Factor Xa.	• Monitor by APTT as the test for dose adjustment; aim for therapeutic interval of 1.5-2.5 prolongation over the normal value. • However, recognise that the decreased antithrombin levels in the plasma of patients with CLD may lead to falsely elevated APTT in cirrhotics treated with heparin (Potze *et al,* 2013); interpret APTT levels with caution.	• *In vitro* data suggest that cirrhotics may have increased sensitivity to the anticoagulant effect of unfractionated heparin (Potze *et al,* 2014). • Increased risk of thrombocytopenia (potentially because of heparin-induced thrombocytopenia) when used in cirrhotic patients (Fuentes *et al,* 2015).	Protamine-sulphate	• Stop at least four hours prior to procedure. • Omit for at least 24 hours following procedure.
	Low molecular weight heparin (LMWH)	Enoxaparin, tinzaparin		• No routine laboratory monitoring required; anti-Factor Xa is probably a poor measure of the anticoagulation effect of LMWH in those with cirrhosis. • Patients who are obese, those with renal insufficiency or pregnant patients should be advised to immediately report any sign suggestive of an adverse event.	• *In vitro* data suggest that cirrhotics may have increased sensitivity to the anticoagulant effect of low molecular weight heparin (Potze *et al,* 2014).	Protamine-sulphate	• Stop at least 12 hours prior to procedure. • Omit for at least 24 hours following procedure.
Vitamin K antagonists (VKA)		Warfarin	Inhibition of the synthesis of vitamin K-dependent clotting factors, II, VII, IX and X.	• Aim for INR in therapeutic interval of 2.0 – 3.0, but recognise the limitations of the use of INR for this purpose in those with chronic liver disease.	• No potential complications specific to those with chronic liver disease beyond those with VKA in general.	Options including vitamin K, prothrombin complex concentrate and fresh frozen plasma, depending upon urgency and/ or product availability	• Stop five days prior to procedure. • Bridging with heparin may be appropriate in people with a very strong indication for continued VKA therapy, e.g.

						thromboembolism within past three months. • Recommence VKA at least 12 hours after procedure, assuming that no concerns about haemostasis.
Direct oral anticoagulants (DOACs)	Dabigatran	Direct thrombin inhibitor	• Very limited experience in chronic liver disease, but no routine laboratory testing used.	• *In vitro* data suggest that cirrhotics may have much increased sensitivity to the anticoagulant effect of dabigatran (Potze *et al,* 2014)	Idarucizumab (Pollack *et al,* 2015).	Experience currently too limited in chronic liver disease to provide specific advice.
	Rivaroxaban, apixiban	Direct Factor Xa inhibitors	• Very limited experience in chronic liver disease, but no routine laboratory testing used.	• *In vitro* data suggest that cirrhotics may have reduced sensitivity to the anticoagulant effect of these agents (Potze *et al,* 2015)	Antidotes still at trial stage but likely to come to market soon, e.g. andexanet (Connolly *et al,* 2016)	Experience currently too limited in chronic liver disease to provide specific advice.

*Adapted from EASL, 2016.

**Adapted from Douketis *et al,* 2012.

Table 1: Summary of the use of anticoagulants in the treatment of thromboembolic disease in those with chronic liver disease.

Prophylaxis:						
Study name:	**Population of study:**	**Anticoagulant used:**	**Screening for and treatment of varices pre-intervention:**	**Primary outcome:**	**Secondary outcomes:**	**Bleeding and other significant complications:**
Villa *et al,* 2012	70 cirrhotic outpatients (Child-Pugh B7-C10) with no PVT; 34 receiving intervention, 36 controls	LMWH (enoxaparin) 4000 IU/ day subcutaneously for 48 weeks	• No portal hypertensive bleeding for three months pre-enrollment. • Exclusion if grade 2 varices with red signs or grade 3 varices unless ligated.	• At 48 weeks: 0 PVT in LMWH group, 6 in controls (p=0.025). • At 96 weeks: 0 PVT in LMWH group, 10 in controls (p=0.001). • At end of follow-up: 3 PVT in LMWH group, 10 in controls (p=0.048).	• 4 episodes of liver decompensation in LMWH group, 21 amongst controls (p<0.0001). • Over the length of follow-up: 8 deaths in LMWH group, 13 deaths amongst controls (p=0.20).	• 2 variceal bleeds in LMWH group, 1 in control group; 1 death from variceal bleed in each group. • 2 episodes of epistaxis in LMWH group, 1 in control group. • 1 patient stopped LMWH because of thrombocytopenia. • No significant difference in haemoglobin during study between LMWH and control arms.
Treatment:						
Francoz *et al,* 2005	Retrospective assessment of 19 cirrhotics listed for OLT receiving anticoagulation, compared to 10 matched patients not receiving intervention	Nadroparin 5700 IU/day subcutaneously until therapeutic on VKA (acenocoumarol), aiming for INR of 2-3	Patients with known varices and previous variceal bleeding still treated with anticoagulation; variceal band ligation used as bleed prophylaxis.	• 8 of the anticoagulated patients had complete recanalisation between starting treatment and OLT (1 of whom had complete thrombosis) • Amongst other anticoagulated patients: thrombosis unchanged in 10, thrombosis extended in 1.	Similar duration of surgery and need for blood transfusions at time of transplant surgery between anticoagulated and non-treated groups.	1 anticoagulated patient had a significant bleed (from ulcer post-variceal banding).
Amitrano *et al,* 2010	Retrospective assessment of 28	Enoxaparin 200U/kg/d	If study participant admitted because of	• 9 anticoagulated patients had complete recanalisation.	12 of the 14 with partial response who continued anticoagulation	• No reported variceal bleeding • Two patients developed

	cirrhotics	subcutaneously for six months; however, continued longer if partial response and on OLT waiting list, or if intestinal ischaemia at presentation	variceal bleeding, LMWH only started after eradication of varices by band ligation; otherwise, beta-blockade used if grade 2/3 varices.	• 14 anticoagulated patients had partial recanalisation. • No recanalisation occurred in 5 patients.	obtained complete recanalisation at median time of 11 months.	modest anaemia attributed to PHG.
Delgado *et al,* 2012	Retrospective analysis of 55 cirrhotics (31 treated for acute/ subacute thrombosis, 24 for progression of previously known PVT)	47 patients treated with LMWH, 8 with VKAs (target INR of 2-3). Of those starting with LMWH, 21 shifted to VKAs, whist 26 remained on LMWH throughout. Anticoagulation continued for a mean of 6.8 months.	24 patients with previous portal hypertensive-related bleeding were included. No specific details given about assessment and management of varices at enrolment.	• Complete recanalisation in 25 patients (16 with recent PVT, 9 with progressive PVT). • Partial recanalisation in 8 patients (3 with recent PVT, 5 with progressive PVT). • No recanalisation in 14 patients.	• Re-thrombosis after complete recanalisation occurred in 5/13 of patients after anticoagulation was stopped, at a median time of 1.3 months. • Those who achieved recanalisation developed less portal hypertensive-related bleeding, ascites or hepatic encephalopathy but not to statistical significance (p=0.1).	• Five bleeding events related to anticoagulation (all in participants taking VKAs), none fatal. Bleeding sites were: lower gastrointestinal bleed, post-dental extraction bleed, obscure gastrointestinal bleed, vaginal bleed, surgical wound bleed. • Six variceal bleeds deemed unlikely related to anticoagulation.
Maruyama *et al,* 2012	Prospective study of 5 cirrhotic patients with acute variceal bleeding found to have PVT.	Endoscopic variceal ligation to ensure haemostasis, then LMWH (75	After initial endoscopic intervention, repeated band ligation or injection sclerotherapy with argon plasma	Complete recanalisation of the portal vein within 2-11 days in all 5 patients.		No episodes of rebleeding.

		IU/kg/day).	coagulation performed until variceal obliteration.			
Senzolo *et al,* 2012	Prospective study of 56 cirrhotics (33 anticoagulated, 21 controls).	LMWH (Nadroparin 95 U/kg of body weight for six months); dose reduced by 40% if platelet count < 50 x 10^9/l. If complete recanalisation, prophylactic dose of 3800 U/d for next six months. Continuous use of prophylaxis if thrombophilia and/ or no recanalisation after one year.	Patients with previous variceal bleeding, grade 2 oesophageal varices with red signs and all with grade 3 varices underwent band ligation. Anticoagulation not started until 15 days after last banding session.	• Complete recanalisation in 12 anticoagulated patients and 1 control. • Partial recanalisation in 9 anticoagulated patients. • Thrombosis unchanged in 7 anticoagulated patients. • Thrombosis progression in 5 anticoagulated patients and 15 controls ($p<0.001$).		• 1 variceal bleed in anticoagulation arm; 5 variceal bleeds and 2 intestinal venous ischaemia episodes in control group. • In anticoagulation arm – 1 patient with epistaxis, 1 patient with haematuria, 1 patient with cerebral haemorrhage. • 1 patient developed likely heparin-induced thrombocytopenia within 1 month of starting LMWH.
Werner *et al,* 2013	Retrospective analysis of 28 cirrhotics.	VKA (warfarin), targeting INR 2-3, at least one year of treatment; longer treatment if partial recanalisation at	Band ligation of grade 2/3 varices prior to initiation of anticoagulation.	• Complete recanalisation in 11 patients. • Partial recanalisation in 12 patients. • No change in 5 patients.		• No gastrointestinal bleeding • 1 significant bleeding event (vaginal bleed).

		one year.				
Chung *et al,* 2014	Retrospective analysis of 28 cirrhotic patients with non-malignant PVT (14 whom received anticoagulation, and 14 matched patients who received no anticoagulation).	VKA (warfarin), with duration of therapy decided on case-by-case basis depending upon extent of PVT detected on follow-up imaging (mean duration of 112 +/- 62 days of therapy). Mean INR of ˜1.6 achieved.	Variceal bleed prophylaxis applied, although details not described.	• Thrombus resolution in 11 anticoagulated patients (including complete resolution in 6 patients), and in 5 patients without anticoagulation (p=0.022). • Progression of PVT in 1 patient in anticoagulated arm, and 3 patients without anticoagulation.		• No bleeding complications within the anticoagulated arm.
Chen *et al,* 2016	Retrospective analysis of 66 cirrhotic patients with non-malignant PVT (33 anticoagulated, 33 untreated).	VKA (warfarin), with target INR of 2.5 (but accepting 2-3). Anticoagulation used for a median of 7.6 months.	Variceal bleed prophylaxis applied, although details not described.	• Improvement in thrombosis in 68.2% of anticoagulated patients (vs 25% of patients with no anticoagulation; p=0.011)). • No change in thrombosis in 18.2% of anticoagulated patients (vs 37.5% of patients with no	No significant difference in the probability of hepatic decompensation after one year of anticoagulation vs no treatment (p=0.847).	• 4 anticoagulated patients required early cessation of anticoagulation because of GI bleeding necessitating hospitalisation/ blood transfusion. • 1 episode of epistaxis and 3 episodes of gingival haemorrhage within the anticoagulated group.

				anticoagulation). • Progression of PVT in 13.6% of anticoagulated patients (vs 37.5% of patients with no anticoagulation).		

Table 2: Clinical studies of prophylaxis and treatment of non-malignant portal vein thrombosis with anticoagulation in people with cirrhosis.