Splanchnic vein thrombosis and myeloproliferative neoplasms: molecular-driven diagnosis and long-term treatment

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Summary
Splanchnic vein thrombosis (SVT) encompasses Budd-Chiari syndrome (BCS), extrahepatic portal vein obstruction (EHPVO), and mesenteric vein thrombosis. Philadelphia-negative myeloproliferative neoplasms (MPNs) are the leading systemic cause of non-cirrhotic and non-malignant SVT and are diagnosed in 40% of BCS patients and one-third of EHPVO patients. In SVT patients the molecular marker JAK2 V617F is detectable up to 87% of those with overt MPN and up to 26% of those without. In the latter, other MPN molecular markers, such as mutations in JAK2 exon 12, CALR and MPL genes, are extremely rare. Immediate anticoagulation with heparin is used to treat acute patients. Upon clinical deterioration, catheter-directed thrombolysis or a transjugular intrahepatic portosystemic shunt is used in conjunction with anticoagulation. Orthotopic liver transplantation is the only reliable option in BCS patients with a lack of a response to other treatments, without contraindication due to MPN. Long-term oral anticoagulation with vitamin K–antagonists (VKA) is recommended in all SVT patients with the MPN-related permanent prothrombotic state; the benefits of adding aspirin to VKA are uncertain. Cytoreduction is warranted in all SVT patients with an overt MPN, but its appropriateness is doubtful in those with molecular MPN without hypercythaemia.

Keywords
Budd-Chiari syndrome, extrahepatic portal vein obstruction, mesenteric vein thrombosis, Philadelphia-negative myeloproliferative neoplasms, antithrombotic treatment

Introduction
Budd-Chiari syndrome (BCS), extrahepatic portal vein obstruction (EHPVO), and mesenteric vein thrombosis (MVT) are three autonomous diseases that largely involve localized sites within the body, although the contemporary involvement of additional regions is not rare, and clinical presentations and risk factors can be shared (1, 2).

The term splanchnic vein thrombosis (SVT) encompasses either BCS and EHPVO and any multiple or isolated occlusions of veins that constitute the portal venous axis.

The annual incidence is 0.4 to 0.8 per million individuals in Western countries (3–5) and 0.1 per million in Japan (3) for BCS and 2.7 per 100,000 individuals for superior MVT (6). In a population-based study conducted on the all autopsies performed in the city of Malmö, the rate of portal vein thrombosis found at autopsy was 1% of cases: the leading causes were malignancy or cirrhosis, whereas non-malignant and non-cirrhotic EHPVO was 0.3% of cases (7).

Risk factors for SVT can be local or systemic, and the latter are influenced by inherited or acquired conditions. Malignancy, cirrhosis, infectious or inflammatory diseases, abdominal surgery or trauma, thrombophilia and myeloproliferative neoplasms (MPNs) are common conditions associated with SVT; important sex-associated risk factors are use of oral contraceptives, hormone replacement therapy, pregnancy and puerperium (8). The combination of multiple concurrent factors is present in up to half of the patients with BCS and up to two-thirds of patients with portal vein thrombosis (8).

Inherited thrombophilia is found in a high percentage of patients with non-cirrhotic and non-malignant SVT. In a meta-analysis the pooled prevalence of deficiency of natural anticoagulants antithrombin, protein C and protein S was 9.1% for BCS and 12.1% for EHPVO (9). A high prevalence near 10% of the prothrombin G20210A mutation has been consistently reported in patients with EHPVO (10–13), whereas factor V Leiden mutation appears to be more common in BCS patients up to 25% (13–15).

Meta-analyses showed a four- to five-fold increased risk for prothrombin G20210A mutation in EHPVO patients and a two- to six-fold increased risk for factor V Leiden mutation in BCS patients (12, 13).

The leading cause of non-cirrhotic and non-malignant SVT are MPNs, which are diagnosed in 40% of BCS patients and one-third of EHPVO patients (8, 13, 14, 16–19). Recently, the pathogenetic...
and clinical features of the SVT which are MPN-related have been extensively reviewed (20); in the present review on this issue, we will further focus on the diagnostic tools at molecular and histological level of the underlying MPN, including information on the recently identified calreticulin (CALR) mutations, and we will discuss the strategies of long-term antithrombotic and cytoreductive treatments.

Review criteria

The information for this narrative review article was retrieved by searching the MEDLINE database for relevant studies published in English up to June 2015, using as key words the MeSH terms and other pertinent terms. The main search terms were: “Budd-Chiari syndrome”, “portal vein thrombosis”, “extrahepatic portal vein obstruction”, “mesenteric vein thrombosis”, “splanchnic vein thrombosis”, “Philadelphia-negative myeloproliferative neoplasms”, “polycythemia vera”, “essential thrombocytopenia”, “primary myelofibrosis”, “JAK2 mutation”, “JAK2 46/1 haplotype” “MPN mutation” “CALR mutation”, “TET2 mutation”, “antithrombotic treatment”, “cytoreductive treatment”. We considered only full-text papers, including electronic early-release publications, and the meeting abstracts published in 2015 and with contents not available in a full-text paper. We included retrospective and prospective patient cohort studies, as well as narrative reviews and meta-analyses. A complementary manual search of the reference lists of relevant articles was also performed.

Splanchnic vein thrombosis and myeloproliferative neoplasms

A meta-analysis demonstrated that the prevalence of MPNs was 40.9% and 31.5% in 1,062 patients with BCS and 855 patients with EHPVO in whom cirrhosis and hepatobiliary cancers were excluded, respectively (19). Polycythemia vera (PV) is the most common type of MPN in patients with SVT (52.9% in BCS and 27.5% in EHPVO), followed by essential thrombocythaemia (ET) (24.6% in BCS and 26.2% in EHPVO) and primary myelofibrosis (PMF) (6.7% in BCS and 12.8% in EHPVO) (19).

The incidence of major thrombosis in PV and ET derives mainly from observational and retrospective studies (21). Thromboses involve arteries in approximately two-thirds of cases in both disorders. The incidence of major and minor arterial and venous thromboses ranged from 1.1% to 4.9% per year in PV and from 1.3% to 6.6% per year in ET (21). Such figures vary mainly according to age and previous thrombosis, which are the two main factors consistently identified as predictors of thrombosis and are currently used for risk stratification (22).

SVT occurs in 0.9-5% of patients with PV (19, 23) and 3-10% of those with ET (23–27) and accounts for 7.5% of first thromboses (28). The annual incidence of SVT during follow-up is 0.1% for both PV and ET patients (26, 29), suggesting in them a risk exceedingly higher than in the general population. The current practice guidelines recommend the routine screening for MPN in SVT patients (30, 31). However, the diagnosis of MPN in this setting is somewhat difficult. Because splenomegaly is mistakenly associated with the occurrence of portal hypertension from SVT alone, hypereosinophilia is often masked by portal hypertension-related hypereosinophilia and haemodilution or gastrointestinal bleeding, and an inappropriately elevated level of erythropoietin can originate from hepatic ischaemia in BCS patients (32, 33).

Molecular-driven diagnosis of MPN-related splanchnic vein thrombosis

According to the high probability of association with MPN, the patients with SVT should be deeply investigated by either molecular and histological tools in order to unravel underlying diseases. In this part we will focus on such diagnostic tools, with emphasis on the molecular markers allowing to disclose the presence of a clonal disorder.

Until the mid-1990s, the so-called occult MPN was diagnosed based on spontaneous endogenous erythroid colonies (EEC) (growth of erythroid colonies in the absence of exogenous erythropoietin) (18), which allowed recognition of MPN in the early stages. However, the assay demands special technical facilities and is not fully standardised, with a specificity less than 80% (32, 34).

In the last decade, knowledge of the somatic mutations associated with MPNs has been greatly improved (35) and is a cornerstone of the diagnosis of Philadelphia-negative MPN (36). The novel findings on the molecular stratification of MPNs have been recently updated. Almost all patients with PV harbour a somatic activating mutation in JAK2 exon 14 (approx. 96%, V617F) and in JAK2 exon 12 (approx. 3%). JAK2 V617F also occurs in ET and PMF, with respective mutational frequencies of 55% and 65%. CALR is a multi-functional calcium-binding protein mostly localised in the endoplasmic reticulum. CALR mutations are rare in PV but occur in 25–35% of patients with PMF and 15–24% with ET. MPL mutations occur in approximately 4% of ET patients, 8% of PMF patients, and rarely in PV. MPL mutations cluster in exon 10, the most frequent being MPL W515L/K. MPL S505N is both a germline (hereditary thrombocytopenia) and somatic (ET) mutation (37).

JAK2 V617F mutation

The close relationship between MPNs and SVT has been confirmed by the current high prevalence of the JAK2 V617F mutation among patients with BCS and EHPVO (Table 1) (19, 38, 39). Evidence that the splanchnic vessels’ endothelium harbours the JAK2 V617F mutation (40, 41) reinforces the role of the clonal myeloproliferation as directly involved in the pathogenesis of thrombosis possibly via a site-specific endothelial dysfunction.

Currently, the JAK2 V617F mutation is widely applied in the diagnostic approach to SVT: in a meta-analysis of 831 patients, the mutation was detected in 33% of patients overall and in 49% of idiopathic cases (38). In contrast, JAK2 V617F mutation was
detectable in less than 1% of patients with venous thrombosis of the common sites, confirming a strong site-linked specificity of JAK2 V617F-associated thrombosis (38). In a subsequent meta-analysis of 555 patients with BCS and 858 with portal vein thrombosis, patients were stratified according to the site of thrombosis: in patients who had undergone a complete diagnostic work-up for MPN, the pooled prevalence of JAK2 V617F mutation was 44% and 25% in patients with BCS and portal vein thrombosis, respectively. After pre-existing MPN was excluded, the pooled prevalence decreased to 27% and 13% (39) (Table 1).

In the aforementioned meta-analysis conducted by Smalberg et al. (19), JAK2 V617F screening in patients without typical hematologic features of MPN was positive in 17% of BCS patients and 15% of EHPVO patients (Table 1). However, it should be noted that the JAK2 V617F mutation has a low negative predictive value, being absent in approximately 40% of patients with ET or PMF.

Additionally, several recent studies suggested that the JAK2 V617F mutation is rare in Chinese patients with BCS (42–44). Further studies also confirmed the difference in the etiological distribution of BCS between Western countries and China (45, 46). Although the presence of a membranous web that obstructs the terminal portion of the inferior vena cava is a rare cause of BCS in Western countries, it causes a large majority of cases in Oriental countries (3). There is evidence that these occluding membranous webs are not congenital, but are the late-stage sequelae of a previous thrombotic obstruction of the inferior vena cava (3). As a consequence, the role of JAK2 V617F in this setting can be strongly downsized in Oriental countries.

By comparison, the prevalence of the JAK2 V617F mutation in Chinese patients with EHPVO was comparable to the Western data (42, 47).

**CALR mutations**

Recently, the prevalence of CALR exon 9 mutations, highly represented in ET and PMF patients, has been further evaluated in SVT patients (Table 2). Turon et al. (48) screened the CALR mutations in 209 SVT patients. Only four (1.9%) had a positive CALR mutation. In another large study on 308 SVT patients, five (2%) had a positive CALR mutation (49). Despite such a low probability of the CALR mutation in SVT, its potential applications should be further emphasised. In these two studies an overt MPN was diagnosed in 74 (35.4%) and 69 (22.4%) patients, respectively. Among them, 61 (82.4%, 61/74) and 56 (81.1%, 56/69) patients with MPN had a positive JAK2 V617F mutation; pooling the two studies, all the 9 patients with positive CALR mutations were attributed to the JAK2 V617F mutation-negative MPN group (n=26). Thus, the prevalence of CALR mutations in SVT patients with MPN and without the JAK2 V617F mutation should be higher (34.6%, 9/26). This finding suggests that screening for CALR mutations would be appropriate only in the absence of the JAK2 V617F mutation. On the opposite, in other studies of smaller size (50–55) CARL mutations were detected in SVT patients only anecdotally (Table 2).

**MPL exon 10 and JAK2 exon 12 mutations**

Kiladjian et al. screened the MPL exon 10 and JAK2 exon 12 mutations in 212 and 123 SVT patients, respectively. However, the prevalence of the two mutations was null (34). Similar results were obtained in a series of 66 BCS patients (56). Moreover, Fiorini et al. (57) did not find any positive JAK2 exon 12 mutations in 52 SVT patients. Only four (1.9%) had a positive CALR mutation. In another large study on 308 SVT patients, five (2%) had a positive CALR mutation (49). Despite such a low probability of the CALR mutation in SVT, its potential applications should be further emphasised. In these two studies an overt MPN was diagnosed in 74 (35.4%) and 69 (22.4%) patients, respectively. Among them, 61 (82.4%, 61/74) and 56 (81.1%, 56/69) patients with MPN had a positive JAK2 V617F mutation; pooling the two studies, all the 9 patients with positive CALR mutations were attributed to the JAK2 V617F mutation-negative MPN group (n=26). Thus, the prevalence of CALR mutations in SVT patients with MPN and without the JAK2 V617F mutation should be higher (34.6%, 9/26). This finding suggests that screening for CALR mutations would be appropriate only in the absence of the JAK2 V617F mutation. On the opposite, in other studies of smaller size (50–55) CARL mutations were detected in SVT patients only anecdotally (Table 2).

**Table 1: Prevalence of myeloproliferative neoplasms (MPNs) and the JAK2 V617F mutation in patients with splanchnic vein thrombosis (SVT), Budd-Chiari syndrome (BCS), and portal vein thrombosis (PVT).**

| Reference | Type of SVT | Patients (n) | JAK2 V617F % | Overt MPN % | JAK2 V617F % | JAK2 V617F %
<table>
<thead>
<tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>All patients</td>
<td>MPN patients</td>
<td>No-MPN patients</td>
</tr>
<tr>
<td>Dentali et al. 2009 [38], meta-analysis</td>
<td>not specified</td>
<td>831</td>
<td>280/831 (32.7%)</td>
<td>77/131 (59.5%)</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Qi et al. 2011 [39], meta-analysis</td>
<td>BCS + PVT + not specified</td>
<td>1697</td>
<td>42/1697 (25.1%)</td>
<td>280/1063 (26.3%)</td>
<td>343/1063 (32.2%)</td>
<td>213/280 (76.1%)</td>
</tr>
<tr>
<td></td>
<td>BCS</td>
<td>555</td>
<td>177/555 (31.8%)</td>
<td>77/242 (31.8%)</td>
<td>106/242 (43.8%)</td>
<td>62/77 (80.5%)</td>
</tr>
<tr>
<td></td>
<td>PVT</td>
<td>858</td>
<td>250/858 (29.1%)</td>
<td>86/532 (16.1%)</td>
<td>136/532 (25.5%)</td>
<td>75/86 (87.2%)</td>
</tr>
<tr>
<td>Smallberg et al. 2012 [19], meta-analysis</td>
<td>BCS</td>
<td>1062</td>
<td>159/401 (41.1%)</td>
<td>180/440 (40.9%)</td>
<td>188/440 (42.7%)</td>
<td>144/180 (80.3%)</td>
</tr>
<tr>
<td></td>
<td>PVT</td>
<td>855</td>
<td>166/595 (27.7%)</td>
<td>188/615 (31.5%)</td>
<td>228/615 (37.0%)</td>
<td>162/188 (86.6%)</td>
</tr>
</tbody>
</table>

*Including only patients with non-cirrhotic and non-malignant SVT who received a complete diagnostic work-up for MPN. § including 91 patients with cirrhosis, 5 of them JAK2V617F-positive. N/A: not available.
SVT patients. Only three patients had a positive MPL W515K mutation, but two of them had been previously diagnosed as ET based on a regular blood test and bone marrow biopsy, and another one had a positive JAK2 V617F mutation. In addition, neither MPL W515L nor JAK2 exon 12 mutations were positive. MPL mutations were not detected in another series of 132 patients with EHPVO (55).

**JAK2 46/1 haplotype**

A series of studies demonstrated that the germline JAK2 46/1 haplotype is strongly associated with the JAK2 V617F somatic mutation, and its presence also has been associated with either JAK2 V617F-positive or JAK2 V617F-negative MPNs (59–61). Therefore, if a certain JAK2 haplotype associated with the JAK2 V617F somatic mutation can represent a predisposition to MPN, it is conceivable that it may be an independent risk factor for SVT. This hypothesis has been explored in a case-control study on 90 SVT patients selected without a diagnosis of MPN and without the JAK2 V617F mutation and 181 healthy controls; the 46/1 genotype is tagged by the C allele, and the CC homozygous genotype frequency was significantly higher than that observed in controls (11.1% vs 2.8%, odds ratio [OR] 4.4, 95% confidence interval [CI] 1.5–13.3). The association was higher in patients with portal-mesenteric venous thrombosis, and no CC carriers were found among patients with BCS (62).

Smalberg et al. (63) investigated 199 patients with SVT and 100 healthy controls. The overall C allele frequency was increased in the JAK2 V617F-positive BCS patients (43%, p=0.01) and EHPVO patients (40%, p=0.1) compared to the controls (27%); no increase was found either in the JAK2 V617F-negative BCS and EHPVO patients (33% and 24%, respectively).

Similar results were obtained by Villani et al. (64) on 164 SVT patients (56 without a diagnosis of MPN) and 56 healthy controls. Patients with no MPN or with JAK2 V617F-negative MPN had a C allele frequency similar to the controls, whereas in the JAK2 V617F-positive MPN patients, the C allele frequency was significantly increased compared to the controls (50.6% vs 26.7%, p=0.0001). A recent meta-analysis of 26 observational studies involving 8,561 cases and 7,434 controls provides evidence that the JAK2 46/1 haplotype is significantly and independently associated with an increased risk of MPN and SVT. This study also suggests an association between the 46/1 haplotype and the development of JAK2 V617F-positive SVT, whereas no association was observed in V617F-negative SVT patients compared to control groups (65). Overall, such observations suggest that the 46/1 haplotype is a susceptibility factor for the JAK2 V617F mutation rather than an independent risk factor for SVT.

**TET2 mutations**

The DNA base 5-hydroxymethylcytosine (5-hmC) is the product of the hydroxylation of 5-methylcytosine (5-mC) by the ten-eleven translocation (TET) oncogene family members. One of them, TET oncogene family member 2 (TET2), is mutated in a variety of myeloid malignancies, including in 15% of MPN. Although its precise function remains partially unknown, TET2 appears to be an important regulator of hematopoietic stem cell biology (66).

In a series of 66 BCS patients, the JAK2 V617F mutation was present in 52% of cases; MPL and JAK2 exon 12 mutations were not detected in any cases. Forty-three patients were analysed for a TET2 mutation, and eight were identified. Of the six patients with a deleterious TET2 mutation, one had an MPN at diagnosis, and one developed an MPN 22 months after presentation; both patients also had the JAK2 V617F mutation. None of the patients with a TET2 mutation in isolation (n=3) or both TET2 and JAK2 mutations (n=1) developed overt MPN after a median follow-up of 45 months. In conclusion, testing for TET2 mutations identified in this cohort 7% (3/43) of BCS patients with this only known molecular marker of MPN (56).

**Other tools for diagnosis of MPN**

**Bone marrow biopsy**

In two series of 93 and 241 non-cirrhotic and non-malignant SVT patients, JAK2 V617F mutation was detected in 36% and 39% of

### Table 2: Prevalence of CALR mutations in patients with splanchnic vein thrombosis (SVT), Budd-Chiari syndrome (BCS), and portal vein thrombosis (PVT).

<table>
<thead>
<tr>
<th>Reference</th>
<th>SVT patients, n</th>
<th>CALR mutations, n (%)</th>
<th>CARL-mutated patients</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Type of MPN Type of SVT</td>
</tr>
<tr>
<td>Turol et al. 2015 [48]</td>
<td>209</td>
<td>4 (1.9%)</td>
<td>ET= 3 PMF= 1</td>
</tr>
<tr>
<td>Marzac et al. 2015 [49]</td>
<td>308</td>
<td>5 (2%)</td>
<td>ET= 1 PMF= 4</td>
</tr>
<tr>
<td>Haslam et al. 2015 [50]</td>
<td>144</td>
<td>0</td>
<td>N/A</td>
</tr>
<tr>
<td>Roques et al. 2015 [51]</td>
<td>66</td>
<td>1 (1.5%)</td>
<td>not specified</td>
</tr>
<tr>
<td>Castro et al. 2015 [52]</td>
<td>40</td>
<td>0</td>
<td>N/A</td>
</tr>
<tr>
<td>Iurlo et al. 2015 [53]</td>
<td>29</td>
<td>0</td>
<td>N/A</td>
</tr>
<tr>
<td>Plompen et al. 2015 [54]</td>
<td>141</td>
<td>1 (0.7%)</td>
<td>PMF PVT</td>
</tr>
<tr>
<td>Colaizzo et al. 2015 [55]</td>
<td>132</td>
<td>0</td>
<td>N/A</td>
</tr>
<tr>
<td>Total</td>
<td>1,066</td>
<td>10 (0.9%)</td>
<td>ET= 4 PMF= 6</td>
</tr>
</tbody>
</table>

ET: essential thrombocythaemia; N/A: not available; PMF: primary myelofibrosis.
cases, respectively. Among the JAK2 V617F-negative cases, bone marrow biopsy (BMB) was diagnostic for MPN in 28% and 7%, respectively (34, 67). In the large cohort of 241 SVT patients, the rate of ET and PMF diagnosed by BMB alone in the absence of JAK2 V617F, JAK2 exon 12, and MPL 515 mutations was 7% (10/144) (34). Conversely, the JAK2 V617F mutation has been found to be positive in 6% and 18% of SVT patients with negative BMB, respectively (34, 67). Such high discrepancy in the reported diagnostic yield obtained by BMB likely mirrors the substantial inter-observer variability that has been reported in applying the histological criteria described in the WHO classification (68, 69). However, in the setting of non-cirrhotic and non-malignant SVT BMB is recommended in either JAK2 V617F-positive patients in order to refine the diagnosis of MPN according to the WHO criteria, and in JAK2 V617F-negative patients in order to capture additional cases of MPN (Figure 1).

Measurement of red cell mass

In a cohort of 241 patients with SVT, the measurement of red cell mass (RCM) allowed for a definite diagnosis of PV in the JAK2V617F-positive SVT cases with masked erythrocytosis (34). In the same cohort, RCM demonstrated absolute erythrocytosis in 11 patients with EHPVO without the JAK2 V617F mutation and no evidence for MPN in BMB. In 10 patients, serum erythropoietin levels were elevated, suggesting reactive erythrocytosis. Therefore, RCM seems of limited value in the diagnostic work-up of JAK2 V617F-negative patients (34).

In conclusion, RCM could be useful in refining diagnosis of the patients JAK2 V617F-positive and maybe could be applied in the patients JAK2 V617F-negative who have bone marrow histology for MPN.

Diagnostic strategy

SVT patients should be first investigated for neoplasia and liver diseases, which are the commonest underlying causes. Investigation of the JAK2 V617F mutation and a complete laboratory work-up for thrombophilia is mandatory in patients with non-cirrhotic and non-malignant SVT. In those with the JAK2 V617F mutation BMB could help to refine diagnosis according to the WHO criteria; in this setting the RCM could give additional useful information to identify patients with masked PV. On the other hand, BMB could capture additional diagnosis of MPN in a not trivial portion of patients JAK2 V617F-negative. In the latter, a complete molecular diagnostic work-up including CALR, MPL, and exon 12 mutation should be reserved only for those with BMB highly suggestive of MPN (Figure 1).

Overall, it should be acknowledged that not all centres have the ability to perform a complete molecular screening and that not all centres can count on a pathologist skilled in the diagnosis of MPN. In addition, the RCM is becoming difficult to obtain because the $^{51}$Cr isotope needed to perform the test is no longer readily available, and institutions willing to perform the test are few as a result of small demand and lack of profit in performing the test. Therefore, multicentre networks for centralised diagnosis of MPN are warranted.

Follow-up and long-term treatment

Treatment of patients with SVT associated with MPN should be based on either antithrombotic and cytoreductive treatment. In this part we will focus on the long-term therapeutic strategies and the prognosis of such patients as for either event-free survival and overall survival.

Treatment at diagnosis

In the acute phase, the treatment of patients with SVT and with Philadelphia-negative MPN does not differ from that of patients without MPN. They should be treated promptly with low molecular or unfractionated heparin followed by vitamin K antagonists (VKA), sodium restriction, diuretic therapy and paracentesis, if necessary (1, 2, 30). In the case of clinical deterioration despite anticoagulation, patients with BCS should be considered for invasive procedures, such as angioplasty with or without stenting, transjugular intrahepatic portosystemic shunt (TIPS) or surgical portosystemic shunt (1). In patients with SVT, systemic thrombolytic therapy with tissue plasminogen activator is of little value, whereas
catheter-directed thrombolysis may be effective in acute and partially occlusive thrombosis (70–72).

In a multicentre prospective registry of SVT patients anticoagulant drugs are employed in almost the totality of MPN patients (48/50) and only in 60% of those with liver cirrhosis (101/166) and 69% of those with solid cancer (94/136), likely mirroring the higher prevalence of thrombocytopenia in the latter populations (73). In this cohort 29.8% of patients had incidental diagnosis of SVT, likely due to the increased use of routine imaging tests. However, 62.5% of them (110/176) received an anticoagulant treatment (73). Current guidelines from the American College of Chest Physicians (ACCP) suggest no anticoagulation over anticoagulation in patients with SVT incidentally detected; indeed, the presence of a permanent risk factor such as MPN is considered an acceptable reason to support anticoagulant treatment (74).

Orthotopic liver transplantation
Failure of the aforementioned interventions occurs in 10–20% of patients with BCS, who are therefore candidates for orthotopic liver transplantation (OLT) (15). In a series of 36 BCS patients, the one-year survival rate was 84% and the five-year survival rate was 69%; the mortality rate after OLT was not affected by the presence of a molecular MPN (56). In another series of 25 BCS patients, the overall mortality rate after OLT was not different between MPN patients (3/18, 16.7%) and the non-MPN patients (1/7, 14.3%) (75).

In a recent retrospective cohort of 78 BCS patients, there was no significant difference between the MPN (n=41) and the non-MPN (n=37) groups with regard to long-term survival (5-year survival 78% vs 76%, respectively, p=0.81; 10-year survival 68% vs 73%, respectively, p=0.66). Twelve of the 41 MPN patients (29%) died within the first three years after OLT, but death was related to the haematologic disease only in one case with recurrent BCS (76). Among survivors, no progression to myelofibrosis or acute leukaemia was observed during a mean follow-up time of 12.4 years (range 3–28.4 years) (76), confirming the absence of MPN evolution reported in a series of 17 BCS patients even at long-term follow-up of up to 20 years after OLT (77).

Follow-up
Patients with SVT who show no additional signs of haematologic disease other than the JAK2 V617F mutation at the time of thrombosis have an overt MPN development rate as high as 52% during the follow-up period (38). In a more recent meta-analysis, among the reported JAK2 V617F-positive SVT patients without typical haematologic MPN features, 11 of 28 with BCS (41%) and 6 of 48 with EHPVO (13%) developed characteristic laboratory or morphologic features of MPN, ranging from 0.7 to 10 years after the diagnosis of thrombosis (19).

We should not neglect the probability that MPNs can develop in SVT patients without any evidence of mutations or diagnostic BMB. Colalizzo et al. (78) identified 80 JAK2 V617F mutation-negative SVT patients without overt MPN from a cohort of 121 patients investigated for the mutation. Among those JAK2 V617-negative cases, 10% (8/80) developed MPNs during the follow-up period. This finding suggests that all SVT patients should be carefully observed for a future development of MPN independently of the detection of a diagnostic mutation.

Prognosis
The prognosis of BCS is greatly improving with time (79). Evaluating the effect of MPNs on the survival of SVT patients is clinically important. If MPNs predicted a worse survival of SVT, early diagnosis is advisable. To clarify this issue, the results from several representative studies should be emphasised.

First, Thatipelli et al. (80) have reported the largest number of SVT patients from a single centre. Among the 832 SVT patients included, 329 had portal vein thrombosis alone, 76 had MVT alone, 62 had splenic vein thrombosis alone, 45 had hepatic vein thrombosis alone, and 320 had multi-segment involvement. In the multivariate analysis, MPN was identified as the independent predictor of mortality (hazard ratio [HR] 1.92, 95% CI 1.41–2.61); it should be noted that active cancer and liver cirrhosis were not excluded from their study.

Second, Kiladjian et al. (34) also conducted a large retrospective study in three European hospitals, in which 241 SVT patients, including 137 non-cirrhotic and non-malignant EHPVO patients and 104 BCS patients, were enrolled. Neither the event-free nor overall survival was related to the presence of MPN in non-cirrhotic and non-malignant EHPVO patients. Additionally, the presence of MPN was significantly associated with the event-free survival in BCS patients (p=0.0145 by log-rank test) but not the overall survival (p=0.961 by log-rank test). According to the viewpoints from the investigators, this finding could be explained by the two following points: 1) BCS-related events developed in patients with MPN more frequently and earlier, and 2) early treatment should be immediately and effectively employed, thereby improving survival. However, it appeared to be inconsistent with the findings from a prospective European multi-centre study by Darwish-Murad et al. (15), where the presence of MPN or the JAK2 mutation was not associated with a higher rate of invasive interventions in BCS patients. Indeed, the presence or absence of MPN was not included in any important prognostic indexes of BCS (81–83).

Third, in 2001, Janssen et al. (16) studied 172 adult EHPVO patients in eight Dutch University hospitals. Among them, 24 were diagnosed with MPN. The five-year survival rate was not significantly different between patients with and without MPN (88% vs 56%, p=0.12). In another study from the same centre, 40 patients with BCS were analysed, 13 of whom had MPN; the 10-year survival rate did not significantly differ between patients with and without MPN (92% vs 53%, p=0.18) (82). Since 2010, the same study team conducted another three studies regarding the prognosis of EHPVO patients (85–87). In contrast to the previous findings (16), they found that the underlying MPNs significantly increased mortality in non-cirrhotic and non-malignant patients with EHPVO (85–87). Notably, nearly half of death events were
attributed to the end-stage MPNs or acute myeloid leukaemia in EHPVO patients with underlying MPN (86). Certainly, the inclusion of malignancy and liver cirrhosis in the earlier study might diminish the prognostic significance of MPNs in EHPVO patients (16). Additionally, the diagnostic strategy of MPNs has been greatly improved during the periods, so that in the latter studies more MPN patients might be diagnosed with more accuracy according to the results of molecular analyses. Considering that the present findings were heterogeneous among studies, we could not conclude any definitive associations between diagnosis of MPN and survival of SVT.

On the other hand, in a cohort of 460 consecutive ET patients, a group of 17 female patients with abdominal vein thrombosis displayed a higher rate of major bleeding during follow-up, a higher conversion rate into myelofibrosis/acute leukaemia, and a shorter median survival in respect to a comparison group matched for sex, age, and year of diagnosis (25).

In a recent multicentre prospective cohort of 604 consecutive patients with SVT, 49 had MPN. In this group the mortality rate was 3.4% patient-years during the two-year follow-up period of prospective observation, much lower than that observed in patients with liver cirrhosis (16.8%) and solid cancer (39.5%), and slightly higher than that observed in patients with SVT unprovoked (2.3%) or associated with transient risk factors (2.5%) (88).

Long-term antithrombotic treatment

In unselected patients with SVT gastroesophageal varices and VKA treatment are independent predictors of bleeding (80). However, in patients with non-cirrhotic and non-malignant SVT there is evidence that therapy with VKA favours recanalisation of vessels and reduces the recurrence rate, without increasing the risk of bleeding (10, 89, 90) or the severity of variceal bleeding (87).

In a recent multicentre retrospective study on 375 unselected SVT patients treated with VKA, the incidence of major bleeding and vascular events was 1.24% and 1.37% patient-years, with gastrointestinal bleeding in 40% of the haemorrhagic events. The presence of esophageal varices was an independent predictor of major bleeding (HR 5.4, 95% CI 1.4–21.1) (91). However, beta-adrenergic blockers and eradication of varices are warranted in patients with previous variceal bleeding or with large gastroesophageal varices (30).

The optimal duration of VKA is unknown, but in general a minimum of 3–6 months for EHPVO and life-long for BCS are suggested; patients with EHPVO should receive life-long anticoagulation in the presence of permanent risk factors for thrombosis (1, 2, 30). More recently, Baveno VI consensus regarding the management of SVT also suggests that there is scarce information to recommend anticoagulation in patients with chronic EHPVO but without prothrombotic disorders; by contrast, long-term anticoagulation is recommended in patients with a persistent prothrombotic state (i.e. MPN), recurrent thrombosis or intestinal infarction (92).

In a retrospective cohort of 494 PV or ET patients with previous thrombosis, recurrence occurred in 166 patients (33.6%), with an incidence of 7.6% patient-years. Significant prevention of re-thrombosis was independently achieved in patients with venous thromboembolism by both VKA (HR 0.32; 95% CI 0.15–0.64) and antiplatelet agents (HR 0.42; 95% CI 0.22–0.77), in those with acute coronary syndrome by cytoduction (HR 0.30; 95% CI 0.13–0.68), and in those with cerebrovascular disease by antiplatelet agents (HR 0.33; 95% CI 0.16–0.66). The overall incidence of major bleeding was 0.9% patient-years and rose to 2.8% in patients receiving both antiplatelet and VKA (28).

Specific data on patients with MPN-related SVT are scarce. In a series of SVT patients, recurrent thromboses occurred in 39% of those with MPN and in 3.9% of those without, in all cases in the absence of anticoagulation (90). In a multicentre prospective cohort of 604 patients with SVT, 49 of them had MPN and showed a nine-fold increased risk of recurrent thrombosis during follow-up (88).

In a retrospective cohort of 44 patients with EHPVO and MPN (median follow-up 5.8 years, range 0.4–21), 21 (48%) received long-term therapy: nine with VKA, six with VKA plus aspirin, and six with aspirin. In addition, cytoduction was initiated with hydroxyurea in 21 cases (48%); other interventions were phlebotomies (n=10), alpha-interferon (n=8), busulfan (n=3), anagrelide (n=1). Recurrent thrombosis events occurred in 12 patients (27%), nine in the absence of antithrombotic prophylaxis and three during VKA treatment. Thus, those treated with aspirin (with or without VKA) had no recurrent thromboses, at variance with those receiving VKA alone or no antithrombotic therapy (86). However, the evaluation of such data is difficult, due to the absence of details about the association of the different cytoductive treatments with the antithrombotic prophylaxis employed. During follow-up, 17 patients (39%) experienced at least one episode of gastrointestinal bleeding. Twelve patients (27%) had progression of the underlying MPN. Seventeen patients (39%) died at a median age of 64 years (range 30–88). Death was directly related to end-stage MPN in eight patients (47%) and to a new thrombotic event in three patients (18%). No patient died from gastrointestinal bleeding (86). A weak efficacy of VKA has been reported also in a series of 36 BCS patients who had recurrent thrombosis after OLT in 42% of cases (15/36), with no difference in the mean INR between patients who developed thrombosis and patients who did not (2.73 vs 2.70, p=0.47) (56).

The use of direct factor Xa oral inhibitors (rivaroxaban) has been anecdotally reported in a patient with PV and BCS (33).

Cytoreductive treatment

In MPN patients with previous thrombosis, cytoduction is warranted (22). In the aforementioned retrospective cohort of 494 PV or ET patients with previous thrombosis, cytoduction halved the risk of recurrence (HR 0.53; 95% CI 0.38–0.73); however, the combination with antiplatelet agents or VKA was more effective than administration of single drugs (28).

Whether it is justified to give cytoduction to patients with SVT and JAK2 V617F but who do not meet the diagnostic criteria for MPN is unexplored. Approximately half of JAK2 V617F--
positive SVT patients will not develop MPN during the follow-up (38); accordingly, caution is due in prescribing cytoreductive regimens that are not evidence-based. On the other hand, JAK2 V617F mutations have been reported to be risk factors either for post-transplant thrombotic complication in BCS patients having received OLT (56) or for recurrent thrombosis after SVT (78, 93). Therefore, the use of treatments aimed at reducing the growth of the mutant clone appears reasonable.

In a small retrospective cohort of 17 patients with BCS and MPN who underwent OLT and were treated with hydroxyurea and aspirin, only one recurrent EHPVO case was recorded (77). In another small series of 18 patients with BCS and MPN, the rate of recurrence was 22% (4/18); none of the patients with recurrence had received cytoreductive treatment (75).

An overall strategy of long-term treatment based upon either antithrombotic and cytoreductive therapy according to the results of the diagnostic work-up is summarised in Figure 2.

Conclusions

The strong association between MPN and SVT is confirmed. Molecular diagnosis of MPN has greatly improved in the last decade, allowing early diagnosis in a significant portion of SVT patients, even in the absence of overt signs of haematologic disease.

Nevertheless, optimising the diagnosis of MPNs in the setting of SVT is considered by the experts as an unmet clinical need (94). In fact, the possibility that the presence of SVT-related factors potentially confounds the WHO criteria and that BMB can result in falsely negative results highlights the need for innovative studies based on molecular analyses (94).

Thrombotic potential appears dependent on the presence of the JAK2 V617F mutation much more than on the other molecular diagnostic-drivers. The optimal regimen of antithrombotic prophylaxis (VKA, aspirin or both) remains to be defined. The impact of cytoreduction with hydroxyurea has been reported to be effective in preventing recurrent thrombosis in small series of patients, but the appropriateness of using antiproliferative drugs in patients with uncertain progression to overt forms of MPN needs to be established by controlled multicentre studies (94).

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Conflicts of interest

None declared.

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