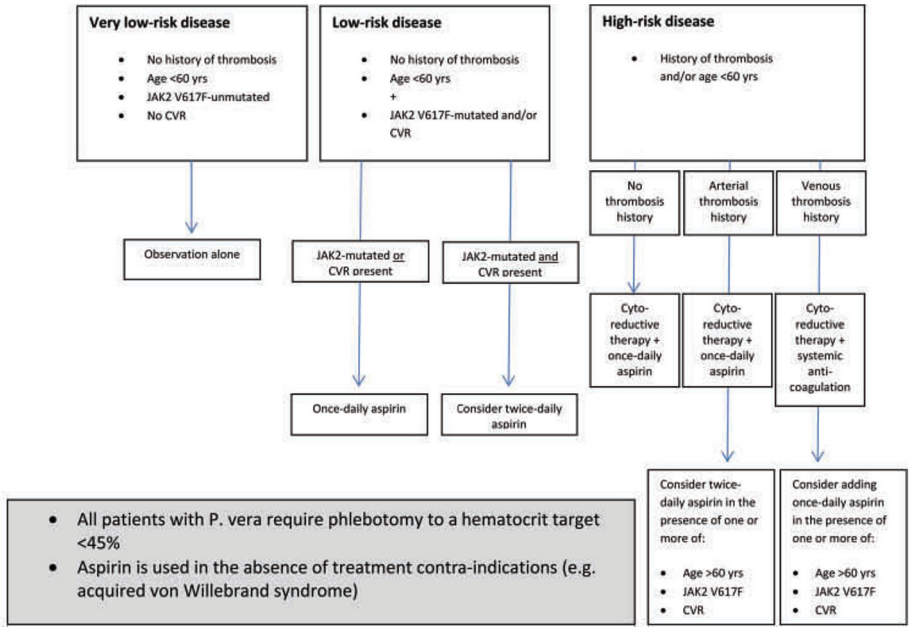

Figure 1. Possible new treatment algorithm in polycythemia vera and essential thrombocythemia (CVR = cardiovascular risk factors). Adapted from: Tefferi A, Barbui T. Am J Hematol 2015;90(8):683–5

MPN III

The impact of thrombophilia in the management of MPN

J. Schwarz
CZEMP (Czech Group for Ph– Myeloproliferative Disorders), Prague, Czech Republic

The overall thrombotic risk in a normal healthy population is always based on a combination of multiple risk factors present in one individual. The risk parameters for arterial and venous events differ. MPD-T represents a situation in which the specific MPD-related risks (such as the *JAK2* mutation) are combined with other risk factors present in the general population. The Czech group for Ph– MPD (CZEMP) had postulated that all known thrombophilic risks (or prothrombotic factors) known in the general population may play a role in MPD-T as well, also based on an institutional study from Prague. This was the basis of the risk stratification used in their first guidelines published in 2005 [1] (updated 2011 [2]). The thrombophilic risk factors comprise both inherited and acquired states. The specific thrombophilic factors include deficiencies (both hereditary and acquired) of proteins C and S and antithrombin, and the hereditary thrombophilias, such as the prothrombin gene G20210A mutation and the factor V "Leiden" G1691A mutation. On the other hand, an acquired thrombophilia may be any hypercoagulation state (often leading to DIC) due to widespread severe infections, cancer, large wounds and burns, as well as the physiological state of pregnancy.

The literature on thrombophilia in Ph– MPD was reviewed. Only the Italian guidelines issued in 2004 used the presence of the thrombophilic markers to decide the indication of cytoreducing therapy in a subset of the so-called "intermediate-risk" patients with ET [3]. However, the current guidelines, such as the most widely used LeukemiaNet guidelines [4], usually do not take the thrombophilias into account. Even the more recent risk stratification of thrombosis in ET – the IPSET-thrombosis criteria [5] – does not consider them. Only the Czech and Slovak guidelines take them into account, as well as the drafted Central European Myeloproliferave Neoplasms Organization (CEMPO) ones.

For many years, there were only retrospective studies available to evaluate different thrombophilic states as prothrombotic risk factors in MPD-T – a lot of them indicated the increased risk. Ten years ago, CZEMP decided to study the thrombophilic factors in a prospective manner within the Czech part of the international registry ("Registry") of anagrelide (Thromboreductin®)-treated patients.

The recent analysis of the "Registry" [6] included altogether 1179 patients having MPD-T – either ET, PV or PMF according to PVSG criteria. In 812 patients, the WHO/CZEMP diagnosis could be established: ET – 445 (54.8%), PMF – 206 (25.4%), PV – 107 (13.2%), and other (mostly MPN-unclassifiable) – 54 (6.7%) cases. The M/F ratio was 2:3, the median age of patients was 52 years (6–91 years) at diagnosis. The incidence of vascular events was compared in the history (before entering the Registry) and during follow-up (on anagrelide treatment). History and follow-up represented 4149 and 4742 patient-years, respectively. For arterial events, there was a decrease in the incidence of events from 5.04 to 2.74 per 100 patient-years ($P < 0.001$) when historical and follow-up events were compared. Microvascular events decreased from 1.76 to 1.03 ($P = 0.001$), and for venous ones, the decrease was most striking: from 4.24 to 0.63 per 100 patient years ($P < 0.001$). For bleeding events, an increase was observed from 1.35 to 2.68 ($P < 0.001$), mostly on behalf of minor events [6].

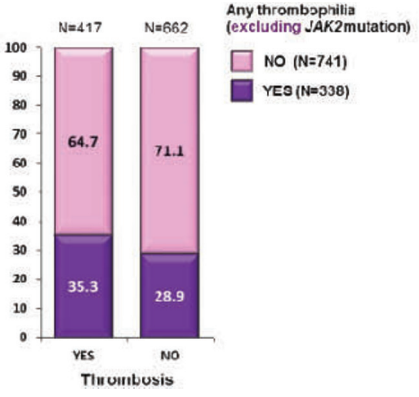

Figure 1. Thrombosis related to thrombophilia (excluding *JAK2*) (N=1079).

In univariate analyses, aside from the most significant predictor – the *JAK2*^{V617F} mutation –, several thrombophilic factors were significantly associated with all thrombotic events, more conspicuously with venous thrombotic events. This was true for the specific thrombophilic markers (protein C, S and antithrombin deficiencies plus F. V "Leiden" and

prothrombin gene mutations) evaluated jointly (Figure 1), and even for protein C and F. V "Leiden" when evaluated separately. Also the presence of antiphospholipid antibodies and elevated F. VIII levels reached statistical significance for venous events. In a multivariate analysis for venous events (Table 1), the specific thrombophilic markers preserved their statistical impact, along with the *JAK2* mutation and non-elevated cholesterol levels (we speculate that this surprising result is caused by the protective effect of statin treatment of hypercholesterolemia). None of the thrombophilias had an impact in multivariate analyses of arterial events [6].

Table 1
Incidence of venous thrombosis related to risk factors – multivariate analysis

Prognostic factor	OR	95% CI	P
Specific thrombophilic markers jointly*	1.797	1.159–2.786	0.009
JAK2 mutation	1.562	1.040–2.347	0.032
Cholesterol elevation	0.617	0.381–1.000	0.050

*Prothrombin gene and f. V "Leiden" mutations and protein C and S deficiencies. Antithrombin levels were not incorporated into the analysis due to low numbers of out of range results and lack of impact in univariate analysis. OR, odds ratio; CI, confidence interval (lower–upper).

Taken together, the first large prospective study of the thrombophilic factors in MPD-T (to our knowledge) shows that, according to the Registry results, the specific thrombophilic markers are the strongest predictors of venous events and deserve screening at diagnosis. Thrombophilia-positive patients should be included in the high-thrombotic risk category and should be treated as such. These patients, if treated according to the CZEMP guidelines, receive thromboreducing agents (patients under 65 years at diagnosis are treated with anagrelide or interferon, regardless of the platelet count, ± ASA, older ones with hydroxyurea), which leads to a dramatic decrease of the incidence of venous events.

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Treatment of high risk ET – data from the EXELS study

G. Birgegård[1], C. Besses[2], M. Griesshammer[3], L. Gugliotta[4], C. Harrison[5], M. Hamdani[6], H. Achenbach[7], J.-J. Kiladjian[8]
[1]Department of Haematology, Uppsala University, Uppsala, Sweden; [2]Department of Haematology, Hospital del Mar-IMIM, Barcelona, Spain; [3]Hematology and Oncology, Johannes Wesling Medical Center, Minden, Germany; [4]Department of Haematology, 'L e A Seragnoli', St Orsola-Malpighi Hospital, Bologna, Italy; [5]Department of Haematology, Guy's and St Thomas' NHS Foundation Trust, London, UK; [6]Global Biometrics, Shire Pharmaceuticals, Wayne, PA, USA; [7]Research & Development, Shire AG, Eysins, Switzerland; [8]APHP, Hôpital Saint-Louis, Centre d'Investigations Cliniques, Paris, France

Background: The Evaluation of Xagrid Efficacy and Long-term Safety (EXELS) study (NCT00567502) is the largest prospective observational cohort of high-risk patients with essential thrombocythemia (ET) reported to date.
Objectives: The primary objective were safety and pregnancy outcomes of anagrelide (ANA) compared with other cytoreductive therapies (CRT). Secondary objectives included efficacy, measured by the incidence of thrombohemorrhagic events and platelet reduction.
Methods: High-risk patients (≥1 of age >60 years, previous thrombotic event, platelet count >1000 × 10^9/L) with ET were enrolled across 13 countries in Europe between 2005 and 2009. Pts were required to be receiving CRT. Data, including events predefined in the protocol (PDEs), were collected every 6 months for 5 years for all patients. Event rates are presented as number of patients per 100 patient-years exposure and by treatment at time of event. Event rates are provided rather than p values due to the observational nature of the study. Preliminary final data are presented and final data, including platelet response and pregnancy results, will be available at ASH. Recently, results have remained stable and conclusions are not expected to change.
Results: 3649 patients were categorized according to treatment at registration as follows: ANA (n=804), ANA + other CRT (n=141), other CRT (n=2666) and no CRT (n=38). Over 80% of patients received either hydroxycarbamide (HC) or ANA, and 69.8% of patients received anti-aggregatory therapy. At registration, median age was lower in the ANA (55.5 years, range 18–89) and ANA + other CRT (59.0 years, range 22–88) groups vs the other CRT group (70.0 years, range 17–95).
The arterial thrombotic event rate was similar in ANA (1.63) and other CRT (1.62) groups, whereas venous thrombotic event rates differed (0.35 vs 0.57). The major hemorrhagic event rate was highest in the ANA group, especially in patients also treated with anti-aggregatory therapy (1.24).
105 patients transformed to myelofibrosis (MF) and 62 to acute leukemia (AL). Transformation to MF rates were similar in the ANA (1.31) and ANA + other CRT (1.27) groups, but lower in the other CRT (0.32) group. Rate of transformation to AL was 0.17, 0.46, and 0.33, respectively. In patients who had only ever received either ANA or HC, rate of transformation to MF was higher in the ANA vs HC group (0.78 vs 0.17) whereas transformation to AL was higher in the HC vs ANA group (0.22 vs 0). All patients who ever received ANA and transformed to AL had also received prior HC.
PDEs of greatest interest are displayed in Table 1. Non-hematological malignancy was the most frequent PDE in the other CRT group. 57.4% of deaths were attributed to a PDE; transformation (event rate, 1.9), most frequently to AL (1.3), and non-hematological malignancies (1.6) were the most frequent causes of PDE-related death. No unexpected side effects were noted.
There were 54 pregnancies, of which 41 were successful (76%).
The proportion of patients with a white blood cell (WBC) count >15 x 10^9/L at any time was higher in patients who died (12.5%) vs alive patients (6.1%) and in patients who had transformed (15.7%) vs those who did not transform (5.7%).
Conclusion: Patients receiving ANA were younger than those receiving other CRT. Thrombotic event rates were low; arterial events were similar between ANA and other CRT groups, and venous events were lower in the ANA vs other CRT group. Hemorrhage was most frequent in the ANA +