On Acute Mesenteric Venous Thrombosis

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DOCTORAL DISSERTATION

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On Acute Mesenteric Venous Thrombosis

Abstract

Background: Mesenteric venous thrombosis (MVT) is a rare but life-threatening condition which without treatment can develop into bowel ischaemia, bowel gangrene, peritonitis, and death. Main causes of MVT are coagulation disorders, abdominal inflammatory conditions, malignancies, and liver diseases. Currently available investigations fail to identify a causal factor in about 20 % of patients. Since MVT is extremely seldom diagnosed on clinical grounds, computed tomography (CT) with intravenous contrast enhancement and imaging in the portal phase has become the most important, reliable, and accurate imaging for diagnosis of MVT. Immediate anticoagulation therapy after diagnosis has been proposed as the first-line treatment option. When to perform thrombophilia testing in venous thromboembolism, and how to interpret the results, is debatable.

Aims:

The aims were to study:

- Prognostic factors, outcome, failure rate of anticoagulation as monotherapy, and to identify when bowel resection was needed.
- Clincal efficacy and safety of direct oral anticoagulants (DOACs) and vitamin K antagonists (VKA) in MVT patients
- The association of CT findings at admission and bowel resection rate in patients with MVT.
- Differences in risk factor profiles between patients with MVT and systemic venous thromboembolism (VTE).

Methods: Retrospective study of consecutive patients with MVT diagnosed between 2000 and 2017 at Skåne University Hospital, Sweden. For the comparative study, 1465 consecutive patients with VTE between 1998 and 2008 were retrieved from the Malmö Thrombophilia Study (MATS).

Results: Among 120 patients, seven died due to autopsy-verified MVT without bowel resection and 15 underwent immediate bowel resection without prior anticoagulation therapy. The remaining 98 patients received anticoagulation monotherapy, wherof 83 (85%) were treated successfully. Computed tomography showed successful recanalization of thrombois in 71% of patients on VKA and 69% of patients with DOACs (p=0.88). No difference in major bleeding (p=0.54) was found between VKA and DOACs. The presence of mesenteric oedema (p=0.014), small bowel wall oedema(p<0.001), small bowel dilatation (p=0.005), and ascites (p=0.021) were associated with increased bowel resection rate. Patients with MVT have a higher prevalence of cancer (19.2% versus 12.1%; p=0.026) and lower prevalence of factor V Leiden mutation (26.6% versus 38.9%; p=0.031) than those with systemic VTE.

Conclusion: Contemporary data show that monotherapy with anticoagulation is an effective first choice in acute MVT patients if diagnosed early in the course. Anticoagulation treatment with DOACs appears to be able to replace VKA in patients with MVT. The presence of abnormal intestinal findings secondary to MVT confers an excess risk of need of bowel resection due to infarction. The high prevalence of factor V Leiden mutation in patients without cancer in both MVT and VTE groups, suggests that screening for factor V Leiden mutation in this population should be considered in both groups.

Key words: Mesenteric venous thrombosis, Intestinal ischaemia, Venous thromboembolism, Thrombophilia, Anticoagulation, Direct oral anticoagulants, Vitamin K antagonists.

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On Acute Mesenteric Venous Thrombosis

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Cover photo: The Sea Serpent Fountain placed in the Grand Square in Trelleborg, Sweden. The sea serpent sprays out its venom with anticoagulative power to rescue the sea mermaid's life by dissolving her deadly mesenteric venous thrombosis.

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*To my **family***

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List of Publications

This thesis is based on the following publications, referred to in the text by their Roman numerals and reprinted with permission from their respective publishers.

I. Salim S, Zarrouk M, Elf J, Gottsäter A, Ekberg O, Acosta S. Improved prognosis and low failure rate with anticoagulation as first line therapy in mesenteric venous thrombosis. World J Surg 2018; 42: 3803-3811

II. Salim S, Ekberg O, Elf J, Zarrouk M, Gottsäter A, Acosta S. Evaluation of direct oral anticoagulants and vitamin K antagonists in mesenteric venous thrombosis. Phlebology 2019; 34: 171-178.

III. Salim S, Ekberg O, Elf J, Zarrouk M, Gottsäter A, Acosta S. Clinical implications of CT findings in mesenteric venous thrombosis at admission. Emerg Radiol 2018; 25: 407-13

IV. Salim S, Zarrouk M, Elf J, Gottsäter A, Sveinsdottir S, Svensson P, Acosta S. Clinical implications of different risk factor profiles in patients with mesenteric venous thrombosis and systemic venous thromboembolism: a population-based study. J Thromb Thrombolysis 2019; 47: 572-577.

Thesis at a glance

Paper	Aim	Method	Main results
I. Improved prognosis and low failure rate with anticoagulation as first-line therapy in mesenteric venous thrombosis.	Evaluate outcome, prognostic factors, and failure rate of anticoagulation as monotherapy, and to identify when bowel resection was needed	Retrospective study of consecutive patients with MVT diagnosed between 2000-2015	Among the 98 patients receiving anticoagulation treatment, 83 (85%) were successfully treated with heparin as monotherapy without need for surgical intervention. Overall 30-day mortality rate was 10.8%.
II. Evaluation of direct oral anticoagulants and vitamin K antagonists in mesenteric venous thrombosis.	Evaluate clinical efficacy and safety of DOACs and VKA in patients with MVT	Retrospective study of 102 patients with MVT treated between 2004 and 2017 at a centre with a conservative medical first approach. Median clinical follow-up was 4 years.	Computed tomography showed successful recanalization of thrombosis in 71% of patients on VKA and 69% of patients on DOACs (p=0.88). No difference in major bleeding (p=0.54) was found between VKA and DOACs.
III. Clinical implications of CT findings in mesenteric venous thrombosis at admission	Evaluate the association of computed tomography (CT) findings at admission and bowel resection rate in patients with MVT	Retrospective study of MVT patients treated between 2004 and 2017. CT images at admission and at follow-up were scrutinized according to a predefined protocol	The presence of mesenteric oedema (p=0.014), small bowel wall oedema (p<0.001), small bowel dilatation (p=0.005), and ascites (p=0.021) were associated with increased bowel resection rate.
IV. Clinical implications of different risk factor profiles in patients with mesenteric venous thrombosis and systemic venous thromboembolism: a population-based study	To compare acquired and inherited risk factors in MVT versus VTE	Retrospective study of consecutive patients with MVT diagnosed between 2000-2015. VTE patients were retrieved from the Malmö Thrombophilia Study (MATS), including 1465 consecutive unselected VTE patients between 1998 and 2008.	Patients with MVT have a higher prevalence of cancer and lower prevalence of factor V Leiden mutation than those with systemic VTE.

Populärvetenskaplig sammanfattning

Akut blodpropp i den övre stora tarmvenen (mesenterialvenstrombos)

Bakgrund

Mesenterialvenstrombos (MVT) är en sjukdom som innebär att patienten utvecklat en blodpropp i en av de stora tarmvenerna. Sjukdomen är ovanlig, och leder mycket ofta till svår syrebrist i tarmen (tarminfarkt) och död. Det är en av de svåraste akuta buksjukdomarna att diagnosticera på kliniska grunder. För bara några årtionden sedan upptäcktes en ansenlig del av patienterna först genom fyndet av död tarm vid obduktion, medan allt fler patienter numera kan diagnostiseras mycket tidigare med hjälp av moderna röntgenundersökningar. Sjukdomen indelas i primär och sekundär MVT beroende på om det föreligger en utlösande orsak till sjukdomen. Primär MVT innebär att man inte finner orsak till sjukdomen medan sekundär, som är den vanligare formen, innebär att det finns en bakomliggande förklaring såsom ärftliga orsaker som gör att blodets levringsförmåga ökar, cancersjukdomar eller inflammatoriska tillstånd i buken, exempelvis bukspottkörtelinflammation.

Syfte med studierna avseende akut blodpropp i den övre stora tarmvenen

- Att studera prognostiska faktorer, utfall, frekvensen av misslyckad behandling med blodförtunnande läkemedel och identifikation när tarmkirurgi behövs.
- Att studera behandlingseffekten och säkerheten av nya och gamla blodförtunnande läkemedel.
- Att studera kopplingen mellan röntgenfynd och tarmkirurgi.
- Att studera skillnader i riskfaktorer mot patienter som drabbats av blodpropp i andra kroppsdelar och lungor.

Sammanfattande metod och resultat av avhandlingens studier

Sammantaget bygger avhandlingen på fall av patienter diagnostiserade med MVT på Skånes universitetssjukhus mellan åren 2000-2017. Sjukdomens kliniska förlopp och utfall studeras först (delarbete I), och i dagens moderna sjukvård diagnostiseras trots allt majoriteten av patienter i tid med röntgenundersökningar (skiktröntgen) och dessa kan i huvudsak behandlas med blodförtunnande läkemedel utan kirurgi. Införandet av nya blodförtunnande läkemedel på marknaden gav oförändrat med

blödningskomplikationer och var lika effektivt att lösa upp blodproppen som gamla blodförtunnande läkemedel (delarbete II). I delarbete III studerades skiktröntgenfynden vid MVT med avseende på utbredning av venpropp och tarmpåverkan samt dess kliniska betydelse. Patienter med tarmförändringar vid skiktröntgen löper större risk att genomgå kirurgi. Riskfaktorer vid MVT jämfördes sedan med annan form av propp i vensystemet i samma befolkning efter sammanslagning av två databaser. Patienter med MVT hade i högre frekvens cancer och lägre frekvens av genmutationen kallad ''faktor V Leiden'' (delarbete IV).

Slutsatser

Blodförtunnande läkemedel är en effektiv förstahandsbehandling vid akut MVT. Behandling med nya blodförtunnande läkemedel förefaller vara lika bra som det gamla blodförtunnande läkemedlet warfarin. Det är viktigt att behandlade läkare detaljstuderar röntgenbilderna tillsammans med röntgenläkare för att identifiera högriskpatienter för kirurgi. Den höga förekomsten av trombofili faktorn,''faktor V Leiden mutation'', stödjer att man bör screena för den faktorn i vår population för att kunna ge patienten en förklaring till att denne drabbats, såvida patienten inte har en sekundär MVT t.ex. cancersjukdom.

Abbreviations

BMI	Body mass index
CT	Computed tomography
DOAC	Direct oral anticoagulants
DVT	Deep vein thrombosis
ESVS	European Society for Vascular Surgery
FVL	Factor V Leiden
GFR	Glomerular filtration rate
INR	International normalized ratio
JAK2 V617F	Janus-activated kinase gain of function substitute of valine to phenylalanine at position 617
LMWH	Low molecular weight heparin
MATS	Malmö Thrombophilia Study
MVT	Mesenteric venous thrombosis
PE	Pulmonary embolism
PT	Prothrombin
PVT	Portal vein thrombosis
SMA	Superior mesenteric artery
TIPS	Transjugular intrahepatic portosystemic shunt
VKA	Vitamin K antagonists
VTE	Venous thromboembolism

Introduction

Normal mesenteric circulation

The mesenteric blood circulation consists primarily of three major arteries (celiac artery, superior mesenteric artery, and inferior mesenteric artery) and two major veins (superior and inferior mesenteric veins) which are connected by smaller arterioles, capillaries and venules. This cascade, also known as the splanchnic circulation, courses through the mesentery, providing blood to and draining it from the digestive organs. The celiac artery is the first major branch of the abdominal aorta and, together with its branches, provides oxygenated blood to the stomach, proximal duodenum, part of the pancreas, spleen, liver, gallbladder, and biliary tree. The superior mesenteric artery (Figure 1) arises just inferior to the celiac artery and supplies arterial blood to the rest of the duodenum and pancreas, the entire small intestine, and the large intestine up to the splenic flexure. The inferior mesenteric artery is the third main branch of the abdominal aorta and provides blood to the remainder of the colon and rectum. The inferior mesenteric vein joins the splenic vein, and the superior mesenteric vein and anastomose to form the portal vein (Figure 2)[1].

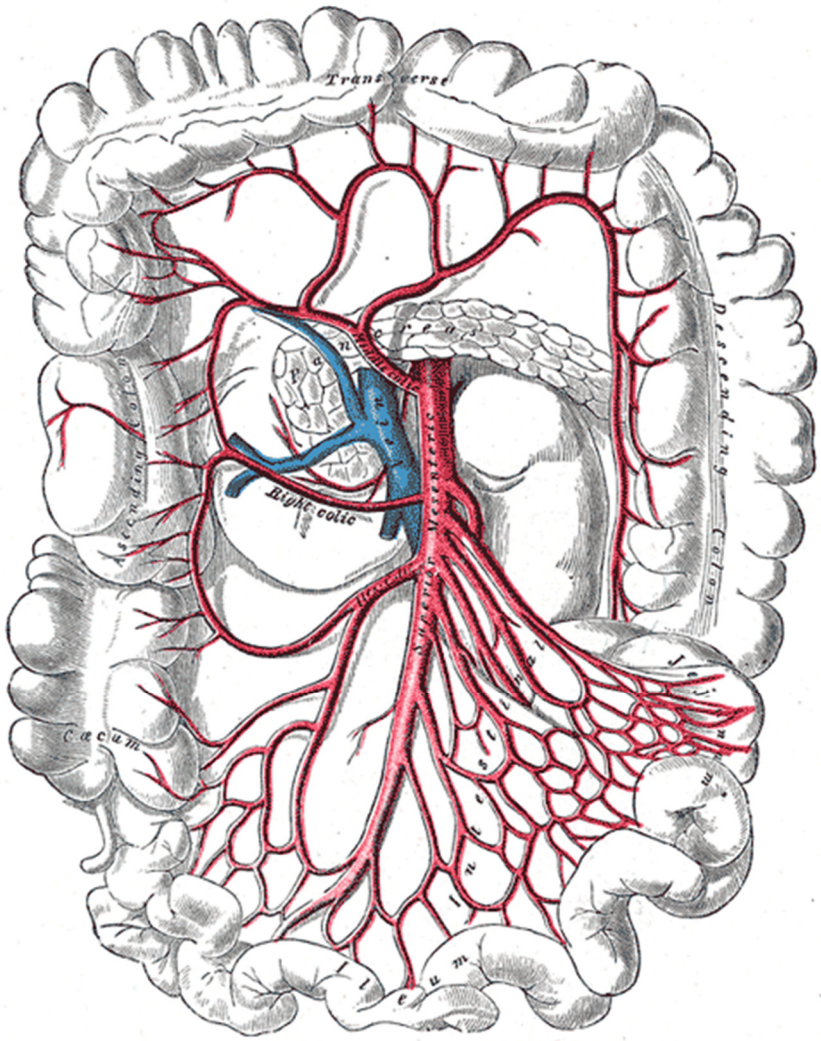

Figure 1. Frontal view of the superior mesenteric artery (SMA) and its branches. The large vessel (blue) beside the SMA is the superior mesenteric vein. Wikimedia Commons.

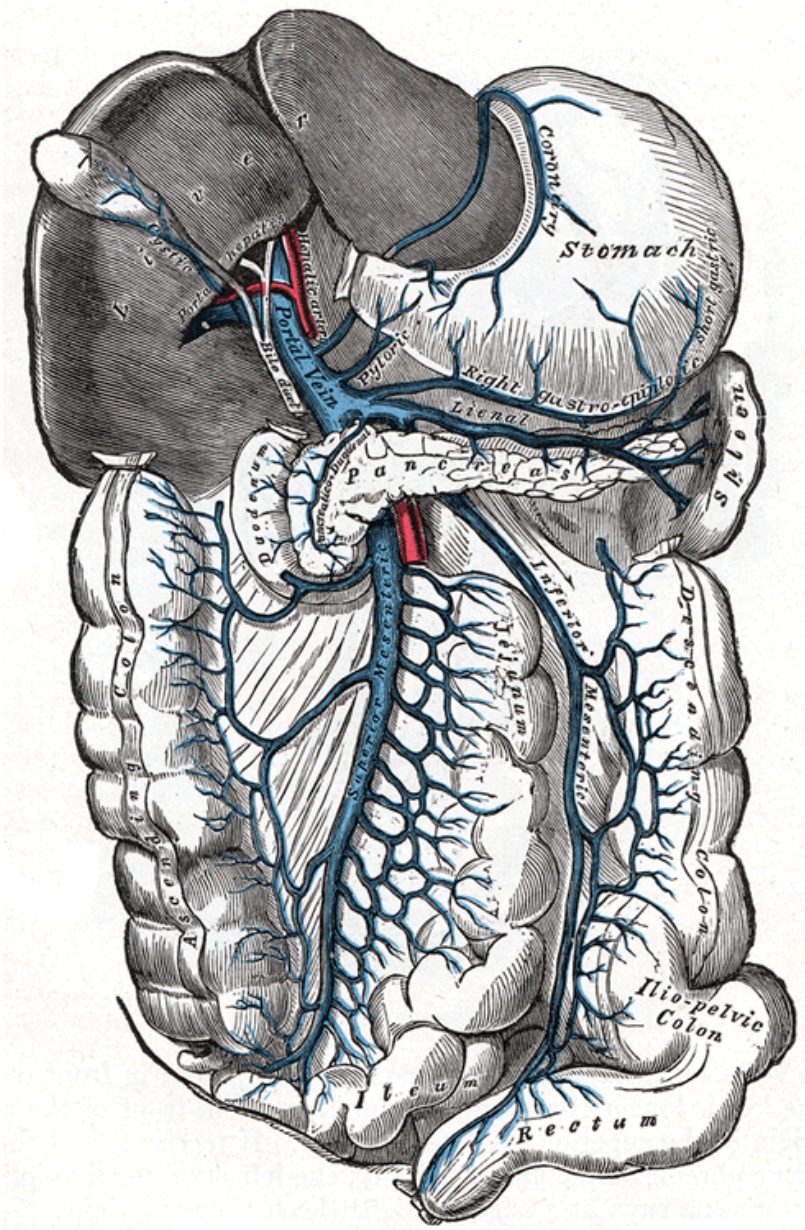

Figure 2. The portal vein and its tributaries. It is formed by the superior mesenteric vein, inferior mesenteric vein, and splenic vein. Wikimedia Commons.

Mesenteric ischaemia

Mesenteric ischaemia occurs when the blood flow in the mesenteric circulation does not meet the metabolic demands of the bowel, resulting in ischaemia, intestinal necrosis, and eventually patient death if untreated[2]. Acute mesenteric ischaemia accounts for about 1:1000 acute hospital admissions in Europe and in USA[3]. Although mesenteric ischaemia is relatively uncommon, it can be life-threatening, and its recognition is therefore crucial to reduce the high mortality rates (50 to 80%)[4-7]. Four different etiological forms of mesenteric ischaemia have been identified: arterial embolism, arterial thrombosis, venous thrombosis and nonocclusive (low-flow) mesenteric ischaemia. Arterial embolism is the most frequent cause, accounting for 45 % of acute intestinal ischaemia[8]. The majority of emboli arise from the heart in the setting of cardiac arrythmia. Other sources of emboli include intracardiac thrombosis, valve vegetations, and atheromatous plaque in the aorta. Arterial thrombosis accounts for approximately 25% of cases of acute mesenteric ischaemia[8]. This entity occurs in the setting of severe atherosclerosis of the superior mesenteric artery (SMA), typically at its origin[9, 10]. The exact aetiology of the SMA occlusion, embolism or thrombosis, is sensitive to changes of preventive activity towards cardiovascular disease in terms of prophylaxis against arterial embolism, smoking cessation, medication against atherosclerotic disease. The embolism/thrombosis ratio of acute SMA occlusion today is probably near 1. There will always be a number of indeterminate cases of acute SMA occlusions, even if this percentage will decrease with time due to increased activity with high resolution computed tomography angiography (CTA)[11].Nonocclusive mesenteric ischaemia accounts for about 20 % of cases of mesenteric ischaemia. It is poorly understood but is thought to occur as a result of splanchnic hypoperfusion and vasoconstriction. MVT causes 10% of cases of acute intestinal ischaemia. This condition occurs in a variety of clinical settings, such as trauma, hypercoagulable states, liver cirrhosis, and malignancies[12]. Dissection of the SMA, either isolated or in combination with aortic dissection, does not belong to the classical aetiologies of acute mesenteric ischaemia. Differences and similarities in clinical presentation for acute embolic and thrombotic SMA occlusion, and MVT are outlined in Table 1.

Table 1. Clinical presentation at admission to hospital in patients with acute mesenteric ischaemia[13]

	SMA embolus	SMA thrombus	MVT
Age ≥ 80 years	++	+	-
Age < 50 years	-	-	+
Women > Men	+	+	+/-
Atrial fibrillation	++	-	-
Previous myocardial infarction	++	+	-
Stroke	+	++	-
Previous symptoms of chronic mesenteric ischaemia	-	++	-
Previous DVT or PE	-	-	++
Symptoms			
Sudden onset	++	+/-	-
Insidious onset	-	+	+
Abdominal pain	++	+	+
Vomiting	++	++	+
Diarrhoea	+	+	+
Bloody stools	+	+	+/-
Synchronous embolism	++	-	-

++, Factors likely to be present, +, factor perhaps present, -, factor unlikely to be present. DVT: deep vein thrombosis. MVT: Mesenteric venous thrombosis. PE: Pulmonary embolism. SMA: Superior mesenteric artery.

History of MVT

In 1921, Dr. Cokkinis stated: ‘’Occlusion of the mesenteric vessels is regarded as one of those conditions of which the diagnosis is impossible, the prognosis is hopeless, and the treatment almost useless’’[14]. This pessimism expressed by Dr. Cokkinis for almost 100 years ago, is unfortunately still shared by many physicians today. Such an attitude results from the continued poor outcome of most patients with acute mesenteric ischaemia. However, remarkable advances in medical and surgical aspects since Cokkinis era, has now made it possible to save lives of a substantial proportion of patients with mesenteric ischaemia[15]. MVT was recognized as a cause of intestinal gangrene already in 1895 by Elliot, who treated the infarcted bowel by resecting it, creating two stomas, and reanastomosizing them two weeks later[16]. Before recognition of nonocclusive mesenteric ischaemia, MVT was thought to be the principal cause of acute mesenteric ischaemia, and it was not until 1935 it was described as a distinct cause of mesenteric ischaemia, differentiated from mesenteric arterial occlusion by Warren and Eberhard[17]. During the same year, Donaldson and Stout performed dog experiments showing that MVT might not lead to gangrene, may allow spontaneous recovery, and was probably related to the same factors causing venous thrombosis in other parts of the body[18]. Following the development of heparin, anticoagulants were first used to treat MVT in 1940[19], and were shown to be associated with improved outcome

by Naitove and Weisman in 1965[20]. The first thrombectomy was described by Bergentz as an adjunctive treatment during laparotomy in 1974[21], and Yankes reported the first use of percutaneous transhepatic local thrombolytics to treat MVT in a high-risk surgical candidate in 1988[22].

Epidemiology of MVT

A population based study in the city of Malmö, Sweden, including 402 patients with acute mesenteric ischaemia with an autopsy rate of 87 %, showed that 16 % of patients were diagnosed with MVT[23]. The estimated overall incidences of MVT in Malmö 1970 to 1982[24] and 2000 to 2006[25] were similar, 2.7/100.000 person-years in 2000 to 2006 with equal incidences in both genders.

Thrombophilia

Thrombophilia (also called hypercoagulability) is the predisposition to thrombosis (formation of a clot within a blood vessel) secondary to an inherited or acquired condition[26]. The pathogenesis of thrombosis is multifactorial, already described in 1856 by the German pathologist Dr. Rudolf Virchow. He postulated three major factors that contribute to thrombosis, including: stasis (slow blood flow), endothelial injury (intravascular vessel wall damage) and hypercoagulability. The interplay between these factors, known as Virchow's triad, has influenced the present's day understanding of thrombus pathogenesis and is still a valid and useful concept. Virchow was referring to venous thrombosis, however his concepts are also relevant to the development of arterial thrombosis[27]. Stasis of blood flow mainly occurs in the setting of venous thrombosis due to the higher blood pressure in arteries as compared to veins[28]. Reduced venous blood flow during, for instance, liver cirrhosis, long-distance travel, immobilization, or in obese or pregnant woman, has convincingly shown to increase the risk of deep vein thrombosis (DVT)[29]. Endothelial injury and alteration of the vessel wall mostly occur in arteries due to several diseases and conditions such as smoking, chronically elevated blood pressure, and atherosclerotic disease secondary to hyperlipidaemia. Hypercoagulability can occur due to several clinical conditions, such as pregnancy, use of oral contraceptive medications, malignancies (paraneoplastic syndrome) and inherited thrombophilias[30].

Inherited thrombophilia

At present time, only a small number of genetic mutations have been shown to markedly increase the risk for VTE (major thrombophilia). These include: different loss-of-function mutations of the inhibitors of plasma coagulation that lead to deficiencies of antithrombin, protein C, and protein S, gain-of-function mutations (known as factor V Leiden) that results in resistance to activated protein C, and the guanin to adenine mutation at nucleotide 20210 of the prothrombin gene (FII20210A). Further hereditary conditions which may increase the risk of thrombosis are non-O blood group, elevated factor VIII, IX and XI levels, certain types of fibrinogen disorders, and hyperhomocysteinemia[31]. There are a growing number of, perhaps less important genetic mutations, that appears to be associated with VTE[32].

Antithrombin deficiency

This was the first recognized inherited risk factor for VTE, identified by Egeberg in 1965. He demonstrated that antithrombin activity was subnormal in affected members of a Norwegian family who suffered from venous thrombosis[33]. Antithrombin plays a key role in anticoagulation and inhibits the thrombin-mediated formation of fibrin clot and the generation of thrombin by activated factor X. Antithrombin deficiency is however very rare, the prevalence rates of 1 in 500 to 1 in 5000 in the general population have been reported[34, 35].

Protein C deficiency

A couple of years later, in the early 1980s, deficiencies of two other anticoagulant proteins, protein C and its co-factor protein S were discovered as distinct hereditary risk factors of VTE[36, 37]. The principal function of protein C is its anticoagulant property as an inhibitor of coagulation factors V and VIII. A deficiency of protein C leads to an inability of the normal cleaving of factor Va and VIIIa, ultimately increasing the propensity to thrombosis. The prevalence of heterozygous protein C deficiency in the general population is estimated to about 1 per 200 to 500[38, 39].

Protein S deficiency

Protein S deficiency and its connection with VTE was first reported in 1984[36]. Protein S physiologically serves as a co-factor for activated protein C and enhances its capacity to inactivate factor Va and factor VIIIa. Deficiency of protein S thus results in loss of the normal cleaving of factor Va and VIIIa and consequently increased risk of thrombosis. The prevalence in the general population remains unknown but is estimated to be less than 0,5%[40].

Activated Protein C resistance and Factor V Leiden mutation

Another decade later, in 1993, a major breakthrough came from Prof. Dahlbäck's laboratory in Malmö, Sweden, where they described a poor anticoagulant response to activated protein C on plasma samples taken from Swedish families with recurrent VTE. They named this phenomenon as ‘’activated protein C resistance’’[41]. It was later found that activated protein C resistance, in at least 90 % of the cases, was caused by a single point mutation in the gene for coagulation factor V[42]. Bertina et al, reported this genetic defect in 1994 (a single G to A nucleotide change at position 1691, leading to the substitution of arginine by glutamine at amino acid position 506) and named it as factor V Leiden mutation(FVL)[43]. This mutation renders factor V relatively resistant to degradation by protein C. As a result, factor V remains active which allows for longer duration of thrombin generation and predisposes to VTE. FVL is the most common genetic risk factor for VTE in northern Europe, found in approximately 20-25 % of patients with VTE and 50 % of patients with familial thrombophilia[44, 45]. The prevalence of FVL varies widely by population, it is most prevalent in people of northern European descent (ranging from 3-15%) and extremely rare in African, Asian and Australian indigenous population[46].

Prothrombin G20210A mutation

Prothrombin (factor II) is the precursor molecule of thrombin, which activates coagulation factors V and VIII and converts fibrinogen to fibrin. Prothrombin G20210A gene mutation, first described in 1996, is a single G to A point mutation at nucleotide position 20210 at the 3´-untranslated region of the prothrombin gene, resulting in increased plasma prothrombin levels. It is the second most common hereditary risk factor for venous thrombosis after FVL in healthy individuals of Caucasians origin. The prevalence of this mutation is 2-5 % in the general population and 6-18% in VTE patients[47].

Acquired thrombophilia

Surgery and trauma

Major general surgery (abdominal or thoracic surgery that require general anesthesia ≥ 30 minutes) and major orthopaedic surgery (lower extremity orthopaedic operations) are well known transient risk factors leading to a temporarily increased risk for VTE[48, 49]. Studies have shown that without antithrombotic prophylaxis, the incidence of thrombosis has been reported as high as 30 % while it was around 5 % when prophylaxis were given[49-51]. The surgical procedures with the highest VTE risk are hip and knee arthroplasty, major vascular surgery and neurosurgery[51-55].

Trauma, particularly multiple trauma, is also a well-established risk factor for developing VTE[56, 57]. Studies have shown that nearly 60 % of high risk trauma patients will develop a deep vein thrombosis if no prophylaxis is given[58, 59].

Age

The risk of VTE is strongly associated with age. VTE is uncommon in children and the risk increases exponentially with increased age for both men and women. The incidence rate increases from <5 cases per 100.000 persons <15 years old to almost 500 cases per 100.000 persons at age 80 years[60].

Immobilization and long-distance travel

Immobilization has been difficult to define, and it is challenging to estimate what effect it has on the risk for VTE. However, a study performed by Gibbs et al.[61] found that 15% of patients of patients on bed rest for < 1 week before death had venous thrombosis at autopsy, while the incidence rose to 80% when in bed for a longer period. The influence of immobility on VTE is striking in studies of hemiplegia; Warlow et al.[62] found asymptomatic deep vein thrombosis in 60% of paralyzed limbs of stroke patients compared with 7 % in the non-paralyzed limbs. Although immobility and prolonged bed rest alone does not provide adequate reason for prescribing antithrombotic prophylaxis, combined with the presence of other risk factors, it is usually motivated.

Long distance air travel, the so called ‘’economy class syndrome’’ and its associated risk for VTE has gained a lot of interest in the popular press the last decades. It was first reported as a risk factor in 1954, where the first case of VTE after a flight from Australia to the United Kingdom was described[63]. In a randomized controlled study of 231 participants without a prior history of VTE who were boarded on flights of >8 hours in duration, were randomized to compression stockings or not. Those randomized to compression stockings had no evidence of DVT on following duplex ultrasonography. Contrariwise, 10 % of untreated individuals developed asymptomatic DVT[64]. Despite these findings, there is general consensus that clinically significant VTE after air travel is rare[65, 66], and that the benefits of providing VTE prophylaxis during long distance flights are doubtful[67].

There are no studies prior to this thesis on the association between immobilization, long distance travel and MVT.

Obesity

Obese (body mass index [BMI] > 30 kg/m^2) individuals are at an increased risk for VTE compared with individuals who are of normal weight. The extent of the effects of obesity on VTE depends not only on total body fat, but also on the distribution of adipose tissue (e.g., central obesity)[68-70].

Malignancy

Cancer has been one of the best-known acquired risk factors for VTE. Already in 1865, Armand Trousseau, reported the relationship between cancer and thrombosis. Occurrence of venous thrombosis may be caused by venous obstruction due to local cancer growth and/or being part of a paraneoplastic syndrome. Several studies have established that thrombosis is a common complication for patients with malignancies, contributing to the second-leading cause of mortality in cancer patients[71, 72]. Studies have shown, that cancer patients undergoing surgery, have a 2-3-fold higher risk of VTE compared to patients undergoing surgery for non-malignant conditions. However, since malignancy is associated with other risk factors, the direct effect of malignancy on VTE is still uncertain. The incidence of VTE varies depending on which type and stage of cancer the patient has, where metastatic cancer disease is the strongest risk factor[73]. In general, patients with cancer have a 4-5 fold increase in their risk of VTE compared to the general population, and chemotherapy treatment is an additional risk factor for these patients[74-76].

Pregnancy and puerperium

Pregnant women have a 4-5 higher VTE risk than non-pregnant women[77, 78]. In postpartum, the risk is even higher (20-fold)[77]. This can be explained by physiological changes that normally occur during pregnancy with a shift towards a hypercoagulable state due to elevated coagulations factors, Von Willebrand factor, and fibrinogen[79]. The hypercoagulable state has likely been evolved to protect women from fatal bleeding during delivery and the postpartum period. Indeed, in the developing world, bleeding at the time of miscarriage or childbirth is still the leading cause of maternal death. The overall incidence of VTE during pregnancy is about 2 per 1000 births[80-82].

Oral contraceptives and hormone replacement therapy

The combined estrogen/progestogen oral contraceptive pill became available as contraceptives in the 1960s, shortly thereafter, reports suggested an alarming incidence of VTE in otherwise healthy young women taking these drugs[83]. Woman in their postmenopausal age treated with estrogen/progestogen compounds as a part of hormone replacement therapy (HRT) also have increased risk of VTE, about 2-4 fold[84-87]. There are numerous different brands of oral contraceptives with different chemical compositions. The VTE risk differs depending on the estrogen dose, type of progestin, duration of use, and administration route[88]. Consequently, this has led to a gradual reduction in the estrogen dose over the past couple of years[89]. Large studies have shown that the risk for VTE within women on combined oral contraceptives is around 3-5 fold compared with non-use[90]. However the incidence of VTE among combined oral contraceptive users remains low (8-10 events per 10 000 women-years of exposure), which is much lower than

the incidence of VTE during pregnancy and the postpartum period[91, 92]. The risk for VTE is lower when using low dose second generation combined oral contraceptives[93-96] but with the use of ‘’mini-pills’’ (containing only progestogen), there is almost no increased risk[95].

JAK-2 V617F mutation

The janus-activated kinase gain of function substitute of valine to phenylalanine at position 617 (JAK-2 V617F) mutation is present in the majority of patients with myeloproliferative cancer, nearly 100% incidence in patients with polycythaemia vera and in about 50 % in patients with essential thrombocytosis and primary myelofibrosis[97-101]. Numerous studies have found that JAK-2 V617F is frequent in patients with splanchnic venous thrombosis, but rare in patients with venous thrombosis at other locations or with arterial thrombosis[102].

Lupus anticoagulant and Cardiolipin antibodies

Lupus anticoagulant and cardiolipin antibodies fall under the category of antiphospholipid antibodies (a heterogenous group of immunoglobulins directed against phospholipids, protein-phospholipid complexes and plasma proteins). They have both been recognized as markers for increased risk of thrombosis, spontaneous abortion, and cerebral ischaemia. Antiphospholipid antibodies is present in approximately 5 % of the general population and has been found in up to 30 % of patients with systemic lupus erythematosus[103]. Of note, administering direct oral anticoagulants (DOACs) instead of vitamin K antagonists (VKA) to patients with antiphospholipid syndrome has recently been warned for due to failure of prevention of venous thromboembolism[104].

Pathogenesis of MVT

Mesenteric venous thrombosis is classified as either primary or secondary. Primary MVT is an idiopathic condition whereas secondary MVT implies that an etiologic factor has been found. There are three major pathways for the pathogenesis of MVT[105]:

1. Direct injury such as abdominal trauma, post-surgical trauma, acute pancreatitis and inflammatory bowel disease. Surgical procedures at higher risk of MVT are splenectomy and bariatric surgery.
2. Local venous congestion or stasis such as portal hypertension/liver cirrhosis, severe congestive heart failure (ejection fraction < 20 %) and morbid obesity (BMI ≥ 40 kg/m^2).

3. Thrombophilia. Acquired thrombophilia such as cancer, especially pancreatic, and oral contraceptive use. Inherited thrombophilia such as Factor V Leiden mutation.

As our ability to diagnose inherited thrombotic disorders improves, the proportion of patients with primary MVT continues to decline. Currently, an etiologic factor can be identified in about 75 % of patients [106]. Systemic factors predisposing to MVT include inherited and acquired hypercoagulable states. Inherited thrombophilic states include factor V Leiden, prothrombin gene mutation, protein C and protein S deficiency, and antithrombin III deficiency, whereas acquired thrombophilic states include cardiolipin antibodies, lupus anticoagulants and JAK2 V617F mutation[105].

Clinical presentation

MVT can present in different clinical forms, acute, sub-acute and chronic[107]. The acute form is most common, accounting for 60 % to 80 % of MVT, characterized by acute onset of symptoms within 24-72 hours of thrombus formation whereas the sub-acute type presents during days to weeks of nonspecific symptoms[108, 109]. The chronic form is usually detected as an incidental finding on radiological examinations, typically together with evidence of portal hypertension, such as gastro-oesophageal varices and splenomegaly[110]. The abdominal pain of acute or sub-acute MVT is mid abdominal and colicky, suggesting an origin from the small intestine. Melena, hematemesis, or haematochezia occurs in only 15 %, whereas occult bleeding may be present in 50 % of the cases[106]. Fever and signs of peritonitis suggests progression of ischaemia to intestinal infarction[111].

Diagnosis

Given its nonspecific symptoms, low incidence and low awareness among clinicians, MVT is an insidious and difficult diagnosis to make. The disease may lead to life threatening complications such as bowel ischaemia, bowel gangrene and peritonitis if left untreated. Therefore, an early diagnosis and prompt effective treatment are critical to improve clinical outcome.

Clinical examination

Within the spectrum of patients presenting with acute abdominal pain, it is difficult to delineate those with MVT. There are no clinical features (symptoms, abdominal

findings, laboratory tests) that are specific for MVT, therefore a high index of suspicion is necessary to make an early diagnosis in patients with the acute or subacute forms or identify those with chronic thrombosis. The abdominal examination varies highly from nonspecific discomfort during palpation to severe, pain out of proportion to the examination. Fever is typically absent or low grade unless peritonitis or sepsis has developed[112].

Laboratory evaluation

No single biomarker is sensitive or specific for the diagnosis of MVT. The presence of increased serum lactate levels and metabolic acidosis may serve to identify patients with established bowel infarction, but this is a late finding[106]. Leukocytosis may be the only initial abnormal laboratory finding[113]. Plasma D-Dimer testing at presentation has a role in the diagnosis of acute venous thromboembolism. Especially normal plasma D-dimer can together with a low probability at clinical examination be used to rule out VTE[114]. Plasma D-dimer is reported to be elevated in MVT[25, 115], but the test is unspecific for any form of acute mesenteric ischaemia[116].

Imaging

Until recently it has been difficult to diagnose MVT without laparotomy. However, recent advancement in radiology has led to earlier diagnosis, making it possible to treat patients early in the course of the disease[24]. There are a number of potential imaging modalities for diagnosis of MVT such as ultrasound, computed tomography (CT), magnetic resonance imaging (MRI) and angiography. There has not been any comparative studies between the different imaging modalities. Contrast enhanced helical CT-imaging with three-phase scan is currently the golden standard diagnostic test for MVT [117]. CT can accurately visualize both the extent of thrombosis within the portomesenteric venous system and secondary abnormal intestinal findings (Figure 3). Thrombosis within the superior mesenteric vein is, in contrast to isolated portal vein thrombosis, associated with symptoms related to intestinal ischaemia in the overwhelming majority (92%)[118], and often results in intestinal infarction if left untreated[23, 118]. In retrospective studies, the accuracy of abdominal CT for the diagnosis of MVT is at least 90 percent [119-124]. On CT, the diagnosis of MVT is made by the presence of venous filling defects or absent flow in the mesenteric veins during the venous phase. A central low attenuation within a sharply defined, enhanced venous wall defines the defect[120]. Other associated findings include enhanced bowel wall and/or mesenteric strandings related to edema, and changes associated with bowel obstruction or intestinal infarction (bowel wall thickening >3mm, intestinal pneumatosis, portal vein gas, bowel dilatation, unexplained ascites)[125].

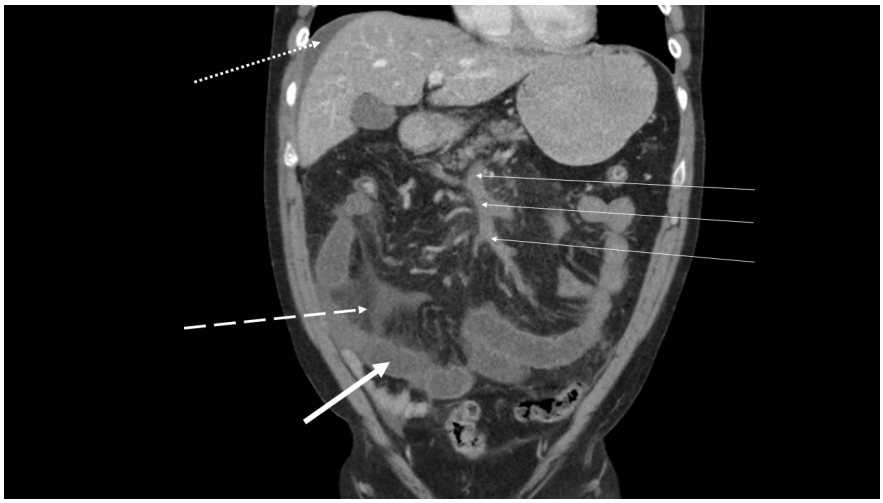

Figure 3. CT features of MVT

A 53-year-old man with previous history of treatment with VKA for three months due to DVT. Blood screening for thrombophilic disorders showed that he had activated protein C resistance in the homozygous form. The patient was admitted with acute abdominal pain, and CT with intravenous contrast enhancement in the portal phase showed MVT (multiple thin arrows). Note the secondary intestinal abnormalities such as dilated small bowel loops (thick arrow), mesenteric oedema (dashed line) and ascites (dotted line).

Treatment

Successful treatment of MVT rests on (I) preventing intestinal infarction and thereby minimizing the extent of bowel resection in acute MVT; (II) Diagnosing patients with hypercoagulable states and treating them with long-term anticoagulant therapy[126]. After diagnosing acute MVT, the treatment is predominantly conservative, consisting of systemic anticoagulation to minimize extension of thrombus, full bowel rest, total parenteral nutrition, analgesia, and careful, close monitoring for any signs of clinical deterioration[127-132].

Anticoagulation

Immediate unfractionated heparin therapy intravenously has been proposed as first-line treatment option as its effect can be reversed immediately if an emergency operation is needed[25]. Low molecular weight heparin (LMWH) administered subcutaneously is often used in clinical practice to patients with milder symptoms at presentation. LMWH may also be used following intravenous heparin therapy when the patient has improved. Once the patient's condition has stabilized, and no further intervention is planned, the patient can be transitioned to an oral anticoagulant (vitamin K antagonist or direct oral anticoagulants)[133]. According to the European Society for Vascular Surgery (ESVS) guidelines[134], anticoagulation is given for six months in the presence of an identifiable transient risk factor, whereas patients with underlying thrombophilia or idiopathic MVT may

be considered for lifelong anticoagulation since relapse of MVT is highly fatal[127, 135, 136].

Vitamin K antagonist

Vitamin K antagonists (VKA) has been around since the late 1950's[137]. Lifelong anticoagulation with VKA with a targeted international normalized ratio (INR) of 2.0 to 3.0 is the standard of care in patients where long-term management is indicated. Increased percentage of time in therapeutic range is important to decrease bleeding and thromboembolic complications[138]. Warfarin is the most commonly used VKA and acts by inhibiting enzymes involved in the hepatic synthesis of the vitamin K-dependant coagulation factors II, VII, IX, and X, as well as the natural anticoagulants protein C and protein S[139]. Despite its effective pharmacological properties, VKA treatment is limited by factors such as a narrow therapeutic index, drug-drug interactions, food interactions, slow onset and offset of action, and the need for routine monitoring of the INR. Thus, the shortcomings associated with VKA have spurred the search for oral anticoagulants with better pharmacokinetics. VKA is, however, still considered first choice option in patients on dialysis/severe renal insufficiency (estimated glomerular filtration rate [GFR]<30 ml/min/1.73m^2)[140] and in antiphospholipid syndrome[104].

Direct oral anticoagulants (DOACs)

The novel direct oral anticoagulants were introduced on and after 2008[141]. Currently, there are five DOACs on the market including direct thrombin inhibitor (dabigatran) and factor Xa inhibitors (apixaban, betrixaban, edoxaban, rivaroxaban). Several randomized controlled trials have shown that they are non-inferior to conventional treatment (parenteral anticoagulation with unfractionated heparin or LMWH followed by VKA) for the treatment of acute VTE[142-147]. Apixaban[148], rivaroxaban[149] and edoxaban[150] are the three DOACs shown to be effective treatment options similar to LMWH in cancer associated venous thromboembolism. All DOACs should be avoided in patients with gastrointestinal cancer due to increased bleeding risk[151]. Given their predictable anticoagulant response, they do not require regular monitoring. Other advantages, as compared to VKA, include rapid onset and offset of action and fewer drug, supplement and dietary interactions. One important concern has been that there was no specific antidote for DOACs. This is however no longer the case. Two specific antidotes have been approved by the U.S. Food and Drug Administration (FDA): idarucizumab (Praxbind®) for reversal of dabigatran (Pradaxa®) and andexanet alfa (AndexXa®) for the reversal of apixaban (Eliquis®) and rivaroxaban (Xarelto®)[152, 153]. DOACs are well established as first-line treatment for deep vein thrombosis (DVT) and pulmonary embolism (PE) but have, however, been scarcely studied in MVT. The properties of the different anticoagulation drugs are summarized in Table 2.

Table 2. Anticoagulation in VTE.

	Heparin	LMWH	Apixaban	Rivaroxaban	Edoxaban	Dabigatran	Vitamin K antagonist
Target	Antithrombin III facilitator	Antithrombin III facilitator	Factor Xa inhibitor	Factor Xa inhibitor	Factor Xa inhibitor	Factor IIa inhibitor	Inhibits vitamin K dependant clotting factors (II, VII, IX, X) and protein C and S
Time to peak effect	2-3 h	2-4 h	1 – 2 h	2 – 4 h	1 – 2 h	1 – 3 h	4 h (peak therapeutic effect 5-7 days)
Half-life	1-2 h	3-4h	8-14 h	7 – 11 h	5 – 11 h	14 – 17 h	20-60h
Renal elimination		80 %	27 %	33 %	50 %	80 %	
Contraindication/not recommended	Active bleeding. Septic endocarditis. Known hypersensitivity or adverse reaction.	Previous heparin-induced thrombocytopenia/thrombosis. Known hypersensitivity or adverse reaction. Severe renal impairment (CrCl <30mL/min) Active bleeding. Active peptic ulceration.	CrCl <15 mL/min. Severe hepatic impairment (Child Pugh C) or hepatic disease associated with coagulopathy.	CrCl <30 mL/min (FDA); CrCl <15 mL/min (EMA). Moderate or severe hepatic impairment. (Child Pugh B and C) or hepatic disease associated with coagulopathy.	CrCl <15 mL/min. Moderate or severe hepatic impairment. (Child Pugh B and C) or hepatic disease associated with coagulopathy.	CrCl <30 mL/min. Concomitant treatment with P-gp inhibitors in patients with CrCl <50 mL/min.	Known hypersensitivity or adverse reaction. Decompensated liver disease. Pregnancy.
Reversal agent	Protamine sulphate	Protamine sulphate	Andexanet	Andexanet	Andexanet	Idarucizumab	Prothrombin complex concentrate
Severe obesity (BMI ≥ 40kg/m^2)	++	++	+/-	+/-	+/-	+/-	++
Active cancer	++	++	+	+	+	-	-
Pregnancy	++	++	-	-	-	-	-
Increased risk of bleeding (prediction model VTE-BLEED[154]; 0-1=low risk, ≥2=high risk)	+/-	+/-	Active cancer(1.5) Male patient with uncontrolled hypertension (2) Anaemia (1) History of bleeding(1.5) Age>60 years (1.5) Renal dysfunction (CrCl 30-60 mL/min) (1.5)	Active cancer(1.5) Male patient with uncontrolled hypertension (2) Anaemia (1) History of bleeding(1.5) Age>60 years (1.5) Renal dysfunction (CrCl 30-60 mL/min) (1.5)	Active cancer(1.5) Male patient with uncontrolled hypertension (2) Anaemia (1) History of bleeding(1.5) Age>60 years (1.5) Renal dysfunction (CrCl 30-60 mL/min) (1.5)	Active cancer(1.5) Male patient with uncontrolled hypertension (2) Anaemia (1) History of bleeding(1.5) Age>60 years (1.5) Renal dysfunction (CrCl 30-60 mL/min) (1.5)	Active cancer(1.5) Male patient with uncontrolled hypertension (2) Anaemia (1) History of bleeding(1.5) Age>60 years (1.5) Renal dysfunction (CrCl 30-60 mL/min) (1.5)

++, Recommended, + Might be recommended, - Not recommended, +/- Indifferent. CrCl: Creatinine clearance, EMA: European Medicines Agency, FDA: US Food and Drug Administration, P-gp: Plasma-glycoprotein. VTE: Venous thromboembolism. Child-Pugh score is used to assess the prognosis of chronic liver disease, mainly cirrhosis. The score employs five clinical measures of liver disease, each measure is scored 1-3 with 3 indicating most severe derangement. Class A: 5-6 points, Class B: 7-9 points, Class C: 10-15 points. The table is based on the following references:[140, 149, 150, 155-157]

Surgery

Surgical exploration is limited to patients with peritonitis and definite signs of bowel infarction. When there is indication for abdominal exploration, an open approach is preferred over laparoscopic technique, since the extent of oedema and resulting abdominal distension, make laparoscopic approach problematic. Furthermore, insufflation of the abdomen can exacerbate mesenteric venous hypertension[107]. The aim of resection is to conserve as much bowel as possible. Determining the extent of bowel resection during abdominal explorations is challenging. The border between ischemic bowel and viable bowel is often diffuse and subtle in the acute stage of MVT[158](Figure 4). A way to avoid resecting bowel that might be viable, is to perform a follow-up (second-look) laparotomy 24 hours later. This is especially useful in patients who have extensive bowel involvement but some venous flow[159, 160]. Grossly infarcted small bowel should be resected (Figure 5). The bowel ends can be left without performing anastomosis or stoma until second look, or can be primarily anastomosed. Heparin therapy should start immediately after the operation.

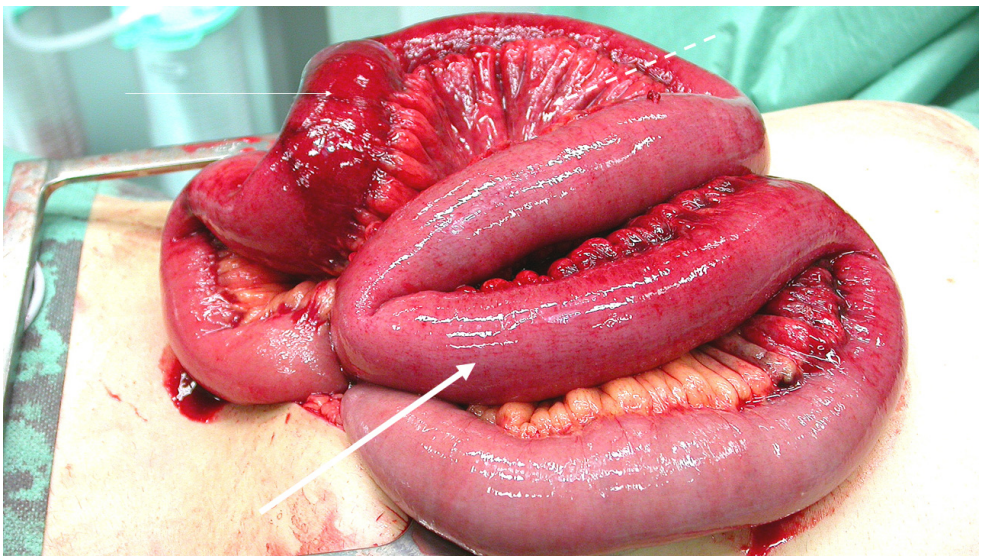

Figure 4. Ischemic bowel due to MVT

A 47-year-old man with a history of DVT and PE treated with a vena cava filter presented with a 3-day history of lower abdominal pain and obstipation a few days after discontinuation of VKA treatment. He developed signs of generalized peritonitis 12 hours after admission. At laparotomy, 0.4 m of the most reddish and severely ischaemic segment (thin arrow) was resected and anastomosed. Note the distended small bowel loops (thick arrow) and the oedema in the adjacent mesentery (dashed line). The patient recovered and was prescribed lifelong treatment with VKA.

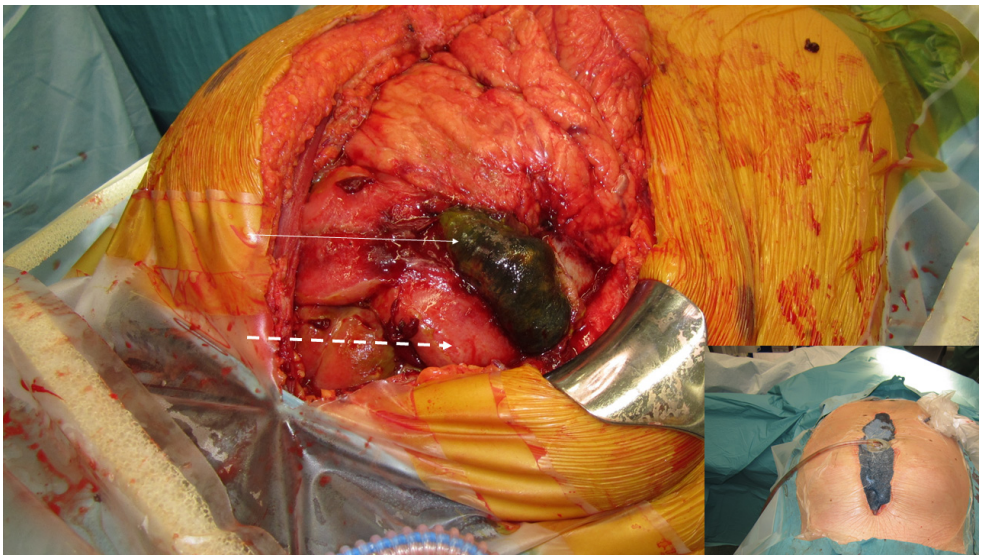

Figure 5. Development of transmural bowel necrosis after failure of conservative anticoagulation therapy

A 50-year old male patient was treated with three weeks of LMWH due to a CT verified MVT. Explorative laparotomy was performed due to clinical deterioration and showed a demarcated 1 meter long transmural green necrosis of the jejunum (arrow) with a large perforation. Note the dilated small bowel loop with apparent normal colour lying in parallel (dashed line). The patient recovered after bowel resection, open abdomen therapy with negative pressure wound therapy (separate mini image at the lower right corner), and reanastomosis of the stapled bowel ends at second look. Screening for thrombophilia showed that the patient was positive for JAK2 V617F mutation and a bone marrow biopsy diagnosed a polycythemia vera. The patient is scheduled for life long VKA therapy, and therapy against his hematologic malignancy.

Endovascular therapy

Currently there are no studies with comparative data, to help establish the indication for endovascular treatment of MVT. Endovascular treatment might be an option in selected patients unresponsive to conventional anticoagulation[25]. During recent years, a number of different endovascular procedures for the treatment of MVT have been developed.

These include percutaneous transhepatic mechanical thrombectomy[161], percutaneous transhepatic thrombolysis (Figure 6A)[162, 163], percutaneous transjugular intrahepatic portosystemic shunting (TIPS)[164] with mechanical aspiration thrombectomy and direct thrombolysis (Figure 6B)[165, 166], thrombolysis via the SMA(Figure 6C)[167], and thrombolysis via a surgically placed mesenteric vein catheter (Figure 6D)[168].

These techniques can provide rapid thrombus removal or dissolution, especially after TIPS and stent placement to create a low-pressure run-off[169]. Mechanical thrombectomy is most effective in cases of acute rather than chronic thrombus. Thrombolysis via the SMA is less effective and more time-consuming since it

requires longer infusion times and higher doses of thrombolytic agent. Furthermore, it is also associated with an increased risk of bleeding. An alternative technique for clot fragmentation in cases of refractory thrombus and fixed venous stenosis is balloon angioplasty. Aspiration thrombectomy is another technique that relies on vacuum and suction force to remove the clot, it is performed with at stiff, large-diameter (at least 8 Fr), angled catheter connected to a Luer-Lok™ syringe (Bluebird Medical, Gothenburg, Sweden) to create vacuum effect[165].

Figure 6A-D. Schematic drawings of various ways of local delivery of thrombolysis for MVT. ***Artist ©Robin Tran***

Usually a special catheter with multiple side holes will be placed directly in the thrombus (Figures A, B, D). An occluding ball wire at the catheter tip end hole (not shown) will allow for even pressure distribution of lytic agent at the side holes. Typically, an intestinal segment of the jejunum and/or ileum[24] will be swollen and ischaemic.

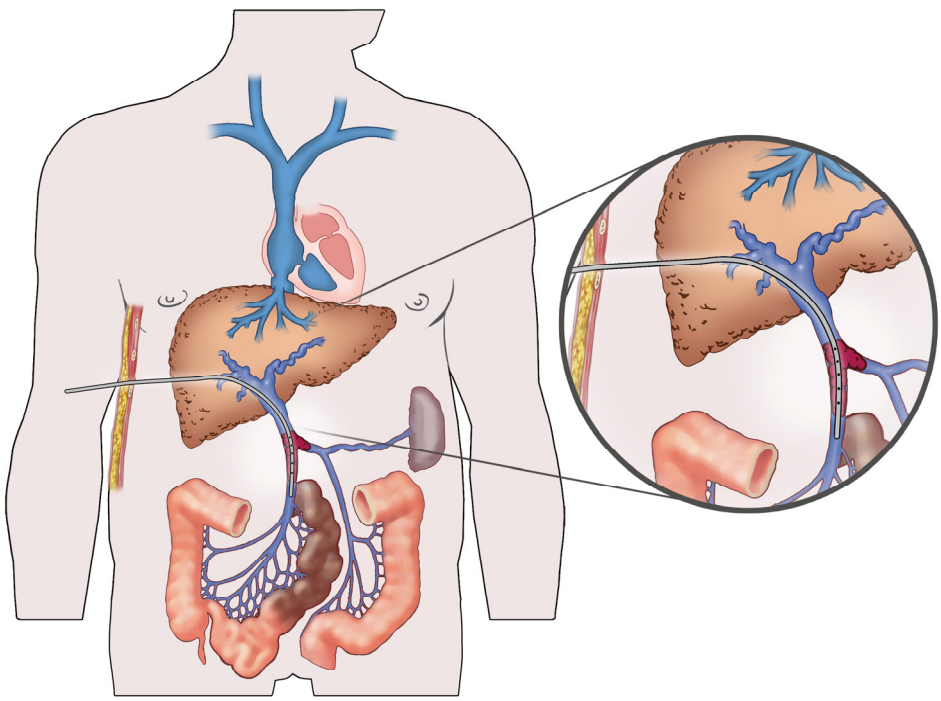

Figure 6A. Percutaneous transhepatic access.

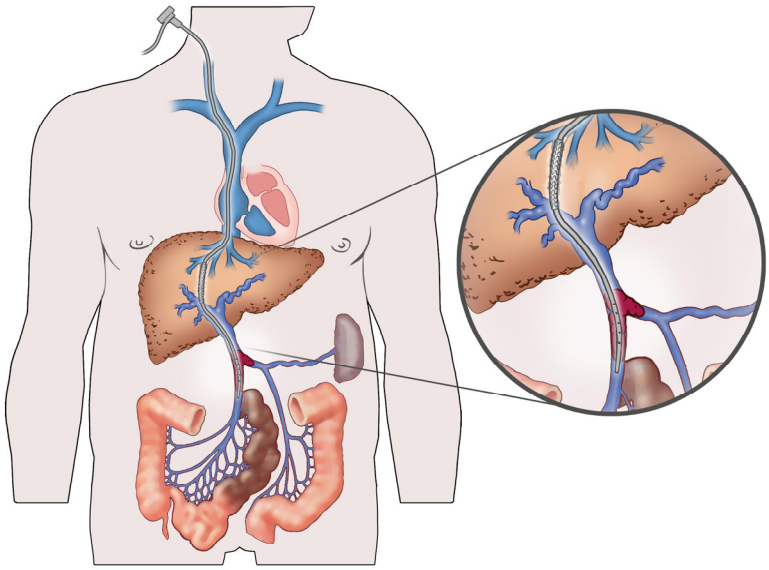

Figure 6B. Percutaneous transjugular intrahepatic portosystemic shunt including stentgraft placement in the shunt.

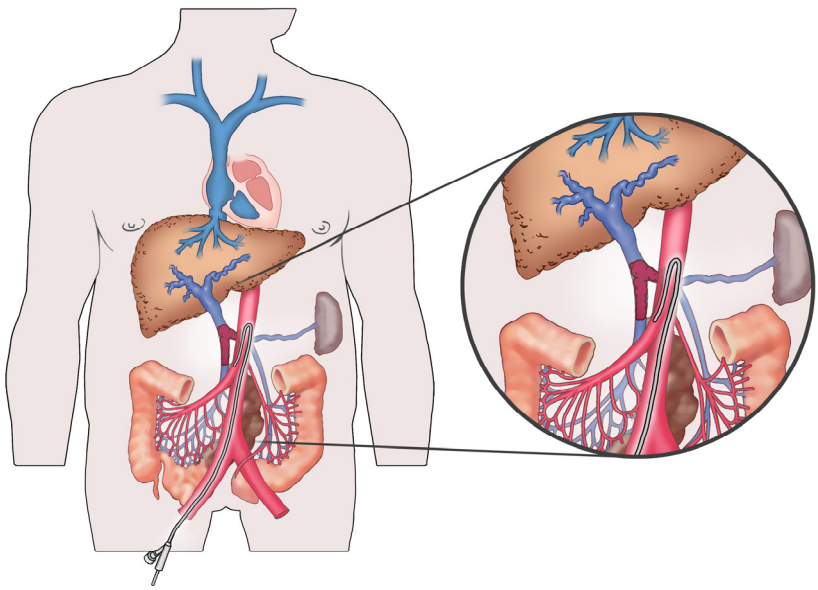

Figure 6C. Percutaneous transfemoral access and indirect thrombolysis by an endhole catheter placed in the superior mesenteric artery.

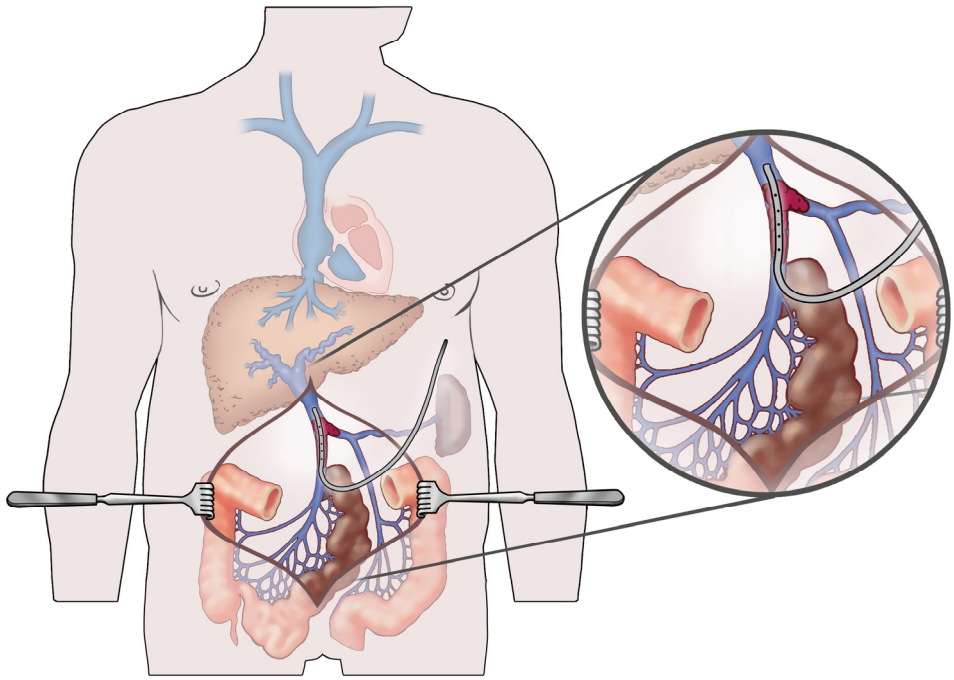

Figure 6D. Intra-operatively placed catheter in the superior mesenteric vein at laparotomy.

Open and hybrid vascular surgery

Open surgical thrombectomy after laparotomy and exposure of the superior mesenteric vein was first described in 1968[170]. During a pancreaticoduodenectomy for pancreatic cancer, the small bowel was found to be deeply cyanotic and oedematous. The superior mesenteric artery and superior mesenteric vein were explored, and a superior mesenteric vein thrombosis was detected, which was immediately treated with open surgical thrombectomy without need of bowel resection. The second described case was reported from former colleagues at Malmö General Hospital in 1974[21]. Bowel resection was followed by open surgical thrombectomy with the use of Fogarty balloon catheter. After venotomy of the superior mesenteric vein, at the lower border of pancreas and just below the entrance of the splenic vein, thrombectomy of the extrahepatic porta, intrahepatic portal branches, splenic vein and superior mesenteric vein, was performed. A baby-feeding tube was left in the peripheral mesenteric vein after abdominal closure for delivery of continuous heparin infusion for five days, whereafter the catheter was removed without complications. A larger series of 31 patients treated surgically for acute portomesenteric thrombosis was reported in 1997[171]. Surgical thrombectomy was performed in eleven patients, and in five of those, additional treatment with continuous local thrombolysis with high-dose recombinant tissue plasminogen activator was administered via a catheter placed into a distal mesenteric vein for 2-3 days (Figure 6D). The catheter was removed after thrombolytic therapy without complications. In a modern series of nine patients[172], bowel resection was followed by fluoroscopic guided balloon thrombectomy followed by completion control venography. When the balloon catheter could not pass from the superior mesenteric vein into the portal vein, a guidewire was used to gain access for proper thrombectomy of the portomesenteric system. Postoperative systemic anticoagulation was administered, followed by long-term peroral anticoagulation treatment.

Outcome

Compared to other forms of acute mesenteric ischaemia, MVT has a better prognosis. In a large systematic review of nearly 3700 cases of acute mesenteric ischaemia, the overall mortality rate of patients with MVT was 44 %[7]. Due to better recognition and earlier treatment, morbidity and mortality related to MVT have improved[24, 131, 132, 173, 174]. With prompt diagnosis and treatment with anticoagulation, mortality rates for acute MVT in modern studies have been reported to be 10-20 % [24, 120, 130, 175-177]. The reported MVT recurrence rate seems to be low while patients are receiving anticoagulation [178, 179].

Aims of the studies

Paper I

To evaluate outcome, prognostic factors, and failure rate of anticoagulation as monotherapy, and to identify when bowel resection was needed.

Paper II

To assess the clinical efficacy, safety, and thrombus recanalization of DOACs and VKA therapy in MVT.

Paper III

To evaluate the association of CT findings at admission and bowel resection rate in patients with MVT.

Paper IV

To compare acquired and inherited risk factors in MVT versus VTE.

Methods

Ethics

All studies were performed according to the principles of the Helsinki Declaration of Human Rights. The four responsible hospital area managers gave written permission to retrieve patient record data on patients with MVT between 2000 and 2006 after written request. Retrieving data on patients with MVT between 2007 and 2017 and conducting the prospective Malmö Thrombophilia Study (MATS) were approved (diary numbers 2015/143 and 2007/237, respectively) by the Regional Ethical Review Board in Lund, Sweden.

Setting

The four studies included in this thesis (Table 3) were performed on patients diagnosed with MVT between 2000-2015 (paper I+IV) and 2004-2017 (paper II+III) at Skåne University Hospital (SUS) in the southern part of Sweden. SUS is one of the largest hospitals in the country with a primary catchment area of 800.000 inhabitants.

Overview of the studies

Table 3. Overview of study designs and patients

Paper	Design	n patients	Timeframe
I	Retrospective cohort study	120	2000-2015
II	Retrospective cohort study	102	2004-2017
III	Retrospective cohort study	102	2004-2017
IV	Population-based study	120 MVT patients 1452 VTE patients	2000-2015

Data collection

Retrieval of patients with MVT

Data collection was carried out between 1st January 2000 - 31st of December 2015 (**paper I+IV**) and between 1st of January 2004 - 29th of September 2017 (**paper II+III).** Identification of all MVT patients treated surgically or conservatively at SUS was performed in (1) hospital records based on the International Statistical Classification of Diseases and Related Health Problems (ICD), tenth edition, codes I81(portal vein thrombosis or MVT) and K55 (mesenteric ischaemia), and (2) *AuriculA*. The Auricula registry (*AuriculA)* is a Swedish national quality registry started in 2004 for patients treated with anticoagulation on various indications. All patient records and CT images in patients with PVT or MVT as well as unclear cases of mesenteric ischaemia were scrutinized and validated. Only patients with symptomatic thrombosis in the superior mesenteric vein with or without anatomical involvement of portal or splenic vein, diagnosed by radiological imaging (CT), laparotomy and/or autopsy, were included in the studies.

The patient series was pragmatically divided at the study protocol stage into two periods, the former (2000-2007) and the latter (2008-2015), for analysis of changes in patient characteristics, risk factor profiles, mode of diagnosis and outcome. Mortality data were obtained from the Swedish population Registry (**paper I)**.

Median clinical follow-up time was 48 months (**paper II+III)**, 62 months (**paper I**) and 64 months (**paper IV)**.

Retrieval of patients with VTE

The Malmö Thrombophilia Study (MATS) is a prospective population-based study conducted at Skåne University Hospital in Malmö, a city of 300.000 inhabitants in southern Sweden. This is the only hospital in the area treating patients with VTE. The MATS cohort includes 1465 consecutive unselected VTE patients that were followed after inclusion of this study (March 1998) until death or the end of the study (September 2017)[180]. Thirteen patients with portal and/or mesenteric vein thrombosis were excluded from this cohort, but those with CT verified MVT were included in the MVT cohort. Seventy percent of all patients treated for VTE at SUS were included in the study. The remaining 30 % were excluded due to unwillingness to participate, language barrier, dementia, or other severe illness that prevented the patient from participating. The patients had to have objectively verified DVT or PE with phlebography, duplex ultrasound, CT, lung scintigraphy or magnetic resonance imaging (MRI). Other inclusion criteria in MATS were age >18 years and ability to communicate in the Swedish language. All patients were treated in accordance to the standard treatment protocol of SUS. Included patients were required to submit

blood samples, answer a questionnaire and were evaluated concerning risk factors for VTE. Malignancies were present or diagnosed at the time of VTE diagnosis. No documentation of myeloproliferative disease was done. End of follow-up for VTE patients was September 6, 2017. Median follow up time were 11.4 (interquartile range |IQR] was 6,5-13.7) years. The DNA mutations for factor V Leiden and Prothrombin were analysed using Taqman allele discrimination with gene specific assays for the two factors (Applied Biosystems, Life Technologies Corporation, Carlsbad, CA, USA).

Treatment strategy at the study centre

After diagnosis of MVT with CT, the mainstay of treatment was conservative with immediate full anticoagulation with either intravenous unfractionated heparin infusion or subcutaneous LMWH, full bowel rest, total parenteral nutrition, and analgesia. Patients admitted with peritonitis or rapid progression toward peritonitis underwent laparotomy and bowel resection. Patients not responding to anticoagulation underwent endovascular measures with or without local thrombolysis, and those not responding to this therapy were subjected to laparotomy. Clearly necrotic and demarcated bowels were resected and anastomosed. Bowels with unclear viability were usually evaluated at a second-look laparotomy, and bowel resections were followed by anastomoses or diverting stomas. Patients with identified transient risk factors were usually treated with oral anticoagulation for 6 months, whereas those with permanent risk factors or unidentified risk factors were prescribed lifelong anticoagulation. DOACs were introduced for treatment of MVT at the study centre in 2015. There was no evidence of non-compliance in patients with DOACs and time in therapeutic range (TTR) during warfarin treatment in our country is as high as 76.5 %[181]. Median follow-up time in patients with DOACs was 25 months (**paper II)**.

Definitions

Primary MVT is defined as an idiopathic condition, whereas secondary MVT is defined by an identified etiologic factor. Patients with abdominal pain of less than 4 weeks duration were classified as having acute MVT. Those with symptoms for 4 weeks or more but without bowel infarction, and those with asymptomatic MVT diagnosed incidentally on abdominal imaging as a clinically nonsignificant finding were defined as chronic MVT. Extensive thrombosis was defined as having mesenteric (both central and peripheral), portal, and splenic vein thrombosis. The first 5 cm of the proximal superior mesenteric vein was defined as central. Small

bowel dilatation was defined as ≥ 4 cm in bowel diameter. Patients initially treated with LMWH for some weeks, and later changed for VKA or DOACs were considered as treated with either of the respective oral anticoagulants. Major bleeding was defined according to the criteria of the International Society on Thrombosis and Haemostasis[182], as a fatal and/or symptomatic bleeding in a critical area or organ, bleeding leading to a reduction of 2 g/dl or more in haemoglobin concentration, or necessitating transfusion of two or more blood units. Gastrointestinal bleeding included oesophageal variceal bleeding. Previous cardiovascular disease was defined as previous myocardial infarction, angina pectoris, history of coronary artery bypass grafting, percutaneous coronary intervention, stroke, or transient ischemic attack. Glomerular filtration rate (GFR) was calculated as a simplified variant of Modification of Diet in Renal Disease Study Group (MDRD)[183]. Advanced renal insufficiency was defined as GFR<25 ml/min/1.73m^2. Renal insufficiency by serum creatinine alone was defined as a serum creatinine higher than 105 mmol/l (1.2 mg/dl) in men and 90 mmol/l (1.0 mg/dl) in women. The term thrombophilia was used as a common denominator for factors that might provoke MVT, such as cancer, coagulation disorders, previous or concomitant venous thromboembolism (VTE), oral contraceptive use, or estrogen substitution. Inherited thrombophilic factors were defined as factor V Leiden mutation, prothrombin gene mutation, or deficiencies of protein C, protein S, or antithrombin. Acquired thrombophilic factors were defined as JAK2 V617F mutation, lupus anticoagulant, or cardiolipin antibodies. Malignancy was defined as the presence of solid cancer or myeloproliferative disease. A transient risk factor was defined as either recent surgery within 6 weeks, abdominal trauma or inflammatory disease such as acute pancreatitis. Short bowel syndrome was defined as bowel resection leading to unable to meet nutrition needs with enteral supplements and requires parenteral nutrition[184]. Follow-up CT was defined as the last available CT of the abdomen with intravenous contrast and imaging in the parenchymal/venous phase. Successful recanalization was defined as partial or complete recanalization of the portomesenteric venous system at the follow-up CT after treatment.

Computed tomography

Clinical data provided in the referral letter for initial radiological examination at admission were retrieved in a Sectra radiological information system (Sectra AB, Linköping, Sweden). Multi-detector row CT (MDCT) was usually performed with a 0.75-mm slice thickness (Siemens Sensation 16, Erlangen, Germany). Multi-planar reconstruction in axial, coronal, and sagittal planes was usually obtained with a 5-mm thickness. Single-slice CT was usually performed with slice thickness of 3–5 mm. Patients were examined in the portomesenteric venous phase. Intravenous contrast medium was non-ionic contrast medium 300–320 mg I/ml with a total dose

of 90 ml, flow rate of 3 ml/s, and delay of 70 s. The diagnostic and follow-up CT scan images of all patients were scrutinized and evaluated by an experienced radiologist (Olle Ekberg) aware of the diagnosis but blinded concerning which treatment the patient received. The main objective was to describe vascular and intestinal findings systematically in a predefined protocol[119]. Bowel wall thickness was assessed on non-contracted intestinal segments and defined as normal if 3 mm or less[185]. The patency of the portomesenteric venous system at follow-up CT was categorized as progression, unchanged, partial regression, and complete regression.

Statistical methods

In all papers the data management and statistical analyses were carried out by using SPSS statistics software, version 22.0 and 23.0 (Chicago, Illinois, USA) with the addition of GraphPad in paper II and III.

In **paper I**, age and gender-specific total incidence rates were based on the number of patients diagnosed with MVT residing in Malmö and expressed as number of cases per 100,000 person-years. Population data, overall and gender-specific, for Malmö in 2008 obtained from Statistics Sweden were used for calculation of incidence. Differences in proportions were evaluated using chi-square or Fisher's exact test. Age was expressed as median (range). Variables associated with 30-day mortality ($p<0.1$) were further tested in a multivariable binary logistic regression model and expressed in terms of odds ratios (OR) with 95 % confidence interval (CI). A p-value < 0.05 was considered significant.

In **paper II**, **III** and **IV**, distribution of variables was expressed with median value and IQR. Differences in proportions were evaluated using the chi-square or the Fisher's exact test. Quantitative differences between groups were assessed with the Mann-Whitney U test.

In **paper II,** The Spearman rank test was used for calculating correlations. A p-value < 0.05 was considered significant.

In **paper III**, when risk factor evaluation for bowel resection was performed, factors with $p < 0.1$ in the uni-variable analysis were entered in a multi-variable regression analysis and expressed in odds ratio (OR) with 95 % confidence interval. The Spearman rank test was used for calculating correlations. A p-value < 0.05 was considered significant.

In **paper IV**, cumulative survival was analysed using the Kaplan-Meier method and life table analysis. Log rank test was used in the overall comparison of survival curves for the MVT versus systemic VTE group. Patients were censored for death in both groups until end of follow-up, September 6, 2017. A p-value < 0.05 was considered significant.

Results

Paper I

Incidence

One hundred and twenty patients, 67 men (31 residing in Malmö) and 53 women (27 residing in Malmö), were diagnosed with MVT from 2000 to 2015. The overall incidence rate of MVT in Malmö was estimated to 1.3/100,000 person-years (1.4/100,00 person-years in men and 1.2/100,000 person-years in women).

Patient characteristics

Median age at admission was 58 (range 19–95) years. Median BMI was 27.5 (IQR 25.2–30.0; n=50) in men and 25.8 (IQR 23.7–33.4; n=38) in women. Acute MVT was found in 115 (96%) patients, and primary and secondary MVT in 26 (22%) and 94 (78%) patients, respectively. Risk factors such as any direct injury to the vein due to disease or surgery were found in 35 (29%) patients, local or systemic venous congestion in 19 (16%), and thrombophilia in 72 (60%). Twenty (17%) patients had abdominal malignancies. History of previous venous thromboembolism was documented in 24 (20%) patients.

Among 89 tested, 39 (44%) patients had positive tests for inherited or acquired coagulation disorder. The most common thrombophilia was activated protein C resistance (Factor V Leiden mutation), occurring in 22 (18% of all patients or 25% of tested patients) patients (19 in heterozygous and three in homozygous genotype). In nine patients with myeloproliferative disease, eight (89%) were JAK-2 V617 mutation positive. Patients diagnosed in the former period (2000–2007) were older (p=0.013) and had higher proportions of abdominal malignancy (p=0.009) and activated protein C resistance (p=0.002) compared to those diagnosed in the latter period (2008–2015) (Table 4).

Table 4. Patient characteristics and risk factors for MVT in the former (2000-2007) and the latter (2008-2015) parts of the study

Factors	Former period (n = 58)	Latter period (n = 62)	Uni-variable analysis (*p* value)
Median age (years; IQR)	64 (50-73)	54 (47-65)	0.013
Women (%)	27 (47)	26 (42)	0.61
Acute pancreatitis(%)	10 (17)	7 (11)	0.35
Recent abdominal surgery	5 (9)	3 (5)	0.35
Thrombophilia	40 (69)	32 (52)	0.053
History of previous venous thromboembolism	12 (21)	12 (19)	0.86
Abdominal malignancy	15 (26)	5 (8)	0.009
Positive test for inherited or acquired coagulation disorder	20/36 (56)	19/53 (36)	0.066
Activated protein C resistance (Factor V Leiden mutation)	15/36 (42)	7/53 (13)	0.002

IQR: Interquartile range. MVT: Mesenteric venous thrombosis.

Mode of establishing diagnosis

During the latter time period, all patients were diagnosed by radiological imaging, in 97% of cases by CT with intravenous contrast enhancement. During this period, CT was more frequently used for MVT diagnosis compared to the former time period ($p < 0.001$). During the former time period, there were six autopsy-verified deaths in patients not undergoing bowel resection, of whom two died outside of hospital.

Bowel resection

Bowel resection rates did not differ between the two periods. Among the 98 patients receiving anticoagulation treatment, 83 (85%) were successfully treated with heparin as monotherapy without need for surgical intervention (Figure 7). Throughout the study period, fifteen patients underwent explorative laparotomy and bowel resection without preoperative diagnosis, and another 15 patients underwent bowel resection or endovascular therapy due to failure of anticoagulation as monotherapy. Endovascular therapy was performed in eight patients, out of whom three underwent bowel resection.

Late small bowel complications

Small bowel resections of 0.05 and 0.1 m of length due to late small bowel strictures at five and three months after index admission, respectively, were performed in two patients. One of these patients had severe heart failure, malnutrition and a low serum albumin of 20 g/L, why an ileostomy was created instead of bowel anastomosis. She developed short bowel syndrome and died 1.5 months after this operation. Another

two patients developed transient short bowel syndrome after bowel resection of 3.0 and 1.3 m, respectively, and creation of ileostomies. The remaining lengths of small bowel were 2.5 and 1.5 m, respectively. Both patients were operated with take down of their ileostomies and reanastomosis of the small bowel ends at 13 and 19 months of follow up, respectively, which cured them from short bowel syndrome. Both patients received parenteral nutrition support through a subcutaneous vein port (Port-a-Cath) during the time they had ileostomies and both central venous catheters were infected with septicaemia.

Endovascular therapy

The endovascular procedures performed were thrombolysis via the superior mesenteric artery (n=4), transjugular intrahepatic portal shunt (TIPS) with stenting (n=2), transjugular mechanical thrombectomy (AngioJet® device [MEDRAD, Warrendale, Pennsylvania, USA]) and thrombolysis (n=1), transhepatic stenting (n=1), transhepatic mechanical thrombectomy (AngioJet®), and Fogarty catheter balloon thrombectomy (n=1). Another two TIPS procedures failed. Local thrombolysis via the superior mesenteric artery was not considered first option but was used in combination with other endovascular therapies in three patients. In the fourth patient, TIPS was not considered an option due to the advanced extent of portomesenteric venous thrombosis, and 56 mg recombinant tissue plasminogen activator (rtPA) was continuously infused into the superior mesenteric artery over 60 h with success and without need of bowel resection. The sum of procedures performed exceeds eight, reflecting that a combination of techniques was often used. The median dose of thrombolytic agent, alteplase (Actilyse®; Boehringer, Ingelheim, Germany), administered locally in the mesenteric circulation, was 30 mg (range 14–56) in the four treated patients. One patient underwent a failed TIPS combined with thrombolysis via the superior mesenteric artery, complicated by perihepatic hematoma requiring explorative laparotomy for control of bleeding. Lifelong anticoagulation therapy after successful non-operative management was given to 49% (17/35) of patients in the former period and 71% (34/48) in the latter (p=0.040).

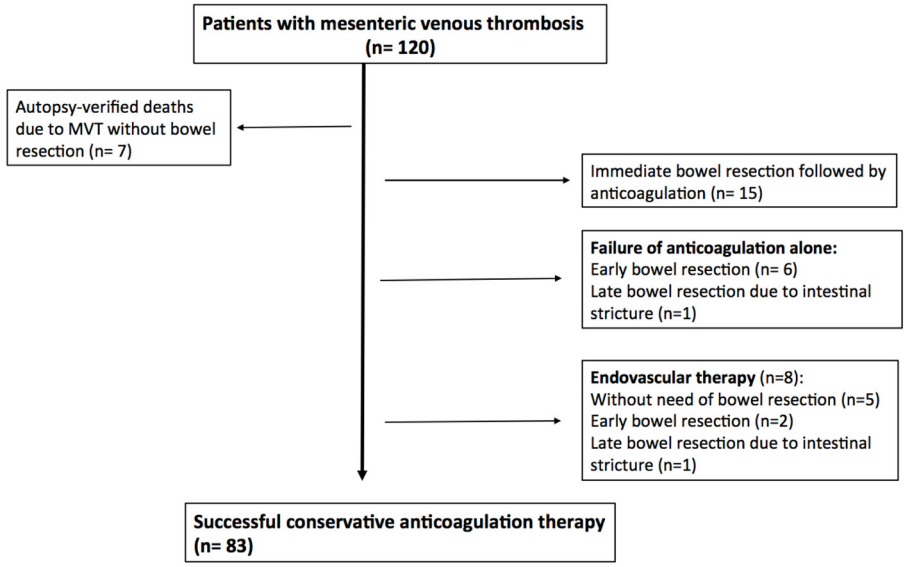

Figure 7. Management in patients with MVT
MVT: Mesenteric venous thrombosis.

Factors associated with 30-day mortality

Overall 30-day mortality rate was 10.8, 19.0% in the former time period versus 3.2% in the latter time period (p=0.006). The 30-day mortality after surgery (bowel resection and/or endovascular therapy) was 12.5% (2/16) in the former period versus 7.1% (1/14) in the latter (p=1.0). Age ≥75 years, management during the former as opposed to the later time period, pancreatic malignancy, and renal insufficiency at admission were all associated with increased 30-day mortality in uni-variable analysis. Age ≥75 years (OR 12.4, 95% CI [2.5–60.3]), management during the former time period as opposed to the latter period (OR 8.4, 95% CI [1.3–54.7]), and renal insufficiency at admission (OR 8.0, 95% CI [1.2–51.6]) were independently associated with increased 30-day mortality in the multivariable analysis. For comparison of bowel resection rate and 30-day mortality rate, results in paper I were compared with contemporary published series on MVT (Table 5).

Table 5. Contemporary published series on MVT

First author (publication year)	Population, Country	Number of patients	Mean or median age	Female sex (%)	Study period	Frequency of bowel resection (%)	Frequency of endovascular procedure (%)	30-day or in-hospital mortality rate (%)	Diagnostic autopsy (%)
Al-Thani[186] (2015)	Qatar	35	45	12 (34.3)	2005 - 2012	28/35 (80)	0 (0)	6/35 (17.1)	0 (0)
Cho[187](2018)*	Korea	41	62	10 (24.4)	2000 - 2017	4/41 (9.8)	0 (0)	2/41 (4.9)	0 (0)
Kim[188] (2017)*	South Korea	66	50	20 (30.3)	2002 - 2016	15/66 (22.7)	0 (0)	3/66 (4.5)	0 (0)
Liu[189] (2019)*	China	68	45	18 (26.5)	2009 - 2014	44/68 (64.7)	49/68 (72.1)	2/68 (2.9)	0 (0)
Maldonado[190] (2016)*	USA	80	58	34 (42.5)	1999 - 2015	4/75 (5.3)	4/75 (5.3)	1/80 (1.2)	0 (0)
Matthaei[191] (2019)	Germany	10	50	5 (50)	2005 - 2015	8/10 (80)	0 (0)	0/10 (0)	0 (0)
Nagaraja[192] (2015)	India	56	50	13 (23.2)	1997 - 2012	51/56 (91.1)	0 (0)	15/56 (26.8)	0 (0)
Wang[193] (2019)	China	78	61	24 (30.8)	2014 - 2018	58/78 (74.4)	0 (0)	Not reported	0 (0)
Yang[194] (2016)	China	32	45	12 (37.5)	2012 - 2014	25/32 (78.1)	15/32 (46.9)	8/32 (25)	0 (0)
Zeng[195] (2017)	China	18	51	6 (33.3)	2013 - 2014	2/18 (11.1)	0 (0)	0 (0)	0 (0)
Salim (paper I 2018)	Sweden	120	58	53/120 (44.2)	2000 - 2015	24/120 (20)	8/120 (6.7)	13/120 (10.8)	6/120 (5)
Salim (paper I, latter time period, 2018)	Sweden	62	54	26/62 (41.9)	2008 - 2015	10/62 (16.1)	6/62 (9.7)	2/62 (3.2)	0 (0)

Searched for original articles in Pub Med 15th Feb 2020. Medical Subject Heading (MeSH) term “Mesenteric venous thrombosis” and including articles from 2015 - 2020. 1703 hits. English language. Only original reports with ≥10 patients with MVT with or without extension to the portal or splenic vein were considered. Reports on portomesenteric venous thrombosis or splanchnic vein thrombosis without further specification on location of thrombosis or no reported patient characteristics or outcome data separately for patients with MVT were excluded. Unvalidated larger (nation or statewide) cohort or register-studies on mesenteric ischaemia were excluded. MVT: Mesenteric venous thrombosis.

*all selected by diagnosis on CT

Comments: The total number of patients in the eleven series was 604, of which 212 were females and 392 males. The pooled estimate of proportion of female sex was 35.1% (95% CI 31.3 – 39.1%).

Paper II

Patient characteristics (paper II and III)

During the 14-year period, 102 patients (61 men and 41 women) were diagnosed with MVT. Their median age was 58 years (IQR 47–68). Men (56 [IQR 47–64] years) were younger (p=0.009) than women (65 [IQR 50–72] years). MVT was defined as acute in 100 (98%) patients, and chronic in the remaining 2 (2%). Median BMI was 27.8 kg/m^2 (IQR 25.5–31.4) in men (n=49) and 25.5 kg/m^2 (IQR 23.5–33.6) in women (n=34). Seventeen (17%) patients had previously been diagnosed with pancreatitis and 26 (26%) with malignancies. Among 85 patients tested for thrombophilia, 17 (20%) had the factor V Leiden mutation (Table 6), and 9 (11%) had the JAK-2 V617 mutation. In 10 patients with myeloproliferative disease, 9 (90%) were JAK-2 V617 mutation positive.

Anticoagulation therapy groups

Lifelong anticoagulation was initiated in 64 patients (63%). Fifty-six (55%) patients received VKA, 22 (22%) LMWH, and 22 (22%) DOACs. The DOAC prescribed were rivaroxaban (n=14), apixaban (n=5), and dabigatran (n=3). Two patients received no medical therapy at all (Table 6). Patients with MVT and malignant disease were more often (p=0.034) treated with LMWH than VKA. Frequencies of renal insufficiency were the same in DOAC- and VKA treated patients (p=0.19), and median GFR for patients treated with DOACs and VKA were 81ml/min/1.73m^2 (IQR 66–96; n=22) and 86 ml/min/1.73m^2 (IQR 70–101; n=54), respectively, p = 0.52.

Table 6. Patient profiles, thrombotic and bleeding complications in 102 patients with MVT verified by CT, and treated with anticoagulation during follow-up.

Variable	All patients (%)	LMWH (%)	VKA (%)	DOACs (%)	No medical treatment (%)
Number of patients	102	22	56	22	2
Median age (IQR); years	58 (47-68)	65 (56-76)	56 (46-65)	58 (48-68)	66 (62-79)
Female sex	41 (40.2)	11 (50.0)	21 (37.5)	7 (31.8)	2 (100)
Lifelong treatment initiated	64 (62.7)	4 (18.2)	41 (73.2)	19 (86.4)	0 (0)
Malignancy	26 (25.5)	10 (45.5)	12 (21.4)	4 (18.2)	0 (0)
Renal insufficiency	16/100 (16)	5 (22.7)	6/54 (11.1)	5/22 (22.7)	0 (0)
Acute pancreatitis	17 (16.7)	5 (22.7)	8 (14.3)	4 (18.2)	0 (0)
Liver cirrhosis	6 (5.9)	2 (9.1)	1 (1.8)	2 (9.1)	1 (50)
Factor V Leiden mutation	17/85 (20.0)	1/11 (9.1)	13/54 (24.1)	3/18 (16.7)	0 (0)
Extensive thrombosis[a] at diagnostic CT	43 (42.2)	5 (22.7)	27 (48.2)	10 (45.5)	1 (50)
Bleeding complications					
Major bleeding	15/102 (14.7)	4/22 (18.2)	8/56 (14.3)	2/22 (9.1)	1 (50)
Oesophageal variceal bleeding	3/102 (2.9)	1/22 (4.5)	2/56 (3.6)	0/22 (0)	0 (0)
Gastrointestinal bleeding	19/102 (18.6)	4/22 (18.2)	8/56 (14.3)	7/22 (31.8)	0 (0)
Intracranial bleeding	3/102 (2.9)	2/22 (9.1)	1 (1.8)	0 (0.0)	0 (0)

CT: Computed tomography; DOACs: direct oral anticoagulants; IQR: interquartile range; LMWH: low molecular weight heparin; MVT: Mesenteric venous thrombosis;VKA: vitamin K antagonist.

[a]Mesenteric (both central and peripheral), portal and splenic vein thrombosis.

Radiological outcome – thrombus recanalization

CT was performed both at diagnosis and after medical treatment in 70 patients after a median follow-up of 6 (IQR 3–28) months. The overall evaluation showed no change in 20 patients, progression of thrombotic status within the portomesenteric venous system in 4, partial regression in 27, and complete regression in 19 patients. Successful recanalization had been achieved in 66% of the 70 patients, 71% of those treated with VKA (n=41) and 69 % of those treated with DOACs (n=16) (p=0.88). Patients with and without extensive thrombosis had complete regression of thrombosis after anticoagulation therapy in 11% (3/27) and 37% (16/43), respectively (p=0.017). When entering extensive thrombosis, age, malignancies, and type of therapy (VKA or DOACs) in a multivariable analysis, none of these variables were associated with successful recanalization. Neither was there any correlation between successful recanalization and the time lapse between diagnostic and follow-up CT (r=0.067, p=0.58). No clinical variable was found to be associated with successful recanalization.

Bowel resection

Among the 102 patients, 17 (17%) underwent bowel resection. There was no difference in bowel resection rate between patients treated with VKA (23% [13/56]) and DOACs (9% [2/22]; p=0.15).

Bleeding complications

The overall rates of major bleeding, intracranial bleeding, gastrointestinal and oesophageal variceal bleeding during anticoagulation were 14.7%, 2.9%, 18.6%, and 2.9%, respectively. The major bleeding rates during VKA and DOAC therapy were 14.3% (8/56) and 9.1% (2/22), respectively (p=0.54). DOAC treatment tended to be associated with a higher rate of gastrointestinal bleeding compared to VKA treatment (p=0.077). Two gastrointestinal bleedings were fatal, one patient with concomitant oesophageal variceal bleeding without anticoagulation died after 12 days, and one duodenal ulcer bleeding died at 1 month after initiation of anticoagulation. Three patients suffered from intracranial bleeding; one patient treated with LMWH suffered a subdural bleeding necessitating neurosurgery after 1 month, another patient treated with LMWH had a subarachnoidal bleeding after 28 months, which was managed conservatively. The third patient treated with VKA had an intracerebral bleeding after 8 months, which was managed conservatively.

Venous thromboembolic complications

No MVT recurrence occurred during or after cessation (n=38) of medical treatment. No VTE recurrence occurred during medical treatment. One patient suffered from a DVT in her leg 9 years after cessation of anticoagulation therapy.

Mortality

The 30-day mortality was 7 % (7/102). There was no difference in 30-day mortality between patients treated with VKA and DOAC (3.6% [2/56] and 0% [0/22]; p=1.0), respectively. Total mortality at the end of follow-up was 20 % (20/102). Median survival times from MVT diagnosis to end of follow-up for patients with malignant (n=26) and non-malignant (n=76) disease were 42 (IQR 5–72) and 50 (IQR 24–101) months, respectively, (p=0.19), whereas survival in patients with nonmetastatic (n=17) and metastatic cancer (n=9) was 66 (IQR 27–84) months and 4 (IQR 2–25) months, respectively (p=0.002).

Paper III

Clinical data from the referral letter for initial radiological examination

Among the 102 patients with MVT, initial radiological examinations had been performed by CT in 69 (68%), ultrasound in 26 (26%), plain abdominal X-ray in 5 (5%), and magnetic resonance imaging in 2 (2%). None of the referral letters for initial radiological examination revealed any suspicion of MVT, whereas intestinal ischaemia was suspected in 3 (3%) patients. In these 3 patients with suspected intestinal ischaemia, intestinal ischaemia was mentioned among two, three, or four diagnostic suggestions in the referral letter. The most frequently asked questions concerned intestinal disorders (n=77), inflammatory disorders (n=65), biliary or urinary tract disorders (n=38), malignancies (n=26), and benign disorders of the liver or spleen (n=10).

Vascular and intestinal CT findings

Central and peripheral MVTs were documented in 98 (96%) and 73 (72%) patients, respectively. Extensive thrombosis at diagnostic CT was found in 43 (42%) patients, and intestinal findings in 66 (65%). The most frequent extra-vascular abnormalities were mesenteric oedema (n=63; 62%), ascites (n=52; 51%), small bowel wall oedema (n=40; 39%), and local small bowel dilatation (n=10; 10%) (Table 7). No abnormalities in the colon were found.

Table 7. Vascular and intestinal findings on CT at diagnosis of MVT in 102 patients

	Frequency (%)
Vascular findings	
Central MVT	98 (96.1)
Peripheral MVT	73 (71.6)
Isolated MVT	14 (13.7)
Portal vein thrombosis	85 (83.3)
Extra-hepatic portal venous thrombosis	80 (78.4)
Intra-hepatic portal venous thrombosis	60 (58.8)
Splenic vein thrombosis	61 (59.8)
Venous collaterals	52 (51)
Extensive thrombosis[a]	43 (42.2)
Intestinal findings	66 (64.7)
Mesenteric oedema	63 (61.8)
Small bowel wall oedema	40 (39.2)
Local small bowel dilatation	10 (9.8)
Extensive small bowel dilatation	2 (2.0)
Gas in the portomesenteric venous system	0 (0.0)
Ascites	52 (51.0)

[a]Mesenteric central, peripheral, portal and splenic vein thrombosis. CT: Computed tomography. MVT: Mesenteric venous thrombosis.

Factors associated with bowel resection

Among the 102 patients, 17 (17%) underwent bowel resection. Previous VTE was associated with increased bowel resection rate (p=0.049). No patient with exclusive transient risk factor (n=15) underwent a bowel resection (p=0.069). No patient with acute pancreatitis (n=17) underwent bowel resection (p=0.068). The presence of any intestinal finding at CT (p=0.026), mesenteric oedema (p=0.014), small bowel wall oedema (p<0.001), small bowel dilatation (p=0.005), and ascites (p=0.021) were associated with increased bowel resection rate (Table 8). After entering small bowel wall oedema, acute pancreatitis, and previous VTE in a multi-variable regression analysis, small bowel wall oedema remained an independent risk factor associated with bowel resection (OR 15.8 [95% CI 3.2–77.2], p=0.001), and previous VTE tended to be a risk factor for bowel resection (OR 3.3 [95% CI 0.9–12.6], p=0.080).

Table 8. Association between vascular and intestinal findings at initial CT and later need for bowel resection in 102 patients with MVT.

CT findings	Bowel resection	*p* value
All	17/102 (16.7)	
Extensive thrombosis[a]	10/43 (23.2)	0.13
Isolated MVT	2/14 (14.3)	1.0
Intestinal findings	15/66 (22.7)	0.026
Mesenteric oedema	15/63 (23.8)	0.014
Small bowel wall oedema	15/40 (37.5)	< 0.001
Small bowel dilatation	6/12 (50.0)	0.005
Ascites	13/52 (25.0)	0.021

[a]Mesenteric central and peripheral, portal, and splenic vein thrombosis. CT: Computed tomography. MVT: Mesenteric venous thrombosis.

Paper IV

Comparison of patient characteristics and acquired risk factors in patients with MVT versus systemic VTE

Patients with MVT (n=120; all symptomatic) were younger (p<0.001), had higher glomerular filtration rate (93 ml/min/1.73m^2 versus 67 ml/min/1.73m^2; p<0.001), lower prevalence of smoking (p<0.001), and had less often undergone recent surgery (p=0.025) compared to patients with systemic VTE. In six individuals with median age 75 years (IQR 60–82) fatal MVT was detected at autopsy. Previous VTE tended to be more prevalent in patients with MVT (p=0.072). The prevalence of cancer (19.2% in MVT versus 12.1% in VTE; p=0.026) and intra-abdominal cancer (16.7% in MVT versus 2.3% in VTE; p<0.001) were both higher in MVT (Table 9). Of nine patients with myeloproliferative neoplasm in the MVT group, eight (89%) were JAK-2 mutation positive. The prevalence of cast therapy, trauma and

immobilization in the VTE cohort were 3.9% (57/1452), 8.2% (119/1452) and 17.1% (248/1452), respectively.

Table 9. Comparison of patient characteristics and acquired risk factors in patients with MVT versus systemic VTE

Variable	MVT	Systemic VTE	*p* value
Number of patients	120	1452	
Median age (IQR); years	58 (47-70)	66 (53-76)	< 0,001
Female sex (%)	53 (44.2)	739 (50.9)	0.16
GFR (ml/min/1.73m^2)	93 (74-116) (n=114)	67 (52-79) (n=970)	< 0,001
Platelet count (x 10^9/L)	260 (177-340) (n=112)	244 (204-299) (n=1411)	0.35
Ongoing VTE prophylaxis (%)	2/116 (1.7)	30 (2.1)	0.80
Acquired risk factors (%)	82/107 (76.6)	1186/1396 (85.0)	0.022
Previous venous thromboembolism (any)	24/120 (20.0)	203/1451 (14.0)	0.072
BMI ≥ 30 kg/m^2	24/88 (27.3)	296/1364 (21.7)	0.22
Smoking (ex or current)	36/103 (35.0)	771/1346 (57.3)	< 0.001
Surgical intervention (≤ 6 weeks)	8/117 (6.8)	207 (14.3)	0.025
Long travel ≥ 3h	7/117 (6.0)	102 (7.0)	0.67
Malignancy (solid cancer)	23 (19.2)	176 (12.1)	0.026
Intra-abdominal malignancy	20 (16.7)	33 (2.3)	< 0.001
Hormone therapy (female only)	7/53 (13.2)	161/739 (21.8)	0.14
Pregnancy	0/53 (0)	17/739 (2.3)	0.62
None of these acquired risk factors	25/107 (23.4)	210/1396 (15.0)	0.022
Strong provocative risk factor (recent surgery or malignancy)	28/119 (23.5)	356 (24.5)	0.81

BMI: Body mass index. GFR: Glomerular filtration rate. MVT: Mesenteric venous thrombosis. VTE: Venos thromboembolism.

Comparison of inherited thrombophilia in tested patients with MVT versus systemic VTE

The prevalence of factor V Leiden mutation was lower in patients with MVT compared to patients with systemic VTE (24.7% versus 37.6%; p=0.015). The prevalence of factor V Leiden mutation without presence of cancer was also lower in MVT compared to VTE (26.6% versus 38.9%; p=0.031). There was no difference in prevalence of the prothrombin (PT) mutation between the two groups (Table 10).

Table 10. Comparison of inherited thrombophilia in tested patients with MVT versus systemic VTE

Variable	MVT	Systemic VTE	p value
Number of patients	120	1452	
Heterozygous FVL mutation(%)	19/89 (21.3)	348/1021 (34.1)	0.014
Homozygous FVL mutation (%)	3/89 (3.4)	36/1021 (3.5)	0.94
FVL mutation (any) (%)	22/89 (24.7)	384/1021 (37.6)	0.015
FVL mutation (any) without malignancy (%)	21/79 (26.6)	360/926 (38.9)	0.031
Heterozygous PT mutation (%)	3/89 (3.4)	58/1259 (4.6)	0.79
Homozygous PT mutation (%)	0/89 (0.0)	0/1259 (0.0)	-
PT mutation (any) (%)	3/89 (3.4)	58/1259 (4.6)	0.79
Compound FVL and PT mutation (%)	0/89 (0.0)	11/1245 (0.9)	1.0
FVL or PT mutation(any) (%)	25/89 (28.1)	429/1036 (41.4)	0.014
No FVL or PT mutation (%)	64/89 (72.0)	605/1036 (58.4)	0.013

FVL: Factor V Leiden, PT: Prothrombin, MVT: Mesenteric venous thrombosis. VTE: Venous thromboembolism.

Comparison of survival in patients with MVT versus systemic VTE

Thirty-day mortality was higher in the MVT group (10.8% versus 0.5% in VTE; $p<0.001$) but did not differ at long-term follow-up according to the Kaplan–Meier analysis ($p=0.73$).

Variability of inherited thrombophilia in patients with MVT around the world.

The prevalence of inherited thrombophilic factors are presented in paper I and IV, and these results are included in the systematic review by Zarrouk[105]. There is a wide variability of inherited thrombophilic factors associated with MVT around the world (Table 11). While the prevalence of FVL was high in Sweden [100], it was rare in China [181] and India [182]. The prevalence of PT mutation was highest in Italy [183], and PS deficiency and AT deficiency were found to be highest in Greece [184]. India had the highest and USA the lowest prevalence of PC deficiency, respectively.

Table 11. The prevalence of inherited thrombophilic factors associated with MVT in different populations.

Variable n (%)	Sutkowska[196] (USA)	Ma[197] (Canada)	Yang[198] (China)	Mutreja[199] (India)	Zarrouk[105] (Sweden)	Primignani[200] (Italy)	Starakis[201] (Greece)	Total n (%)	(95% CI)
No. of patients tested for thrombophilia	341	49	50	34	89	73	29		
Inherited thrombophilic factor									
FVL mutation	35/341 (10.3)	3/49 (6.1)	1/50 (2.0)	0/20 (0)	22/89 (24.7)	2/73 (2.7)	5/29 (17.2)	68/651(10.4)	(8.2-13.1)
PT mutation	13/341 (3.8)	3/49 (6.1)	N/A	0/34 (0)	3/89 (3.4)	15/73 (20.5)	2/29 (6.9)	36/615 (5.9)	(4.1-8.0)
PS deficiency	12/341 (3.5)	2/49 (4.1)	3/50 (6.0)	4/34 (11.8)	5/89 (5.6)	1/73 (1.4)	7/29 (24.1)	34/665 (5.1)	(3.6-7.1)
PC deficiency	1/341 (0.3)	1/49 (2.0)	4/50 (8.0)	7/34 (20.6)	2/89 (2.2)	2/73 (2.7)	5/29(17.2)	22/665 (3.3)	(2.1-5.0)
AT deficiency	5/341 (1.5)	1/49 (2.0)	2/50 (4.0)	0/34 (0)	0/89 (0)	3/73 (4.1)	4/29 (13.8)	15/665 (2.3)	(1.3-3.7)

FVL, Factor V Leiden; PS, Protein S; PC, Protein C; AT, Antithrombin; PT, Prothrombin G20210A. N/A: not analysed

Discussion

Epidemiology

A population based study in the city of Malmö, Sweden, including 402 patients with acute mesenteric ischaemia with an autopsy rate of 87%, showed that 16% of patients were diagnosed with MVT[23, 202]. Such firm epidemiological data is very difficult to obtain from other populations. In fact, there are no epidemiological study with accurate estimate on the distribution of aetiologies of acute mesenteric ischaemia[106, 203, 204].

In contrast to the reported 16% of patients with MVT among all patients with acute mesenteric ischaemia[23], a study performed in the city of Mansoura, Egypt, including 101 patients, found the proportion of MVT as an aetiology to be remarkably high, 77% (78 patients). This discrepancy were perhaps mostly attributed to the high prevalence of chronic liver disease secondary to endemic hepatitis C virus infection in Egypt[205].

Another study performed by Nagaraja et al, studied characteristics of 117 Indian patients (85 males and 32 females) with acute mesenteric ischaemia. MVT was seen in 56 patients (48%) and mesenteric arterial occlusion in 61 (52%). The probable reasons why they found MVT in almost half of their patients might be several: Patients with arterial occlusive disease were probably much sicker with more rapid progression of illness, earlier presentation with peritonitis and either died or got operated at another hospital before reaching the study hospital. Patients with MVT had a much longer duration of symptoms (14 vs 2 days), and less frequent peritoneal signs at presentation, which made them eligible for laparotomy during hospitalization. Five (8.9%) had liver cirrhosis, whereas there was no reported data on inherited thrombophilia.

The population-based estimated overall incidence rate of MVT in Malmö citizens between 2000 and 2015 (paper I) was estimated to 1.3/100.000 person-years, a figure in the lower range of incidence reported in the 1970s[24]. This might partly be related to the markedly reduced autopsy frequency[206], from 85%[207] to 12% in the latter time period of the study (paper I). On the other hand, important improvements in diagnostics and treatment of hypercoagulable states have occurred during this period[208] probably resulting in a decrease in venous thromboembolism. However, since MVT is very rarely suspected already in the

emergency setting[202], or sometimes confused with arterial mesenteric ischaemia at laparotomy, and with the contemporary low autopsy frequency in the population, the contemporary true incidence is hard to estimate.

It is important to distinguish MVT from other forms of splanchnic venous thrombosis (portal vein thrombosis, splenic vein thrombosis) since it is an acute abdominal condition with a high risk of developing intestinal infarction and much higher mortality rates[118, 209, 210].

Aspects on age and gender

MVT seems to typically affect middle-aged adults as it is most common in the fifth and sixth decades of life. In the recent published series (Table 5), the mean or median age of MVT patients at presentation was reported to be between 45-62 years. Age ranges are broad and varies depending on the underlying pathogenesis and aetiology. For example, MVT associated with myeloproliferative disease presents at an older age compared to MVT associated with oral contraceptive use or abdominal trauma[126, 211]. Table 5 supports also that MVT is slightly more common in males compared to females.

Thrombophilia in the population

The prevalence of inherited thrombophilia varies widely in different populations depending on their geographical distribution. For example, the prevalence of FVL mutation, which seems to be overrepresented in patients with MVT, is highest in Sweden, Greece and Lebanon where it approximates 15 % in some areas, while on the other hand, it is almost not present in African, Chinese or Japanese populations[46].

In a systematic review performed by Zarrouk et al[105], the most prevalent inherited thrombophilic factors in patients with MVT were FVL mutation (9%), and prothrombin deficiency (7%), whereas the least prevalent were deficiencies of protein C (4%) and antithrombin deficiency(3%). The wide range of frequency of inherited thrombophilic factors in different populations as outlined in Table 10, indicates the necessity to relate these factors to background population-based data in order to estimate their overrepresentation in MVT.

Hence it was of utmost importance that the case-control study in paper IV, comparing thrombophilias in MVT versus systemic VTE were from the same population

Screening for inherited thrombophilia

Several authors have expressed different opinions regarding the clinical utility of thrombophilia testing in MVT. Whom to screen, when to screen and its role in clinical decision making is still a matter of debate. Data and practices relevant to DVT and PE are often extrapolated to aid in the management of venous thrombosis in unusual sites, such as MVT, even though the underlying predisposing factors and pathophysiology of these entities may be different.

Al-Samkari et al[212] suggests that patients with splanchnic venous thrombosis, including MVT, should firstly be screened for local precipitating factors and any blood cell count disturbances prior to evaluation for inherited or acquired thrombophilia. They state that the majority of these local precipitating factors (pancreatitis, diverticulitis, inflammatory bowel disease) will be diagnosed or excluded on CT. There seems to exist general consensus on the concept of testing for inherited thrombophilia and myeloproliferative diseases when there are no strong trigger factors present. Furthermore, if a patient with MVT is diagnosed with antiphospholipid syndrome, this will alter the treatment regime, since these patients preferably should be treated with VKA and not DOACs[213]. For patients in whom the decision of indefinite anticoagulation is made due to the presence of a non-reversible strong risk factor, such as active cancer, further thrombophilia testing has no clinical consequences.

The high prevalence of inherited and acquired thrombophilic factors present in MVT patients[105] and potential severe clinical consequences of recurrence, makes experts tend to offer patients with identified laboratory-confirmed thrombophilia lifelong anticoagulation treatment, despite insufficient evidence for such treatment. Consequently, routine laboratory screening may be considered in patients with MVT without an identified provocative factor on CT scan. The ESVS guidelines recommend indefinite anticoagulation in MVT patients with proven thrombophilia[134].

Clinical diagnosis – still ‘’impossible’’?

In a cross-sectional survey among experts on emergency evaluation of abdominal pain, 96.7% (29/30 emergency physicians) answered that it was unacceptable not to diagnose mesenteric ischaemia in the emergency department[214]. The results of this survey are, however, in very strong contrast to real life setting. Indeed, none of the 102 referral letters for the initial radiological examination in paper III expressed suspicion of MVT. Only three referral letters stated ‘’intestinal ischaemia’’ as one of several possible differential diagnosis. The statement by Cokkinis – ‘’Occlusion of the mesenteric vessels is regarded as one of those conditions of which the

diagnosis is impossible, the prognosis is hopeless, and the treatment almost useless''[14] for almost 100 years ago is still valid, in particular for clinical suspicion of MVT.

Early diagnosis

The diagnosis of acute mesenteric ischaemia is a collaborative effort of emergency department physicians, gastrointestinal and vascular surgeons, and radiologists. In contrast to acute arterial occlusive mesenteric ischaemia, early diagnosis prior to development of transmural bowel infarction is often possible in MVT due to the often insidious onset of abdominal pain with a symptom duration of typically two to three days. The availability of high-resolution CT scanners around the clock has had a tremendous impact on early detection, increased rate of conservative anticoagulation therapy alone and improved prognosis in patients with MVT as clearly demonstrated in paper I. The four series[187-190] that diagnosed all patients by CT in Table 5, had all a low 30-day mortality rate, ranging from 1.2 % to 4.9 %. It is well known that detecting acute mesenteric ischaemia in acute abdomen on CT is more likely if there is a clinical suspicion stated in the referral letter[215]. However, since there rarely are any clinical suspicion of intestinal ischaemia in MVT patients, radiologists have a great responsibility to diagnose this disease whenever possible and routinely describe the mesenteric vessels in acute abdomen when the CT images allows examination, even if the CT protocol not is optimal with contrast enhancement in the arterial and venous phase. Thus, CT scan is most important for diagnosis MVT. In one large series on patients with suspected acute mesenteric ischaemia[216], CT had a sensitivity of 89 % and was false-negative in 19/180 patients. All 19 false-negative patients had surgically proven non-occlusive mesenteric ischaemia. CT had a sensitivity for MVT of 100% (10 correctly diagnosed/10 MVT patients) and a specificity for acute mesenteric ischaemia of 99.5%. Correctness of CT report by the first reader for the diagnosis of MVT was 100% (9/9) in a recent report[215]. In a retrospective study based on 109 patients with diagnosis of acute mesenteric ischaemia between 2006 and 2014, the inter-reader agreement for 30 patients with MVT and various secondary intestinal abnormalities on CT were 94% and 70-100%, respectively[217]. This report concluded that multiphasic CT scan protocol, including unenhanced, arterial phase and venous phase images, without positive oral contrast agent, improves the inter-reader agreement for vascular and intestinal abnormalities secondary to acute mesenteric ischaemia.

Summary of initial management

Since no referral letter for the initial radiological examination indicated clinical suspicion of MVT among the 102 patients with confirmed MVT in paper III, it seemed very theoretical and unjustified to start the management algorithm (Figure 8) with "patient with suspected mesenteric venous thrombosis" prior to imaging confirmation by CT. CT with intravenous contrast enhancement and imaging in the portal phase has become the most important, reliable and accurate imaging for diagnosing MVT[218, 219]. A low percentage of patients with MVT will be diagnosed as an incidental finding. The protocol for urgent CT of the abdomen varies with the clinical history provided by the referring physician, and sometimes a second CT with an optimized protocol for imaging may be needed. Diagnosis of portal vein thrombosis with colour Doppler ultrasound alone is not sufficient to evaluate the extent of thrombosis, whether there is an extension to the superior mesenteric vein, and cannot evaluate secondary intestinal abnormalities, and needs to be complemented by CT.

The importance to scrutinize the CT images

When the diagnosis of MVT has been established, it is very important that the responsible physicians taking care of the patient, gastrointestinal surgeon, general surgeon, vascular surgeon or internal medicine physician, scrutinizes the CT images together with the radiologist who has assessed the images and written the preliminary report. In paper III, it was clearly found that secondary intestinal abnormalities such as small bowel wall oedema, small bowel dilatation, mesenteric oedema, and ascites, were prognostic indicators for increased need of bowel resection. Findings of bowel wall thickening, decreased enhancement of bowel wall and ascites were recently found to be associated with increased bowel resection rate in MVT[188]. In paper III, small bowel wall oedema was found to be associated with bowel resection after multi-variable adjustment. In another report performing adjustment for confounders, CT verified dilated small bowel loops, defined as ≥ 2.0 cm, was associated with intestinal necrosis and bowel resection[193]. Patients with thrombosis extending into the portal vein or complete (as opposed to partial) thrombosis of the superior mesenteric or portal vein were also recently reported to have an increased risk of needing a bowel resection[188]. Such information should alert the physicians. Even though no association between extensive thrombosis defined as thrombosis of the central and peripheral part, portal and splenic vein thrombosis, could be shown in paper III, it is highly likely that less extensive thrombosis is associated with more complete radiologic recovery[190] and less risk of long-term sequalae of portal venous hypertension[190, 220].

The place of DOACs in MVT

DOACs are well established as first-line treatment for systemic VTE but have, however, been scarcely studied in MVT. Due to the absence of clinical experience with the use of DOACs in the setting of MVT, there are currently no evidence for or against their use[221]. However, if a decision to use these agents are made, their use should be considered off-label and careful patient counselling and clinical monitoring should follow. Patients receiving DOACs should ideally be included in prospective cohort studies aimed to fill this knowledge gap. Although the use of DOACs in patients with MVT is limited[195], it is better documented than in any other group of venous thromboembolism at unusual sites[222]. Even though paper II is a retrospective study with a small sample size of 22 patients treated for MVT with DOACs, efficacy and safety were the same as the group of patients treated with VKA. In view of the disadvantages of VKA therapy including narrow therapeutic window, extensive food and drug interactions, highly variable dose response, and requirements of frequent dose adjustments and monitoring, DOACs appears to be a better alternative. At present time, renal function (estimated GFR based on serum creatinine, age and gender) is monitored in patients receiving DOACs in Region Skåne every three months the first year and thereafter the intervals are based on the GFR levels. It should also be acknowledged that long term VKA therapy in patients with VTE is associated with a relatively high risk of major bleeding, 0.4-3.8%, compared to DOACs which has a major bleeding risk of 0.1-0.9%[223].

DOACs are 19 times more expensive than VKA therapy according to FASS (Farmaceutiska Specialiteter i Sverige; accessed 2 April 2020, standard VTE dose Xarelto® [rivaroxaban] versus Waran®[warfarine] for one year of therapy). However, the level of maximal yearly cost for each patient is set to 2350 Swedish Crona (213 Euros; www.oanda.com; accessed 1 April 2020), which means that the difference in costs between types of anticoagulants has little influence on choice of anticoagulant in Sweden. DOACs has been considered more cost-effective than VKA for VTE therapy due to increased costs during VKA therapy associated with anticoagulation monitoring and the occurrence of major bleeds[224]. The advantage of DOACs shown from such report[224] can, however, not be easily extrapolated and applied in patients with MVT due to the increased risk of gastrointestinal bleeding that may be further increased during DOAC therapy[151]. It may be wise to treat the patients with LMWH during the first weeks of therapy until clinical stabilization, before changing therapy to DOACs. Such management may decrease the risk of gastrointestinal bleeding. Despite that firm evidence from prospective comparative studies or randomized controlled trials in medical management of MVT are lacking, anticoagulation treatment with DOACs appears to be able to replace VKA in patients with MVT. Hence, DOACs has been first-choice anticoagulation therapy in MVT at the present thesis centre for several years. Suggested anticoagulation management in MVT are shown in Table 12.

Table 12. Suggested anticoagulation in MVT.

	Heparin	LMWH	Apixaban	Rivaroxaban	Edoxaban	Dabigatran	VKA
Initial therapy	++	++	-	-	-	-	-
Peritonitis	++	+	-	-	-	-	-
Gastrointestinal bleeding (mild, no blood transfusion needed)	+	+[#]	-	-	-	-	-
Maintenance therapy	-	+	++	++	++	++	+
Severe renal impairment	+	++	-	-	-	-	+
Severe liver failure	+	+	-	-	-	-	-
Severe obesity (BMI ≥ 40kg/m^2)	+	++	+/-	+/-	+/-	+/-	++
Active cancer	+	++	-	-	-	-	-
Pregnancy	+	++	-	-	-	-	-

++, Recommended, + Might be recommended, - Not recommended, +/- Indifferent. BMI: Body mass index. LMWH: Low molecular weight heparin. MVT: Mesenteric venous thrombosis. VKA: Vitamin K antagonist. The table is based on the following references:[140, 155, 157] and paper II. [#] LMWH may be administered subcutaneously as half of the full dose twice daily to reduce the risk of bleeding.

The place of endovascular therapy

A number of endovascular procedures for the treatment of MVT have been developed as outlined. There are no comparative studies between anticoagulation first-strategy and endovascular first-strategy treatment to help us establish the indication for endovascular therapy. In clinical practice, clinical deterioration during anticoagulation will end up with laparotomy with probable bowel resection or an endovascular procedure in centres with experience of endovascular therapy for MVT as outlined in paper I. These procedures may be performed by vascular surgeons or interventional radiologists, depending on organizational structure.

In modern series (Table 5), endovascular therapy was not at all performed in the majority of centres, whereas two centres performed endovascular therapy in 46.9%[194] and 72.1%[189] of the patients, respectively. Both these series had a case-control design, retrospectively comparing different treatment strategies: In the Liu study[189], stratification in three different groups, endovascular local thrombolysis and aspiration of thrombus without need of surgery (n=24), bowel resection (n=19) and both endovascular therapy and bowel resection (n=25). When comparing bowel resection length between the bowel resection group and the combination therapy group, the latter group had a mean of 0.7 m bowel spared. Twenty patients were excluded from the study, of whom ten underwent bowel resection directly and six patients received anticoagulation. Local thrombolysis was given via the percutaneous transhepatic or TIPS approach, or indirect thrombolysis via the SMA, for five days with only two reported haemorrhagic complication. In the Yang study[194], one group underwent emergent laparotomy, open thrombectomy of the superior mesenteric vein, and bowel resection in 13 out of 17 patients followed by anticoagulation versus emergent laparotomy, open thrombectomy of the superior mesenteric vein, with bowel resection in 12 out of 15 patients followed by local indirect thrombolysis via the SMA for three days. Major abdominal haemorrhage was reported for three (20%) in the postoperative thrombolysis group. Of note, mean hospital stay length in group 1 and group 2 were 46 and 23 days, respectively. All patients in group 2 was included after termination of inclusion of all patients in group 1. Repeat bowel resection, short-bowel syndrome and 30-day mortality rate was lower in group 2.

The impression of these two studies from China, compared to the study presented in paper I, latter time period, is that bowel resection rate was too high, 64.7% and 78.1%, respectively. These patients were simply diagnosed too late for being eligible for successful anticoagulation therapy alone, which may be due to factors related to patient delay, doctor´s delay or organizational issues. These centres should focus to organize themselves to be able to earlier diagnose MVT to avoid any interventional therapy. The design of the study by Yang[194] is strange by first performing laparotomy and bowel resection and then thrombolysis, which in most

centres would be a contraindication after surgery. The study by Liu[189] could show a benefit of thrombolysis, even though the comparative groups were non-randomized and highly prone to selection bias. The exclusion of the ten patients that immediately underwent bowel resection was also uncalled for.

As shown in paper I, it is possible to treat the majority of MVT patients with anticoagulation monotherapy if timely diagnosed. Endovascular therapy should preferably be performed in experienced centres in the few patients that clinically deteriorate in order to avoid progression towards bowel infarction and need of bowel resection. In paper I, five out of eight patients did not need bowel resection after successful endovascular therapy. Suggested management algorithm of patients with MVT is presented in Figure 8.

Suggested algorithm for management of MVT

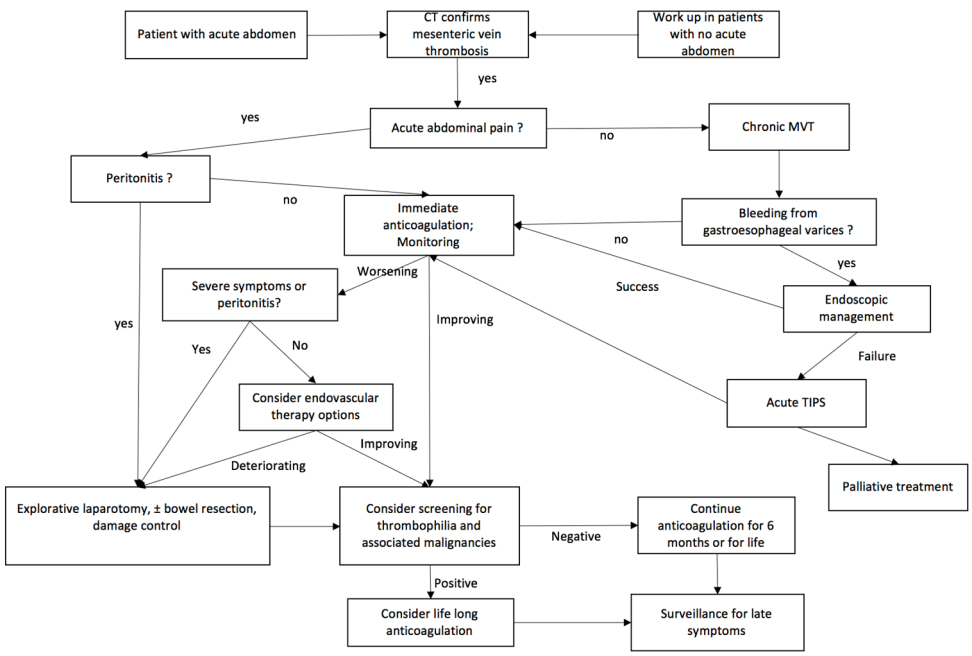

Figure 8. Extented management algorithm of MVT

CT: Computed tomography. MVT: Mesenteric venous thrombosis. TIPS: Transjugular intrahepatic portosystemic shunt

Chronic MVT

This thesis deals with acute MVT. The distinction between acute and chronic MVT is, however, not always clear cut. In addition, a substantial proportion of patients with MVT will develop CT features of chronic MVT such a cavernoma (cavernous transformation of the portal vein) and presence of numerous collateral veins around a thrombosed portomesenteric vein system after anticoagulation therapy[220], whereas a minor, but not insignificant, proportion of patients will develop clinical features of portal hypertension and bleeding from oesophageal or gastric varices at the time of presentation[190] or later. It is therefore justified to cover aspects of chronic MVT as outlined in the extended management algorithm (Figure 8).

In case of acute variceal haemorrhage, placement of a balloon tamponade device before, or after failed, endoscopic therapy may be used as a bridge to more definitive therapy[225]. Endoscopic therapy is used to arrest bleeding varices as well as to prevent early re-bleeding. The combination of vasoconstrictor and endoscopic therapy is superior to vasoconstrictor or endoscopic therapy alone for control of acute oesophageal variceal haemorrhage[226].

TIPS creation is a well-established therapy for refractory variceal bleeding. Experience and technical improvements including covered stents have led to improved TIPS outcomes that have encouraged an expanded application such as in portomesenteric venous thrombosis[227]. Emergency TIPS should be considered early to decompress the portal venous hypertension in patients with refractory variceal bleeding once endoscopic sclerotherapy and medical treatment fail, before the clinical condition worsens[228].

Late small bowel stricture

A percentage of patients with MVT will develop a late small bowel stricture. The reported frequencies were 3.0%[188], 5.6%[195] and 9.4%[194] in modern series. These strictures develop as a consequence of the healing process in parallel to the ischaemic insult ending up with fibrosis of the small bowel wall. This fibrosis may be so severe that it completely or almost completely narrows the small bowel lumen resulting in ileus. This condition requires an operation to relief the ileus. Two patients in paper I had to be operated for small bowel stricture after three and four months, respectively. As outlined in the management algorithm (Figure 8), responsible physicians need to be aware of this late bowel complication.

Short bowel syndrome

Apparently, a high percentage of patients will suffer from small bowel syndrome. The reported frequencies were 5.9%[189], 25%[194], 31%[186] and 40%[191] in modern series. These percentages appear to be similar to the historically high rate, 23%[122], of short bowel syndrome, which was thought to be attributed to unnecessarily long bowel resections or failure to recognize the advantage of anticoagulation therapy. Only one patient suffered from a permanent short bowel syndrome after creation of an ileostomy after a small bowel resection of only 0.05 m due to a stricture in paper I. This patient died after 1.5 months after this operation due to multiple comorbidities and short bowel syndrome as a contributory cause of death. Two other patients had transient short bowel syndrome after creation of ileostomies, which resolved after take down and re-anastomosis of bowel ends after 13 and 19 months, respectively. Both had nutritional parenteral support through a subcutaneous venous port (Port-a-Cath), which resulted in further complications with infection of their central venous catheters including septicaemia. These three patients illustrate that the occurrence of short bowel syndrome increases morbidity and mortality and should, if possible, be avoided.

Strengths and limitations of the studies

The main strengths of the studies included in this thesis were the relatively large number of patients and the included autopsy data in paper I. Since thrombophilia profiles may vary greatly in different populations (Table 11), the fact that the compared cohorts in the case-control study (paper IV) are from the same population constitutes an important strength of the study. The studies in this thesis had some limitations. One main limitation is attributed to the retrospective design of data collection (paper I-IV) with missing data. Frequency of former or current smokers were retrieved from patient records, but not reported in paper I, due to difficulties to obtain reliable information. The reported lower frequency of smoking among patients with MVT compared to the prospectively collected data on patients with systemic VTE in paper IV, should therefore be interpreted very cautiously.

The studies spans over almost two decades with potential changes on thrombosis prophylaxis, medication and smoking cessation, which might affect the incidence and mortality of MVT. This confounding factor, time period, has to some extent been accounted for in paper I, where this factor was included in the multi-variable analysis together with other factors associated with 30-day mortality in the uni-variable analysis

The diagnosis of MVT is rare and extremely difficult to establish clinically without CT, and a prospective study is almost impossible to design. Hence, MVT studies will either by necessity be retrospective, with all the inherent limitations of this study design, or be prospective after diagnosis at CT. A prospective single-centre study will, inevitably take too many years to complete and few investigators are prepared to undertake such a mission.

The series are relatively small in a general perspective, but rather large in comparison with other series (Table 5). The small sample sizes in each anticoagulation therapy group makes group comparison prone to type 2 statistical error. A high-quality evaluation of differences in outcomes between patients treated with DOACs and VKA was therefore not possible (paper II). Follow up CT was performed in less than 70% of patients, mainly attributable to the absence of clear treatment recommendations for MVT patients (paper III). Furthermore, CT protocols at diagnosis and follow-up were often different, due to the wide diversity of questions asked in the referral letter for initial CT. Some initial CT-examinations were performed with oral contrast media, which was never used at the follow-up CT evaluating the extent of portomesenteric venous thrombosis. Moreover, the changes in thrombotic status were assessed by a semi-quantitative ordinal scale between CT-examinations. With a prospective study design, a more modern quantitative evaluation using computer software for automatical or semi-automatical measurements of differences in thrombus volume might be possible.

In paper IV, only factor V Leiden mutation and prothrombin mutation was documented for systemic VTE patients in MATS, whereas a full thrombophilia panel with eight tests including JAK-2 mutation also was available for 74% in the MVT cohort. It would have been very interesting to evaluate differences in prevalence of JAK2 mutation and clinical consequences in JAK2 mutation positivity between these two groups, considering the relative high incidence of myeloproliferative neoplasm in the MVT groups.

Conclusion

- Short-term prognosis in patients with MVT seems to have improved. Contemporary data show that monotherapy with immediate anticoagulation is an effective first-line therapy in patients with MVT
- DOACs and VKA anticoagulation therapy in patients with MVT was clinically and radiologically effective. Bleeding complications during treatment was a concern in both groups, whereas recurrent VTE was not.
- Abnormal intestinal CT-findings secondary to MVT are related to excess risk of bowel resection due to intestinal infarction. Responsible physicians should therefore scrutinize initial CT images together with the radiologist to better tailor clinical surveillance.
- Patients with MVT have different risk factor profiles than those with systemic VTE; higher prevalence of cancer and lower prevalence of factor V Leiden mutation. Intra-abdominal cancer should be excluded in MVT patients, and the high prevalence of factor V Leiden mutation without cancer in both groups suggests that screening for thrombophilia in patients without cancer should be considered in this population.

Future perspectives

There are a number of randomized controlled trials that are warranted in MVT. These RCTs need to be multi-centre due to the rarity of disease. From an ethical point of view, it would be difficult to randomize between surgery and medical therapy when diagnosed. However, a contemporary trial investigating best medical treatment would be appropriate, to randomize between LMWH followed by warfarin versus LMWH followed by DOACs. Endpoints would be bowel resection, survival, quality of life and major bleeding. A cost-effectiveness analysis should follow. On the other hand, it is notably difficult to recruit a high proportion of randomized patients in clinical trials in surgery among those eligible[229], and low rate of included patients in RCTs will not reflect real life setting. Therefore, data from national and international[178] registries will continue to be very important for research purposes.

Non-leg and non-lung VTE or VTE at unusual sites such as MVT represent special conditions. Several aspects of MVT need to be considered when initiating medical therapy. First, MVT is associated with a unique spectrum of several risk factors. Secondly, and very important, MVT is associated with intestinal ischaemia and the ischaemia starts from the mucosa side first, which means that there should be an increased susceptibility for anticoagulation induced gastrointestinal bleeding. Long-term sequalae's due to portal hypertension has not been studied in depth in this thesis, but presence of oesophageal varices possesses a special high-risk for major bleeding, which needs to be considered in patients with MVT. The latest 2016 American College of Chest Physicians treatment guidelines for VTE has identified that determination of optimal anticoagulant management for patients with MVT is one key research priority[140, 230].

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Paper I

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ORIGINAL SCIENTIFIC REPORT

Improved Prognosis and Low Failure Rate with Anticoagulation as First-Line Therapy in Mesenteric Venous Thrombosis

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Abstract

Background Monotherapy with anticoagulation has been considered as first-line therapy in patients with mesenteric venous thrombosis (MVT). The aim of this study was to evaluate outcome, prognostic factors, and failure rate of anticoagulation as monotherapy, and to identify when bowel resection was needed.

Methods Retrospective study of consecutive patients with MVT diagnosed between 2000 and 2015.

Results The overall incidence rate of MVT was 1.3/100,000 person-years. Among 120 patients, seven died due to autopsy-verified MVT without bowel resection and 15 underwent immediate bowel resection without prior anticoagulation therapy. The remaining 98 patients received anticoagulation monotherapy, whereof 83 (85%) were treated successfully. Fifteen patients failed on anticoagulation monotherapy, of whom seven underwent bowel resection and eight endovascular therapy. Endovascular therapy was followed by bowel resection in three patients. Two late bowel resections were performed due to intestinal stricture. The 30-day mortality rate was 19.0% in the former (2000–2007) and 3.2% in the latter (2008–2015) part of the study period ($p = 0.006$). Age ≥75 years (OR 12.4, 95% CI [2.5–60.3]), management during the former as opposed to the latter time period (OR 8.4, 95% CI [1.3–54.7]), and renal insufficiency at admission (OR 8.0, 95% CI [1.2–51.6]) were independently associated with increased mortality in multivariable analysis.

Conclusions Short-term prognosis in patients with MVT has improved. Contemporary data show that monotherapy with anticoagulation is an effective first choice in MVT patients.

Background

Within the spectrum of patients presenting with acute abdominal pain, it is difficult to delineate those with mesenteric venous thrombosis (MVT). MVT is a rare but life-threatening condition which without treatment can develop into bowel ischemia, bowel gangrene, peritonitis, and death [1]. Main causes of MVT are coagulation disorders, abdominal inflammatory conditions, malignancies, and liver diseases [2]. Currently available investigations fail to identify a causal factor in about 20% of patients [3, 4]. Improved diagnostic workup with computed tomography (CT) may possibly lead to increased detection rates and earlier diagnosis of MVT [3, 4]. Immediate

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anticoagulation therapy after diagnosis has been proposed as the first-line treatment option [5].

To prospective study, MVT is challenging due to the low incidence of the condition, and large cohort studies would provide a valuable insight into the optimal management. This retrospective study was designed to evaluate prognostic factors and trends in prognosis over time in a large cohort of patients with MVT. Secondary aims were to evaluate the failure rate with anticoagulation as monotherapy, to identify when failures occurred, and when bowel resection was needed.

Methods

Identification of all patients with MVT treated surgically or non-surgically in Malmö University Hospital between 2000 and 2015 based on the International Statistical Classification of Diseases and Related Health Problems (ICD), tenth edition, codes I81 (portal vein thrombosis [PVT] or MVT) and K55 (mesenteric ischemia), and *AuriculA* [6] (national quality register for anticoagulant treatment). Patient records and all CT images in patients with PVT or MVT as well as unclear cases of mesenteric ischemia were scrutinized. Patients with thrombosis in the superior mesenteric vein with or without anatomical involvement of portal or splenic veins were included in the present study. Patients diagnosed 2000–2006 have been reported upon previously [7]. The patient series was pragmatically divided at the study protocol stage into two periods, the former (2000–2007) and the latter (2008–2015), for analysis of changes in patient characteristics, risk factor profile, mode of diagnosis, and outcome. In emergencies, single-detector row CT was performed between 2000 and 2003, and multidetector row CT from 2004 and onwards [8]. Mortality data were obtained from the Swedish Population Registry. Median follow-up after diagnosis for patients with MVT was 62 (interquartile range [IQR] 24–128) months. End of follow-up was September 29, 2017. The study was approved by the Research Ethical Review Board in Lund (Dnr 2015/143).

Treatment strategy

After diagnosis of MVT with CT, the mainstay of treatment was conservative with immediate full anticoagulation with either intravenous heparin infusion or subcutaneous LMWH, full bowel rest, total parenteral nutrition, and analgesia. Patients admitted with peritonitis or rapid progression toward peritonitis underwent laparotomy and bowel resection. Patients not responding to anticoagulation underwent endovascular measures with or without local thrombolysis, and those not responding to this therapy was subjected to laparotomy. Clearly necrotic and demarcated bowels were resected and anastomosed. Bowels with unclear viability were usually evaluated at a second-look laparotomy, and bowel resections were followed by anastomoses or diverting stomas. Patients with identified transient risk factors were usually treated with oral anticoagulation for 6 months, whereas those with permanent risk factors or unidentified risk factors were prescribed lifelong anticoagulation. Up to 2014, the vitamin K antagonist (warfarin) was the only oral anticoagulation therapy, whereas direct-acting oral anticoagulants were gradually introduced as a treatment option from 2012.

Definitions

Primary MVT is defined as an idiopathic condition, whereas secondary MVT is defined by an identified etiologic factor. Patients with abdominal pain of less than 4-week duration were classified as having acute MVT. Those with symptoms for more than 4 weeks, but without bowel infarction, and those with asymptomatic MVT diagnosed incidentally on abdominal imaging as clinically nonsignificant findings, were defined as chronic MVT. The term thrombophilia was used as a common denominator for factors that may promote MVT, such as coagulation disorders, malignancy, previous or concomitant venous thromboembolism, and use of oral anticonceptives or estrogen substitution. The presence of inherited thrombophilia such as Factor V Leiden mutation and acquired thrombophilia as JAK2 V617F (janus-activated kinase gain of function substitute of valine to phenylalanine at position 617) mutation was registered. Previous cardiovascular disease was defined as previous myocardial infarction, angina pectoris, history of coronary artery bypass grafting, percutaneous coronary intervention, stroke, or transient ischemic attack. Renal insufficiency was defined as a serum creatinine level higher than 105 μmol/l (1.2 mg/dl) in men and 90 μmol/l (1.0 mg/dl) in women.

Statistical analysis

Data management and statistical analysis were performed using SPSS for Windows (SPSS, version 23.0, Chicago, Illinois, USA). Age and gender-specific total incidence rates were based on the number of patients diagnosed with MVT residing in Malmö, and expressed as number of cases per 100,000 person-years. Population data, overall and gender-specific, for Malmö in 2008 obtained from Statistics Sweden were used for calculation of incidence. Differences in proportions were evaluated using χ^2 or Fisher's exact test. Age was expressed as median (range). Variables associated with 30-day mortality ($p < 0.1$) were further

tested in a multivariable binary logistic regression model and expressed in terms of odds ratios (OR) with 95% confidence interval (CI). $p < 0.05$ was considered significant.

Results

Incidence

One hundred and twenty patients, 67 men and 53 women, were diagnosed with MVT from 2000 to 2015. The overall incidence rate of MVT in Malmö was estimated to 1.3/100,000 person-years (1.4/100,000 person-years in men and 1.2/100,000 person-years in women).

Patient characteristics

Median age at admission was 58 (range 19–95) years. Median body mass index (BMI) was 27.5 (IQR 25.2–30.0; $n = 50$) in men and 25.8 (IQR 23.7–33.4; $n = 38$) in women. Acute MVT was found in 115 (96%) patients, and primary and secondary MVT in 26 (22%) and 94 (78%) patients, respectively. Risk factors such as any direct injury to the vein due to disease or surgery were found in 35(29%) patients, local or systemic venous congestion in 19 (16%), and thrombophilia in 72(60%). Twenty (17%) patients had abdominal malignancies. History of previous venous thromboembolism was documented in 24 (20%) patients. Among 89 tested, 39 (44%) patients had positive tests for inherited or acquired coagulation disorder. The most common thrombophilia was activated protein C resistance (Factor V Leiden mutation), occurring in 22 (18%) patients (19 in heterozygous and three in homozygous genotype). In nine patients with myeloproliferative disease, eight (89%) were JAK-2 V617 mutation positive.

Patients diagnosed in the former period (2000–2007) were older ($p = 0.013$) and had higher proportions of abdominal malignancy ($p = 0.009$) and activated protein C resistance ($p = 0.002$) compared to those diagnosed in the latter period (2008–2015) (Table 1).

Mode of establishing diagnosis

During the latter time period, all patients were diagnosed by radiological imaging, in 97% of cases by CT with intravenous contrast enhancement. During this period, CT was more frequently used for MVT diagnosis compared to the former time period ($p < 0.001$) (Table 2). During the former time period, there were six autopsy-verified deaths

Table 1 Patient characteristics and risk factors for mesenteric venous thrombosis in the former (2000–2007) and the latter (2008–2015) parts of the study

Factors	Former period ($n = 58$)	Latter period ($n = 62$)	Univariable analysis (p value)
Median age (years; IQR)	64 (50–73)	54 (47–65)	0.013
Women (%)	27 (47)	42 (42)	0.61
Acute pancreatitis (%)	10 (17)	7 (11)	0.35
Recent abdominal surgery	5 (9)	3 (5)	0.35
Thrombophilia	40 (69)	32 (52)	0.053
History of previous venous thromboembolism	12 (21)	12 (19)	0.86
Abdominal malignancy	15 (26)	5 (8)	0.009
Positive test for inherited or acquired coagulation disorder	20/36 (56)	19/53 (36)	0.066
Activated protein C resistance (Factor V Leiden mutation)	15/36 (42)	7/53 (13)	0.002

Table 2 Mode of establishing diagnosis in the former (2000–2007) and the latter (2008–2015) parts of the study

Factors	Former period ($n = 58$)	Latter period ($n = 62$)	Univariable analysis (p value)
Autopsy frequency (%)	25	12	<0.0001
Primary mode of diagnosis			
Autopsy	6 (10.3)	0 (0.0)	
Computed tomography (with intravenous contrast)	41 (70.7)	60 (96.8)	
Ultrasound	0 (0.0)	2 (3.2)	
Operation	11 (19.0)	0 (0.0)	<0.001
Bowel resection rate (excluding autopsy cases)	14/52 (26.9)	10 (16.1)	0.16

in patients not undergoing bowel resection, of whom two died outside of hospital.

Bowel resection and endovascular therapy

Bowel resection rates did not differ between the two periods (Table 2). Among the 98 patients receiving anticoagulation treatment, 83 (85%) were successfully treated with heparin as monotherapy without need for surgical intervention (Fig. 1). Throughout the study period, fifteen patients underwent explorative laparotomy and bowel resection without preoperative diagnosis, and another 15 patients underwent bowel resection (Fig. 2) or endovascular therapy due to failure of anticoagulation as monotherapy. Endovascular therapy was performed in eight patients, out of whom three underwent bowel resection. The two late bowel resections due to intestinal stricture were performed after 3 and 5 months, respectively, after index admission. The endovascular procedures performed were thrombolysis via the superior mesenteric artery ($n = 4$), transjugular intrahepatic portal shunt (TIPS) with stenting ($n = 2$), transjugular mechanical thrombectomy (AngioJet® device [MEDRAD, Warrendale, Pennsylvania, USA]) and thrombolysis ($n = 1$), transhepatic stenting ($n = 1$), transhepatic mechanical thrombectomy (AngioJet®), and Fogarty catheter balloon thrombectomy ($n = 1$). Another two TIPS procedures failed. Local thrombolysis via the superior mesenteric artery was not considered first option, but was used in combination with other endovascular therapies in three patients. In the fourth patient, TIPS was not considered an option due to the advanced extent of portomesenteric venous thrombosis, and 56 mg recombinant tissue plasminogen activator (rtPA) was continuously infused into the superior mesenteric artery over 60 h with success and without need of bowel resection. The sum of procedures performed exceeds eight, reflecting that a combination of techniques was often used. The median dose of thrombolytic agent, alteplase (Actilyse®; Boehringer, Ingelheim, Germany), administered locally in the mesenteric circulation, was 30 mg (range 14–56) in the four treated patients. One patient underwent a failed TIPS combined with thrombolysis via the superior mesenteric artery, complicated by perihepatic hematoma requiring explorative laparotomy for control of bleeding. Bowel resection due to late intestinal stricture was performed in two patients (Fig. 3). Lifelong anticoagulation therapy after successful non-operative management was given to 49% (17/35) of patients in the former period and 71% (34/48) in the latter ($p = 0.040$).

Factors associated with 30-day mortality

Overall 30-day mortality rate was 10.8, 19.0% in the former time period versus 3.2% in the latter time period ($p = 0.006$). The 30-day mortality after surgery (bowel resection and/or endovascular therapy) was 12.5% (2/16) in the former period versus 7.1% (1/14) in the latter ($p = 1.0$). Age ≥75 years, management during the former as opposed to the later time period, pancreatic malignancy, and renal insufficiency at admission were all associated with increased 30-day mortality in univariable analysis. Age ≥75 years (OR 12.4, 95% CI [2.5–60.3]), management during the former time period as opposed to the latter period (OR 8.4, 95% CI [1.3–54.7]), and renal

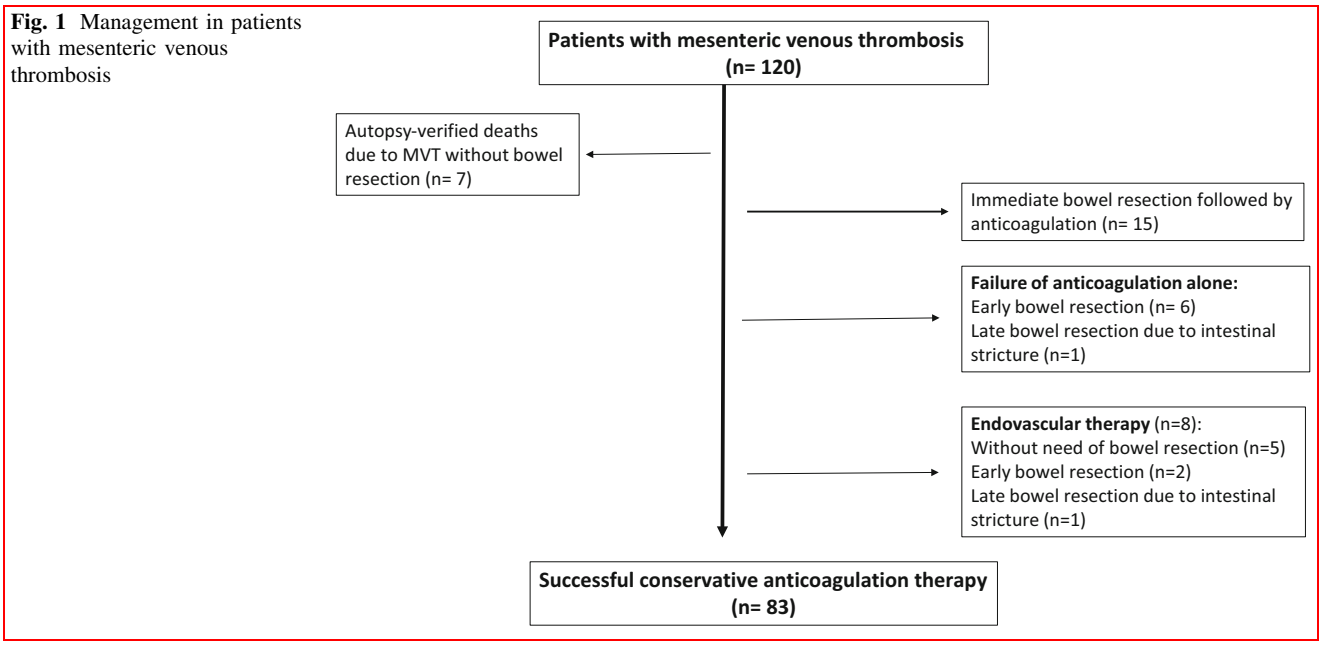


Fig. 1 Management in patients with mesenteric venous thrombosis

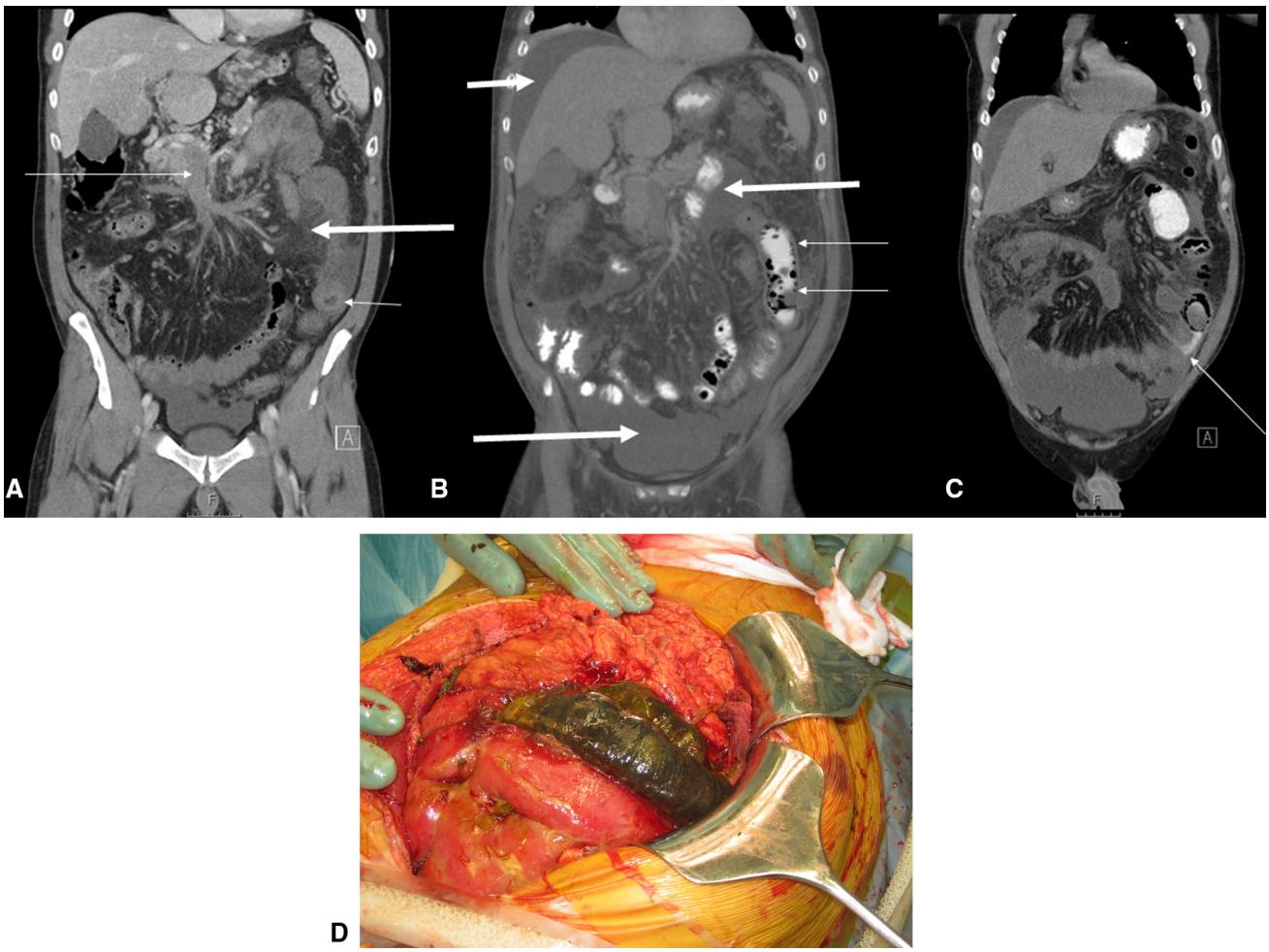
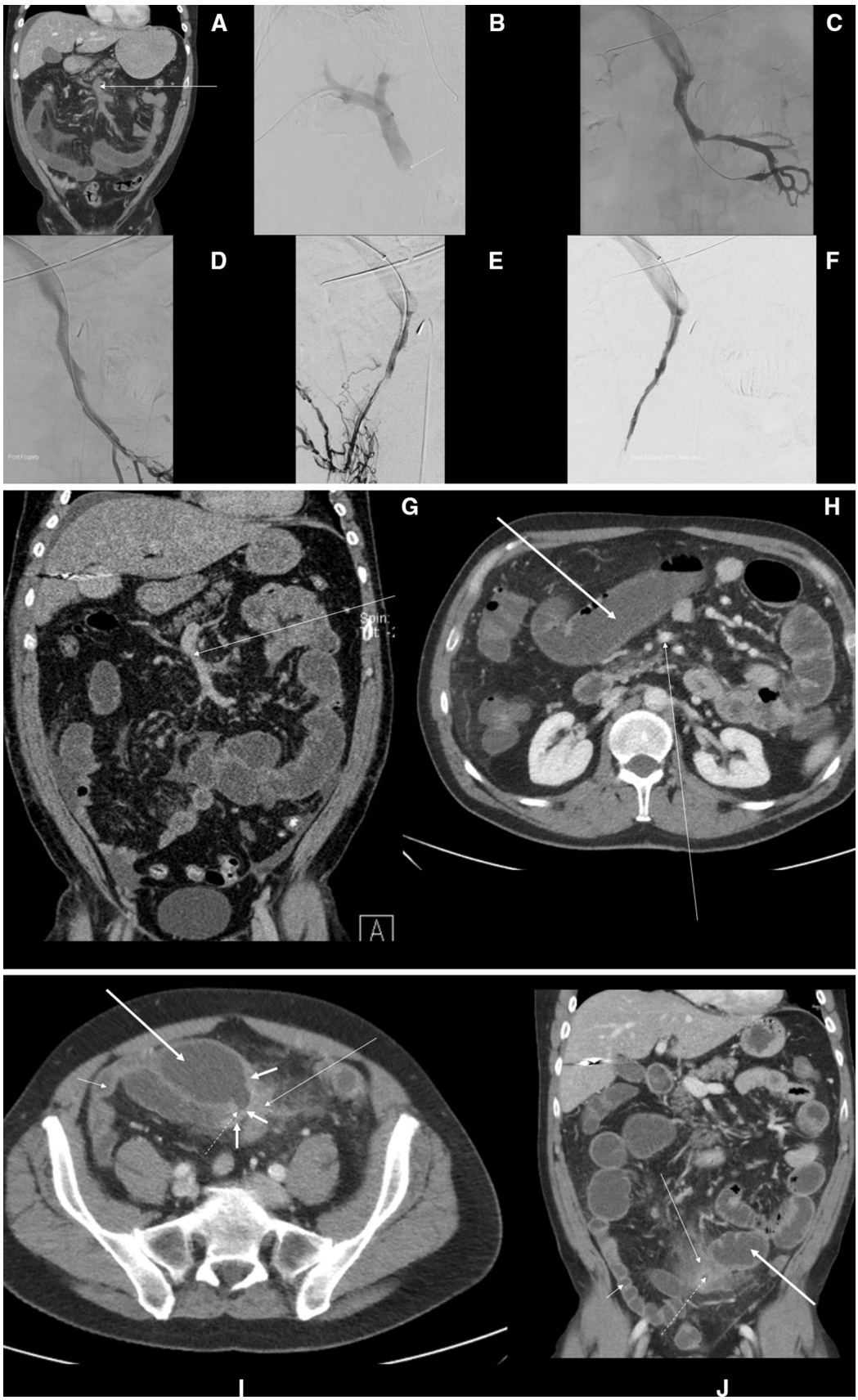


Fig. 2 Failure of anticoagulation therapy. A 50-year-old male patient with a history of ulcerative proctitis who was admitted with 3 days of abdominal pain and C-reactive protein (CRP) of 161 mg/L. Diagnosis of mesenteric venous thrombosis (Fig. 2a, long thin arrow) was achieved after computed tomography (CT) with intravenous contrast enhancement and imaging in the portal/parenchymal phase. Note thickening of the jejunum (short arrow) and the mesenteric edema (long thick arrow). The patient had localized signs of peritonitis to the left in the abdomen and absent bowel sounds at the time of diagnosis. Full-dose heparin infusion was started, whereafter the patient improved temporarily but later deteriorated. A new CT (Fig. 2b) after 13 days of heparin therapy showed progression of ascites (thick arrows) and occurrence of gas bubbles (thin arrows) in the jejunal wall. Continued conservative therapy resulted in further clinical deterioration, and after 20 days of heparin therapy a CT (Fig. 2c) showed leakage of perorally administered contrast outside of the bowels (arrow). Explorative laparotomy showed a well-demarcated 1-meter-long transmural green necrosis of the jejunum (Fig. 2d) with a large perforation. The patient recovered after bowel resection, open abdomen therapy, and reanastomosis of the stapled bowel ends. Testing for thrombophilia showed that the patient was positive for JAK2 V617F mutation and a bone marrow biopsy diagnosed a polycythemia vera. The patient is scheduled for lifelong vitamin K antagonist therapy, and cytoreductive therapy with interferon, and is also undergoing regular venesection

insufficiency at admission (OR 8.0, 95% CI [1.2–51.6]) were independently associated with increased mortality in the multivariable analysis (Table 3).

Discussion

The adjusted results of the present population-based study on 120 patients showed that prognosis for patients with MVT improved during the study period. The increased diagnostic and therapeutic activity, including possibility to perform endovascular therapy, should be related to the current low 30-day mortality rate of 3.2%. Interestingly, the proportions of patients with activated protein C resistance [9], abdominal malignancy [10], and age were lower in the latter period, perhaps reflecting an increased activity in preventing venous thromboembolism including prophylactic anticoagulation therapy in high-risk patients. Since randomized trials comparing safety and efficacy of various treatments most likely will be impossible to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◀**Fig. 3** Endovascular therapy of mesenteric venous thrombosis after failure of anticoagulation treatment. A 53-year-old man with history of 3 months of anticoagulation treatment for deep venous thrombosis in the lower leg and Factor V Leiden mutation in the homozygous form. The patient fell ill with acute abdominal pain, and CT diagnosed an extensive MVT (**a**, arrow). He underwent transhepatic puncture and access to the portal vein. Venography showed total occlusion of the superior mesenteric vein (SMV) (**b**, arrow). Mechanical thrombectomy with an AngioJet® device (MEDRAD, Warrendale, Pennsylvania, USA) and endovascular Fogarty catheter thrombectomy were carried out, followed by thrombolysis with recombinant tissue plasminogen activator (rtPA) into the branches of the SMV and superior mesenteric artery. After a total dose of 25 mg rtPA over 25 h, improved flow in the SMV was noted. Endovascular rethrombectomy with a Fogarty catheter was performed owing to residual clots in the SMV branches (**c**–**f**). CT venography before discharge showed no signs of thrombus within the SMV and the proximal parts of the major venous branches (**g**, arrow). The patient did not recover fully and was readmitted after 3 months with symptoms of bowel obstruction. CT venography showed fully patent SMV (**h**, arrow), but severe localized fibrosis in the small bowel wall (**i**, thick short arrows) and adjacent mesenteric fat (**i**, **j**, thin long arrow) causing a bowel stricture. Note the narrow bowel lumen at the stricture (**i**, **j**, interrupted line). There is a prestenotic bowel dilatation (**h**, **i**, **j**, thick long arrow) and a poststenotic normalized bowel (**i**, **j**, thin short arrow). The patient underwent immediate bowel resection of the stricture, recovered and is on lifelong vitamin K antagonist medication

conduct in these patients, evidence will rely upon prospective cohort studies. International, multicenter collaboration is necessary, as exemplified by the prospective study promoted by the International Society on Thrombosis and Hemostasis (ISTH), in which affiliated centers worldwide were invited to participate [11]. In similar future studies, in which a larger proportion of patients will likely receive endovascular therapy [12], it would be preferable to not only report on therapy-related major bleeding complications, thrombotic events, bowel necrosis, and mortality. High-quality data on patency rates of the portomesenteric venous system, and patient-reported outcomes such as quality of life and pain scores before and after conservative and endovascular therapy, would also be helpful to supply physicians and patients with important data to support decision making.

The overall incidence rate of MVT in Malmö was estimated to 1.3 per 100,000 person-years, a figure in the lower range of incidence reported in the 1970s [1]. This might partly be related to the markedly reduced autopsy frequency [13], from 85% [14] to 12% in the latter time period of the present study. On the other hand, important improvements in diagnostics and treatment of hypercoagulable states have occurred during this period [15] probably resulting in a decrease in venous thromboembolism. However, since MVT is very rarely suspected already in the emergency setting [16], or sometimes confused with arterial mesenteric ischemia at laparotomy, and with the contemporary low autopsy frequency in the population the contemporary true incidence is hard to estimate.

The decrease in 30-day mortality from 19.0% during the former half of the study period to 3.2% during the latter has several explanations. Earlier diagnosis by the use of

Table 3 Factors associated with 30-day mortality in 120 patients with mesenteric venous thrombosis

Factors	Number of patients	30-day mortality (%)	Univariable analysis (*p* value)	Multivariable analysis	
				OR (95% CI)	*p* value
All patients	120	10.8	–		
≥75 years	17	47.1	<0.001[a]	12.4 (2.5–60.3)	0.002
Female gender	53	17.0	0.054[a]	2.4 (0.5–11.7)	0.29
Period (2000–2007 vs. 2008–2015)	58 vs. 62	19.0 vs. 3.2	0.006[a]	8.4 (1.3–54.7)	0.026
Malignancy	23	17.4	0.26	–	
Abdominal malignancy	20	20.0	0.15	–	
Pancreatic malignancy	7	42.9	0.027[a]	5.1 (0.6–43.6)	0.13
Metastatic malignancy	14	28.6	0.045	–	
History of previous venous thromboembolism	24	12.5	0.77	–	
Activated protein C resistance	22/89	0.0	1.0	–	
Pancreatitis	17	0.0	0.21	–	
Liver cirrhosis	6	33.3	0.13	–	
Inflammatory bowel disease	7	0.0	1.0	–	
Renal insufficiency at admission	20	25	0.035[a]	8.0 (1.2–51.6)	0.029
Bowel resection	24	8.3	1.0	–	

[a]Entered into a multivariable logistic regression model

available high-resolution, high-speed CT scanners around the clock in patients with unexplained abdominal pain would probably help to avoid development of bowel gangrene and peritonitis and the poor prognosis in these cases. CT with intravenous contrast and imaging in the portal phase is clearly the most accurate method of diagnosing the condition [17]. Corroborating other reports [18, 19], the present study showed that a non-operative approach with immediate anticoagulation therapy with unfractionated or low molecular weight heparin at the time of diagnosis was an effective treatment for acute MVT. Explorative laparotomy and bowel resection due to bowel gangrene and peritonitis will always be a way to rescue these patients in cases of rapid development of intestinal infarction, overlooked diagnosis, or late presentation as shown in Fig. 1. The clinician should also remember that the possibility of intestinal infarction is not ruled out until full resolution of pain occurs [2]. The study identified failure of anticoagulation therapy in a small proportion of patients, occurring mainly after days to weeks of medical therapy (Fig. 1).

Endovascular therapy was selectively performed in a few patients and proved to be successful in the majority of these, in whom bowel resection could be avoided. Two patients were operated after 3 and 5 months, respectively, due to late development of severe intestinal stricture with ileus (Fig. 3). CT features such as extensive thrombosis and ascites seem to be predictive factors of poor recanalization on anticoagulant therapy [20]. Clinicians should be aware of the severity of thrombotic and intestinal ischemic lesions on the CT images to be able to proceed with more aggressive approaches, either with endovascular therapy or laparotomy with bowel resection when needed. The 30-day mortality of 3.2% in the present study supports a conservative anticoagulation-first treatment approach (Fig. 4). Endovascular therapy may have a role in patients with extensive portomesenteric thrombosis at diagnosis, but this has to be proven in a large multicenter randomized trial.

The limitations of the present study include mainly its retrospective design. Information on bleeding complications due to anticoagulation therapy was not possible to accurately retrieve. The sample sizes of the patients in the two periods were probably not sufficiently large to be able to show a difference in bowel resection rates. Assuming that the six patients primarily diagnosed at autopsy in the former period would have undergone bowel resection if timely diagnosed, the bowel resection rate would have been significantly higher in the former compared to the latter period (20/58 vs. 10/62, respectively, $p = 0.02$). The low autopsy frequency during the latter time period might have led to an underestimation of the contemporary 30-day mortality in comparison with the former time period when autopsies were more frequently conducted. Nevertheless, the comparably large sample size in our study enabled us to evaluate our study results with multivariable testing.

In conclusion, short-term prognosis in patients with MVT seems to have improved. Contemporary data show that immediate anticoagulation is an effective first-line therapy in patients with MVT.

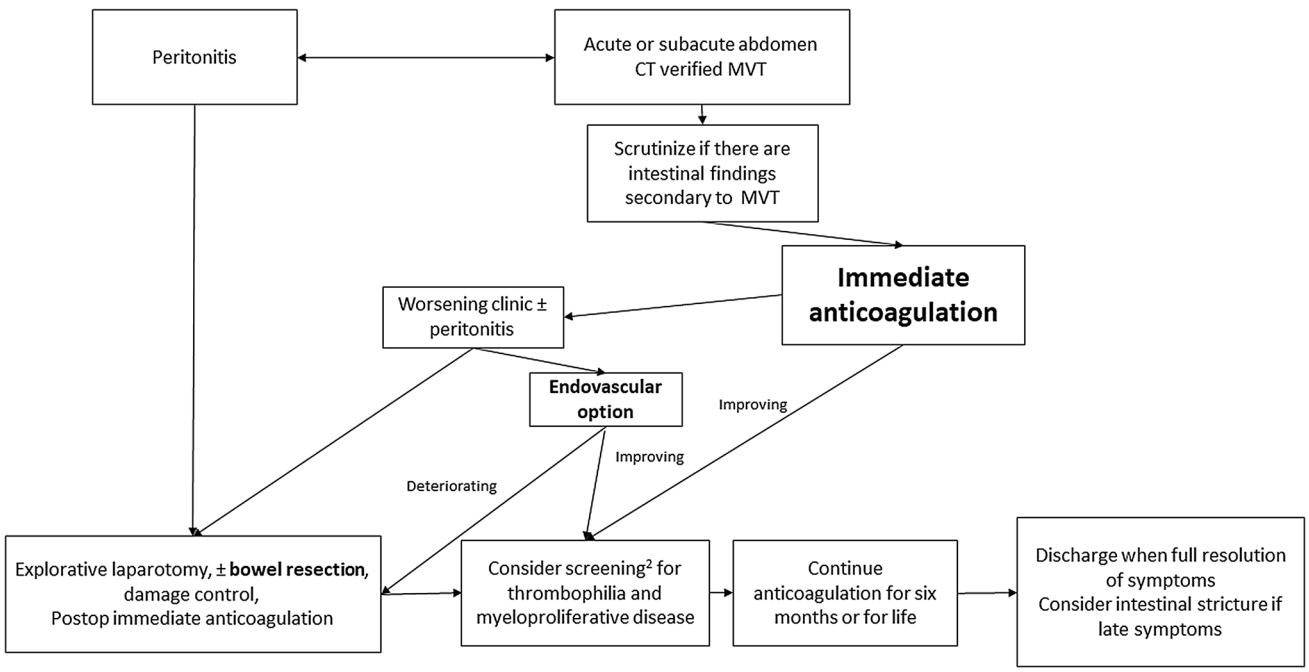

Fig. 4 Proposed management algorithm in patients with acute MVT

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Compliance with ethical standards

Conflict of interest The authors declared that they have no conflict of interest.

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Paper II

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Evaluation of direct oral anticoagulants and vitamin K antagonists in mesenteric venous thrombosis

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Abstract

Background/aim: Mesenteric venous thrombosis is a rare lethal disease. The main aim of the present study was to evaluate clinical efficacy and safety of direct oral anticoagulants and vitamin K antagonists in mesenteric venous thrombosis patients.

Methods: Retrospective study of 102 mesenteric venous thrombosis patients treated between 2004 and 2017 at a center with a conservative medical first approach. Median clinical follow-up was 4 years.

Results: Computed tomography showed successful recanalization of thrombosis in 71% of patients on vitamin K antagonists and 69% of patients on direct oral anticoagulants ($p = 0.88$). Overall major and esophageal variceal bleeding rate was 14.7% and 2.9%, respectively. No difference in major bleeding ($p = 0.54$) was found between vitamin K antagonists and direct oral anticoagulants. No mesenteric venous thrombosis recurrence occurred during follow-up, and one venous thromboembolism occurred after cessation of anticoagulation.

Conclusion: Anticoagulation with direct oral anticoagulants and vitamin K antagonists was efficient in patients with mesenteric venous thrombosis. Bleeding complications was a concern during treatment in both groups.

Keywords

Mesenteric venous thrombosis, direct oral anticoagulants, anticoagulation, efficacy, safety, recanalization, computed tomography

Introduction

Mesenteric venous thrombosis (MVT) remains an important cause of intestinal ischemia,[1] though less common than mesenteric arterial thromboembolism. Prothrombotic inherited and acquired factors, and local factors such as malignancies, liver cirrhosis, and inflammatory conditions, are important conditions that predispose for MVT.[2] MVT is most often diagnosed by contrast-enhanced computed tomography (CT) with imaging in the venous phase in patients with acute abdomen.[3] Initial conservative medical approach with anticoagulation therapy is advocated in patients without peritonitis.[4]

Immediate unfractionated heparin therapy intravenously has been proposed as first-line treatment option as its effect can be reversed immediately if an emergency operation is needed.[5] Patients with less severe disease may be given low molecular weight heparin (LMWH) for 1–2 weeks, usually followed by oral vitamin K antagonist (VKA) therapy. According to the European Society of Vascular Surgery (ESVS) guidelines,[1] anticoagulation is given for 6 months in the presence of an identifiable reversible risk factor, whereas patients with underlying thrombophilia or idiopathic MVT may be considered for lifelong anticoagulation since relapse of MVT is highly fatal. Lifelong anticoagulation with VKA with a targeted international normalized ratio (INR) of 2.0:3.0 is the standard of care in patients where long-term management is indicated.[6] Despite its effective pharmacological properties, VKA

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treatment is limited by factors such as a narrow therapeutic index, drug–drug interactions, food interactions, slow onset and offset of action, and the need for routine monitoring of the INR.[7] Thus, the shortcomings associated with VKA have spurred the search for oral anticoagulants with better pharmacokinetics. The novel direct oral anticoagulants (DOAC), that is, dabigatran, rivaroxaban, apixaban, and edoxaban are well-established as first-line treatment for pulmonary embolism (PE) and deep vein thrombosis (DVT)[8] but have, however, been scarcely studied in MVT.[9] The main aim of the present study was to assess the clinical efficacy, safety, and thrombus recanalization of DOAC and VKA therapy in MVT. On the basis of previous comparative studies in PE and DVT,[10–14] it was hypothesized that VKA therapy was associated with a higher major bleeding complication rate than DOAC in MVT.

Methods

Retrieval of patients with MVT

Ethical approval was obtained from the Regional Ethical Review Board in Lund (Dnr 2014/287). MVT patients treated surgically or conservatively at Skåne University Hospital between 1 January 2004 and 29 September 2017, were identified in hospital records and *AuriculA*[15] (Swedish quality registry for patients treated with anticoagulation), based on the International Statistical Classification of Diseases and Related Health Problems (ICD), tenth edition, codes I81 (portal vein thrombosis (PVT) or MVT) and K55 (mesenteric ischemia). All patient records and CT images in patients with PVT or MVT as well as unclear cases of mesenteric ischemia were scrutinized. Only patients with symptomatic thrombosis in the superior mesenteric vein with or without the anatomical involvement of portal or splenic vein were included in the present study. The median clinical follow-up time was 48 months (IQR 22–86).

Definitions

Patients with abdominal pain of less than 4 weeks duration were classified as having acute MVT. Those with symptoms for 4 weeks or more but without bowel infarction, and those with asymptomatic MVT diagnosed incidentally on abdominal imaging as a clinically nonsignificant finding were defined as chronic MVT. Extensive thrombosis was defined as having mesenteric (both central and peripheral), portal, and splenic vein thrombosis. The first 5 cm of the proximal superior mesenteric vein was defined as central. Small bowel dilatation was defined as $\geq$4 cm in bowel diameter. Patients initially treated with LMWH for some weeks, and later changed for VKA or DOAC were considered as treated with either of the respective oral anticoagulants. Major bleeding was defined according to the criteria of the International Society on Thrombosis and Haemostasis,[16] as a fatal and/or symptomatic bleeding in a critical area or organ, bleeding leading to a reduction of 2 g/dl or more in hemoglobin concentration, or necessitating transfusion of two or more blood units. Gastrointestinal bleeding included esophageal variceal bleeding.

Glomerular filtration rate (GFR) was calculated as a simplified variant of Modification of Diet in Renal Disease Study Group (MDRD).[17] All patients were white Caucasians, and advanced renal insufficiency was defined as GFR < 25 ml/min.

Renal insufficiency by serum creatinine alone was defined as a serum creatinine higher than 105 µmol/l (1.2 mg/dl) in men and 90 µmol/l (1.0 mg/dl) in women. The term ''thrombophilia'' was used as a common denominator for factors that might provoke MVT, such as cancer, coagulation disorders, previous or concomitant venous thromboembolism (VTE), oral contraceptive use, or estrogen substitution. Inherited thrombophilic factors were defined as factor V Leiden mutation, prothrombin gene mutation, or deficiencies of protein C, protein S, or antithrombin. Acquired thrombophilic factors were defined as JAK2 V617F (Janus-activated kinase gain of function substitute of valine to phenylalanine at position 617) mutation, lupus anticoagulant, or cardiolipin antibodies. Malignancy was defined as the presence of solid cancer or myeloproliferative disease. A transient risk factor was defined as either recent surgery within 6 weeks, abdominal trauma or inflammatory disease such as acute pancreatitis. Follow-up CT was defined as the last available CT of the abdomen with intravenous contrast and imaging in the parenchymal/venous phase. Successful recanalization was defined as partial or complete recanalization of the portomesenteric venous system at the follow-up CT after treatment.

Computed tomography

Multi-detector row CT (MDCT) was usually performed with 0.75 mm slice thickness (Siemens Sensation 16, Erlangen, Germany). Multiplanar reconstruction in axial, coronal, and sagittal planes was usually obtained with 5 mm thickness. Single-slice CT was usually performed with slice thickness of 3–5 mm. Patients were examined in the portomesenteric venous phase. Intravenous contrast medium was nonionic

contrast medium 300–320 mg I/ml with a total dose of 90 ml, flow rate of 3 ml/s, and delay of 70 s. The diagnostic and follow-up CT scan images of all patients were scrutinized and evaluated by an experienced radiologist (OE) aware of the diagnosis but blinded concerning which treatment the patient received. The main objective was to describe vascular and intestinal findings systematically in a predefined protocol.[18] The patency of the portomesenteric venous system at follow-up CT was categorized as progression, unchanged, partial regression, and complete regression of thrombosis.

Treatment strategy at the study center

After diagnosis of MVT with CT, the mainstay of treatment is conservative with immediate full anticoagulation with either intravenous heparin infusion or subcutaneous LMWH, full bowel rest, total parenteral nutrition, and analgesia. Patients admitted with peritonitis or rapidly progressing toward peritonitis undergo laparotomy and bowel resection. Patients not responding to anticoagulation may undergo endovascular treatment with or without local thrombolysis, and nonresponders are subjected to laparotomy. Clearly, necrotic and demarcated bowels are resected and anastomosed. Bowels with unclear viability may be evaluated at a second look laparotomy, and bowel resections may be followed by anastomoses or diverting stomas. Patients with identified transient risk factors are usually treated with oral anticoagulation for 6 months, whereas those with permanent risk factors or unidentified risk factors are prescribed lifelong anticoagulation. Patients with a malignancy were usually treated with LMWH. DOAC was introduced for treatment of MVT in 2015 at the study center and used at the discretion of the responsible physician. There was no evidence of noncompliance in patients with DOAC and time in therapeutic range (TTR) during warfarin treatment in our country is as high as 76.5%.[19] Median follow-up time in DOAC patients was 25 months.

Statistical methods

Data management and statistical analysis were performed using the SPSS for Windows program package (SPSS version 22.0, Chicago, IL) or GraphPad (GraphPad Software, Inc. La Jolla, CA). Distribution of variables was expressed with median value and interquartile range (IQR). Differences in proportions were evaluated using the chi-square or the Fisher's exact test. Quantitative differences between groups were assessed with the Mann–Whitney U test. The Spearman rank test was used for calculating correlations. A p-value < 0.05 was considered significant.

Results

Patient characteristics

During the 14-year period, 102 patients (61 men and 41 women) were diagnosed with MVT. Their median age was 58 years (IQR = 47–68). Men (56 (IQR = 47–64) years) were younger ($p = 0.009$) than women (65 (IQR = 50–72) years). MVT was defined as acute in 100 (98%) patients, and chronic in the remaining 2 (2%). The two patients with chronic MVT had diffuse abdominal pain for 1 month and unspecific intermittent symptoms for several months prior to diagnosis, respectively. Median body mass index (BMI) was 27.8 (IQR = 25.5–31.4) in men ($n = 49$) and 25.5 (IQR = 23.5–33.6) in women ($n = 34$). One (1.0%; 1/100) 95-year-old woman with advanced renal insufficiency received LMWH but died due to intestinal infarction after 1 day of anticoagulation therapy. Seventeen (17%) patients had previously been diagnosed with pancreatitis and 26 (26%) with malignancies. Among 85 patients tested for thrombophilia, 17 (20%) had the factor V Leiden mutation (Table 1), and 9 (9%) had the JAK-2 V617 mutation. In 10 patients with myeloproliferative disease, 9 (90%) were JAK-2 V617 mutation positive.

Anticoagulation therapy groups

Lifelong anticoagulation was initiated in 64 patients (63%). Fifty-six (55%) patients received VKA, 22 (22%) LMWH, and 22 (22%) DOAC. The DOAC prescribed were rivaroxaban ($n = 14$), apixaban ($n = 5$), and dabigatran ($n = 3$). Two patients received no medical therapy at all (Table 1): One patient suffered from concomitant severe bleeding from esophageal varices and died at the intensive care unit 12 days after admission. The second patient with Chron's disease had an MVT at CT, which was dismissed by an ultrasound examination 3 weeks later. CT-enterography was performed 2 months later, and there was no mention of suspicion of MVT in the referral letter and no statement at all regarding the portomesenteric system. The review of the CT images showed unchanged extent of thrombosis in the portomesenteric system. No anticoagulation treatment has been given. Patients with MVT and malignant disease were more often ($p = 0.034$) treated with LMWH than VKA. Frequencies of renal insufficiency were the same in DOAC- and VKA-treated patients ($p = 0.19$), and median GFR for

Table 1. Patient profile, thrombotic and bleeding complications in 102 patients with mesenteric venous thrombosis verified by computed tomography, and treated with anticoagulation during follow-up.

Variable	All patients (%)	LMWH (%)	VKA (%)	DOAC (%)	No medical treatment (%)
Number of patients	102	22	56	22	2
Median age (IQR); years	58 (47–68)	65 (56–76)	56 (46–65)	57.5 (47.5–68.3)	66.0 (61.8–78.5)
Female sex	41 (40.2)	11 (50.0)	21 (37.5)	7 (31.8)	2 (100)
Lifelong treatment initiated	64 (62.7)	4 (18.2)	41 (73.2)	19 (86.4)	0 (0)
Malignancy	26 (25.5)	10 (45.5)	12 (21.4)	4 (18.2)	0 (0)
Renal insufficiency	16/100 (16)	5 (22.7)	6/54 (11.1)	5/22 (22.7)	0 (0)
Acute pancreatitis	17 (16.7)	5 (22.7)	8 (14.3)	4 (18.2)	0 (0)
Liver cirrhosis	6 (5.9)	2 (9.1)	1 (1.8)	2 (9.1)	1 (50)
Factor V Leiden mutation	17/85 (20.0)	1/11 (9.1)	13/54 (24.1)	3/18 (16.7)	0 (0)
Extensive thrombosis[a] at diagnostic CT	43 (42.2)	5 (22.7)	27 (48.2)	10 (45.5)	1 (50)
Bleeding complications					
Major bleeding	15/102 (14.7)	4/22 (18.2)	8/56 (14.3)	2/22 (9.1)	1 (50)
Esophageal variceal bleeding	3/102 (2.9)	1/22 (4.5)	2/56 (3.6)	0/22 (0.0)	0(0)
Gastrointestinal bleeding	19/102 (18.6)	4/22 (18.2)	8/56 (14.3)	7/22 (31.8)	0(0)
Intracranial bleeding	3/102 (2.9)	2/22 (9.1)	1 (1.8)	0 (0.0)	0 (0)

CT: computed tomography; DOAC: direct oral anticoagulant; IQR: interquartile range; LMWH: low molecular weight heparin; VKA: vitamin K antagonist.
[a]Mesenteric (both central and peripheral), portal and splenic vein thrombosis.

patients treated with DOAC and VKA were 81 ml/min/1.73 m^2 (IQR = 66–96; $n = 22$) and 86 ml/min/1.73 m^2 (IQR = 70–101; $n = 54$), respectively, $p = 0.52$.

Vascular and intestinal CT findings

Central and peripheral MVT were documented in 98 (96%) and 73 patients (72%), respectively. Extensive thrombosis at diagnostic CT was found in 43 patients (42%), and intestinal findings in 66 (65%). The most frequent extra-vascular abnormalities were mesenteric oedema ($n = 63$; 62%), ascites ($n = 52$; 51%), small bowel wall oedema ($n = 40$; 39%), and local small bowel dilatation ($n = 10$; 10%).

Radiological outcome—Thrombus recanalization

CT was performed both at diagnosis and after medical treatment in 70 patients after a median follow-up of 6 (IQR = 3–28) months. The overall evaluation showed no change in 20 patients, progression of thrombotic status within the portomesenteric venous system in 4, partial regression in 27, and total regression in 19 patients. Successful recanalization had been achieved in 66% of the 70 patients, 71% of those treated with VKA ($n = 41$) and 69% of those treated with DOAC ($n = 16$) ($p = 0.88$). Patients with and without extensive thrombosis had complete regression of thrombosis after anticoagulation therapy in 11% (3/27) and 37% (16/43), respectively ($p = 0.017$). The association between extent of thrombosis at diagnosis and complete regression of thrombosis in the respective anticoagulation therapy group are shown in Table 2. One of the 70 patients had no anticoagulation therapy. When entering extensive thrombosis, age, malignancies, and type of therapy (VKA or DOAC) in a multivariable analysis, none of these variables were associated with successful recanalization. Neither was there any correlation between successful recanalization and the time lapse between diagnostic and follow-up CT ($r = 0.067$, $p = 0.58$). No clinical variable was found to be associated with successful recanalization (Table 3).

Table 2. The association between extent of thrombosis at diagnosis and complete regression of thrombosis in respective anticoagulation therapy group.

	Extensive thrombosis at diagnosis		Univariable analysis (p value)
	Yes (%)	No (%)	
Complete regression of thrombosis in respective anticoagulation therapy group			
LMWH ($n = 12$)	0/4 (0)	2/8 (25)	0.52
VKA ($n = 41$)	2/18 (11)	8/23 (35)	0.080
DOAC ($n = 16$)	1/5 (20)	6/11 (55)	0.31

DOAC: direct oral anticoagulant; LMWH: low molecular weight heparin; VKA: vitamin K antagonist.

Table 3. Factors associated with CT-verified recanalization of the portomesenteric venous thrombosis in 70 patients.

Variable	Partial or complete recanalization (%)	Univariable analysis (p value)
All patients	46/70 (65.7)	
≥75 years	4/5 (80.0)	0.65
Female gender	17/25 (68.0)	0.76
Smoking	14/23 (60.9)	0.55
Previous VTE	12/16 (75.0)	0.37
Factor V Leiden mutation	11/15 (73.3)	0.46
Any inherited thrombophilia	14/21 (66.7)	0.90
Any acquired thrombophilia	7/9 (77.8)	0,48
Malignancy	6/11 (54.5)	0.49
Abdominal malignancy	5/9 (55.6)	0.48
Pancreatic malignancy	1/3 (33.3)	0.27
Metastatic malignancy	1/3 (33.3)	0.27
Pancreatitis	11/17 (64.7)	0.92
Liver cirrhosis	2/4 (50.0)	0.60
Inflammatory bowel disease	4/5 (80.0)	0.65
Renal insufficiency at admission	6/9 (66.7)	1.0
Bowel resection	7/8 (87.5)	0.24
Endovascular therapy	4/6 (66.7)	1.0
Medical therapy		
LMWH	6/12 (50.0)	0.21
VKA	29/41 (70.7)	0.29
DOAC	11/16 (68.8)	0.77

CT: computed tomography; DOAC: direct oral anticoagulant; LMWH: low molecular weight heparin; VKA: vitamin K antagonist; VTE: venous thromboembolism.

Bowel resection

Among the 102 patients, 17 (17%) underwent bowel resection. There was no difference in bowel resection rate between patients treated with VKA (23% [13/56]) and DOAC (9% [2/22]; $p = 0.15$).

Bleeding complications

The overall rates of major bleeding, intracranial bleeding, gastrointestinal and esophageal variceal bleeding during anticoagulation were 14.7%, 2.9%, 18.6%, and 2.9%, respectively. The major bleeding rates during VKA and DOAC therapy were 14.3% (8/56) and 9.1% (2/22), respectively ($p = 0.54$). DOAC treatment tended to be associated with a higher rate of gastrointestinal bleeding compared to VKA treatment ($p = 0.077$). Two gastrointestinal bleedings were fatal, one patient with concomitant esophageal variceal bleeding without anticoagulation died after 12 days, and one duodenal ulcer bleeding died at 1 month after initiation of anticoagulation. Three patients suffered from intracranial bleeding; one patient treated with LMWH suffered a subdural bleeding necessitating neurosurgery after 1 month, another patient treated with LMWH had a subarachnoidal bleeding after 28 months, which was managed conservatively. The third patient treated with VKA had an intracerebral bleeding after 8 months, which was managed conservatively (Table 1).

Venous thromboembolic complications

No MVT recurrence occurred during or after cessation ($n = 38$) of medical treatment. No VTE recurrence occurred during medical treatment. One patient suffered from a DVT in her leg 9 years after cessation of anticoagulation therapy.

Mortality

The 30-day mortality was 7% (7/102). There was no difference in 30-day mortality between patients treated with VKA and DOAC (3.6% [2/56] and 0% [0/22]; $p = 1.0$), respectively. Total mortality at the end of follow-up was 20% (20/102); a Kaplan–Meier curve for survival is shown in Figure 1. Median survival times from MVT diagnosis to end of follow-up for patients with malignant ($n = 26$) and nonmalignant ($n = 76$) disease were 42 (IQR = 5–72) and 50 (IQR = 24–101) months, respectively, ($p = 0.19$), whereas survival in patients with nonmetastatic ($n = 17$) and metastatic cancer ($n = 9$) was 66 (IQR = 27–84) months and 4 (IQR = 2–25) months, respectively ($p = 0.002$).

Discussion

The present study showed that anticoagulation treatment of MVT with LMWH, VKA, and DOAC was effective, and not associated with any recurrence of MVT during a median follow-up of 4 years, and no VTE recurrence during treatment. In a multicenter study on splanchnic vein thrombosis in patients with myeloproliferative neoplasms, a 3.3% risk of MVT recurrence was reported.[20] It was, however, unclear if any of the patients suffering recurrence had MVT at the index thrombotic event. In the same report, the proportion of patients diagnosed with VTE outside the splanchnic vein circulation was 7.2% during a mean follow-up of 4.1 years.[20] In addition, increased VTE recurrence rate has previously been reported after treatment discontinuation in 72 patients with MVT followed for a median time of 3 years.[21] There was only one patient with VTE recurrence after cessation of treatment in the present study, which presumably not is

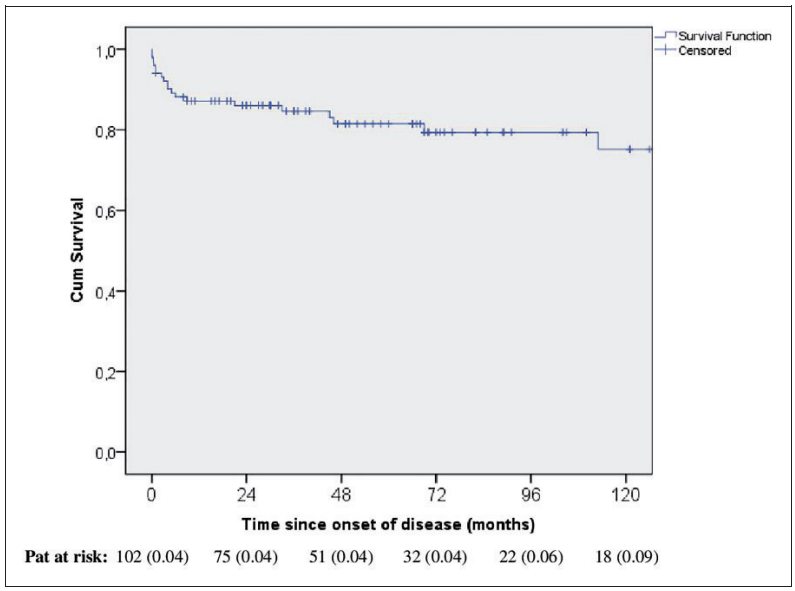

Figure 1. Kaplan–Meier analysis of long-term survival in patients with MVT. Life table showing patients at risk at each occasion. Standard error of cumulative proportion surviving at end of interval is stated within parentheses. Censored patients are marked with ticks.
MVT: mesenteric venous thrombosis.

explained by poor validity of data, since Skåne University Hospital is the only unit treating VTE patients in the catchment area. The rates of both major bleeding and intracranial hemorrhage were of concern in the present study, and as well as in the above-mentioned large study.[20] In particular, patients with esophageal varices and/or a low platelet count may suffer troublesome bleeding, and in a real-world clinical practice, a certain proportion of patients with portomesenteric venous thrombosis will have to discontinue their anticoagulation therapy as risks conferred by treatment are presumed to exceed the benefits.[22] Indeed, two fatal gastrointestinal bleedings were found in the present study, and one of these patients died due to a concomitant esophageal variceal bleeding.

Complete or partial radiological recanalization at follow-up CT was 66% in all patients without difference between those treated with DOAC compared to VKA. It was found that a less extensive initial thrombus burden was associated with a higher rate of complete regression of thrombosis in the 70 evaluable patients, while no such detectable differences were found in the respective small anticoagulation therapy subgroups. The present explorative study was not, however, optimally designed to compare results of VKA and DOAC treatment in MVT. A longer inclusion period and enrolment of a higher proportion of DOAC-treated patients would have been beneficial for our aim. In a recent retrospective comparative study, the factor Xa inhibitor edoxaban was found to be superior to VKA therapy in reducing thrombus volume in cirrhotic patients with PVT.[23] Besides these advantages in cirrhotic patients, DOAC therapy helps to avoid the disadvantages of VKA therapy such as a narrow therapeutic window, extensive food and drug interactions, highly variable dose response, and requirements of frequent dose adjustments and monitoring. Another important issue to consider in MVT patients, however, is the possibility to instantly reverse the anticoagulation effect in case of a life-threatening bleeding or need of immediate surgery due to suspicion of intestinal infarction. Whereas effects of VKA can be reversed by vitamin K, prothrombin complex concentrates, and plasma,[24] and effects of the thrombin inhibitor dabigatran can be reversed by idarucizumab,[25] there are still no commercially available antidotes for factor Xa inhibitors.

LMWH monotherapy is the current mainstay of treatment in cancer-associated venous thromboembolism and reduces venous thromboembolic events.[26] LMWH was also the dominant treatment regime in patients with cancer-associated MVT in the present

study. However, VKA therapy was used in 12 patients with malignancies, both solid cancers and myeloproliferative diseases. This is mainly attributed to the retrospective study design with inclusion of patients from 2004. Secondly, MVT has not been proven to share the same characteristics as systemic venous thromboembolism regarding risk factor profiles,[27] efficacy, and safety of various treatment regimes. Treatment recommendations for cancer and VTE may therefore not apply strictly to cancer-associated MVT. In addition, four patients with malignancies and MVT in the present study used DOAC, which should be considered as experimental since the use of DOAC is not currently recommended for patients with malignancy and VTE.[28] Very recent data from a randomized controlled trial in patients with cancer and VTE has shown that the rate of recurrent VTE was lower but the rate of major bleeding was higher with edoxaban compared to subcutaneous dalteparin.[29]

The present study has limitations. Follow-up CT was performed in only 69% of the study patients, mainly attributable to the absence of clear treatment recommendations concerning MVT patients during the study period and early mortality after the initial admission. As the diagnosis of MVT is rare and extremely difficult to establish clinically without CT, a prospective study is almost impossible to design. Hence, MVT studies will by necessity be retrospective by nature, with all the inherent limitations of this study design. For instance, CT protocols at diagnosis and follow-up were often different, since the questions asked in the referral letter at the initial assessment were very diverse. Some initial CT examinations were performed with oral contrast media, which was never used at follow-up CT evaluating the extent of portomesenteric venous thrombosis. Furthermore, we did not have a fixed time point for follow-up CT examinations, which might have influenced the thrombotic status in the portomesenteric vein system. A semi-quantitative ordinal scale assessed the thrombotic status between CT examinations. Modern CT software is able to automatically measure differences in PVT volume, providing more accurate changes in thrombotic status.[23] Even if the study material is rather large for a rare disease as MVT, appropriate statistical adjustment for several confounding variables in multivariable analysis was not possible. This study included patients diagnosed between 2004 and 2017, and as DOAC treatment for MVT was not introduced until in 2015 better diagnostic and therapeutic measures during the latter part of the study period might have biased our results. Comorbidity such as cancer has also induced a selection bias concerning the choice of anticoagulation therapy in the present study. The small sample sizes in each anticoagulation therapy group make group comparisons prone to type 2 statistical error. A high-quality evaluation of differences in outcomes between patients treated with DOAC and VKA was therefore not possible.

Conclusion

DOAC and VKA anticoagulation therapy in patients with MVT was clinically and radiologically effective. Bleeding complications during treatment was a concern in both groups, whereas recurrent VTE was not. These data are encouraging for a randomized large multicenter trial of DOAC versus VKA in newly CT diagnosed MVT.

Declaration of Conflicting Interests

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Ethical approval

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Guarantor

None.

Contributorship

SS and SA researched literature and conceived the study. OE, SA, SS scrutinized the CT images. JE and AG achieved ethical approval. SS and SA wrote the first draft. All authors reviewed and edited the manuscript and approved the final version of the manuscript.

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Paper III

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ORIGINAL ARTICLE

Clinical implications of CT findings in mesenteric venous thrombosis at admission

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Abstract

Purpose The main aim of this study was to evaluate the association of computed tomography (CT) findings at admission and bowel resection rate in patients with mesenteric venous thrombosis (MVT). It was hypothesized that abnormal intestinal findings on CT were associated with a higher bowel resection rate.

Methods Retrospective study of MVT patients treated between 2004 and 2017. CT images at admission and at follow-up were scrutinized according to a predefined protocol. Successful recanalization was defined as partial or complete recanalization of the portomesenteric venous thrombosis at the latest CT follow-up ($n = 70$).

Results We studied 102 patients (median age 58 years, 61 men). Lifelong anticoagulation was initiated in 64 patients, and bowel resection rate was 17%. No referral letter indicated suspicion of MVT, whereas three indicated suspected intestinal ischemia. Previous venous thromboembolism was associated with increased bowel resection rate ($p = 0.049$). No patient with acute pancreatitis ($n = 17$) underwent bowel resection ($p = 0.068$). The presence of mesenteric oedema ($p = 0.014$), small bowel wall oedema ($p < 0.001$), small bowel dilatation ($p = 0.005$), and ascites ($p = 0.021$) were associated with increased bowel resection rate. Small bowel wall oedema remained as an independent risk factor associated with bowel resection (OR 15.8 [95% CI 3.2–77.2]). Successful thrombus recanalization was achieved in 66% of patients.

Conclusion The presence of abnormal intestinal findings secondary to MVT confers an excess risk of need of bowel resection due to infarction. Responsible physicians should therefore scrutinize the CT images at diagnosis together with the radiologist to better tailor clinical surveillance.

Keywords Mesenteric venous thrombosis · CT · Intestinal ischemia · Bowel resection

Introduction

Mesenteric venous thrombosis (MVT) is an important cause of intestinal ischemia [1], though less common than mesenteric arterial thromboembolism. Unspecific abdominal pain is often present in the early stage of the disease, whereas localized abdominal pain develops later. Melena, hematemesis, or hematochezia occurs in only 15%, whereas occult bleeding may be present in 50% of the cases [2]. Fever and signs of peritonitis suggest progression of ischemia to intestinal infarction [3]. Since MVT is extremely seldom diagnosed on clinical grounds, computed tomography (CT) with intravenous contrast enhancement and imaging in the portal phase has become the most important, reliable, and accurate imaging for diagnosis of MVT [4–7]. CT can accurately visualize both the extent of thrombosis within the portomesenteric venous system and secondary abnormal intestinal findings. Thrombosis within the superior mesenteric vein is, in contrast to isolated portal vein thrombosis, associated with symptoms related to intestinal ischemia in the overwhelming majority (92%) [8] and often results in intestinal infarction if left untreated [8, 9]. Patients with MVT are nowadays, however, often diagnosed by CT in time, enabling a conservative medical approach with anticoagulation therapy [10].

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One previous report suggests that patient characteristics and CT findings in MVT may be associated with increased bowel resection rate [11]. The main aim of the present large retrospective study was to evaluate the association of CT findings at admission and bowel resection due to intestinal infarction. It was hypothesized that abnormal intestinal findings on CT were associated with a higher bowel resection rate.

Methods

Retrieval of patients with mesenteric venous thrombosis

Ethical approval was obtained from the Regional Ethical Review Board in Lund (Dnr 2014/287). Identification of all patients with MVT treated surgically or conservatively at the Skåne University Hospital between 1st of January 2004 and 29th of September 2017 was performed in (1) hospital records based on the International Statistical Classification of Diseases and Related Health Problems (ICD), tenth edition, codes I81 (portal vein thrombosis [PVT] or MVT) and K55 (mesenteric ischemia), and (2) *AuriculA* [12] (a Swedish quality registry for patients treated with anticoagulation). All patient records and CT images in patients with PVT or MVT as well as unclear cases of mesenteric ischemia were scrutinized. Only patients with symptomatic thrombosis in the superior mesenteric vein with or without anatomical involvement of portal or splenic veins were included in the present study. Patients with isolated PVT without thrombotic involvement of the superior mesenteric vein were excluded. Median clinical follow-up was 48 months.

Definitions

Patients with abdominal pain of less than 4 weeks of duration were classified as having acute MVT. Those with symptoms for 4 weeks or more but without bowel infarction, and those with asymptomatic MVT diagnosed incidentally on abdominal imaging as a clinically non-significant finding were defined as chronic MVT. Extensive thrombosis was defined as having mesenteric central and peripheral, portal, and splenic vein thrombosis. The first five centimeters of the proximal superior mesenteric vein were defined as central. Small bowel dilatation was defined as ≥ 4 cm in bowel diameter. Patients initially treated with low molecular weight heparin (LMWH) for some weeks and later changed for VKA (vitamin K antagonists) or DOAC (direct-acting oral anticoagulants) were considered as treated with either of the respective oral anticoagulants.

Glomerular filtration rate (GFR) was calculated with a simplified variant of the Modification of Diet in Renal Disease Study Group (MDRD) equation [13], and advanced renal insufficiency was defined as GFR < 25 ml/min.

Renal insufficiency evaluated by serum (s) creatinine alone was defined as a s-creatinine > 105 μmol/l (1.2 mg/dl) in men and > 90 μmol/l (1.0 mg/dl) in women. Body mass index (BMI) was defined as weight/length^2 expressed in kg/m^2. The term "thrombophilia" was used as a common denominator for factors which might provoke MVT, such as cancer, coagulation disorders, previous or concomitant VTE, oral contraceptive use, or estrogen substitution. Inherited thrombophilic factors were defined as factor V Leiden mutation, prothrombin gene mutation, or deficiencies of protein C, protein S, or antithrombin. Acquired thrombophilic factors were defined as JAK2 V617F (janus-activated kinase gain of function substitute of valine to phenylalanine at position 617) mutation, lupus anticoagulant, or cardiolipin antibodies. A transient risk factor was defined as either recent surgery within 6 weeks, abdominal trauma, or inflammatory disease such as acute pancreatitis. Follow-up CT was defined as the last available CT of the abdomen with intravenous contrast and imaging in the parenchymal/venous phase. Successful recanalization was defined as partial or complete recanalization of the portomesenteric venous system at the follow-up CT after treatment.

Computed tomography

Clinical data provided in the referral letter for initial radiological examination at admission were retrieved in a Sectra radiological information system (Sectra AB, Linköping, Sweden). Multi-detector row CT (MDCT) was usually performed with a 0.75-mm slice thickness (Siemens Sensation 16, Erlangen, Germany). Multi-planar reconstruction in axial, coronal, and sagittal planes was usually obtained with a 5-mm thickness. Single-slice CT was usually performed with slice thickness of 3–5 mm. Patients were examined in the portomesenteric venous phase. Intravenous contrast medium was non-ionic contrast medium 300–320 mg I/ml with a total dose of 90 ml, flow rate of 3 ml/s, and delay of 70 s. The diagnostic and follow-up CT scan images of all patients were scrutinized and evaluated by an experienced radiologist (OE) aware of the diagnosis but blinded concerning which treatment the patient received. The main objective was to describe vascular and intestinal findings (Fig. 1) systematically in a predefined protocol [7]. Bowel wall thickness was assessed on non-contracted intestinal segments and defined as normal if 3 mm or less [14]. The patency of the portomesenteric venous system at follow-up CT was categorized as progression, unchanged, partial regression, and complete regression.

Treatment strategy at the study center

After diagnosis of MVT with CT, the mainstay of treatment was conservative with immediate full anticoagulation with either intravenous heparin infusion or subcutaneous LMWH,

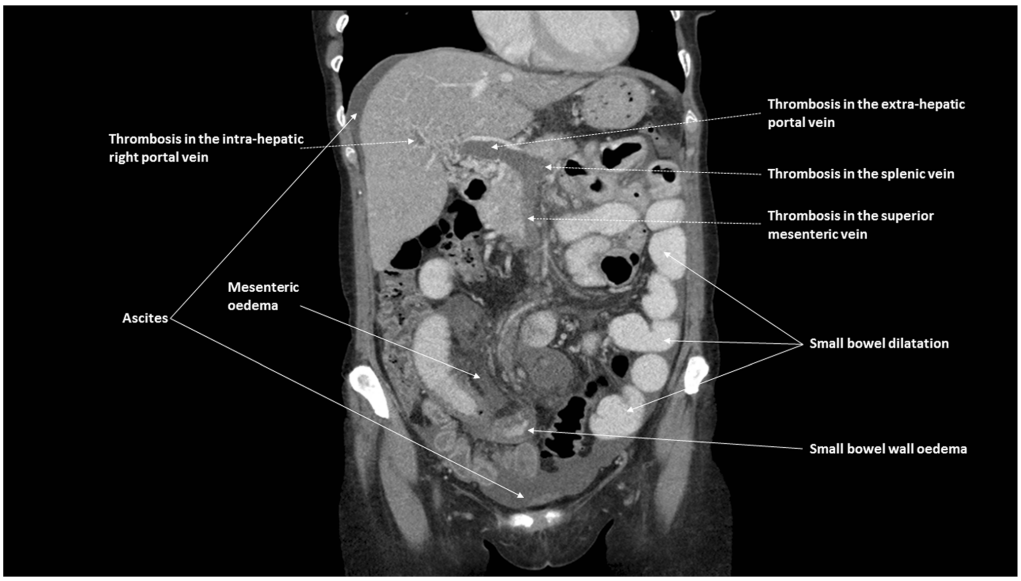

Fig. 1 A 59-year-old woman admitted with 3 days of abdominal pain and vomitus. CT with intravenous and oral positive contrast enhancement showed extensive portomesenteric venous thrombosis with secondary abnormal intestinal findings

full bowel rest, total parenteral nutrition, and analgesia. Patients admitted with peritonitis or rapidly progressing towards peritonitis underwent laparotomy and bowel resection. Patients not responding to anticoagulation may have undergone endovascular treatment with or without local thrombolysis, and non-responders were subjected to laparotomy. Clearly necrotic and demarcated bowels were resected and anastomosed. Bowels with unclear viability were usually evaluated at a second look laparotomy, and bowel resections were followed by reconstructions with anastomoses or diverting stomas. Patients with identified transient risk factors were usually treated with oral anticoagulation for 6 months, whereas those with permanent risk factors or unidentified risk factors were prescribed lifelong anticoagulation. Patients with a malignancy were usually treated with LMWH. DOACs were introduced for treatment of MVT at the study center in 2015.

Statistical methods

Data management and statistical analysis were performed using the SPSS for Windows program package (SPSS version 22.0, Chicago, IL, USA) or GraphPad (GraphPad Software, Inc., La Jolla, CA, USA). Distribution of variables was expressed with median value and interquartile range (IQR). Differences in proportions were evaluated using the chi-square or Fisher's exact test. Quantitative differences between groups were assessed with the Mann-Whitney *U* test. When risk factor evaluation for bowel resection was performed, factors with $p < 0.1$ in the uni-variable analysis were entered in a multi-variable regression analysis and expressed in odds ratio (OR) with 95% confidence interval (CI). The Spearman rank test was used for calculating correlations. A p value < 0.05 was considered significant.

Results

Patient characteristics

During the 14-year period, 102 patients (61 men and 41 women) were diagnosed with MVT. Median age was 58 years (IQR, 47–68), and men (56 [IQR 47–64] years) were younger ($p = 0.009$) than women (65 [IQR 50–72] years). MVT was defined as acute in 100 (98%) patients and chronic in the remaining 2 (2%). Median BMI was 27.8 (IQR 25.5–31.4) in men ($n = 49$) and 25.5 (IQR 23.5–33.6) in women ($n = 34$). One (1.0%; 1/100) patient had advanced renal insufficiency. Seventeen (17%) patients had previously been diagnosed with pancreatitis, and 26 (26%) with malignancies. Among 85 patients tested for thrombophilia, 17 (20%) had the factor V Leiden mutation and 9 (9%) had the JAK-2 V617 mutation. In 10 patients with myeloproliferative disease, 9 (90%) were JAK-2 V617 mutation positive. Lifelong anticoagulation

was initiated in 64 patients (63%). Fifty-six (55%) patients received VKA, 22 (22%) LMWH, and 22 (22%) DOAC.

Clinical data from the referral letter for initial radiological examination

Among the 102 patients with MVT, initial radiological examinations had been performed by CT in 69 (68%), ultrasound in 26 (26%), plain abdominal X-ray in 5 (5%), and magnetic resonance imaging in 2 (2%). None of the referral letters for initial radiological examination revealed any suspicion of MVT, whereas intestinal ischemia was suspected in 3 (3%) patients. In these 3 patients with suspected intestinal ischemia, intestinal ischemia was mentioned among two, three, or four diagnostic suggestions in the referral letter. The spectrum of suspected clinical diagnoses at initial radiological examinations, respectively, is shown in Supplementary Table 1. The most frequently asked questions concerned intestinal disorders ($n = 77$), inflammatory disorders ($n = 65$), biliary or urinary tract disorders ($n = 38$), malignancies ($n = 26$), and benign disorders of the liver or spleen ($n = 10$).

Vascular and intestinal CT findings

Central and peripheral MVTs were documented in 98 (96%) and 73 (72%) patients, respectively. Extensive thrombosis at diagnostic CT was found in 43 (42%) patients, and intestinal findings in 66 (65%). The most frequent extra-vascular abnormalities were mesenteric oedema ($n = 63$; 62%), ascites ($n = 52$; 51%), small bowel wall oedema ($n = 40$; 39%), and local small bowel dilatation ($n = 10$; 10%) (Table 1). No abnormalities in the colon were found.

Radiological outcome—thrombus recanalization

CT was performed both at diagnosis and after medical treatment in 70 patients after a median follow-up of 6 (IQR 3–28) months. The overall evaluation showed no change in 20 patients, progression of thrombotic status within the portomesenteric venous system in 4 patients, partial regression in 27 patients, and total regression in 19 patients. Successful recanalization had been achieved in 66% of the 70 patients (Table 2), 71% of those treated with VKA and 69% of those treated with DOAC ($p = 0.88$). When entering age, malignancies, and type of therapy (VKA or DOAC) in a multi-variable analysis, none of these variables were associated with successful recanalization. Neither was there any correlation between successful recanalization and the time lapse between diagnostic and follow-up CT ($r = 0.067$, $p = 0.58$). No clinical variable was found to be associated with successful recanalization.

Table 1 Vascular and intestinal findings on computed tomography at diagnosis of mesenteric venous thrombosis (MVT) in 102 patients

	Frequency (%)
Vascular findings	
Central MVT	98 (96.1)
Peripheral MVT	73 (71.6)
Isolated MVT	14 (13.7)
Portal vein thrombosis	85 (83.3)
Extra-hepatic portal venous thrombosis	80 (78.4)
Intra-hepatic portal venous thrombosis	60 (58.8)
Splenic vein thrombosis	61 (59.8)
Venous collaterals	52 (51)
Extensive thrombosis[a]	43 (42.2)
Intestinal findings	66 (64.7)
Mesenteric oedema	63 (61.8)
Small bowel wall oedema	40 (39.2)
Local small bowel dilatation	10 (9.8)
Extensive small bowel dilatation	2 (2.0)
Gas in the portomesenteric venous system	0 (0.0)
Ascites	52 (51.0)

[a] Mesenteric central and peripheral, portal, and splenic vein thrombosis

Factors associated with bowel resection

Among the 102 patients, 17 (17%) underwent bowel resection. Previous VTE was associated with increased bowel resection rate ($p = 0.049$). No patient with exclusive transient risk factor ($n = 15$) underwent a bowel resection ($p = 0.069$). No patient with acute pancreatitis ($n = 17$) underwent bowel resection ($p = 0.068$). The presence of any intestinal finding at CT ($p = 0.026$), mesenteric oedema ($p = 0.014$), small bowel wall oedema ($p < 0.001$), small bowel dilatation ($p = 0.005$), and ascites ($p = 0.021$) were associated with increased bowel resection rate (Table 3). After entering small bowel wall oedema, acute pancreatitis, and previous VTE in a multi-variable regression analysis, small bowel wall oedema remained an independent risk factor associated with bowel resection (OR 15.8 [95% CI 3.2–77.2], $p = 0.001$), and previous VTE tended to be a risk factor for bowel resection (OR 3.3 [95% CI 0.9–12.6], $p = 0.080$).

Mortality

The 30-day mortality was 7% (7/102). Mortality at the end of follow-up was 20% (20/102).

Discussion

The present study showed that a number of abnormal intestinal CT findings secondary to MVT such as small bowel wall

Table 2 Recanalization of portomesenteric venous thrombosis verified by computed tomography (CT) after follow-up in 70 patients with mesenteric venous thrombosis (MVT)

Initial CT findings	Frequency of partial or complete recanalization (%)
All patients	46/70 (65.7)
Vascular findings	
Central MVT	45/69 (65.2)
Peripheral MVT	34/46 (73.9)
Portal vein thrombosis	35/57 (61.4)
Extra-hepatic portal venous thrombosis	35/56 (62.5)
Intra-hepatic portal venous thrombosis	28/42 (66.7)
Splenic vein thrombosis	23/43 (53.5)
Venous collaterals	22/39 (56.4)
Extensive thrombosis[a]	17/27 (63.0)
Intestinal findings	29/45 (64.4)
Mesenteric oedema	28/44 (63.6)
Small bowel wall oedema	20/27 (74.1)
Small bowel dilatation	5/7 (71.4)
Ascites	25/36 (69.4)

[a] Mesenteric central and peripheral, portal, and splenic vein thrombosis

oedema, small bowel dilatation, mesenteric oedema, and ascites were all associated with increased bowel resection rate, whereof small bowel wall oedema is the strongest risk factor. It therefore seems to be of utmost importance that CT images at diagnosis are scrutinized by the responsible physician together with the radiologist to better individualize clinical surveillance. The study data suggest that patients with small bowel wall oedema need a more close clinical follow-up than patients without secondary findings, with repeated physical examinations, C-reactive protein (CRP), and temperature measurements. In concordance with the present study, a recent study of 66 patients with CT verified MVT reports that bowel wall oedema, contrast enhancement defects of the bowel wall, and ascites were all associated with bowel resection [11]. The extent of thrombosis, involving both the superior mesenteric and portal veins as opposed to isolated thrombosis of the superior mesenteric vein, was also found to be associated with bowel resection [11], whereas in the present study, there was no increase in bowel resection rate in patients with extensive MVT, defined as SMV, PV, and splenic vein thrombosis. This might, however, be attributed to a type 2 statistical error. The decreased bowel resection rate in patients with a transient risk factor may imply that these patients have a more benign course of the disease and may therefore justify a limited 6-month time period of anticoagulation [11]. In agreement, none of the 15 patients with an exclusive transient risk factor or of the 17 patients with acute pancreatitis, a transient strong provocative trigger, in the present study required bowel resection. In addition, we report a trend towards previous VTE being associated with the need of bowel resection in adjusted analysis, strengthening the indication for lifelong anticoagulation therapy in these patients.

Table 3 Association between vascular and intestinal findings at initial computed tomography (CT) and later need for bowel resection in 102 patients with mesenteric venous thrombosis (MVT)

CT findings	Bowel resection	*p* value
All	17/102(16.7)	
Extensive thrombosis[a]	10/43 (23.2)	0.13
Isolated MVT	2/14 (14.3)	1.0
Intestinal findings	15/66 (22.7)	0.026
Mesenteric oedema	15/63 (23.8)	0.014
Small bowel wall oedema	15/40 (37.5)	< 0.001
Small bowel dilatation	6/12 (50.0)	0.005
Ascites	13/52 (25.0)	0.021

[a] Mesenteric central and peripheral, portal, and splenic vein thrombosis

Complete or partial radiological thrombus recanalization at follow-up CT was 66% among all patients, without difference between those treated with DOAC and those on VKA. However, the present explorative study was not optimally designed to compare results of VKA and DOAC treatment in MVT. In a radiological report on patients with acute MVT, 80% showed signs of evolution towards chronic MVT such as vein stenosis or occlusion and development of collateral veins [15]. It was reported that patients with short, isolated central MVT in a wide vein had a better chance of complete radiologic recovery [16]. Long-term imaging sequelae of portal venous hypertension, defined as esophageal varices, portal vein cavernous transformation, splenomegaly, or hepatic atrophy, were reported in 50% of MVT patients, and these radiological

findings were associated with lower thrombus recanalization rate and more extensive thrombotic disease at initial CT [16]. Among MVT patients with extensive portomesenteric thrombosis in the present study, 63% achieved successful recanalization, a figure comparable with the overall rate of successful recanalization. To date, there is no proof that a follow-up CT evaluating changes of the status of the portomesenteric venous system is necessary. Nevertheless, the result of such a repeated CT can aid long-term decision-making. In case of complete clot resolution and recanalization, discontinuation of anticoagulation may be considered, particularly in patients with transient risk factors [1].

The retrospective design is a limitation of the present study. As the diagnosis of MVT is difficult to establish clinically as shown by the wide spectrum of conditions asked in the referral letters for the initial radiological assessment, a prospective study is impossible to design before a CT has been performed. After confirmation of MVT diagnosis by CT, the rarity of the disease necessitates multi-center design to enable collection of prospective high-quality data. Another study limitation was that follow-up CT was performed in only 69% of our patients, mainly attributable to the absence of clear treatment recommendations for MVT patients. In addition, CT protocols at diagnosis and follow-up were often different, due to the wide diversity of questions asked in the referral letter for initial CT. Some initial CT examinations were performed with oral contrast media, which was never used at the follow-up CT evaluating the extent of portomesenteric venous thrombosis. When CT follow-up was considered, there was no fixed time point between the initial and follow-up CT, which might have influenced the thrombotic status in the portomesenteric venous system. Furthermore, the changes in thrombotic status were assessed by a semi-quantitative ordinal scale between CT examinations. With a prospective study design, a more modern quantitative evaluation using computer software for automatical or semi-automatical measurements of differences in thrombus volume [17] might be possible. Furthermore, appropriate statistical adjustment for several confounding variables in multi-variable analysis was not possible in our study, despite a rather large cohort of patients with MVT.

Conclusion

Abnormal intestinal CT findings secondary to MVT are related to excess risk of bowel resection due to intestinal infarction. Responsible physicians should therefore scrutinize initial CT images together with the radiologist to better tailor clinical surveillance. Thrombus recanalization rate after anticoagulation therapy was acceptable.

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Compliance with ethical standards

Ethical approval was obtained from the Regional Ethical Review Board in Lund (Dnr 2014/287).

Conflict of interest The authors declare that they have no conflict of interest

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Paper IV

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Clinical implications of different risk factor profiles in patients with mesenteric venous thrombosis and systemic venous thromboembolism: a population-based study

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Abstract
It is unknown whether the risk factor profile for mesenteric venous thrombosis (MVT) is different from systemic venous thromboembolism (VTE). The aim of the present population-based study was to compare acquired and inherited risk factors in MVT versus VTE. Identification of all MVT patients at Skåne University Hospital between 2000 and 2015 was performed in patient records and *AuriculA* (Swedish anticoagulation registry). VTE patients were retrieved from the Malmö Thrombophilia Study (MATS), including 1465 consecutive unselected VTE patients between 1998 and 2008. Patients with MVT (n = 120) were younger ($p < 0.001$), had higher glomerular filtration rate ($p < 0.001$), lower smoking rate ($p < 0.001$), and had less often undergone recent surgery ($p = 0.025$). The prevalence of solid cancer (19.2% in MVT versus 12.1% in VTE; $p = 0.026$) and intra-abdominal cancer (16.7% versus 2.3%; $p < 0.001$) were higher in MVT. The prevalence of factor V Leiden mutation without presence of cancer was lower in MVT compared to VTE (26.6% versus 38.9%; $p = 0.031$). Thirty-day mortality was higher in the MVT group (9.2% versus 0.6%; $p < 0.001$), but did not differ at long-term follow-up according to Kaplan–Meier analysis ($p = 0.73$). Patients with MVT have a higher prevalence of cancer and lower prevalence of factor V Leiden mutation than those with systemic VTE. Intra-abdominal cancer should be excluded in MVT patients, and the high prevalence of factor V Leiden mutation in patients without cancer in both groups suggests that screening for thrombophilia in patients without cancer should be considered in this population for both groups.

Keywords Mesenteric venous thrombosis · Venous thromboembolism · Thrombophilia testing · Factor V Leiden mutation · Prothrombin mutation

Highlights

- Risk factor profiles in MVT and VTE has never been compared in the same population.
- MVT patients had a higher prevalence of solid and intra-abdominal cancer.
- VTE patients had higher prevalence of factor V Leiden mutation.
- Factor V Leiden mutation prevalence in patients without cancer was high in both groups suggesting that screening for thrombophilia should be considered.
- The study findings should be externally validated in another population.

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Introduction

Mesenteric venous thrombosis (MVT) is a rare and potentially lethal disease [1]. Unspecific abdominal pain is often present in the early stage of the disease, whereas localized abdominal pain develops later. Melena, hematemesis, or hematochezia occurs in only 15%, whereas occult bleeding may be present in 50% of the cases [2]. However, there is rarely any clinical suspicion of MVT, and diagnosis may come as a surprise for clinicians after radiological imaging [3]. Main causes of MVT are coagulation disorders, abdominal inflammatory conditions, malignancies, and liver diseases [4]. When to perform thrombophilia testing in patients with MVT, and how to interpret the results, is debatable. Importantly, since there is a considerable morbidity and mortality associated with MVT, concern and anxiety regarding the underlying cause may lead to testing for thrombophilia in many patients. MVT may also be the first clinical manifestation of myeloproliferative neoplasms [5]. Although inherited and acquired thrombophilias are acknowledged to increase the risk of systemic venous thromboembolism (VTE) some authors argue that the majority of patients with systemic VTE should not be tested for thrombophilia [6]. It is unknown whether the risk factor profile for MVT is the same as for systemic venous thromboembolism (VTE). However, since population based studies on both MVT [7] and systemic VTE [8] have been performed in Malmö, Sweden, there was a unique opportunity to analyse differences in risk factor profile between these two venous thrombotic groups. The aim of the present population-based study was to compare acquired and inherited risk factors in MVT versus VTE, assuming that the risk factor profile would be similar in both groups.

Methods

Retrieval of patients with mesenteric venous thrombosis

Identification of all MVT patients treated surgically or conservatively at Skåne University Hospital between 1st of January 2000 and 31st of December 2015 was performed in patients records and *AuriculA* (Swedish quality registry for patients treated with anticoagulation; [9]), and based on the International Statistical Classification of Diseases and Related Health Problems (ICD), tenth edition, codes I81 (portal vein thrombosis [PVT] or MVT) and K55 (mesenteric ischemia). All patient records as well as unclear cases of mesenteric ischemia were scrutinized and validated. Only patients with symptomatic thrombosis in the superior mesenteric vein with or without anatomical involvement of portal or splenic vein, diagnosed by radiological imaging (computed tomography [CT]), laparotomy and/or autopsy, were included in the present study. Patients with liver disease were included. Myeloproliferative disease and other malignancies were present or diagnosed at the time of MVT diagnosis. Full thrombophilia panel with eight tests including Janus kinase 2 v617F mutation (JAK2) [7] was available for 74% in the MVT cohort. End of follow-up for MVT patients was September 6, 2017. Median and mean follow up time were 5.4 and 6.2 years, respectively, and interquartile range [IQR] was 2.0–10.6 years.

Retrieval of patients with venous thromboembolism

The Malmö Thrombophilia Study (MATS) is a prospective population-based study conducted at Skåne University Hospital in Malmö, a city of 300.000 inhabitants in southern Sweden. This is the only hospital in the area treating patients with venous thromboembolism (VTE). The MATS cohort includes 1465 consecutive unselected VTE patients that were followed after inclusion in this study (March 1998) until death or the end of the study (September 2017) [10]. Thirteen patients with portal and/or mesenteric vein thrombosis were excluded from this cohort, but those with CT verified MVT were included in the MVT cohort. Seventy percent of all patients treated for VTE at Skåne University Hospital were included in the study. The remaining 30% were excluded due to unwillingness to participate, language barrier, dementia or other severe illness that prevented the patient from participating. The patients had to have objectively verified deep venous thrombosis (DVT) and/or pulmonary embolism (PE) with phlebography, duplex ultrasound, computed tomography (CT), lung scintigraphy or magnetic resonance imaging (MRI). Other inclusion criteria in MATS were age > 18 years and ability to communicate in the Swedish language. All participants provided written informed consent and the study were approved by the Lund University Ethical Committee (Dnr 2015/143). All patients were treated in accordance to the standard treatment protocol of Skåne University Hospital. Included patients were required to submit blood samples, answer a questionnaire and were evaluated concerning risk factors for VTE. Malignancies were present or diagnosed at the time of VTE diagnosis. No documentation of myeloproliferative disease was done. End of follow-up for VTE patients was September 6, 2017. Median and mean follow up time were 11.4 and 10.2 years, respectively, and IQR was 6.5–13.7 years.

The DNA mutations for factor V Leiden and Prothrombin were analysed using Taqman allele discrimination with gene specific assays for the two factors (Applied Biosystems, Life Technologies Corporation, Carlsbad, CA, USA).

Definitions

Glomerular filtration rate (GFR) was calculated as a simplified variant of Modification of Diet in Renal Disease Study Group (MDRD).

Statistics

Data management and statistical analysis were performed using the SPSS for Windows programme package (SPSS version 22.0, Chicago, IL, USA). Distribution of variables was expressed with median value and IQR. Differences in proportions were evaluated using the Chi square or the Fisher's exact test. Quantitative differences between groups were assessed with the Mann–Whitney U test. Cumulative survival was analysed using the Kaplan–Meier method and life table analysis. Log rank test was used in the overall comparison of survival curves for the MVT versus systemic VTE group. Patients were censored for death in both groups until end of follow-up, September 6, 2017. A p-value < 0.05 was considered significant.

Results

Comparison of patient characteristics and acquired risk factors in patients with mesenteric venous thrombosis versus systemic VTE

Patients with MVT (n = 120; all symptomatic) were younger ($p < 0.001$), had higher glomerular filtration rate (93 ml/min versus 67 ml/min; $p < 0.001$), lower prevalence of smoking ($p < 0.001$), and had less often undergone recent surgery ($p = 0.025$) compared to patients with systemic VTE. In six individuals with median age 75 years (IQR 60–82) fatal MVT was detected at autopsy. Previous VTE tended to be more prevalent in patients with MVT ($p = 0.072$). The prevalences of cancer (19.2% in MVT versus 12.1% in VTE; $p = 0.026$) and intra-abdominal cancer (16.7% in MVT versus 2.3% in VTE; $p < 0.001$) were both higher in MVT (Table 1). Of nine patients with myeloproliferative neoplasm in the MVT group, eight (89%) were JAK-2 mutation positive. The prevalences of cast therapy, trauma and immobilization in the VTE cohort were 3.9% (57/1452), 8.2% (119/1452) and 17.1% (248/1452), respectively.

Comparison of inherited thrombophilia in tested patients with mesenteric venous thrombosis versus systemic VTE

The prevalence of factor V Leiden mutation was lower in patients with MVT compared to patients with systemic VTE

Table 1 Comparison of patient characteristics and acquired risk factors in patients with mesenteric venous thrombosis versus systemic VTE

Variable	MVT	Systemic VTE	p value
Number of patients	120	1452	
Median age (IQR); years	58 (47–70)	66 (53–76)	< 0.001
Female sex (%)	53 (44.2)	739 (50.9)	0.16
GFR (ml/min)	93 (74–136) (n = 114)	67 (52–79) (n = 970)	< 0.001
Platelet count ($\times 10^9$/L)	260 (177–340) (n = 112)	244 (204–299) (n = 1411)	0.35
Ongoing VTE prophylaxis (%)	2/116 (1.7)	30 (2.1)	0.80
Acquired risk factors (%)	82/107 (76.6)	1186/1396 (85.0)	0.022
Previous venous thromboembolism (any)	24/120 (20.0)	203/1451 (14.0)	0.072
BMI ≥ 30 kg/m^2	24/88 (27.3)	296/1364 (21.7)	0.22
Smoking (ex or current)	36/103 (35.0)	771/1346 (57.3)	< 0.001
Surgical intervention (≤ 6 weeks)	8/117 (6.8)	207 (14.3)	0.025
Long travel (≥ 3 h)	7/117 (6.0)	102 (7.0)	0.67
Malignancy (solid cancer)	23 (19.2)	176 (12.1)	0.026
Intra-abdominal malignancy	20 (16.7)	33 (2.3)	< 0.001
Hormone therapy (female only)	7/53 (13.2)	161/739 (21.8)	0.14
Pregnancy	0/53 (0)	17/739 (2.3)	0.62
None of these acquired risk factors	25/107 (23.4)	210/1396 (15.0)	0.022
Strong provocative risk factor (recent surgery or malignancy)	28/119 (23.5)	356 (24.5)	0.81

Table 2 Comparison of inherited thrombophilia in tested patients with mesenteric venous thrombosis versus systemic VTE

Variable	MVT	Systemic VTE	p value
Number of patients	120	1452	
Heterozygous FVL mutation (%)	19/89 (21.3)	348/1021 (34.1)	0.014
Homozygous FVL mutation (%)	3/89 (3.4)	36/1021 (3.5)	0.94
FVL mutation (any) (%)	22/89 (24.7)	384/1021 (37.6)	0.015
FVL mutation (any) without malignancy (%)	21/79 (26.6)	360/926 (38.9)	0.031
Heterozygous PT mutation (%)	3/89 (3.4)	58/1259 (4.6)	0.79
Homozygous PT mutation (%)	0/89 (0.0)	0/1259 (0.0)	–
PT mutation (any) (%)	3/89 (3.4)	58/1259 (4.6)	0.79
Compound FVL and PT mutation (%)	0/89 (0.0)	11/1245 (0.9)	1.0
FVL or PT mutation (any) (%)	25/89 (28.1)	429/1036 (41.4)	0.014
No FVL or PT mutation (%)	64/89 (72.0)	605/1036 (58.4)	0.013

FVL Factor V Leiden, *PT* prothrombin

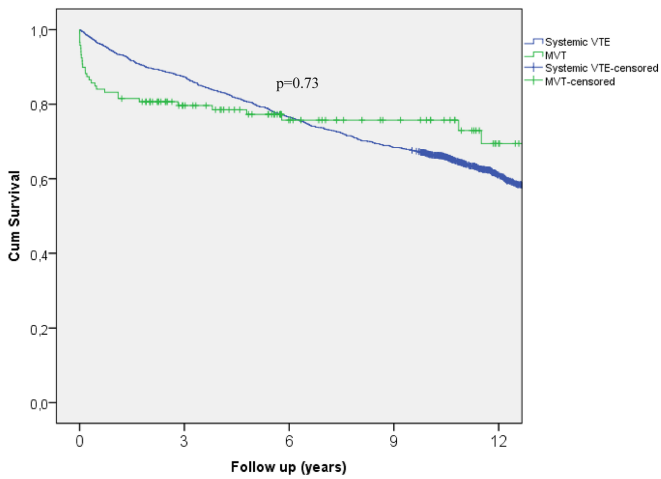

Fig. 1 Kaplan–Meier analysis of long-term survival in patients with mesenteric venous thrombosis (MVT) and systemic venous thromboembolism (VTE). Life table showing patients at risk at each time point. Standard error of cumulative proportion surviving at end of interval is stated within parentheses. Censored patients are marked with ticks

Patients at risk:	120 (0.04)	75 (0.04)	48 (0.04)	36 (0.05)	17 (0.09)	**MVT**
	1452 (0.01)	1267 (0.01)	1111 (0.01)	992 (0.01)	610 (0.02)	**Systemic VTE**

(24.7% versus 37.6%; p = 0.015). The prevalence of factor V Leiden mutation without presence of cancer was also lower in MVT compared to VTE (26.6% versus 38.9%; p = 0.031). There was no difference in prevalence of the prothrombin (PT) mutation between the two groups (Table 2).

Comparison of survival in patients with mesenteric venous thrombosis versus systemic VTE

Thirty-day mortality was higher in the MVT group (10.8% versus 0.5% in VTE; p < 0.001), but did not differ at long-term follow-up according to the Kaplan–Meier analysis (p = 0.73) (Fig. 1). The cause of the 13 deaths in the MVT group at 30 days were the following: Intestinal ischaemia (n = 9), liver cirrhosis (n = 2), pulmonary embolism (n = 2) and pancreatic cancer with metastasis (n = 2). Among these 13 deaths, eight patients underwent clinical autopsy and additional two underwent bowel resection during surgery. The cause of the seven deaths in the VTE group at 30 days were the following: Metastatic cancer (pulmonary [2], pancreatic [1] and unknown [1]) disease (n = 4), operation for gastric cancer (n = 1), pulmonary embolism (n = 3), acute

myocardial infarction with multiple arterial embolization (n = 2) and cerebral haemorrhage (n = 1). Among these seven deaths, three underwent clinical autopsy and additional one was operated upon. As multiple causes of death were registered for some patients, the number of causes exceeds the number of patients in each group.

Discussion

Patients with MVT and systemic VTE have different risk factor profile as shown in this population-based comparative study. Patients with MVT have a higher prevalence of cancer, and the present study data suggests that intra-abdominal cancer should simultaneously be excluded at the diagnostic CT examination of the abdomen for MVT. Screening for occult cancer in the chest, breast, cervix or prostate, showed a low prevalence of occult cancer in patients with first unprovoked systemic VTE, not increasing after adding a CT examination of the abdomen and pelvis [11]. The high prevalence of factor V Leiden mutation without presence of cancer in both groups, 27% in MVT and 39% in systemic VTE, suggests that screening for thrombophilia may be considered in both study groups. The much higher 30-day mortality of 10.8% in the MVT group, mostly caused by intestinal infarction, is of particular concern, and anxiety of recurrence of MVT, development towards intestinal infarction and death, may lead to both unselected screening for thrombophilia and consideration of life-long anticoagulation treatment, especially in the absence of a sole reversible risk factor such as first episode of acute pancreatitis and trauma [12, 13].

The vast majority of patients will receive indefinite anticoagulation treatment due to their high MVT related mortality [1, 4]. For patients in whom the decision of indefinite anticoagulation is made due to the presence of a non-reversible strong risk factor, such as active cancer, further thrombophilia testing has no clinical consequences. The principle of indefinite treatment in patients without detection of any risk factor is in line with current American College of Chest Physicians guidelines for VTE, recommending indefinite anticoagulation treatment for patients "with a first VTE that is an unprovoked proximal DVT of the leg or PE and who have a low or moderate bleeding risk" [14].

Importantly, testing for thrombophilia including both inherited factors such as Factor V Leiden mutation, prothrombin gene mutation, and deficiencies of protein C, protein S, antithrombin, and acquired thrombophilic factors such as Janus kinase 2 v617F (JAK2) mutation, lupus anticoagulant, and cardiolipin antibodies is not expensive in relation to other diagnostic tests. Current price at the present study centre is 302 € [15]. The duration of anticoagulation therapy in patients with an identified non-reversible provoking factor such as Factor V Leiden mutation is a matter of debate on the other hand [4]. In a population-based study including 900 VTE patients, patients with heterozygous FVL mutation had an increased risk (Odds ratio 2.4) for new VTE recurrence during a mean follow up of 5 years [8]. The high rate of inherited and acquired prothrombotic factors present in patients with MVT [7] and potential severe clinical consequences of recurrence makes experts tend to offer patients with identified laboratory-confirmed thrombophilia indefinite anticoagulation, despite low level of evidence. Consequently, routine laboratory screening may be considered in patients with MVT without an identified provocative factor on CT scan. The European Society of Vascular Surgery guidelines recommend lifelong anticoagulation in patients with MVT with proven thrombophilia [4].

The limitations of the study are attributed to the retrospective design of data collection in patients with MVT, whereas systemic VTE data in MATS were prospectively registered. The finding that MVT patients were less likely smokers than patients with systemic VTE might have been attributed to younger age [16] and retrospective data sampling in the MVT group. The younger age of MVT patients is more difficult to explain taking into account that the prevalence of cancer, which increases with age [17], was higher in this group, and that an aged subgroup of six individuals with MVT detected at autopsy were included in the MVT group. This age discrepancy between the two groups needs to be externally validated in another comparative cohort study. In fact, it seems likely that younger age in the MVT group is a factor contributing to the absence of mortality difference at long-term.

Only Factor V Leiden and prothrombin mutation was documented for the systemic VTE patients in MATS, whereas a full thrombophilia panel with eight tests including JAK2 mutation [7] was available for 74% in the MVT cohort. In contrast to the prevalence of heterozygous FVL mutation, the small sample size of patients with homozygous FVL mutation makes evaluation of differences in prevalence between the two groups impossible. It would have been very interesting to evaluate differences in prevalence of JAK2 mutation and clinical consequences between these two groups, considering the relative high incidence of myeloproliferative neoplasm in the MVT group [5]. A prospective large nationwide cohort study with sufficient number of patients with both MVT and systemic VTE is needed to evaluate differences in risk factor profiles of other thrombophilias than factor V Leiden and prothrombin mutation. Novel candidate markers for venous thrombosis such as plasminogen activator inhibitor-1 should then be considered in the test panel [18, 19]. Since thrombophilia profiles may vary greatly in different populations [7, 20], the fact that the compared cohorts are from the same population constitutes an important strength of the present study.

In conclusion, patients with MVT have different risk factor profile than those with systemic VTE; higher prevalence of cancer and lower prevalence of factor V Leiden mutation. Intra-abdominal cancer should be excluded in MVT patients, and the high prevalence of factor V Leiden mutation without presence of cancer in both groups suggests that screening for thrombophilia in patients without cancer should be considered in this population for both groups unless the clinician beforehand irrespective of thrombophilia can decide to give indefinite anticoagulation.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interests.

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