Editorial

Challenges in patients with splanchnic vein thrombosis

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Splanchnic vein thrombosis (SVT) is a heterogeneous disease which involves thrombosis in different abdominal veins, such as portal, mesenteric, splenic and supra-hepatic veins. It also includes different subgroups of patients with peculiar characteristics, such as patients with Budd-Chiari syndrome (BCS), who have a poor prognosis and frequently need interventional procedures or liver transplants (1), and cirrhotic patients, who have a delicate haemostatic balance and a higher incidence of both thromboembolic and bleeding events (2). Given the peculiarities of the cirrhotic population and in order to create a more homogeneous cohort, most studies have focused only on non-malignant non-cirrhotic SVT (3-5).

A recently published study by Jara-Palomares *et al.* (6) retrospectively evaluated 70 non-cirrhotic patients with SVT, including also 28 patients with abdominal malignancies. Of note, 77.2% were anticoagulated with low molecular weight heparin (LMWH) or vitamin K antagonist (VKA). During a median follow-up of almost 12 months, the incidence of overall clinically relevant bleeding events was 16.03 (95% CI 9.5–25.34) per 100 patient-years, while the incidence of major bleeding was 10.65 (95% CI 5.67–18.2) per 100 patient-years (6). The incidence of arterial or venous thrombotic events was 16.28 (95% CI 10.1–24.89) per 100 patient-years, with 62% of the events occurring off anticoagulant treatment (6). These data confirm that SVT patients have both an elevated risk of haemorrhagic complications and recurrent thrombotic events, thus complicating the choice of the most appropriate treatment.

It is difficult to balance the risks and benefits associated with anticoagulant treatment, since all available studies are observational, thus including heterogeneous treatment approaches, and used different definitions of bleeding [e.g., only major bleeding (7,8) or overall gastrointestinal bleeding (3,4)] or provided overall estimates of bleeding on- and off-treatment (4), thus precluding to obtain pooled estimates of the bleeding risk. We studied a prospective cohort of 604 SVT patients, of whom approximately 50% were malignant and/or cirrhotic patients, and we found an incidence of major bleeding complications of 3.9 per 100 patient-years (95% CI 2.6–6.0) during anticoagulant treatment with VKA or heparin (8). Fewer major bleeding events were reported after treatment discontinuation (1.0 per 100 patient-years, 95% CI 0.3–4.2) in patients who received anticoagulant treatment while, interestingly, the incidence rate of major bleeding was highest (5.8 per 100 patient-years, 95% CI 3.1–10.7) in those patients that were never treated (8). The incidence of thrombotic events was 5.6 per 100 patient-years (95% CI 3.9–8.0) on-treatment and 10.5 per 100 patient-years (95% CI 6.8–16.3) off-treatment (8). Thus, our data suggested a favourable risk/benefit ratio for anticoagulant treatment in SVT patients. In another cohort study specifically designed to explore the safety of VKA in 375 patients monitored by 37 Italian anticoagulation clinics, the rates of major bleeding complications on treatment were low (1.24 per 100 patient-years, 95% CI 0.75–2.06) (9).

The uncertain balance between risks and benefits of anticoagulant treatment also impacts on the decision on the optimal duration of secondary prevention of SVT. Guidelines suggest 3–6 months in patients with SVT secondary to transient reversible risk factors, while a longer indefinite treatment duration is suggested for patients with permanent risk factors, unprovoked thrombosis or

particularly severe disease (such as BCS) (10-12). Studies reported treatment durations ranging from less than a year (5) to almost 2 years (3), or even lifelong in the majority of patients (7), thus showing a certain degree of heterogeneity in the management of SVT patients in clinical practice. We found that the risk of recurrence after stopping VKA was higher in patients with permanent risk factors (10.2 per 100 patient-years, 95% CI 4.2–24.4), followed by unprovoked thrombosis (2.4 per 100 patient-years, 95% CI 0.6–9.6) and very low in patients with transient risk factors (13), thus confirming the suggestions provided by international guidelines.

Another important objective of anticoagulation in this setting is represented by vessel recanalization, which is particularly relevant in patients with portal vein thrombosis (PVT). Jara-Palomares *et al.* evaluated also the response to anticoagulant treatment defined as complete or partial resolution of the thrombosis at abdominal imaging performed during follow-up. They found that vessel recanalization was higher in patients receiving anticoagulant treatment compared to non-treated patients (47.8% *vs.* 8.3% respectively, P=0.013) (6). Previous studies reported variable recanalization rates of splanchnic veins during anticoagulant treatment, although some of them considered only complete recanalization (5,14), while others have included also partial recanalization (15,16). Furthermore, the lack of randomization raises questions on the comparability of anticoagulated and non-anticoagulated patients. Finally, it is still a matter of debate whether the lack of recanalization might constitute an additional criterion to continue anticoagulation.

In the study by Amitrano *et al.* anticoagulation achieved complete recanalization in 45.4% of patients with acute SVT (14), while Turnes *et al.* reported complete or partial recanalization in 44% of anticoagulated patients *vs.* 0% of non-anticoagulated patients (15). Furthermore, the latter study showed also that vessel recanalization was more likely to occur in patients who started heparin treatment within the first week, although the sample size was small (27 anticoagulated patients) (15). In the study by Condat *et al.*, among the 27 patients receiving anticoagulation, 37% had a complete recanalization and 56% had a partial recanalization (16). The probability of a complete recanalization was correlated with thrombus extension, being highest in patients with a thrombosis involving only the portal or the superior mesenteric veins (16). So far, the largest cohort of SVT patients in which recanalization has been systematically evaluated includes 95 patients with acute PVT early anticoagulated with heparin followed by VKA and treated for at least 6 months (5). The 1-year recanalization rate was 38% for the portal vein, 61% for the superior mesenteric vein and 54% for the splenic vein (5).

SVT is a serious disease potentially associated with a poor prognosis. Jara-Palomares *et al.* reported a mortality rate of 12.85 per 100 patient-years (95% CI 7.86–19.92), with underlying cancer accounting for 56% of deaths (6). At multivariate analysis, solid cancer increased the risk of death by more than 22 folds [hazard ratio (HR) 22.65, 95% CI 3.13–163.99], while higher albumin levels were protective (HR 0.22, 95% CI 0.08–0.57) (6).

We previously reported an overall mortality rate of 10.3 per 100 patient-years (95% CI 8.5–12.5), and found that it was significantly higher in certain subgroup of SVT patients, such as oncological (39.5 per 100 patient-years, 95% CI 31.1–50.1) and cirrhotic patients (16.8 per 100 patient-years, 95% CI 12.5–22.4) (8). Spaander *et al.*, instead, reported a 90% survival (95% CI 84–96) at 5 years and 70% survival (95% CI 58–82) at 10 years, but this study did not include patients with cancer, cirrhosis or BCS (3). Data from an unselected cohort of SVT patients also show a worse prognosis compared to thrombosis in the lower limbs, with overall survival rates at 10 years of 60% and 68%, respectively (P=0.024) (7). In addition, mesenteric veins thrombosis is associated with intestinal infarction in approximately one third of cases and carries a 30-day mortality of 20% (17), while PVT is frequently associated with the development of portal hypertension, with resulting thrombocytopenia, ascites, oesophageal varices and gastrointestinal bleeding (7).

Finally, SVT can be a marker of occult cancer. A recently published study reported that the risk of being diagnosed with a solid cancer in the first 3 months after SVT is 8%, and concerns mainly liver and pancreatic cancer, with absolute risks of 3.5% and 1.5%, respectively (18). SVT appeared to be a negative prognostic factor for survival in oncological patients: the 3-month survival after diagnosis of liver cancer was 44% in SVT patients *vs.* 55% in those patients without prior SVT, while the 3-month survival after diagnosis of pancreatic cancer was 35% in SVT patients *vs.* 53% in those patients without prior SVT (18). SVT can also be the first clinical manifestation of a myeloproliferative neoplasm (MPN): the prevalence of MPN has been reported to be 31.5% in patients with PVT and 40.9% in patients with BCS but, interestingly, in approximately three fourth of cases MPN diagnosis

actually followed the development of SVT (19).

In conclusion, SVT is a challenging disease with heterogeneous clinical presentations and underlying provoking factors that make therapeutic decisions difficult and that place patients at increased risk of short and long-term morbidity and mortality. There is a clear need to improve our knowledge on this unusual thrombotic disorder, and this can only be achieved by means of large collaborative multicentre studies.

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