Myeloproliferative Neoplasia associated Splanchnic Vein Thrombosis (MPN-SVT)

Frederick Chen FRCP FRCPath PhD

Consultant Haematologist

Risks associated with SVT

Risk factors
Abdominal disorders and interventions
Acute
Pancreatitis
Peritonitis and intraabdominal sepsis
Inflammatory bowel disease
Diverticulitis
Hydatidosis
Splenectomy
General abdominal surgery
Sclerotherapy for esophageal varices
Abdominal trauma
Chronic
Cirrhosis
Abdominal cancer
Portal hypertension
Hematological disorders
Philadelphia chromosome negative chronic MPNs
Polycythemia vera
Essential thrombocythemia
Idiopathic myelofibrosis
PNH
Inherited thrombophilic state
Antithrombin deficiency
Protein C deficiency
Protein S deficiency
Factor V Leiden
G20210A mutation in prothrombin gene
Antiphospholipid syndrome
Hormones
Oral contraceptives
Hormonal replacement therapy
Pregnancy
Puerperium
Virus
Cytomegalovirus
Autoimmune disorders
Behçet's disease
Hypereosinophilic syndrome
Other
Membranous webs
New biological marker of subclinical disorders
JAK2V617 mutation

Ageno et al., *Blood 2014*, 124; No 25: p3685-3691

Meta-analysis of 32 studies of MPN in BCS and PVT
(Smalberg et al Blood 2012)

Budd Chiari Syndrome (n= 1062)

40.9% **MPN** (80.3% JAK2V617F pos)

41.1% JAK2pos

17.1% no MPN features, JAK2mut pos

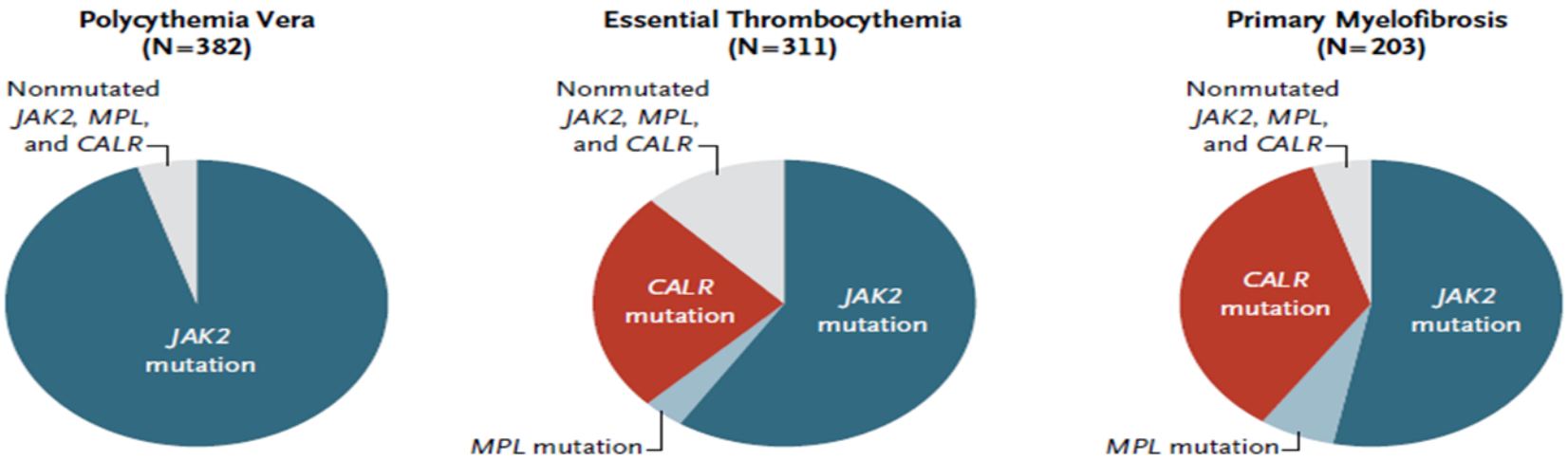
Portal Vein Thrombosis (n= 855)

31.5 % **MPN** (86.6% JAK2V617F pos)
27.7% JAK 2 pos
15.4% no MPN features, JAK2 pos

But in more recent studies including our own, the majority were de novo presentation of SVT with no prior MPN diagnosis

Clinical diagnosis of MPN defined by blood counts and molecular mutations (JAK2, Calreticulin, mpl)

- **Polycythaemia Vera (PV)** — Hb >16; Hct >52(M); >48%(F); RCM>25%;
  Masked PV — normal Hb - not well defined
- **Essential Thrombocythaemia (ET)** — Plts >450
- **Myelofibrosis (MF)** — Cytopenia, BM fibrosis



T. Klampfl, NEJM 2013

G.P. 56 yrs/M

Previously well

Investigated for abdominal symptoms

Portal vein thrombosis

Hb 136

WBC 7.2

Plts 241

Hct 0.42

RCC 5.52 (N<5.7)

MCV 77 (>80)

Ferritin 18 (>30)

Epo 6.2 (low)

JAK2 V617F positive

RCM: predicted=2426 mls

measured= 3280 mls

ratio: 1.35 (0.75-1.25)

UHB: Blood Counts in MPN SVT

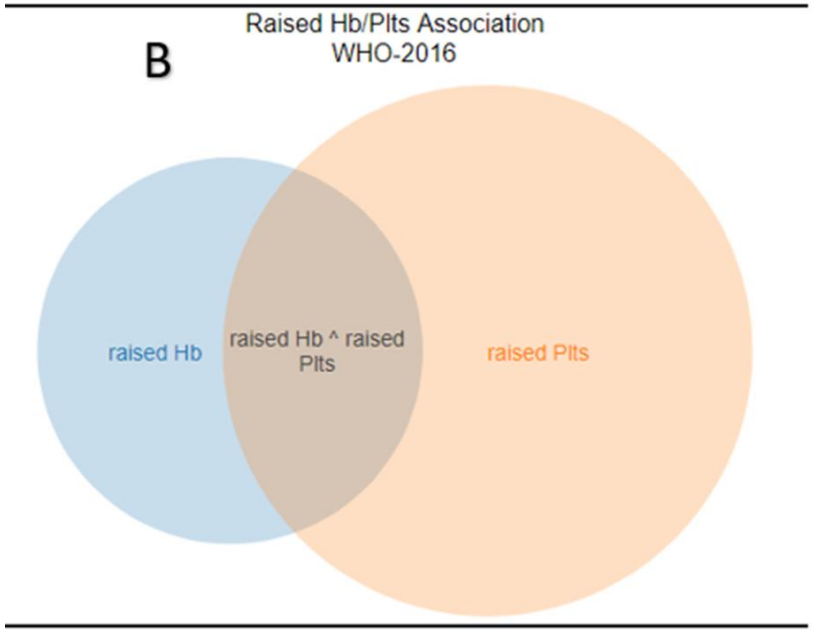
- FBC for 64 patients (No cytoreductive therapy)
- Large no. of patients have normal FBC (37%)

- 26.6% have ↑ platelet (Plts)
- 28.1% ↑ WBC
- 14% have ↑ haemoglobin (Hb)
- 18.7% ↑ haematocrit (Hct)

But:

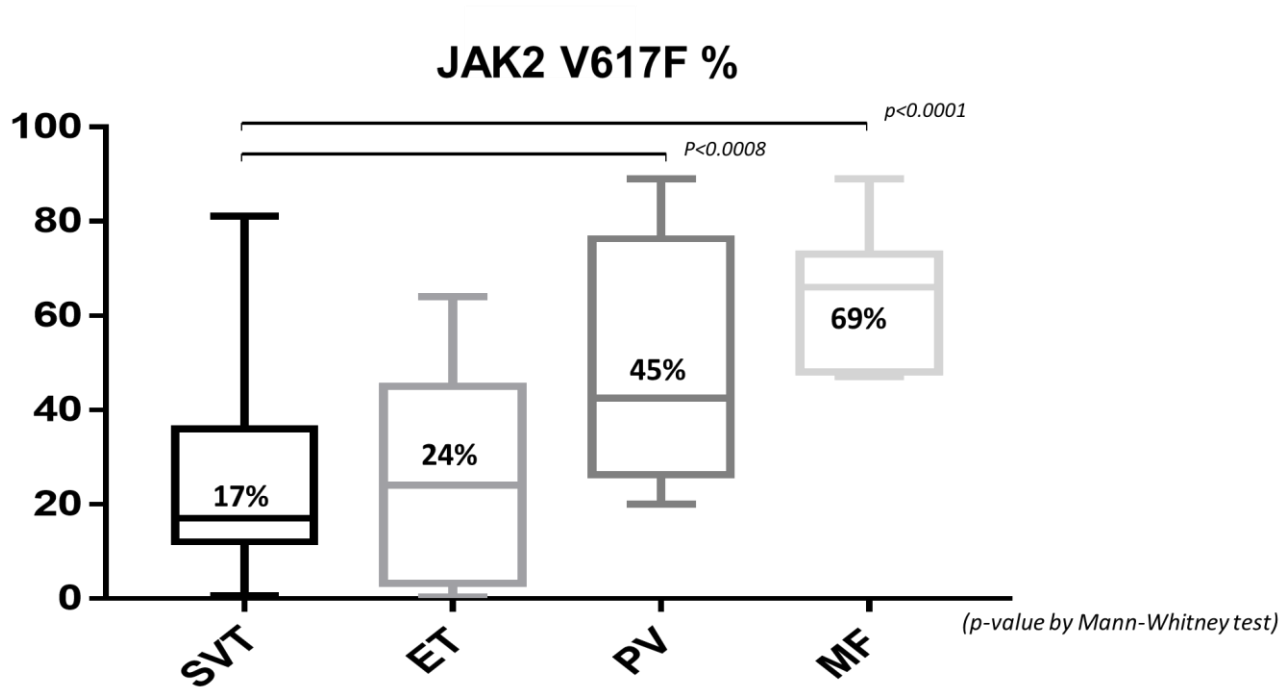
- 53% ↑ RCC
- 51% ↓ MCV

Masked PV



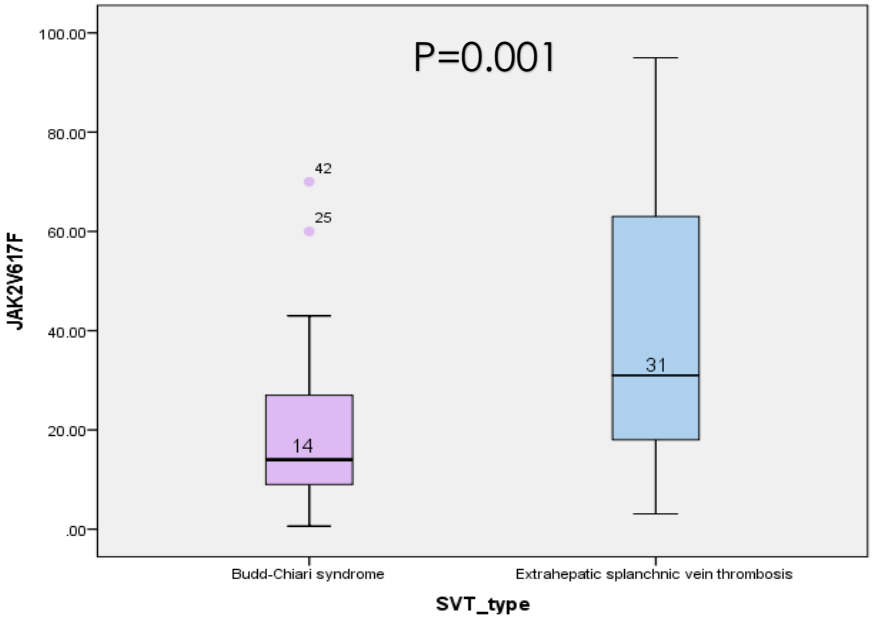
Most Studies show SVT-MPN associated with JAK2 mutation- nly up to 2% is associated with CalR mutation.

UHB data: Analysing the JAK2 617F allele burden in MPN SVT: A distinct group?

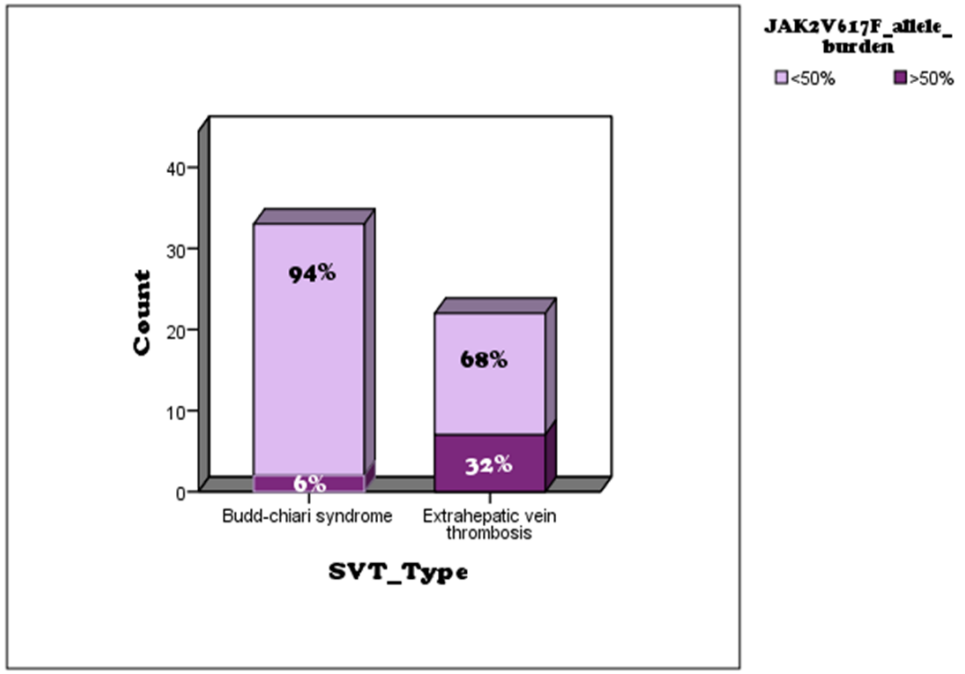


JAK2 V617F allele burden: de-novo SVT 17% (0.6%-81%), SVT diagnosed during MPN follow-up: 17% (4.5%-63%), ET: 24% (0.30%-64%), PV 45% (20%-89%), MF 69% (47%-89%).

BCS vs. EH-SVT ; Different JAK2 allele burden



EH-SVT has higher
JAK2 V617F allele burden than BCS



Homozygous JAK2 mutation
higher in EH-SVT

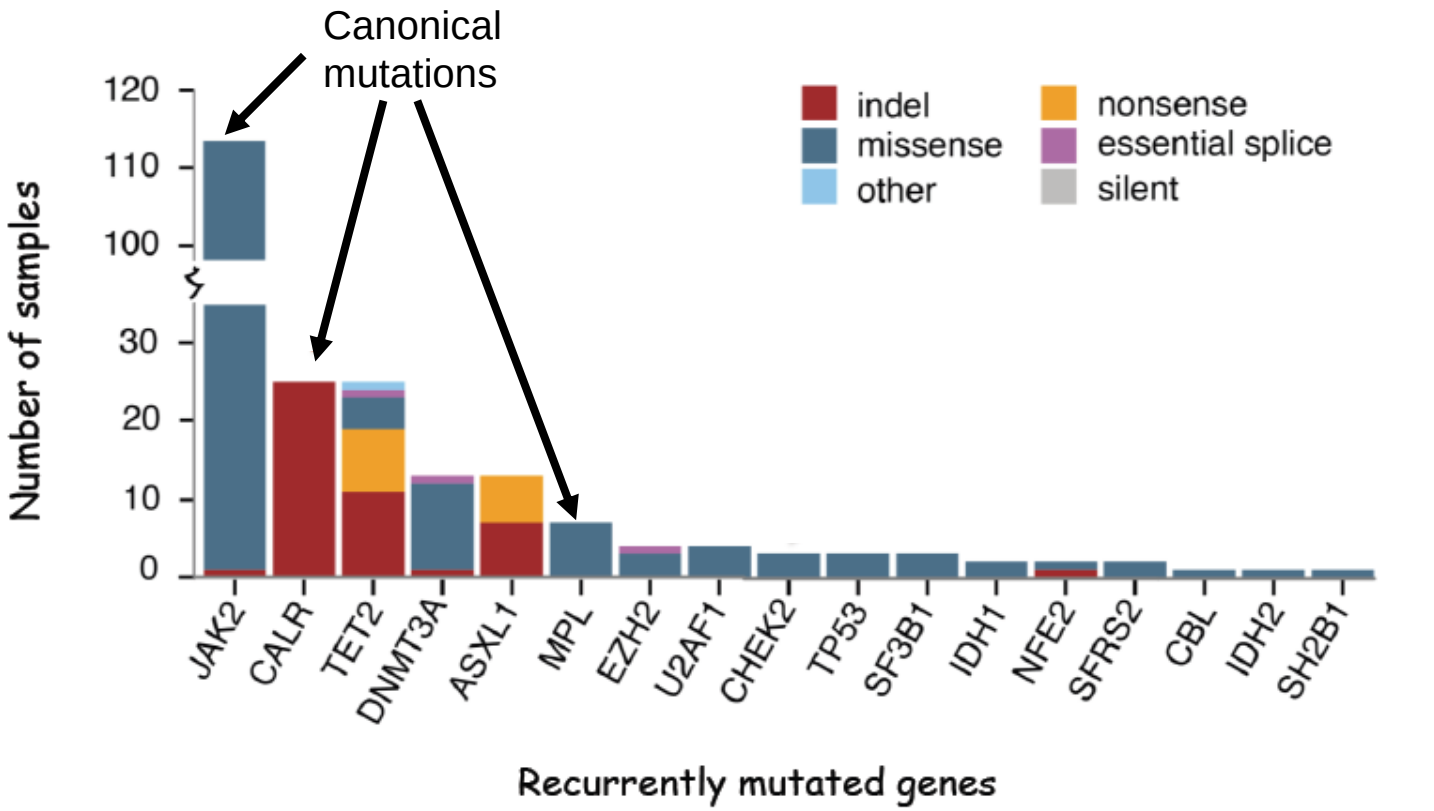
MPN-SVT present with distinctive features

- SVT present at younger age than ET, PV or MF (mean 44 years)
- F>M (F 64%:M 34%)
- Large proportion have normal counts (~40%)
- They have low JAK2 V617F allele burden

- BCS and extra-hepatic vein thrombosis are different at the molecular level

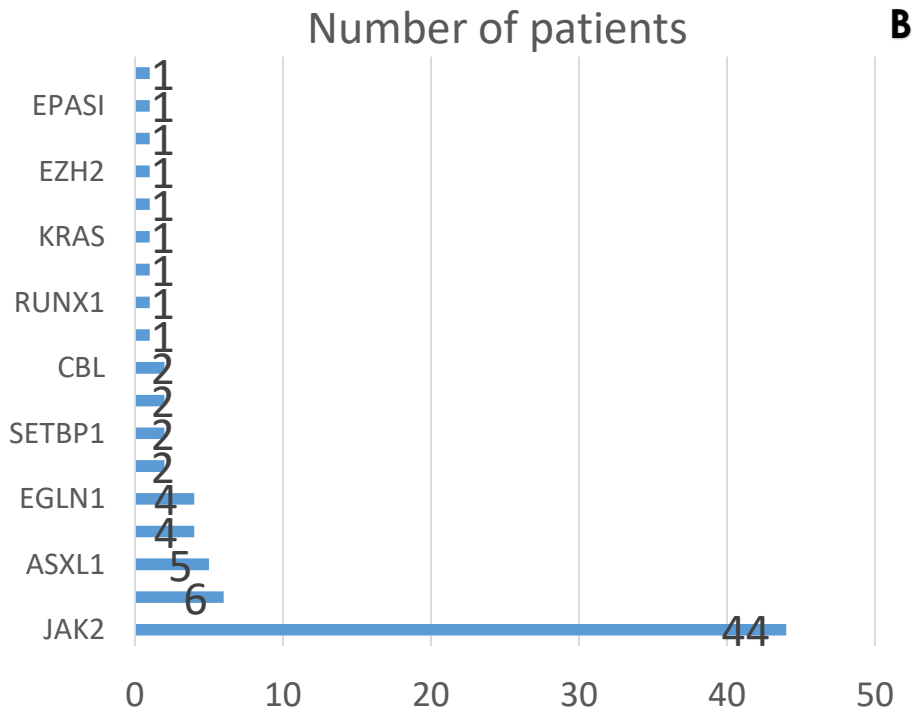
- High frequency of additional myeloid mutations

Recurrently mutated genes



Nangalia et al 2013

Additional mutations by Next Generation Sequencing

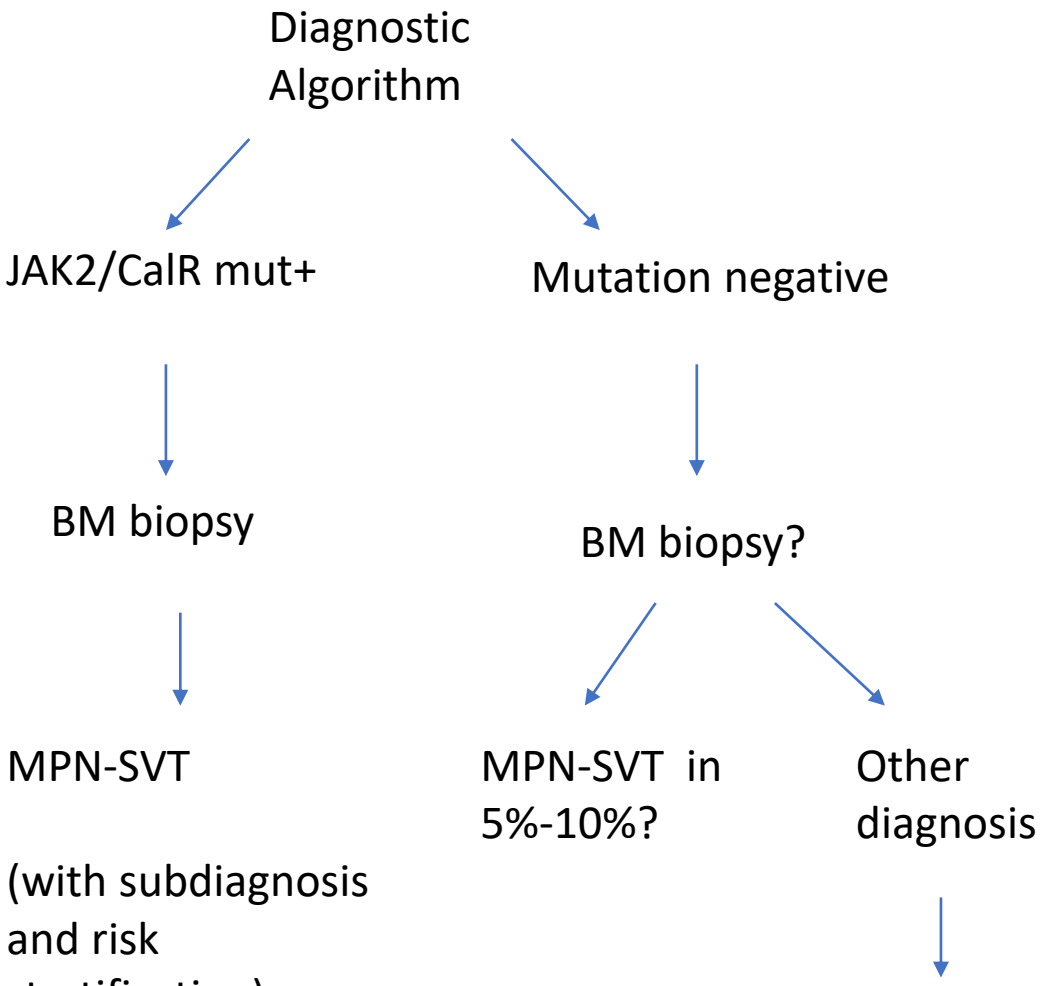


A. (Number of patients with each mutation in NGS-MPN panel for 25 genes

B

No. Additional mutations plus JAK2 V617F	% of MPN SVT patients
1	34.1%
2	11.4%
3	1.0%
Patients with additional mut. 24/44	54.5%

Diagnostic Algorithm



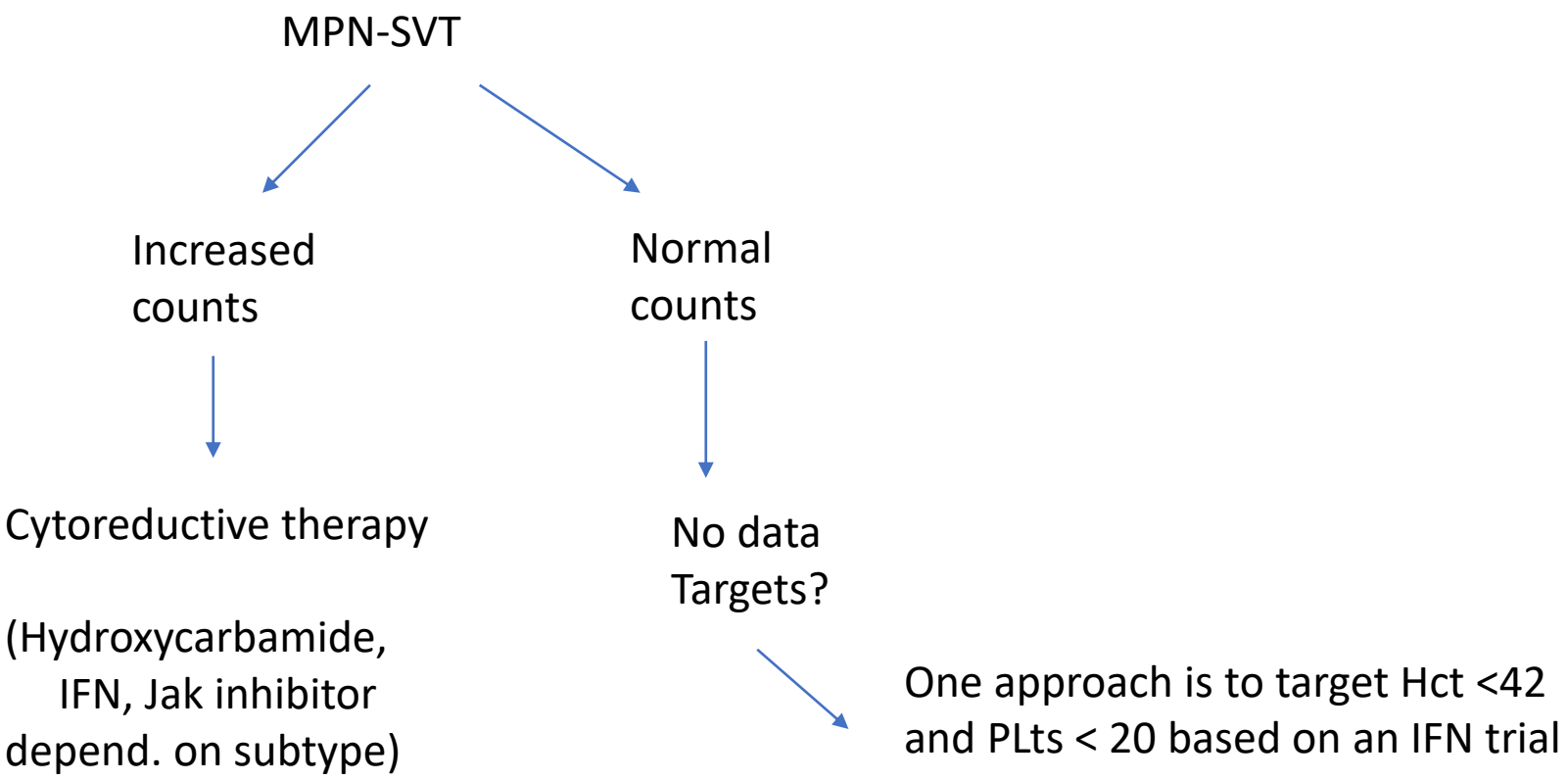
Investigations

- FBC
- Blood Film
- EPO
- JAK2/CALR/Mpl
- Iron studies
- PNH
- LAC/ACA
- (Thrombophilia screen)
- BM biopsy
- Red cell mass

Therapy of thrombosis and MPN: basic principles

1. Indefinite anticoagulation is recommended in the presence of continuing risk/unprovoked
   (NICE 2012; Kearon et al. 2016; Watson et al. 2015)

1. Thrombosis in MPN is high risk and should be cytoreduced. (BCSH, McMullin 2018, ESMO, Vannucchi 2018)



A Multidisciplinary Approach is required

- Interventional radiology
  - TIPSS
- Hepatology/GI
  - Beta Blockers
  - HCC & varices
    surveillance (endoscopy)
  - Liver transplantation
  - Nutritional support
    for bowel resection
- Anticoagulation
  - LMWH /Warfarin
  - Anti-platelet agents?
- Cytoreductive therapy for MPN and FU

Disclosures:

- Novartis Academic Grant for MASCOT trial
- QEHB Charity Grant for supporting The Rare Disease Clinic for MPN SVT Clinic and Research