We retrospectively investigated for the presence of the JAK2 mutation 76 adult patients (greater than 18 years old) with PVT or isolated mesenteric vein thrombosis (MVT) (39 men, 37 women, median age at thrombosis 49 years, range 25-78 years). They had been consecutively referred to our center for screening of thrombophilia (deficiency of natural anticoagulants, factor V Leiden, prothrombin G20210A, hyperhomocysteinemia, antiphospholipids); a preliminary evaluation had ruled out patients with overt cancer or liver cirrhosis. Among the 17 MVT patients, 7 (41%) had inherited or acquired thrombophilia and none carried the JAK2 mutation. Out of the 59 PVT patients, 19 developed thrombosis after a provoking circumstance (oral contraception in 9, surgery in 6, puerperium in 3, and trauma in 1). Twenty-two (37%) had thrombophilia and 24 (41%) the JAK2 mutation; 9 of them (15%) carried both. Eight patients, all with the JAK2 mutation, met the conventional criteria for diagnosis of PV (n = 4) or ET (n = 4) at the time of thrombosis. Two additional patients developed overt ET and myelofibrosis 8 and 4 years after thrombosis, respectively; the ET patient was JAK2-mutated. Therefore, JAK2 mutation allowed strong suspicion of CMD in 15 of the remaining 49 patients (31%). In our series, no difference in the prevalence of the mutation was found in respect to the presence of thrombophilia ($P = 1.0$) or a provoking circumstance ($P = 0.16$), in agreement with Primignani et al.[6] However, among the patients without thrombophilia or overt CMD the rate of the mutation was 43% (9 of 21) in those with unprovoked thrombosis and 9% in those with provoked thrombosis (1 of 11).

In the series of Primignani et al.[6] the mutation was present in 71% of the patients with a bone marrow (BM) biopsy diagnostic for CMD; conversely, the BM biopsy was diagnostic in 93% of the mutated patients. Thus, BM biopsy was the only sign of CMD in 16% of the patients with HVT or PVT, in line with other reports.[3,4] They conclude that BM biopsy is warranted in patients with splanchnic vein thrombosis either JAK2-mutated (in order to precise diagnosis of CMD and to exclude myelofibrosis) or JAK2 wild-type (in order to assist diagnosis of JAK2-negative CMD); this is in line with the recent consideration of BM biopsy as a positive tool for diagnosis of CMD, as established by the WHO criteria.[7] Yet in our opinion such recommendation should be tempered. The adverse events associated with BM biopsy are rare (about 1 per 1000 procedures) but can be serious; moreover, diagnosis of CMD is a risk factor for hemorrhagic complications even in the absence of antiplatelet agents.[8] Finally, most of the PVT patients are on anticoagulant therapy, so that biopsy needs special care. Therefore, the indication to BM biopsy in this particular setting should be balanced with the clinical utility and to the likelihood that the procedure will modify treatment. In adult patients with nonmalignant, noncirrhotic PVT anticoagulant therapy has a favorable benefit-risk ratio[9] and in patients with a prothrombotic state life-long oral anticoagulant treatment has been recommended.[10] However the assumption that the presence of JAK2 mutation or a BM biopsy suggestive for CMD should be considered *per se* a prothrombotic state is to date quite premature and should not influence decision for life-long anticoagulation. In our patients without overt CMD, none had significant splenomegaly and the median values were 12.6 g/l (range 9.6-16.4 g/l) for Hb, $6.84 \times 10^9$/l (range 2.50-20.40) for WBC count, $199 \times 10^9$/l (range 93-400) for platelet count, in agreement with those reported by Primignani et al.;[6] although such values are obviously in part affected by hypersplenism and increased plasma volume, indication to cytoreductive treatment seems remote even in the presence of JAK2 mutation or a BM biopsy suggestive for CMD. As suggested by others, in such patients without clinical or haematological evidence of an active CMD a watchful-waiting attitude is recommended, reserving cytoreduction in the presence of usual haematological symptoms of CMD.[4] At present, the indication to BM biopsy should be given on an individual basis and the routine use of procedures that are invasive and not well-standardized should be necessarily validated by further prospective controlled trials, aimed to improve the diagnostic flow-sheet in such patients.

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## Reply:

The main criticism of De Stefano and colleagues pertains to our suggestion to use bone marrow biopsy in the diagnostic pathway of chronic myeloproliferative disorders (CMPDs) associated with splanchnic vein thrombosis (SVT), together with the search of the JAK2 V617F mutation and clonality assays. Our recommendation is not new, and reinforces a well-documented literature.[1,2] Bone marrow biopsy has for a long time been part of the diagnostic routine in our and other institutions for these patients, as docu-

mented by the fact that in our retrospective series, a bone marrow biopsy was performed in 74 of 93 cases.[3] In our consideration for including bone marrow biopsy in the diagnostic workup of these patients, risk-benefit was not taken into account, because it is considered a trivial argument. The rate of adverse events for a bone marrow biopsy cited by De Stefano and colleagues, derived from 19,259 procedures (both bone marrow biopsies and aspirates) performed from 2001 to 2003 in the United Kingdom, is 0.08%.[4] However, because only 3 of these patients had serious events, we should expect that 1.3 patients in 10,000 would risk serious events from a bone marrow biopsy. This is the reason why hematologists consider bone marrow biopsy a very safe procedure. Our standard policy before performing bone marrow biopsy in patients on oral anticoagulant therapy is to stop this therapy 3 days before and to start low weight molecular heparin (LWMH) until the evening before the procedure, to skip its administration in the morning, and to start again LWMH in the evening together with coumarin derivatives, continuing until the target International Normalized Ratio is reached. This policy is safe, and we observed no adverse events.

Pertaining to the criticism to our suggestion that the presence of the JAK2 mutation or a bone marrow biopsy suggestive for a CMPD should be considered per se a prothrombotic state, several studies indicate that CMPD patients carrying the JAK2 mutation have a higher risk of thrombotic complications[5,6] and such risk is probably due to increased blood cell production and activation, irrespective of the number in the peripheral blood. This is particularly true in patients with extrahepatic portal vein obstruction or Budd-Chiari syndrome in whom typical peripheral blood changes may be lacking, in part or totally, because of increased plasma volume or hypersplenism caused by portal hypertension. The vast majority of CMPD patients in our study, either JAK2-positive or not, as well as in a similar study,[7] indeed lacked the conventional hematological criteria for suspicion of myeloproliferation. These arguments and the experience of a very high risk of re-thrombosis, either splanchnic or not, argue in favor of life-long anticoagulation in patients with SVT and CMPD. Pertaining to the possible indication for cytoreduction, we are aware that there is no evidence to recommend cytoreduction instead of (or together with) anticoagulants in patients with CMPDs with SVT who lack the conventional hematological criteria. It appears however that the conventional criteria for starting cytoreductive treatment in these atypical patients are inconsistent and should be reset at a much lower cut-off of blood peripheral counts, because the rationale should be the suppression of the abnormal clone responsible for myeloproliferation. This approach is perhaps particularly indicated in JAK2-positive patients, whose propensity for thrombosis appears to be higher than that of JAK2-negative patients.

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## Testing for Minimal Hepatic Encephalopathy in the United States: An AASLD Survey

To the Editor:

We read with interest the recent article by Kale et al. describing the MR imaging of patients with cirrhosis with minimal hepatic encephalopathy (MHE) who were diagnosed using a battery of neuro-psychometric tests.[1] MHE is a neurocognitive complication of cirrhosis which is associated with poor quality of life, increased rate of progression to overt hepatic encephalopathy (OHE) and driving skill impairment.[2-6] MHE detection is not possible by clinical examination but can only be performed using neuropsychometric/neurophysiological techniques, as in the paper by Kale et al.[1,7-9]

We set out to determine the diagnostic approaches of U.S.-based members of AASLD toward MHE systematically to identify potential barriers to routine testing. An anonymous questionnaire querying the practice profile, personal opinions regarding MHE diagnostic strategies, fre-