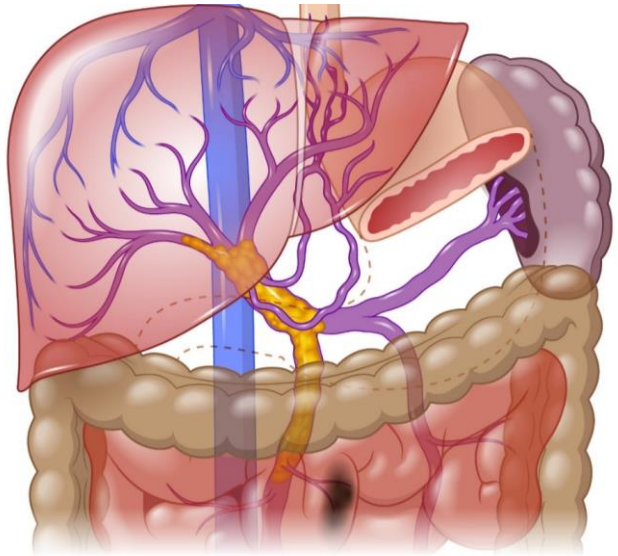
Impact of etiological therapy in non-cirrhotic non-tumoral PVT
Paris 29th 2022

Ch Bureau Toulouse France

In patients with portal vein thrombosis (PVT), the goal of treatment is to limit

- the risk of extension
- the risk of a recurrence in the splanchnic territory
- the risk of a recurrence in the extra splanchnic territory considering that all vascular events are of interest

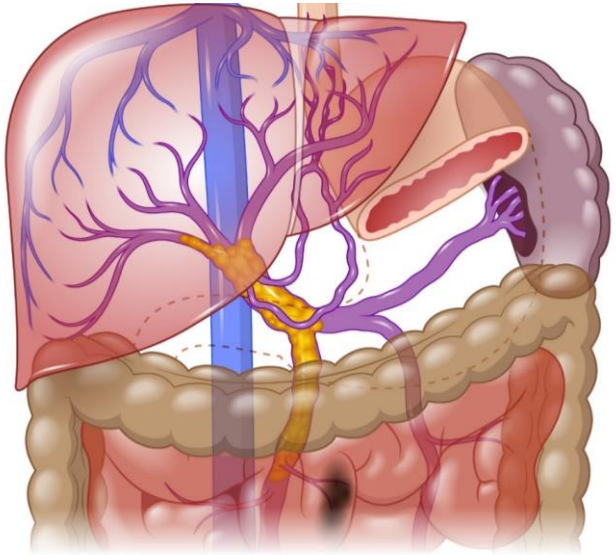


The treatment of an identified risk factor could have a beneficial impact on the risk of recurrence of venous thromboembolism (VTE)

But it remains a difficult question to answer for the following reasons

PVT is a rare disease.

One or more risk factors are identified in less than 2/3 of patients.



An effective treatment is not available in all etiologies.

A relapse remains a rare event and the risk is highly variable among the etiologies.

Up to now, the results of large studies are scarce in splanchnic vein thrombosis: all observational and retrospective.

Main risk factors

Local factors

Infection

Inflammatory states

Surgery

Abdominal trauma

Prothrombotic Conditions

Acquired

Myeloproliferative neoplasm

Behcet Disease

Paroxysmal nocturnal Hemoglobinuria`

Antiphospholipid Syndrome

Congenital

Factor V Leiden mutation

Factor-II Mutation

Protein C or S deficiency

Antithrombin deficiency

General factors

Obesity

Pregnancy

Oral contraceptive

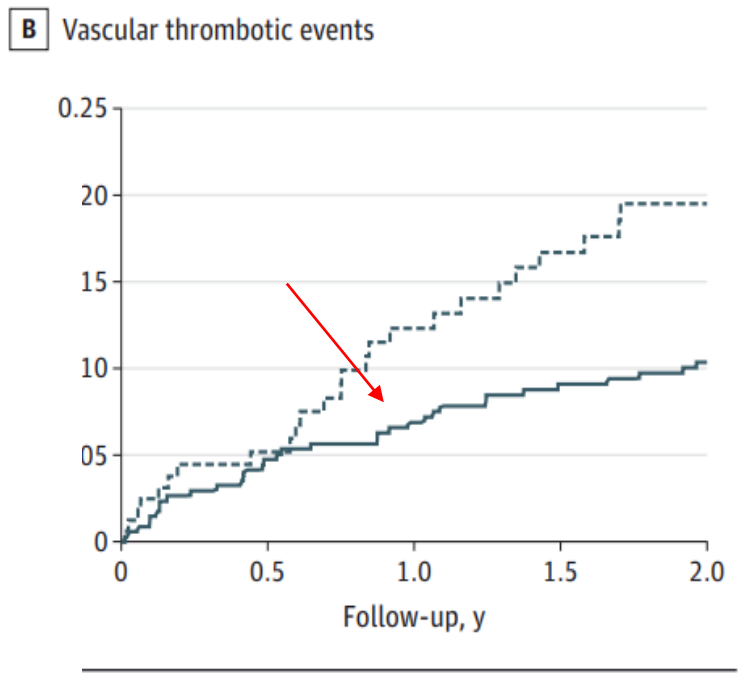
Tobacco

Systemic Disease

Overall the risk of recurrence is decreased with the use of VKA

Figure 2. Cumulative Incidence of Major Bleeding and Thrombotic Events in Patients With Liver Cirrhosis and Nonmalignant, Noncirrhotic Splanchnic Vein Thrombosis (SVT)

Thrombosis recurrence	Incidence rate 100 PY
Total	7.3
With anticoagulation	5.6
Anticoagulation Discontinued	10.5
Untreated	9.2



n =604

Ageno JAMA Intern Med 2015

Thrombosis recurrence	Incidence rate 100 PY
Total	5.5
With anticoagulation	3.8
Anticoagulation Discontinued	6.3

n =139

B Condat et al. Gastro 2001

Myeloproliferative neoplasm (MPN)	Cytoreductive agents
Paroxystical nocturne Hemoglobinuria (PNH)	Eciluzimab
Behçet Disease (BD)	Immunosuppressive agents
Local factors	Surgery/ Antibiotics…

Myeloproliferative neoplasms

ORIGINAL ARTICLE

Splanchnic vein thrombosis in myeloproliferative neoplasms: risk factors for recurrences in a cohort of 181 patients

V De Stefano[1,25], AM Vannucchi[2,25], M Ruggeri[3], F Cervantes[4], A Alvarez-Larrán[5], A Iurlo[6], ML Randi[7], L Pieri[2], E Rossi[1], P Guglielmelli[2], S Betti[1], E Elli[8], MC Finazzi[9], G Finazzi[9], E Zetterberg[10], N Vianelli[11], G Gaidano[12], I Nichele[3], D Cattaneo[6], M Palova[13], MH Ellis[14], E Cacciola[15], A Tieghi[16], JC Hernandez-Boluda[17], E Pungolino[18], G Specchia[19], D Rapezzi[20], A Forcina[21], C Musolino[22], A Carobbio[23], M Griesshammer[24] and T Barbui[23,25]

The IR of recurrence was 3.9 /100 pt-yrs in patients on VKA vs 7.2 /100 pt-yrs in patients off VKA

Treatment Regimen	Events	IR 100 pt-year
With cytoreductive treatment (hydroxyurea +++) n = 130	23 recurrent events over 537 pt-years	4.2
Without cytoreductive treatment n = 51	8 recurrent events over 198 pt-years	4.0
With both cytoreductive treatment and VKA n = 107	20 recurrences over 471 pt-years	4.2

17 of the 31 events (55%) occurred in patients with hypercythaemia not receiving cytoreduction or in patients who failed to reach the haematological response in spite of cytoreduction

De Stefano et al. *Blood Cancer Journal* (2018)8:112
DOI 10.1038/s41408-018-0151-y

Blood Cancer Journal

ARTICLE Open Access

Hydroxyurea prevents arterial and late venous thrombotic recurrences in patients with myeloproliferative neoplasms but fails in the splanchnic venous district. Pooled analysis of 1500 cases

Valerio De Stefano[1,2], Elena Rossi[1,2], Alessandra Carobbio[3], Arianna Ghirardi[3], Silvia Betti[1], Guido Finazzi[4], Alessandro M. Vannucchi[5] and Tiziano Barbui[3]

The efficacy of HU in patients with VTE at common sites was not demonstrated in the first 5 years after the incident event.

Authors failed to show a positive action of HU in preventing recurrences after the first incident episode of splanchnic vein thrombosis.

218 patients with SVT

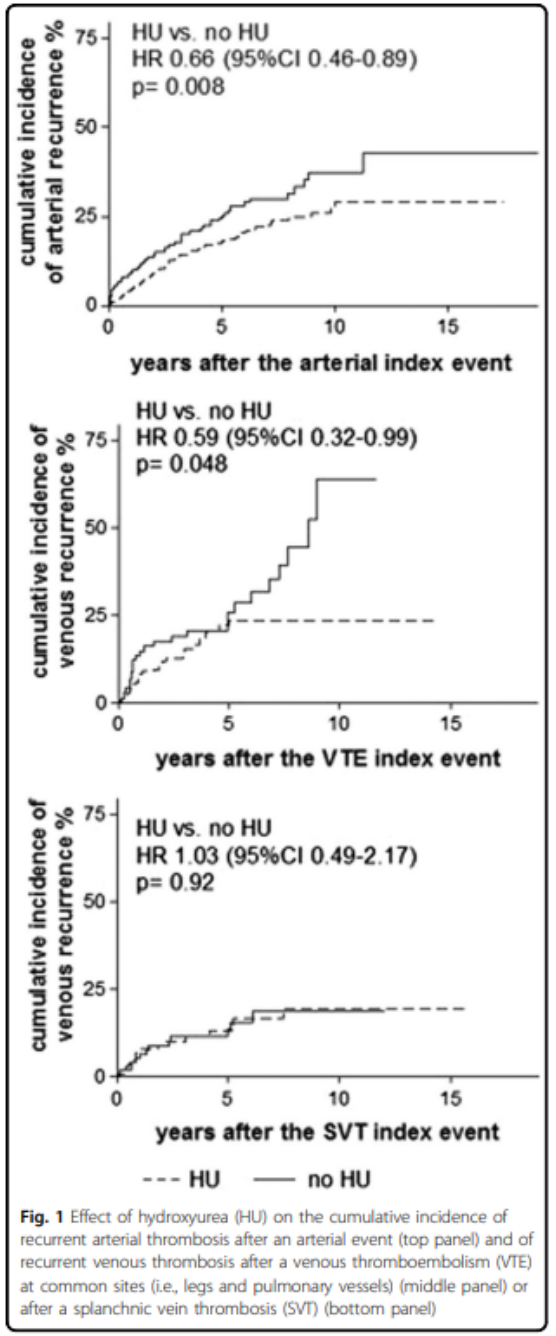


Fig. 1 Effect of hydroxyurea (HU) on the cumulative incidence of recurrent arterial thrombosis after an arterial event (top panel) and of recurrent venous thrombosis after a venous thromboembolism (VTE) at common sites (i.e., legs and pulmonary vessels) (middle panel) or after a splanchnic vein thrombosis (SVT) (bottom panel)

SYSTEMATIC REVIEW

blood advances

Myeloproliferative neoplasms

A systematic review of antithrombotic treatment of venous thromboembolism in patients with myeloproliferative neoplasms

Eva N. Hamulyák,[1] Joost G. Daams,[2] Frank W. G. Leebeek,[3] Bart J. Biemond,[4] Peter A. W. te Boekhorst,[3] Saskia Middeldorp,[1] and Mandy N. Lauw[1,3,4]

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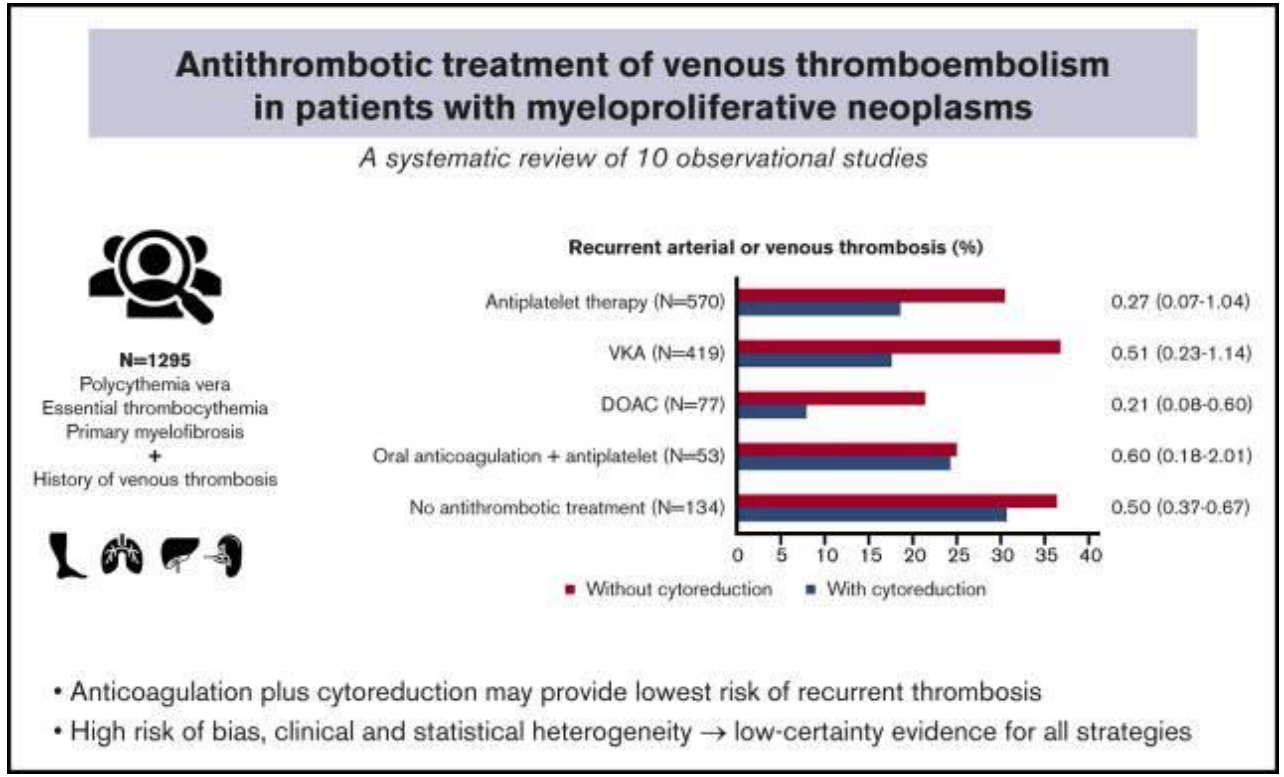
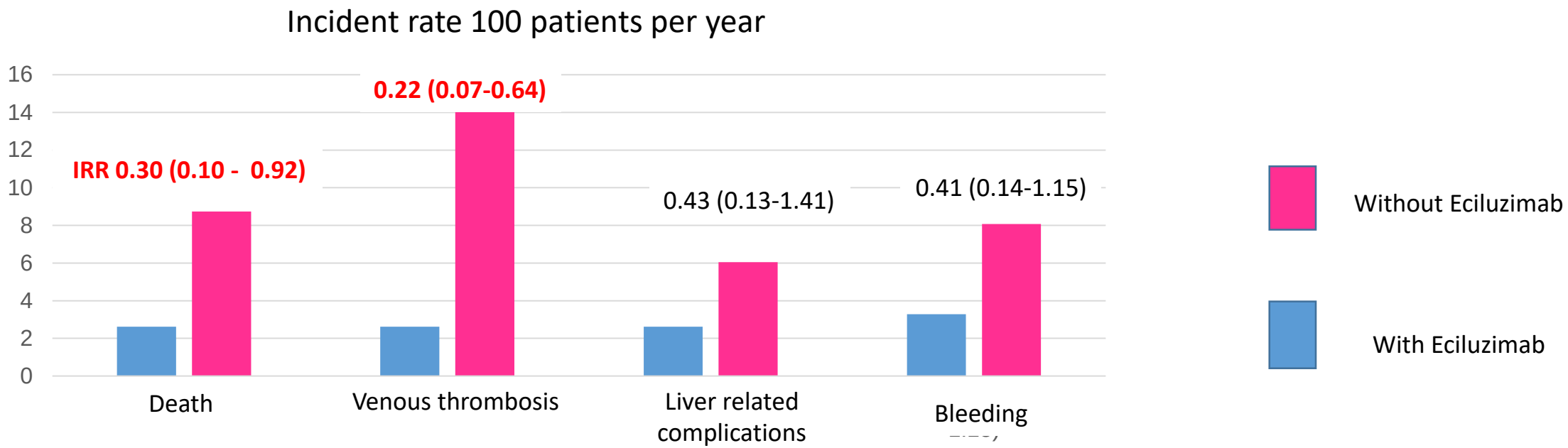
1295 patients

In 738 patients with initial VTE, the combination of cytoreduction and VKAs or DOACs was more effective in preventing recurrences than VKA alone (RR 0.51) or DOACs alone (n = 14) (RR 0.21).

No data on the subgroup of 286 patients with an initial SVT



Paroxysmal nocturnal hemoglobinuria



New venous thrombosis : 2.6 versus 14.2 per 100 PY, IRR 0.22 (0.07–0.64) in treated with eculizumab vs non-treated patients

And increased survival in treated patients

This study strongly suggests that treating the underlying cause favorably impacts on outcome in VLD patients

A Plessier et al. Am J Hematol 2022

Behçet Disease

Frequency of different manifestations of Behcet's disease

Manifestation	Frequency (%)
Oral ulcers	97–99
Genital ulcers	80–85
Papulopustular lesions	75–85
Erythema nodosum	40–50
Pathergy reaction	30–50
Uveitis	40–50
Arthritis	30–50
Deep vein thrombosis	10–15 (more prevalent around Mediterranean) *
Arterial occlusion/aneurysm	5–10 (more prevalent around Mediterranean)
Central nervous system involvement	5–10
Epididymitis	2–3
Gastrointestinal lesions	2–50 (more prevalent in Japan/Korea)

*10 year-incidence of relapse close to 50 %

In a study of 296 BD with venous thrombosis, immunosuppressive agents significantly decreases the relapse of thrombosis by four fold (HR 0.27 [0.14-0.52]).

14 of the of 586 vascular events were Budd Chiari SD

AC Desbois Arthitis Rheum 2012

In 260 patients with VLD, relapse of a vascular event was :

- lower in patients taking Immunosuppressive agents : 25 % vs 86 %, $P < 0.001$
- higher in the group taking only Anticoagulants : 92 % vs 29 %, $P < 0.001$
- similar between the patients taking only IS *vs* AC + IS : 29 % vs 22 %, $P = 0.28$

Alibaz-Oner F, et al. Medicine (Baltimore) 2015

Local risk factor

RCT rivaroxaban vs placebo for secondary prevention of VTE

In patients with a treated local risk factor of PVT, no recurrence of VTE was observed

Thrombosis recurrence	Yes (n=10)	No (n=46)	P
Age	44.6 [36.2-50.7]	49.3 [43.0-64.0]	0.18
IMC>30 n (%)	3 (30)	13 (28)	1.00
Local factor/OP at diagnosis (%)	0	19 (41)	0.012
Repermeabilisation	0	6 (13)	0.25
D-dimers à M1 ≥500 ng/mL n (%)	6 (75)	10 (25)	0.015
Facteur VIII à M1>150% n (%)	4 (50)	16 (40)	0.62

A Plessier et al. In press

Conclusion

The level of evidence of an universal benefit of the etiological therapy is low.

In the situation of an initial SVT, the studies may be underpowered.

Selection bias of high-risk patients when treatment is initiated.

In particular conditions, the recurrence is dramatically decreased suggesting a beneficial impact of etiological therapy.

The indication of the treatment (cause) is often a case by case discussion with a multidisciplinary approach (hematologist, internist, rheumatolgist, …..) taking into account potential other benefits on outcome.

Association des Malades des Vaisseaux du Foie

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