Thrombotic Complications in Cirrhotic Patients: Balancing Risks and Benefits of Anticoagulation Treatment

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ABSTRACT

The risk of excessive bleeding and thrombotic complications coexist in cirrhotic patients due to synthetic reduction in both pro and anticoagulants. However, investigators suggest the prevalence and consequences of thrombotic complications are underestimated. There is convincing evidence that thrombosis causes worsening portal hypertension, hepatic fibrosis and increases patient mortality. New evidence is emerging about the benefits of treating and preventing thrombotic complications in patients with liver disease. In the absence of well-designed trials, clinical experience has become the most consistent guide to choose and dose anticoagulant drugs in this patient population. Practical use of anticoagulants however, is hindered by the lack of simple methods to monitor drug effect. In this review, we present a concise appraisal of current evidence on the most commonly studied indications for anticoagulation in cirrhotic patients. Information about drug action, dosing and monitoring are presented to provide a basis for clinical decision-making. The ongoing challenges in identifying therapeutic targets for treatment and monitoring drug effects are examined to highlight important clinical questions that have not yet been fully addressed.

Key words: liver cirrhosis; coagulation; bleeding; thrombosis

INTRODUCTION

Health care providers have primarily focused upon the prevention and treatment of bleeding episodes in cirrhotic patients (1). A lack of laboratory measures identifying thrombosis risk has given clinicians the impression that patients are "auto-anticoagulated" and at low risk of thromboembolic disease (2-4). Only recently have the importance of thrombosis in cirrhotic patients been recognized and investigators think the frequency and severity of the resulting complications are still underestimated (5).

Pro and anticoagulant factors play a critical role in forming mechanically effective clot that is limited to the site of injury (2,6). The same balance is

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present in patients with compensated liver disease. However, coagulation is “rebalanced” by an equal reduction in factors that build and prevent clotting. Physiological insults such as sepsis or kidney dysfunction easily tip this new and fragile balance to cause bleeding and/ or thrombotic complications.

New clinical findings show that thrombosis can cause acute hepatic decompensation, disease progression and death in cirrhotic patients (7-9). While treatment with anticoagulants reduces morbidity and mortality associated with thrombotic complications in a number of diseases, the data about risks and benefits of anticoagulation in cirrhotic patients is only beginning to accrue. Durable recommendations about indications, dosing and therapeutic safety indices still require more information from well-designed studies.

The aim of this review is to provide a concise yet comprehensive appraisal of current research that outlines the risks and benefits of anticoagulation in cirrhotic patients. We limited our review to the most studied indications for anticoagulation in cirrhotic patients. A summary of up to date information about the pharmacology and monitoring of anticoagulants is provided to assist care providers in clinical decision making. We use the evidentiary base to identify gaps in knowledge that require future work to improve patient outcomes.

MOST COMMONLY STUDIED INDICATIONS FOR ANTICOAGULATION IN CIRRHOTIC PATIENTS

Portal vein thrombosis (PVT)

The prevalence of nonmalignant PVT in cirrhosis is estimated at 10-25% (10). Acute PVT can abruptly increase portal hypertension leading to decompensation and death. Further, transplantation may not be possible if clot propagates into the mesenteric veins. Risk factors for PVT are unknown, but variceal bleeding, low platelet count and reduced portal flow velocity are associated findings (4,11).

Population studies suggest thrombophilic factors occur in up to 39% of patients with PVT (12). The most common were Factor V Leiden, prothrombin 20210A mutation and Plasminogen activator inhibitor 4G-4G. The prevalence of thrombophilia in PVT may be underestimated as standard coagulation profiles often fail to identify increased clotting and routine screening for thrombophilic factors is rarely performed (12-14).

Differences in opinion about anticoagulation for PVT stem from findings showing that nearly half of affected

patients experience some degree of spontaneous recanalization (15). However, a systematic review showed a pooled Odds Ratio of 4.16 (95% CI = 1.88 – 9.20, $P = 0.0004$) for complete recanalization in treated compared to untreated patients (16). Findings from the same systematic review showed that bleeding complications were rare and patient death was not due to treatment (16).

The findings show anticoagulation increases portal vein patency and reduces complications due to PVT. Observations from a small randomized controlled trial in advanced and compensated cirrhosis also suggest the benefits of routine PVT prophylaxis outweigh the risks (17). The findings are promising, but more outcome data is needed to construct a robust therapeutic safety index capable of guiding treatment. Regardless of these limitations, many investigators consider current findings convincing enough to recommend anti-coagulation for treatment and prophylaxis of PVT (17).

Budd-Chiari syndrome (BCS)

Obstruction of outflow between the small hepatic veins and the inferior vena up to the level of the right atrium is rare in Western countries and usually due to multiple thrombophilic disorders including myeloproliferative disease (18). Congenital endoluminal abnormalities explain the higher prevalence in Asian countries (19). Therapeutic options include anticoagulation, recanalization, surgical shunting, transjugular intra-hepatic portosystemic shunting and transplantation. Anticoagulation is a common initial intervention (20). The strategy for anticoagulation is extrapolated from outcomes in patients with venous thromboembolism (VTE) due to thrombophilic disorders. However, anticoagulation as a single therapy is only effective in 10% of BCS cases (21).

Venous thromboembolism (VTE)

The reported incidence of deep vein thrombosis and pulmonary embolism in hospitalized patients with chronic liver disease varies from 0.5 to 6.3% (4,22). Incidence increased with severity of illness measured by Child-Pugh (22). Age less than 45 years increased the risk in compensated (OR 1.23; 95% CI 1.04 to 1.46) and decompensated patients (OR 1.39; 95% CI 1.15 to 1.69)(23).

Investigators suggest VTE is still underestimated because routine screening is rarely performed and standard coagulation tests are not diagnostic (2-4). Patients at increased risk include those with Hepatitis A, B and C in addition to Epstein Barr and Cytomegalovirus (24). Investigators theorize that viral-induced inflamma-

tion activates coagulation factors, downregulates anticoagulants and inhibits fibrinolysis (25).

A pulmonary embolus mortality risk of 35% compared to 16% in noncirrhotic patients and longer hospital stay supports routine surveillance and anticoagulation for VTE in hospitalized cirrhotic patients (26). Few adverse outcomes in patients with decompensated cirrhosis treated for PVT suggest there could be a similar risk-benefit profile for treatment of VTE. To date, prophylaxis for VTE requires additional evaluation (2).

Thrombosis-associated hepatic fibrosis

Human and experimental animal evidence link hepatic microvascular thrombosis with tissue parenchyma fibrosis (26). A similar relationship between microvascular clotting and fibrosis has been reported in progressive lung and kidney diseases and suggests that in situ small vessel thrombosis may be a common end pathway for a number of pathological conditions (24,25). Recent studies show microvascular thrombosis initiates inflammation and stellate cell activation, two molecular pathways associated with increased thrombin generation and fibrin formation (26,27). Theories implicating parenchyma extinction also identify microvascular thrombosis as the first step in a cascade leading to fibrosis (27).

Hepatic fibrosis progresses faster in patients with genetic mutations for Factor V Leiden, protein C deficiency or increased expression of factor VIII than in patients with hemophilia and Hepatitis C (5,28). The fibrotic response is slower in experimental animals with inhibition of endothelial-based Tissue Factor and P-selectin (29,30). Evidence suggests multiple sites in the coagulation cascade initiate inflammation which stimulates the synthesis of interstitial molecules (31).

The current evidence specifically implicates increased clot formation as a cause of progressive fibrosis but, it is unknown if anticoagulation will mitigate this response. The evidence is very compelling and clinical trials are the next logical step.

Use of extracorporeal circuits for life support

Extracorporeal circuits are often used in cirrhotics without anticoagulation due to concerns about heparin-induced bleeding risk. Clot accumulation in extracorporeal circuits is common in cirrhotic patients compared to patients with other causes of renal failure (32). Heparin administration however, failed to increase circuit patency times and was associated with increased bleeding complications (33). Other anticoagulants used to promote extracorporeal circuit patency did not perform better than heparin (34, 35). Citrate anticoagulation can safely be used in liver transplant patients, but the filter running time was still limited to approximately 23 hours (35). There is general agreement that the risk of heparinization exceeds the benefit in renal replacement circuits (33).

PHARMACOLOGY AND MONITORING OF ANTICOAGULANT DRUG

Choice of anticoagulant drugs for clinical use in cirrhotic patients is complicated by a lack of well-designed efficacy and safety trials. Current studies in cirrhotic patients have not tested for differences in response due to factors such as demographic heterogeneity, severity of illness and etiology of disease. Therefore clinicians often draw from their knowledge about the pharmacological behavior of anticoagulant drugs (*fig. 1*).

Figure 1 - Two major classes of anticoagulant drugs are the Heparins and Novel Oral Anticoagulants (NOAC). Unfiltered heparins are larger than Low Molecular Weight Heparin (LMWH). Both groups of heparin-based drugs are activated by binding Antithrombin III (AT III). AT-III activated LMWH have higher affinity for factor Xa than for thrombin. NOAC bind and inactivate either thrombin or factor Xa

Heparin: unfractionated heparin and low molecular weight heparin

Pharmacology

Unfractionated heparin (UFH) is a naturally occurring molecule bound to endothelial cells. Molecules are repeating disaccharide units that vary between 3000 to 30,000 Daltons (36). When given parenterally, UFH, binds Antithrombin III (AT III), inducing conformational changes that causes the UFH-AT-III complex to bind and inactivate thrombin and factor Xa (36). Smaller UFH segments complex with AT III and inactivate factor Xa, while longer segments are required to inhibit thrombin (37). Duration of action is one to two hours (*table 1*).

Low molecular weight heparins (LMWH) are formed by chemical or enzymatic breakdown of large UFH molecular fragments to yield smaller subunits. Purity assays require at least 60% of heparin chains are 8000 Daltons or less (37). LMWH form a complex with AT III to primarily inhibit factor Xa. The preferential inhibition of factor Xa produces more predictable anticoagulant effects than unfractionated heparins.

Duration of action

Steady state drug levels for UFH require 6 hours compared to approximately two to four days for LMWH. The elimination half-life of UFH is 60-150 minutes compared to 4.5 hours for LMWH (33). Heparin half-life is determined by the rate of cellular uptake, renal excretion and binding to Antithrombin III. Human hyaluronic acid receptors for endocytosis (HARE)/ stabilin-2 in liver sinusoidal endothelial cells clear UHF and LMWH (38). Affinity for HARE is higher for UFH than LMWH but uptake for both is facilitated by AT III binding. Renal

excretion becomes the primary route of elimination when cellular uptake is saturated (39). In contrast, LMWH is eliminated by the kidneys only after hepatic partial depolymerization and/or desulfation (40). Therefore renal elimination becomes the primary determinant of half-life during continuous treatment (39).

Monitoring heparin-anticoagulation in cirrhosis

The activated partial prothrombin time (aPTT) is a standard measure of UFH anticoagulant effect, but poorly predicts coagulation inhibition in cirrhosis (41, 42). Baseline aPTT values often exceed normal limits in most cirrhotic patients because the assay only measures procoagulant activity which is reduced due to synthetic failure.

The aPTT does not measure anticoagulant activity and can overestimate bleeding risk, leading to sub-therapeutic dosing. To date there are no evidence-based algorithms to guide UFH dosing that considers the balance between procoagulant and anticoagulant factors. Even tests that use a direct measure of thrombin activity have poor predictability (43,44).

Monitoring is rarely performed in non-cirrhotic patients taking LMWH due to the relatively large therapeutic safety index. When required, the anti-Xa assay is used to determine therapeutic effect (45,46). The assay is performed by adding patient plasma to a known excess of factor Xa and AT III. The amount of remaining Xa is used to extrapolate the degree of coagulation inhibition (46,47).

Results of the anti-Xa assay can be unreliable due to inconsistent sources of commercially available anti-factor Xa substrates and the use of blood samples outside peak activity. Further, the test presumes patients

Table 1 - Pharmacokinetic and pharmacodynamic properties of Unfractionated Heparin (UFH) and Low Molecular Weight Heparins (LMWH)

Property	Unfractionated Heparin	Low Molecular Weight Heparin
Chemical Composition	Polysaccharide with repeating disaccharide units	Same but less heterogeneous
Molecular Weight	3000- 30,000 Daltons	4,000-6,000 Daltons
Administration	Parenteral	Parenteral
Inhibitory activity	Primarily Thrombin	Primarily Xa
Elimination half-life	1.5 hours (1-2)	4.5 hours (4-6)
Metabolism	Hepatic (HARE receptors)	Hepatic (HARE receptors and desulfation or depolymerization)
Elimination	Renal-dose dependent	Renal-dose independent
Standard Laboratory Monitoring	aPTT	Antifactor Xa and thrombin generation
Reversal	Protamine	Partially reversed by Protamine

Abbreviations: Activated Partial Thromboplastin Time (aPTT), Hyaluronic acid receptors for endocytosis (HARE)

have normal AT III levels (41). Most cirrhotic patients develop profound AT III deficiency (<30% activity) due to hepatic synthetic failure. Therefore, the accuracy of the assay declines as the severity of cirrhosis increases (42).

Thrombin generation tests also estimate LMWH anticoagulant effect. The degree of coagulation inhibition measured by the anti-Xa and thrombin generation tests vary and make clinical interpretation difficult (48). Similar discordant findings are also reported in pregnant patients (49). Thrombin generation tests for monitoring are now commonly used as opposed to anti-Xa since the former provides a more detailed pharmacokinetic profile.

Newer low molecular weight heparins

Newer LMWH have a narrower range of mean molecular weights that make the duration of action more predictable (50). The ratio of anti-Xa and anti-thrombin activity varies for each LMWH. Smaller LMWH drugs such as Bemiparin (3,600 D) have the highest anti-Xa to anti-thrombin activity. The relative proportion of anti-thrombin activity increases with molecular weight, explaining why Tinzaparin (6,500 D) has the lowest anti-Xa to anti-thrombin activity. For example, Tinzaparin has much higher dose dependent anti-thrombin activity compared to Enoxaparin (4,400 D) (50).

Lower molecular weight is associated with accumulation in renal disease. Tinzaparin has the highest molecular weight of all marketed LMWH and is least dependent upon renal excretion (38). Studies in elderly patients showed less accumulation of Tinzaparin compared to Enoxaparin with a creatinine clearance <20 mL/min (51).

New oral anticoagulants (NOAC)

Pharmacology

New oral anticoagulants are molecular heterogeneous drugs that bind and inactivate thrombin or Xa (table 2). Dabigatran was the first NOAC released for use. It directly inhibits thrombin, while Endoxaban, Rivaroxaban and Apixaban inhibit free factor Xa and Xa bound to prothrombinase complex (52). The thrombin inhibitor, Dabigatran has a larger anticoagulant effect in cirrhotic versus control patients compared to the direct factor Xa inhibitors, Rivaroxaban and Apixaban which were less potent than in control patients (43).

Advantages of NOAC include oral administration, no requirement for bridging therapy, few drug restrictions, reversal with recombinant prothrombin complexes or specific agents like Idarucizumab for Dabigatran reversal (53) and no need for monitoring in most patient populations (54). Oral administration is particularly advantageous in cirrhotic patients who require long term anticoagulant administration (2,55).

Duration of action

The half-life of NOAC vary between 5 and 17 hours (table 2). The shorter half-life of the factor Xa inhibitor, Rivaroxaban (5-9 hours) improves safety. Up to 33% of the drug is eliminated unchanged by the kidney while 66% is metabolized by the liver before renal elimination. In contrast Dabigatran must be activated by hepatic metabolism (54). The half-life is considerably longer (12-17 hours) than Rivaroxaban, but the mean plasma terminal half-life is independent of dose which improves the ability to predict duration of action. Apixaban is another factor Xa inhibitor with a half-life

Table 2 - A summary of pharmacokinetic and pharmacodynamic information on Novel Oral

NOAC	Dabigatran	Rivaroxaban	Apixaban
Trade name	Pradaxa, Praxaza, Pradax	Xarelto	Eliquis
Site of Action	thrombin	Xa	Xa
Bioavailability	3-7%	80-100%	50%
Metabolism	Hepatic glucuronidation	Hepatic metabolism (66%) CYP3A4 , CYP2J2 and CYP-independent mechanisms	Hepatic CYP3A4, CYP3A5, CYP1A2
Half-life	12-17 hours	5-9 hours	9-14 hours
Elimination	Renal 7% GI 87%	Renal Metabolized (66%) Unchanged (33%)	Biliary (75%) Renal (25%)
Monitor: None	TCT-based tests	Modified chromogenic Anti-Xa assay	Modified chromogenic Anti-Xa assay
Reversal	3 and 4 PTC Idarucizumab	3 and 4 PTC Reversal agents in development	3 and 4 PTC Reversal agents in development

Abbreviations: Anticoagulant Drugs (NOAC). Cytochrome P (CYP), Gastrointestinal (GI), Prothrombin Complex (PTC), Thrombin Clotting Time (TCT)

of 8–15 hours. However, it has the smallest renal clearance of all NOAC drugs (25%). Apixaban and Rivaroxaban are metabolized in the liver by the Cytochrome P450-dependent isozyme pathway prior to elimination (54).

Monitoring

There are no laboratory assays capable of measuring NOAC anticoagulation effect (55). Dilute thrombin generation time, Ecarin clotting and chromogenic assays correlate best with drug concentration, but are not approved by U.S. regulatory agencies for testing (56). In addition, dosing adjustments for age or renal and hepatic disease have not been developed (57).

The Prothrombin Time and Ecarin venom test can be used to estimate clotting inhibition but are unreliable due to differences in thromboplastin assay agents (58). The diluted thrombin time and Ecarin clotting times only estimate plasma drug concentration (59). Therapeutic ranges are unknown and concentration does not reliably predict activity (56). The results from in vitro studies found chromogenic anti-Xa assays may be better estimates of direct Xa inhibitors even though this test underestimates AT III-dependent drug levels in cirrhotic patients (42).

CLINICAL EXPERIENCE WITH ANTICOAGULATION IN CIRRHOSIS

Experience with PVT

There is growing support for routine use of anticoagulation in all cirrhotics with newly diagnosed non-malignant PVT. Most clinical experience is derived from studies using the LMWH, Enoxaparin. Most patients had partial or complete resolution of PVT following treatment over 7-17 months (60-62). However, limited data suggests at least 39% recurrence after treatment was stopped.

The natural history of PVT is similar to spontaneous pulmonary embolism where therapeutic benefit is lost after discontinuing treatment (63). This raises questions about treatment strategies and if long term post thrombotic prophylaxis is of benefit. At least one study showed de novo PVT could be prevented by prophylactic treatment. While it is reasonable to speculate that prophylaxis could reduce the risk of recurrent PVT, this assumption requires confirmatory evidence (17).

There is limited experience with newer anticoagulant drugs for PVT or other thrombotic complications of cirrhosis. Anticoagulant drugs are not necessarily interchangeable even if they belong to the same family of medications. A comparison of half-life, duration of

action and type of elimination within each drug group indicates that each drug has a unique pharmacological profile.

Clinical experience with NOAC in PVT is limited to small studies and case reports as cirrhotic patients were excluded from commercially sponsored Phase III trials. Use of these products in cirrhotics is considered off-label. Successful treatment of PVT with or without mesenteric extension of clot was reported in a series of 5 patients and in a separate single case report (64, 65). All patients were Child A, without varices. Resolution of PVT required six months of therapy. No major bleeding complications were reported (66). Mild hepatic impairment did not seem to alter the pharmacokinetics of Rivaroxaban. However, moderate hepatic impairment significantly increased plasma levels (67).

The decision to treat PVT with anticoagulants appears evidence based and has a sound line of scientific reasoning (68). However, some investigators argue PVT is probably a distant marker of worse patient survival regardless of successful recanalization and the important benchmark is a critical reduction in portal venous velocity that precedes in situ thrombosis (69). This difference in viewpoints has made it difficult to find consensus on anticoagulant management of PVT (60).

Experience with BCS

Investigators suggest limiting anticoagulation for BSC to patients without portal hypertension to reduce risk of bleeding complications and because of a poor long term response rate (70). Heparins (UFH and LMWH) appear to have equal efficacy to Vitamin K antagonists (71). However, Vitamin K antagonists are often preferred due to ease of long term oral administration. There is limited evidence for choice of anticoagulants following percutaneous or surgical recanalization and transplantation. A retrospective single center study of balloon dilation reported complete clot resolution in 12 of 19 and partial resolution in the remaining 7 BCS patients at 15.9 ± 14.4 months using Warfarin (72). The antithrombotic effects of aspirin were equally effective as Vitamin K Antagonists in patients with thrombophilia due to myeloproliferative disorders well controlled on hydroxyurea (73). To date there are no studies using newer LMWH or NOAC in BCS.

Experience with VTE

Evidence suggests VTE prophylaxis improves patient survival and reduces length of hospitalization in cirrhotic patients. Early studies found prophylaxis with LMWH or UFH failed to prevent VTE and increased bleeding complications (44, 74). A reduction in VTE rate however, was reported in a larger study cohort

comprised of younger hospitalized cirrhotics. The diagnostic rate was greater in the younger cohort (1.5% vs. 0.5%) (75). The findings are consistent with previous observations showing a relationship between younger age in cirrhotics and risk of VTE (23). Older age in earlier studies also probably explains the higher number of bleeding episodes (76, 77).

Experience with hepatic fibrosis

There is strong experimental data supporting observations that in situ thrombosis increases the risk of progressive fibrosis. However, there are no corresponding human trials. Select anticoagulants may have additional properties that modulate ischemia and the fibrotic response. Rats treated with Enoxaparin and Nadroparin had significantly less hepatic fibrosis compared to those treated with Tinzaparin (78). A link between Rivaroxaban and inhibition of inflammatory pathways was found in models of ischemic stroke. Better outcome in Rivaroxaban treated rats was related to down regulation ICAM-1 expression and the activation of CD68+-immune cells in addition to thrombin inhibition (79).

Vitamin K antagonists (VKA)

Vitamin K antagonists still form a mainstay of therapeutic intervention at many institutions. Warfarin binds and inactivates Vitamin K epoxide reductase, the enzyme that returns Vitamin K1 to an active form. This depletes Vitamin K1, the substrate needed to activate coagulation proteins (II, VII, IX, X, protein C, and S). Onset of action is delayed for two to three days until there is natural attrition of activated coagulation proteins. Protein C and S levels drop faster than procoagulant factors leaving a vulnerable period where the risk of thrombosis is theoretically increased. Short acting anticoagulants with rapid onset are therefore often used to initiate anticoagulation during treatment with VKA. Treatment requires regular monitoring. The most common monitoring test is the International Normalized Ratio (INR).

Monitoring

The therapeutic target for INR in cirrhotic patients is often unclear due to prolongation of the INR caused by reduced procoagulant synthesis (2). A comparison of assays including INR shows thrombin generation captures more detailed information about the global coagulation cascade. However, there was a large variation across a narrow range of INR values even in thrombin generation testing (80).

Shortfalls in clinical monitoring

The prothrombin time was previously used to measure therapeutic effect in patients taking VKA. Different sourcing of assay thromboplastin substrates gave rise to variable test results. The World Health Organization endorsed use of a normalized value based upon a single thromboplastin source (81). The resulting international sensitivity index (ISI) corrects prothrombin times into values that can be compared over time and between institutions (81,82). The resulting INR values can only be used in patients without pre-existing coagulation defects and there is no simple approach to normalize the INR in cirrhosis (82).

Investigators suggested using plasma from healthy and cirrhotic patients to normalize the INR (82). Each thromboplastin would have 2 ISI values: one for patients on VKA and one for cirrhotic patients. This should reduce inter-laboratory variability for INR values. However, it is unlikely that a single ISI for liver would work equally well in all cirrhotic patients due to differences in coagulation profiles caused by severity of illness. The other remaining alternative is to measure factor levels (2).

Clinical outcomes

There are no large randomized trials and most evidence supporting use of VKA in cirrhotic patients comes from small single center reports. Treatment appears to improve PVT with and without thrombophilia (83). Few bleeding complications have been reported following PVT treatment with either VKA or LMWH (84, 85). Similar findings were reported in a single center study of VKA thrombosis prophylaxis in liver transplant recipients (86). Patients with splanchnic thrombosis have been safely treated with VKA after initiation treatment with LMWH. Patients in this study had an average MELD score of 13 and the INR was kept between values of 2-3 during treatment (87).

A single study found cirrhotic patients with atrial fibrillation experienced more bleeding complications when treated with VKA (88). Bleeding complications were mostly due to varices and hemorrhagic stroke. However, a higher prevalence of neurological vascular accident and hypertension in this population prior to VKA treatment may explain these findings. Endoscopic treatment of varices was not reported. Further, the only test that guided VKA administration was the INR and end points for treatment were unclear. The authors still concluded however, that the risk compared to benefit of VKA use seemed favorable for patients with earlier stages of cirrhosis (88,89).

CONCLUSIONS

A focus upon the most commonly studied indications for anticoagulation in cirrhotic patients allowed us to compile enough evidence to uncover trends in anticoagulant treatment and identify knowledge gaps that cause uncertainty in clinical decision making. We found general agreement that treatment of thrombosis in cirrhosis reduces morbidity and mortality. The strongest evidence came from studies of PVT.

Evidence outlining the risks and benefits of PVT prophylaxis were more controversial. However, the findings were encouraging and can be considered a launch point for future investigation. Larger and better designed studies are needed to confirm observations about the benefits of anticoagulation prophylaxis and treatment for PVT and VTE. The ability of some anticoagulant drugs to modulate the fibrotic response in experimental animals is an exciting finding that still needs translation into human studies.

There are few reliable tests to monitor anticoagulant activity in cirrhotic patients and standard tests have inherent faults that limit clinical use. The desire to monitor anticoagulant effects is driven by the lack of steady state in coagulation synthesis and drug metabolism and elimination. Developing reliable and validated tests for measuring coagulation profiles and therapeutic effect will be one of the most important pieces of the puzzle for developing a rational approach to anticoagulation in cirrhosis.

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