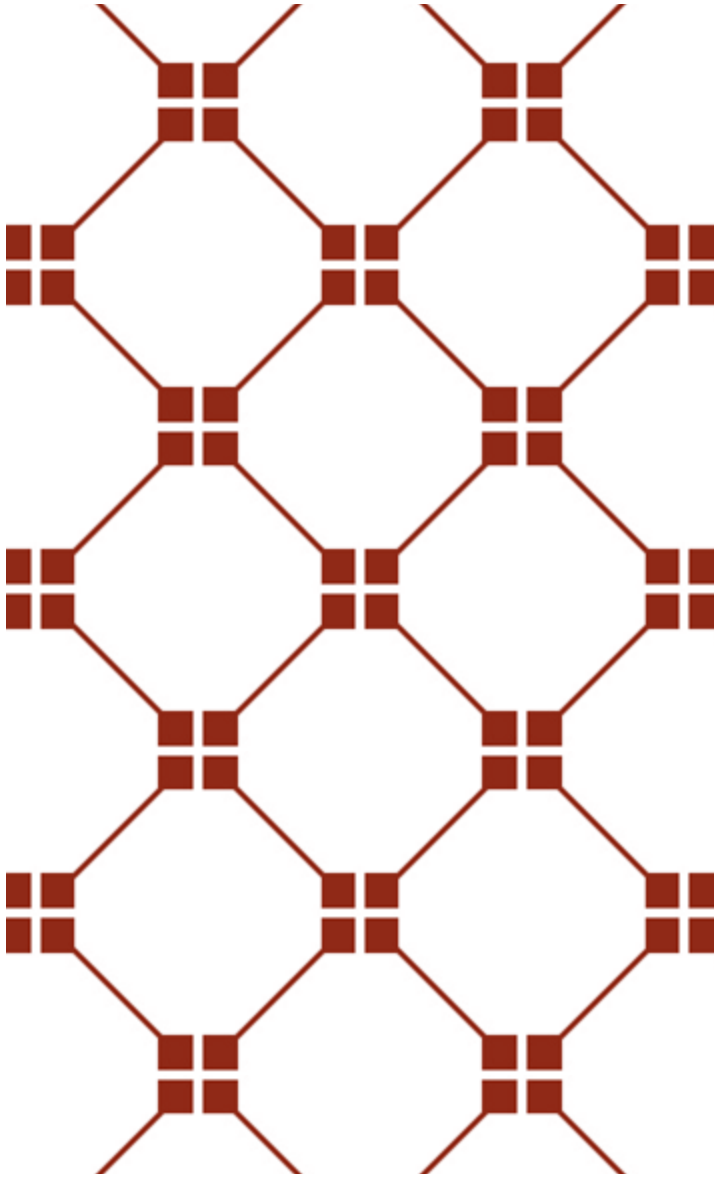
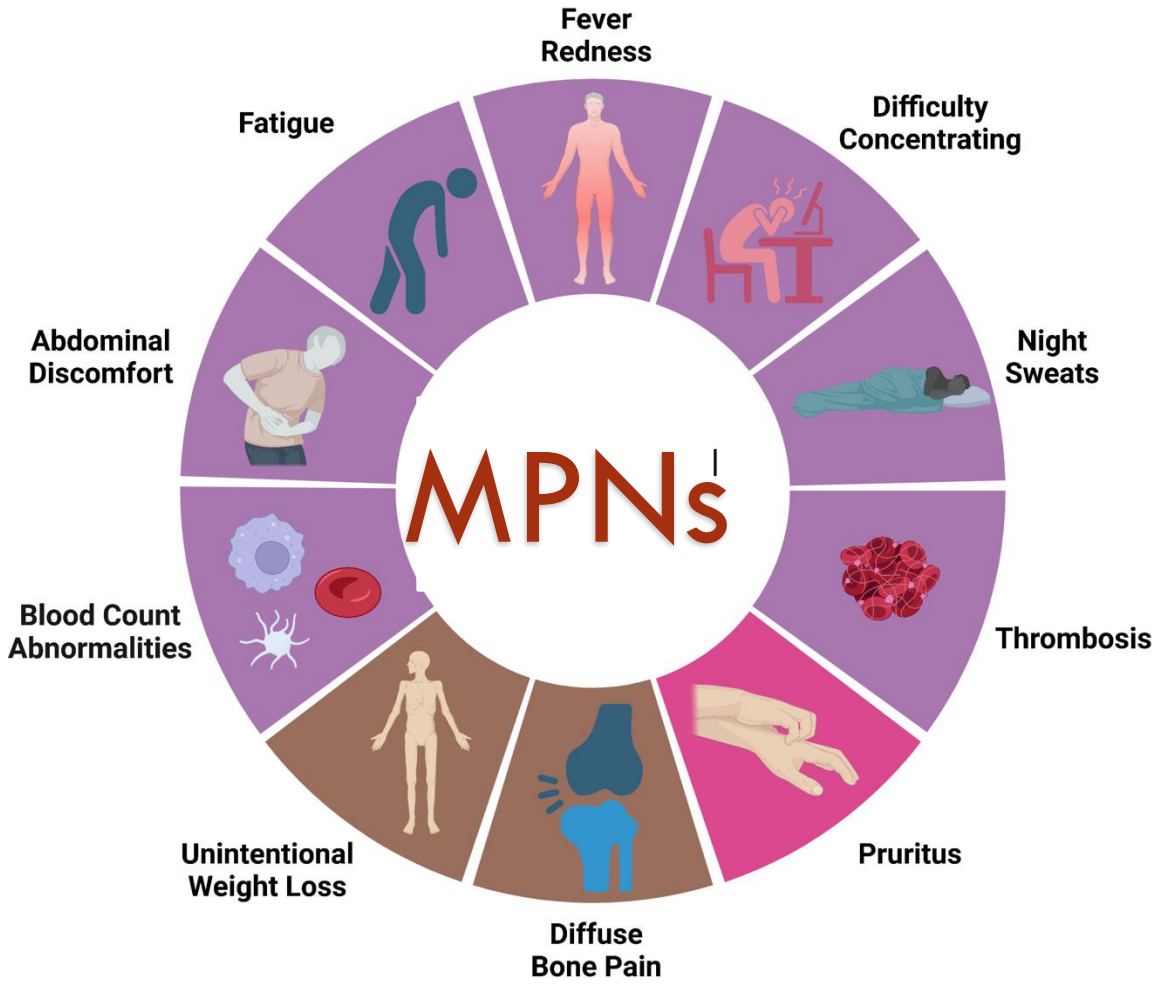


MPNS AND THROMBOSIS

Dr Cecily Forsyth

MPN CLINICAL FEATURES

- High blood counts often with splenomegaly
- Potential for progression
  - Acute leukaemia (blast phase disease)
  - Myelofibrosis
- **Thrombosis - arterial or venous**
  - Macrovascular complications
    - Stroke, heart attack, DVT, pulmonary emboli
  - Microvascular events
    - Headaches, visual disturbances, acral paraesthesia (numbness in fingers/toes), digital discolouration
- Haemorrhagic complications
  - Minor bleeding
  - Major internal organ haemorrhage



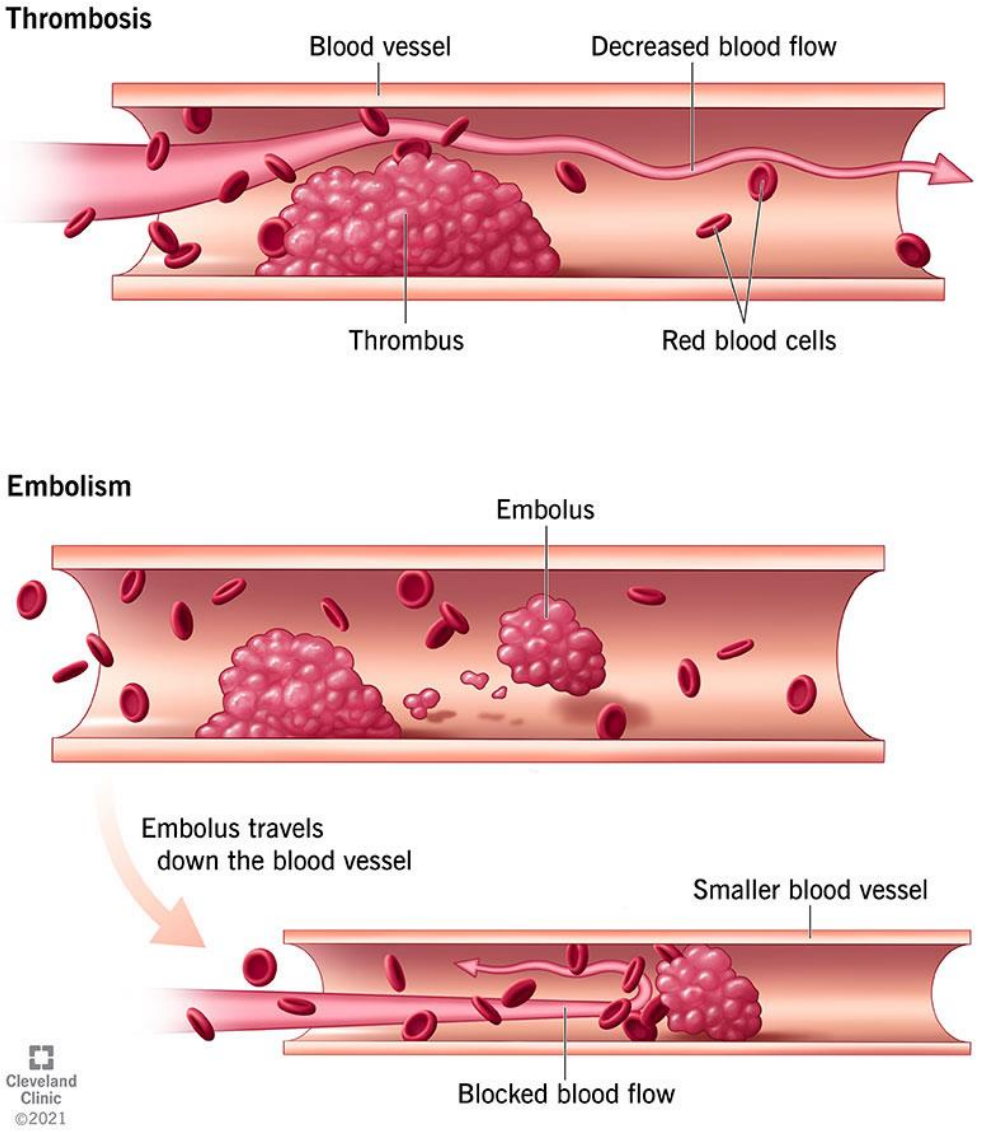
THROMBOSIS

Thrombosis - formation of a blood clot (thrombus) inside a blood vessels

Clots can block blood flow in blood vessels or break free and travel elsewhere in the body

If a clot gets stuck in a critical location like the lungs or brain, it can disrupt blood flow to that organ and result in a life-threatening emergency

Symptoms vary based on the clot's location



THROMBOSIS – ARTERIAL AND VENOUS

- Arterial thrombosis
  - Blood clot forms in an artery
  - Arteries carry blood from your heart to the rest of your body
  - Examples include
    - Heart attacks
    - Strokes/TIA
    - Peripheral arterial disease
- Venous thrombosis
  - Blood clot forms in a vein
  - Veins carry blood back to your heart from your body
  - Examples include
    - Deep vein thrombosis
    - Pulmonary embolism (blood clot in your lung)
    - Portal vein thrombosis (vein to liver)
    - Cerebral venous sinus thrombosis (veins in brain)

THROMBOTIC EVENTS AT DIAGNOSIS

Thrombosis is primary complication of MPNs

- Most common cause of morbidity and mortality
- Impacts on quality-of-life

Diagnostic event in 20% patients

- Arterial events - 16.2%
  - Stroke, heart attack, peripheral arterial occlusions
- Venous events - 6.2%
  - DVT, pulmonary emboli (lung clots), abdominal blood vessels (e.g. portal), cerebral (brain) veins

Risk at diagnosis varies among MPNs

- Highest prevalence in PV
- Lowest prevalence in PMF

Disease	Thrombosis	Haemorrhage
PV	28.6%	6.9%
ET	20.7%	7.3%
PMF	9.5%	8.9%

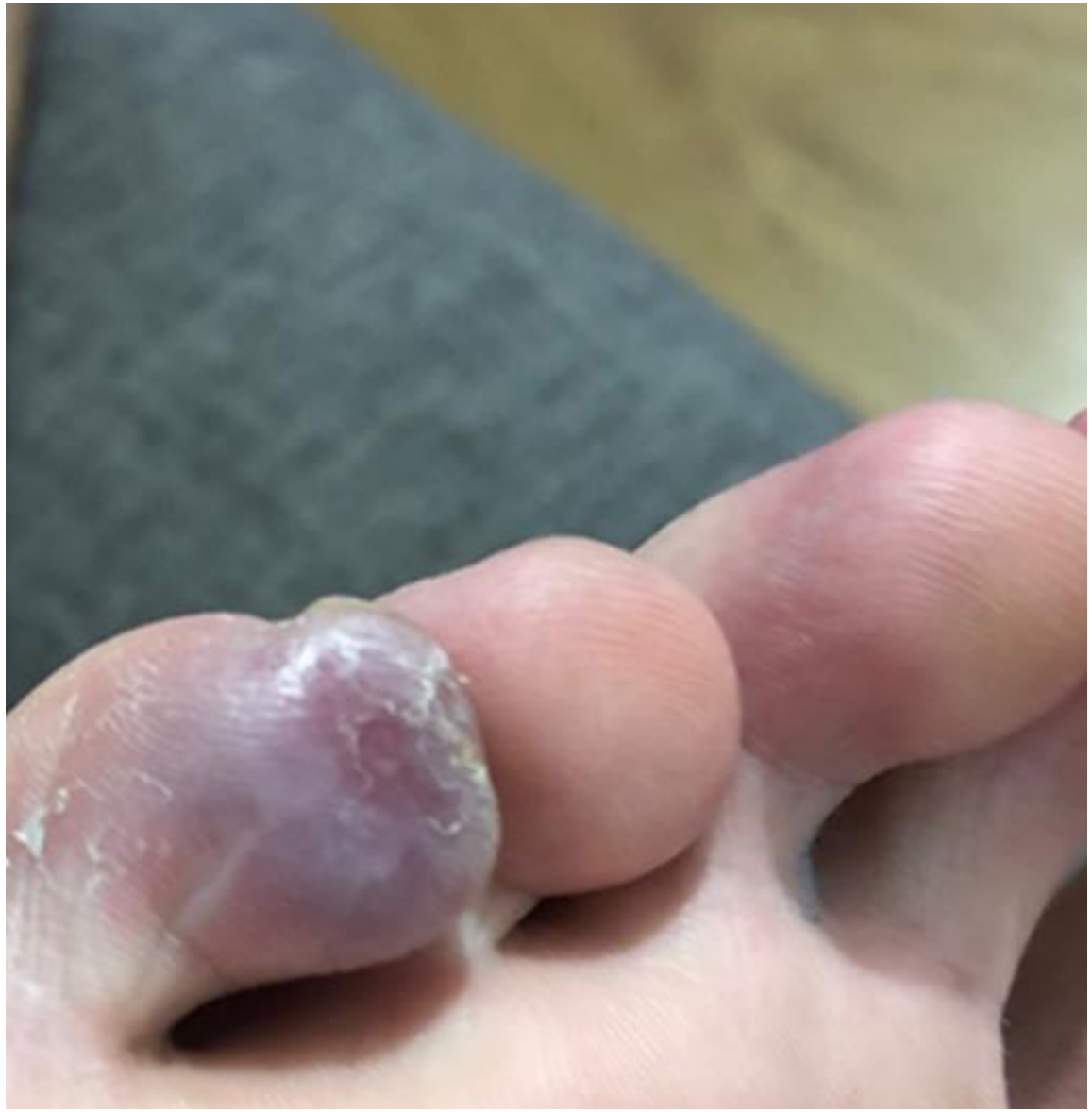
Rungjirajittranon BMC Cancer 2019;19(1):184

WHY DO MPN PATIENTS CLOT?

Complex interplay between blood cells, clotting systems, endothelial cells (line blood vessels) and inflammatory mediators due to dysregulated JAK/STAT signaling

All circulating blood cells and some vascular lining cells have abnormalities that are influenced by the MPN driver mutations present (e.g. *JAK2* V617F)

When blood cells and endothelial cells are activated, their interactions create a highly pro-adhesive and pro-thrombotic milieu in the circulation that predisposes patients to venous, arterial, and microvascular thrombosis



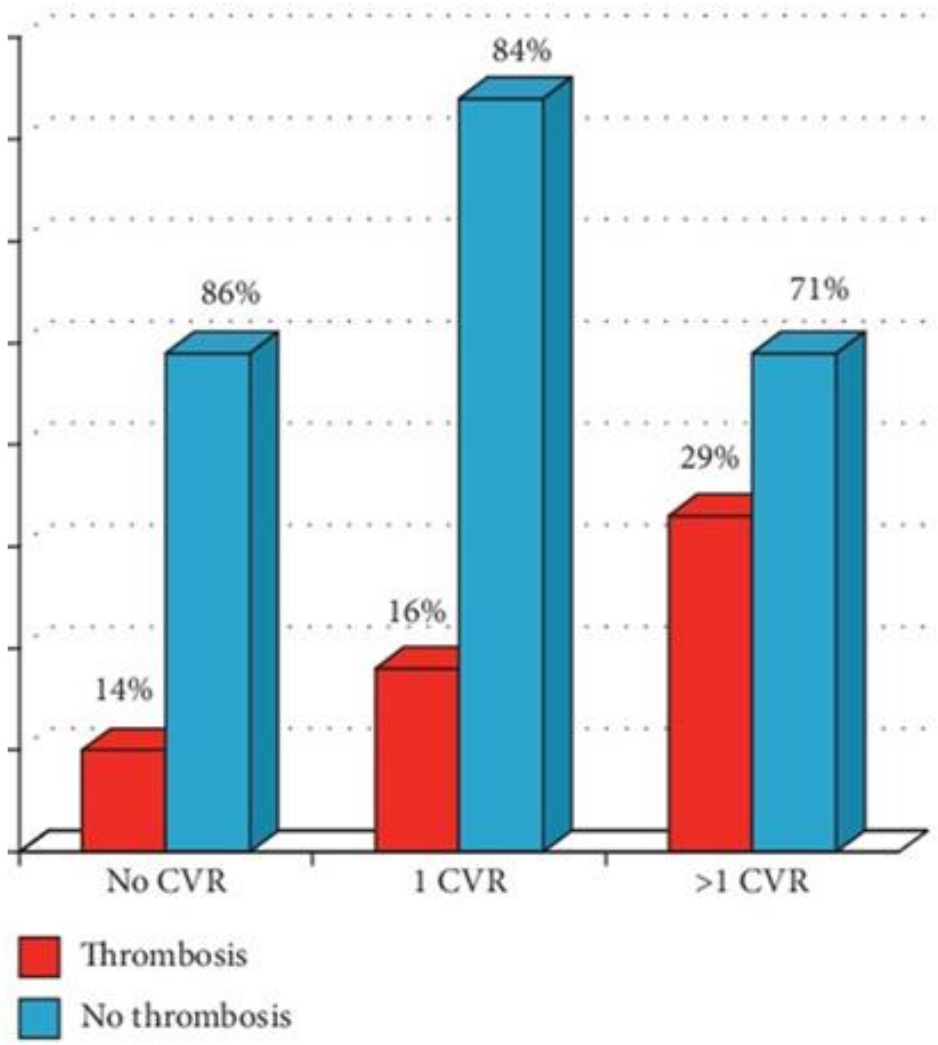
CLOTTING: DISEASE SPECIFIC FACTORS

- JAK2 positivity
  - Increases risk of thrombosis (2 x increase)
  - Allele burden (amount) of >50% is associated with higher clot risk
- Quantitative and qualitative abnormalities in blood cells
  - High red cells in PV
    - CYTO-PV study: rate of thrombosis was 3- to 4-times higher in pts with Hct 45-50% c/w Hct <45%
    - Change in structure and function of red cells results in pro-adhesive (sticky) properties
  - Neutrophils
    - High levels associated with arterial events
    - Activation (extracellular traps)
  - Platelet activation
    - Especially in JAK2-positive patients
- Endothelial cells
  - Activated with pro-adhesive features
  - Especially important for thrombosis in abdominal blood vessels

CLOTTING: PATIENT SPECIFIC FACTORS

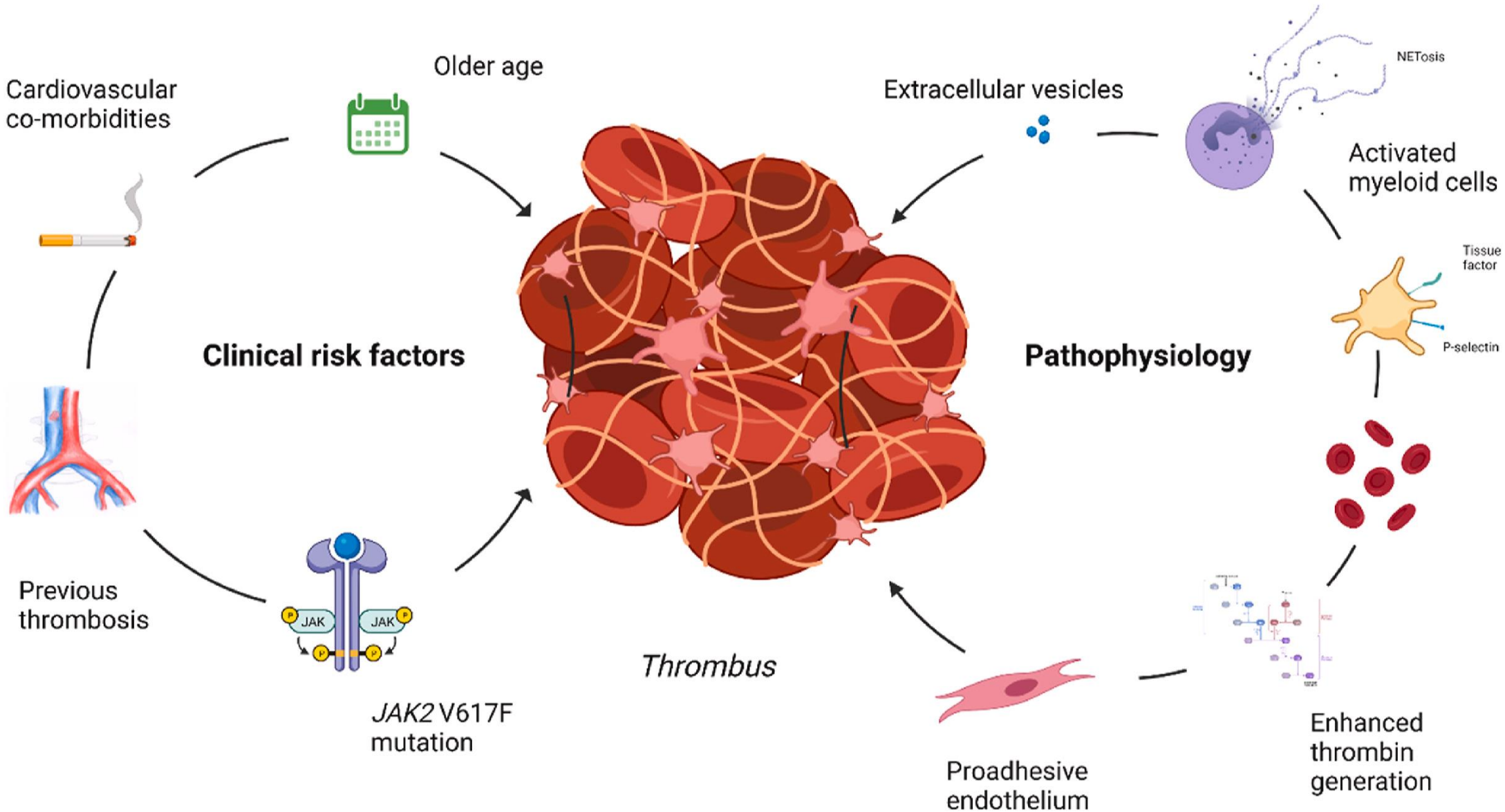
- Age >60 yrs
- Prior thrombosis
- Cigarette smoking
- Hypertension
- Diabetes
- High cholesterol

Recurrent events often in same place (arterial or venous) as initial event



Mancuso Adv Hematol 2020:9124821

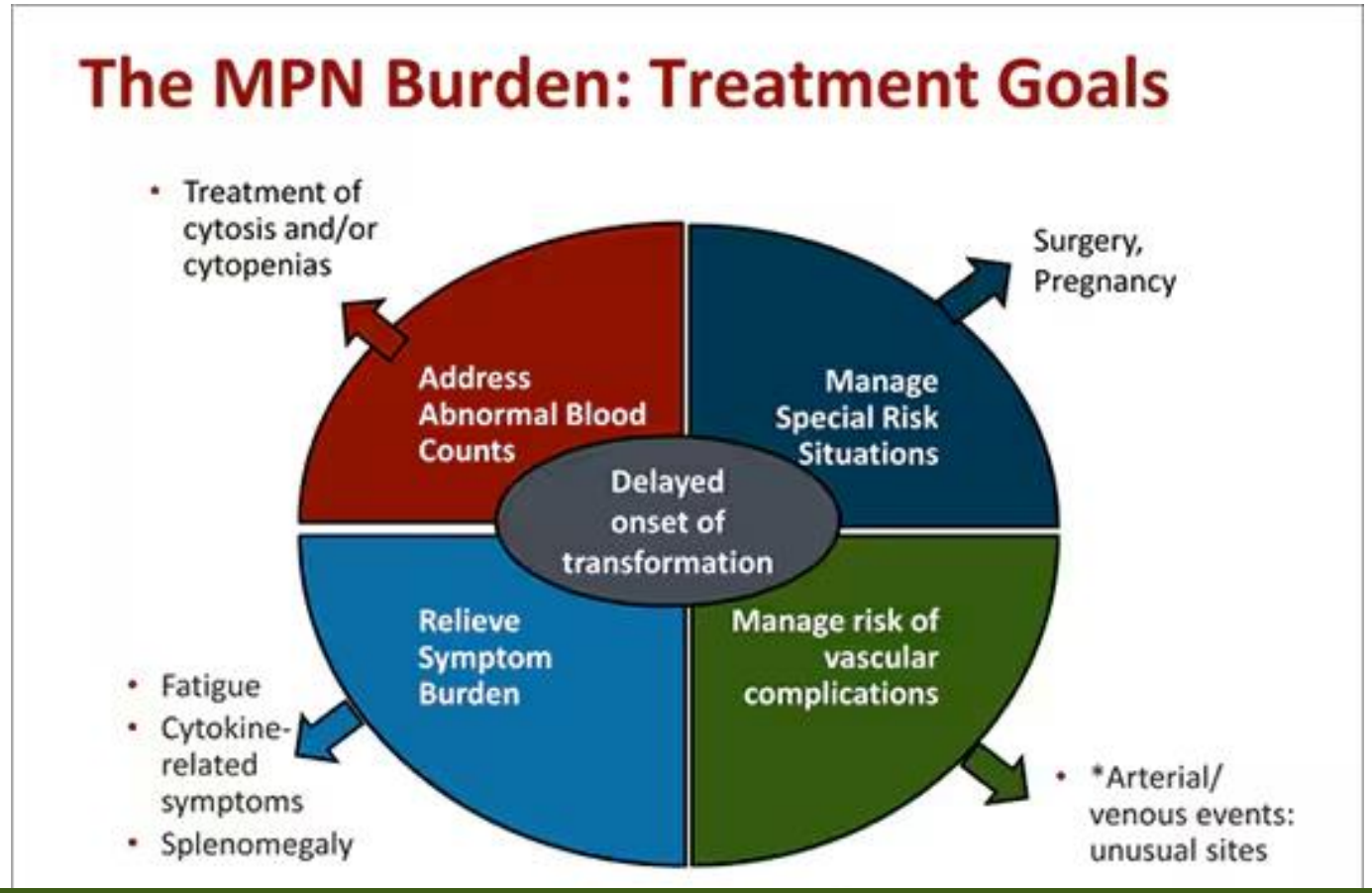
Thrombogenesis in Myeloproliferative Neoplasms



Thrombosis Risk Scores in MPN pts

Scores	MPN	Criteria					Risk groups
		Age	Prior clot	JAK2+	DNMT3A, TET2 variants	CVRF	
Conventional risk score	PV/ET/MF	Yes	Yes	No	No	No	0: low ≥1: high
IPSET-thrombosis	ET	Yes (1 pt)	Yes (2 pt)	Yes (2 pt)	No	Yes	0-1: low 2: intermed ≥3: high
Revised IPSET-thrombosis	ET	Yes	Yes	Yes	No	No	4 risk gps: very low, low, intermed, high
Arterial thrombosis score (ARTS)	PV/ET/MF	Yes (2 pt)	Yes (arterial) (1 pt)	No	Yes (1 pt)	Yes (3 pt)	0-3: low 4-7: high
Venous thrombosis score (VETS)	PV/ET/MF	No	Yes (venous) (1 pt)	Yes (if VAF>50%) (1 pt)	No	No	0: low 1: intermed 2: high

Guy. Blood. 2025;145(16):1769-1778



MPN MANAGEMENT GOALS

Preventing thrombosis
- Antiplatelet +/or anticoagulant treatment
- Cytoreductive agents

Controlling MPN-related symptoms
Optimising QoL

Preventing disease progression/transformation
- Blast-phase MPN
- Post ET/PV myelofibrosis

MANAGEMENT OF THROMBOSIS

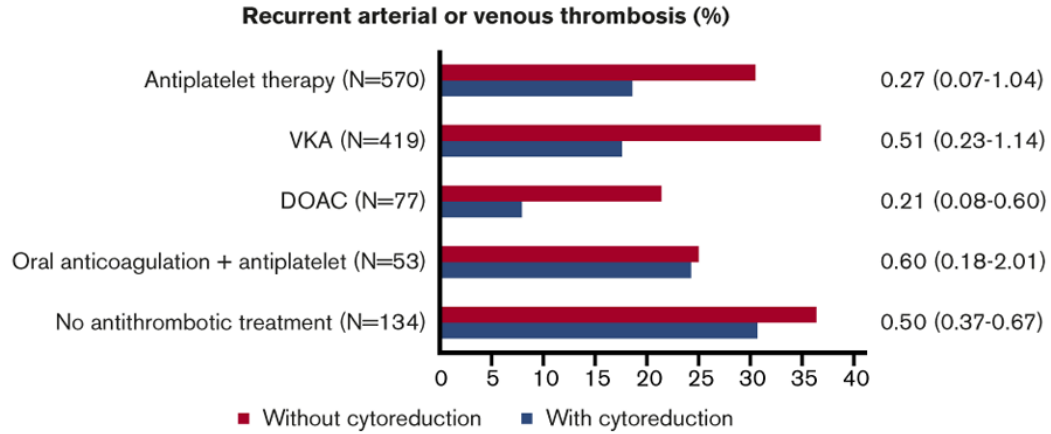
Primary goal is to prevent thrombosis occurrence/recurrence

- Antithrombotic therapy
  - Arterial thrombosis
    - Dual antiplatelet therapy (2 drugs) or twice daily aspirin
      - Initial therapy if cardiac event and sometimes also if stroke/TIA
    - Indefinite low-dose aspirin
  - Venous thrombosis
    - Full dose therapeutic anticoagulation initially
    - After 6 mths if MPN under good control consider
      - Lower dose anticoagulation or
      - Low-dose aspirin especially if bleeding risk high
- **Splanchnic vein thrombosis management much more complex!*

Antithrombotic treatment of venous thromboembolism in patients with myeloproliferative neoplasms

A systematic review of 10 observational studies

N=1295
Polycythemia vera
Essential thrombocythemia
Primary myelofibrosis
+
History of venous thrombosis



- Anticoagulation plus cytoreduction may provide lowest risk of recurrent thrombosis
- High risk of bias, clinical and statistical heterogeneity → low-certainty evidence for all strategies

Venous thrombosis therapy

Based on data from 10 observational studies:

- High risk of recurrent thrombotic events in MPN pts with a history of venous thrombosis even with long-term anticoagulation
- Combination of anticoagulation & cytoreduction results in lowest risk of recurrent thrombosis
- Information from randomised controlled trials would provide more evidence but isn't currently available

Hamulyak Blood Adv 2021;5(1):113-121

MANAGEMENT OF THROMBOSIS

Normalising blood counts with cytoreductive drugs

- Essential to reduce incidence of arterial and venous thrombosis
- Main strategy for preventing initial and recurrent events
- Target counts:
  - ET and pre-PMF patients: Platelets <400
  - PV patients: Haematocrit <45%
  - PMF patients: Platelets <400

Choice of cytoreductive therapy in PV and ET

- Individualised, must include patient preference
- Insufficient evidence of clinically significant efficacy advantages of one therapy over another
- Large and long trials required to provide better data…

Tremblay Hematology Am Soc Hematol Educ Program 2023(1):660-666

CYTOREDUCTION – WHICH AGENT?

Hydroxycarbamide

- Older studies in PV show reduction in thrombosis incidence c/w venesection alone
- May have greater effect at reducing risk of recurrent arterial rather than venous events
- Residual incidence rate of thrombosis in HC-treated pts with PV remains high
  - Approx three-fold higher than the general population

Interferon

- May reduce thrombosis by normalising FBC, reducing *JAK2* and anti-inflammatory properties
- Two big studies (not randomised trials) suggest low rates of thrombosis in PV and ET pts on IFN

Ruxolitinib

- Action as a cytoreductive and anti-inflammatory drug suggests it should reduce vascular events
- Review of published studies in PV
  - Number of thrombotic events reported with RUX was consistently lower than with best available therapy

Barbui Res Pract Thromb Haemost 2022;6:e12657
Masciulli Blood Adv 2020;4(2):380-386

PREVENTION OF VTE
(VENOUS THROMBOEMBOLISM)

Maintain healthy weight
- Obesity - 4-6-fold increased risk

Remain physically active
- Regularly move if sitting for extended time

Travel precautions
- Long-haul flights
  - Aisle seat, mobilise, ECS, hydration
  - Aspirin or prophylactic anticoagulant

- Obtain specialist advice in situations of increased risk
  - Surgery, pregnancy
  - Oestrogen use (OCP, MHT)
  - Lower limb injury/immobilisation

FROM HEAD TO TOE,
TAKE CONTROL:
PREVENT THROMBOSIS,
PROTECT YOUR HEALTH

WORLD THROMBOSIS DAY
13 OCTOBER

UNDERSTANDING THROMBOSIS: TYPES AND WARNING SIGNS

Arterial Thrombosis

Ischemic Stroke

Sudden weakness, vision problems, speech difficulty, limb paresthesia/paralysis

Myocardial Infarction (Heart Attack)

Chest pain, shortness of breath, nausea

Peripheral Arterial Thrombosis

Sudden limb pain, cold or pale skin, numbness or tingling, weak or absent pulse, muscle weakness, blue or mottled skin

Venous Thrombosis

Deep Vein Thrombosis (DVT)

Swelling, pain, warmth, redness

Pulmonary Embolism (PE)

Shortness of breath, chest pain, rapid heart rate

Cerebral Sinus Venous Thrombosis (CSVT)

Severe headache (often the first symptom), vision problems, seizures, nausea or vomiting, stroke-like symptoms (weakness, difficulty speaking, confusion)

Abdominal Vein Thrombosis (AVT)

Abdominal pain, bloating, nausea, vomiting, blood in stool, swelling in abdomen, fever

WorldThrombosisDay.org

Seek medical attention if you have one or more of these signs.

REDUCING RISK OF ARTERIAL THROMBOSIS

Cease smoking

Ensure lipid levels in target range

Control hypertension

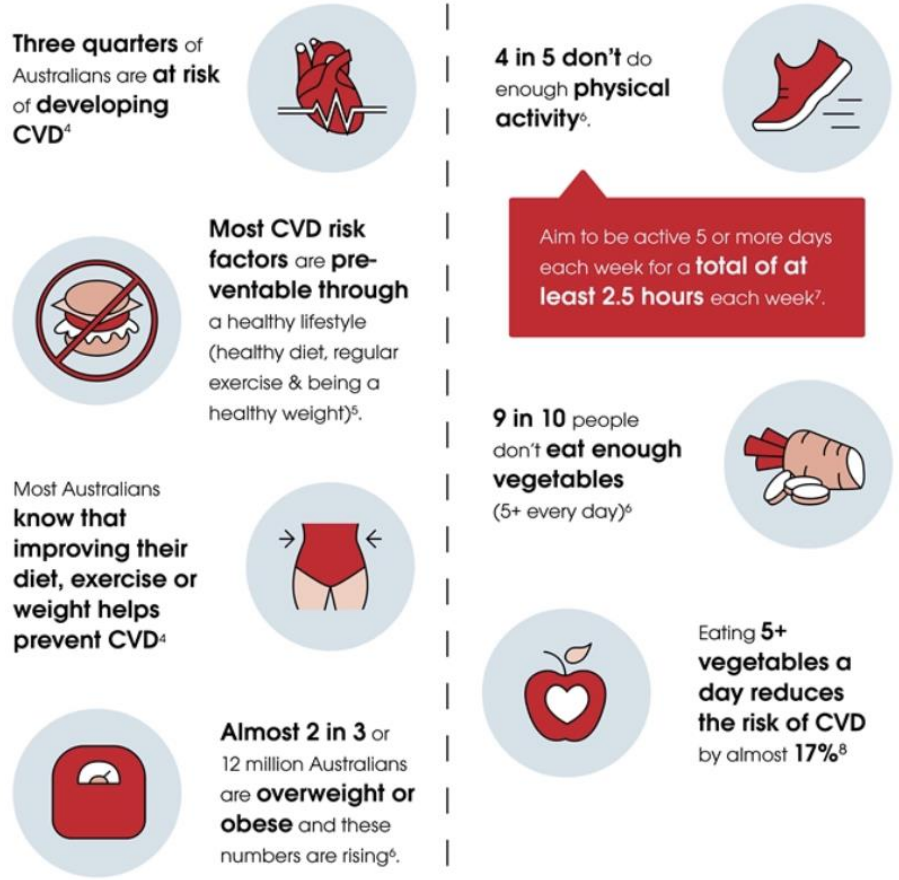
- ACE inhibitors - simultaneously control HTN & may reduce erythropoiesis

Ensure good control of diabetes

Optimise diet

Aim for a healthy weight

Exercise regularly



National Heart Foundation of Australia

Barbui Blood. 2017;129(9):1226-1227

SMOKING

Increased risk of MPNs in smokers c/w non-smokers (Danish population-based study)

- 2.5-fold higher among daily smokers
- 1.9-fold higher among occasional/ex-smokers

Tobacco smoking is the single greatest preventable cause of mortality

Smoking cessation

- Reduces cardiovascular mortality
- Reduces incidence of hypertension, diabetes, heart failure
- Earlier cessation is better
  - Quit at 25 to 34 years - 10-year survival gain
  - Quit at about 39 years - 9-year survival gain
  - Quit between 55 and 64 years of age - 4-year survival gain
- Lower risk of cardiovascular disease within 5 years and slowly declines over decades

Okorare Cureus. 2023;15(3):e35966
Pedersen Cancer Med. 2018;7(11):5796-5802

LIPID TARGETS

Current approach stratifies pts into risk groups with lipid target based upon CV risk

- All MPN pts, especially JAK2-positive pts
  - High-risk (similar to pts with diabetes or CKD)
    - Target LDH <1.8 mmol/L
- Prior acute coronary syndrome/myocardial infarct/stent/CABG
  - Very-high risk
    - Target LDL target <1.4 mmol/L, and at least 50% reduction from baseline

Management

- Lifestyle modifications will lower LDL-C by 5-10% only
- Statin +/- ezetimibe required in most circumstances
- There is no adverse lower limit (can go low)

Nelson. Aust Prescr 2024;47:7-14

Treatment targets and goals for cardiovascular disease prevention

Smoking	No exposure to tobacco in any form
Diet	Healthy diet, low in saturated fat Focus on wholegrain products, vegetables, fruit, and fish
Physical activity	3.5–7 h moderately vigorous physical activity per week, or 30–60 min most days
Body weight	BMI 20–25 kg/m^2 Waist circumference <94 cm (men), <80 cm (women)
Blood pressure **(**HTN Dx ≥130/80)	Treat if 130-139/80-89 and high CV risk Target SBP <120, DPB ≤70-80
LDL-C	Very-high risk: LDL <1.4 mmol/L & ≥50% LDL-C reduction from baseline High risk: LDL <1.8 mmol/L & ≥50% reduction Moderate risk factors: <2.6 mmol/L, lower preferable
Triglycerides	No goal, <1.7 mmol/L indicates lower risk
Diabetic	HbA1c: <7%

STATINS

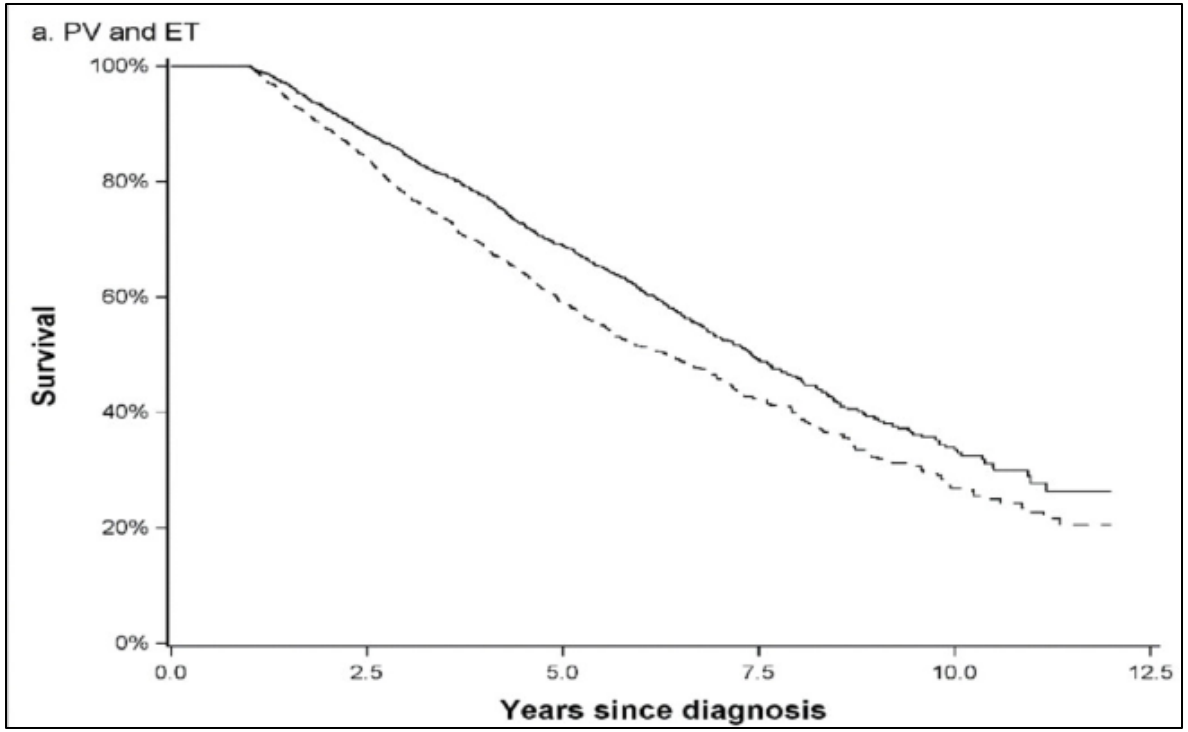
Statins users have a lower likelihood of an MPN dx (Danish Study)

Statins may enhance efficacy of IFN

- Higher rates of CHR and PMR with lower dose of IFN

US data of 4010 pts with MPNs (PV and ET)

- Statin use
  - 22% reduction in all-cause mortality
  - Reduced risk of thrombosis
    - Entire group
    - PV and ET subgroups



Statin users - significantly better overall survival than nonusers

Kristensen Blood Adv.2023;7(14):3450-3457
Hansen Blood. 2024;144(1):3184
Podoltsev Cancer Med. 2023;12:18889–18900

BENEFITS OF EXERCISE

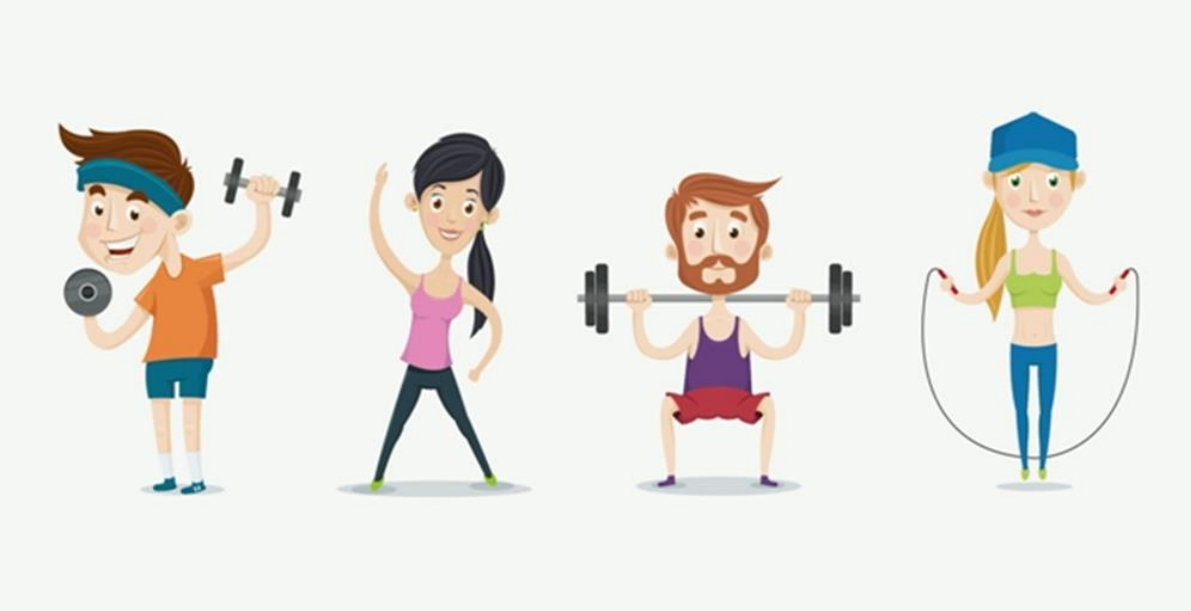
Reduced risk of heart disease & stroke

Improved BP & lipid levels

Increased energy levels & overall well-being

Strength training

- Increases muscle mass & reduces risk of injury
- Stimulates bone growth & reduces osteoporosis risk
- Improves metabolism & weight
- Improves flexibility & balance
- Improves mood & mental well-being
- Reduces depression & anxiety



Singh. Current Oncology Reports. 2024;26:1135-1145

BENEFITS OF EXERCISE

Exercise in cancer pts improves

- Treatment-related adverse effects
- Quality of life
- Psychosocial distress
- Fatigue
- Cognitive function
- Sexual health

TO IMPROVE CV HEALTH

150-300 mins of moderate-intensity activity/wk

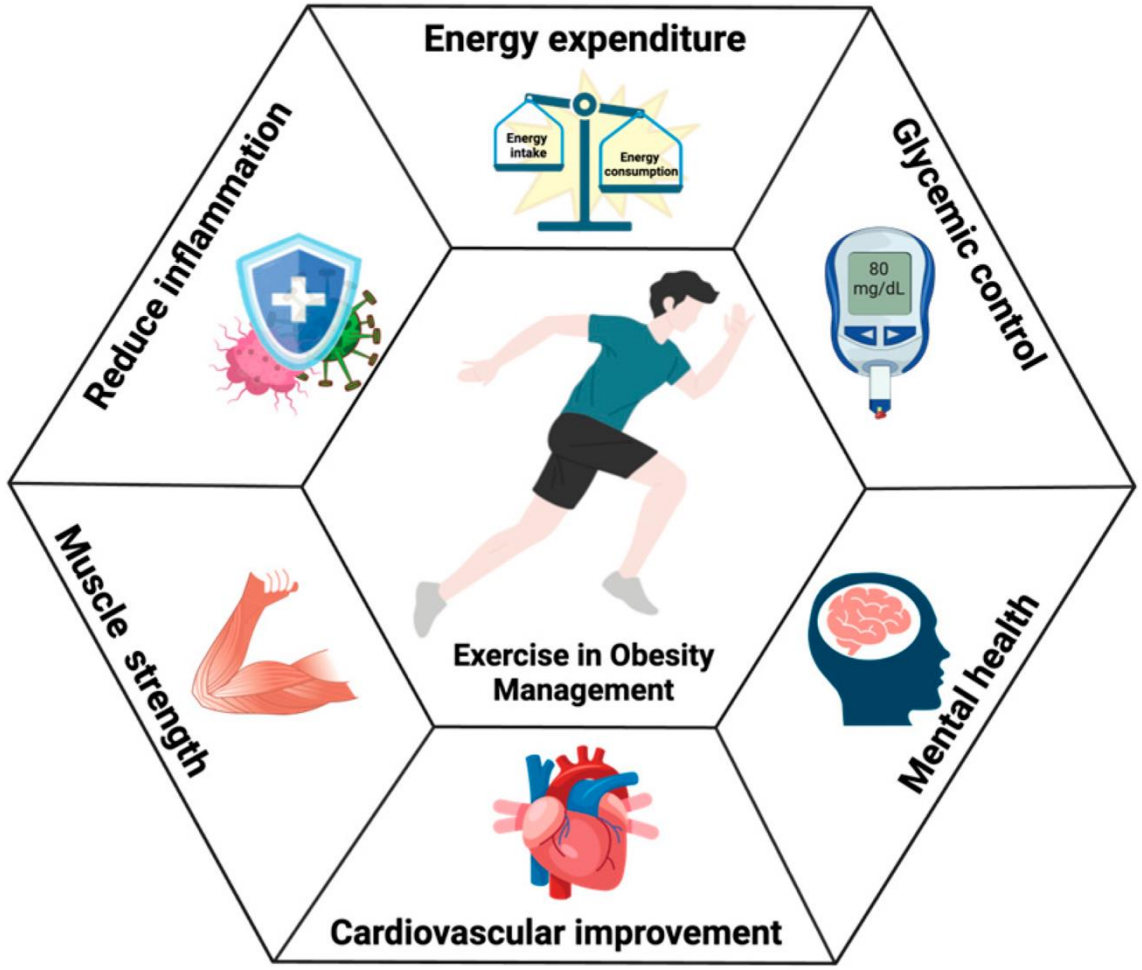
- Brisk walking, swimming or cycling

75-150 mins of vigorous-intensity activity/wk

- Jogging, aerobics, netball, soccer

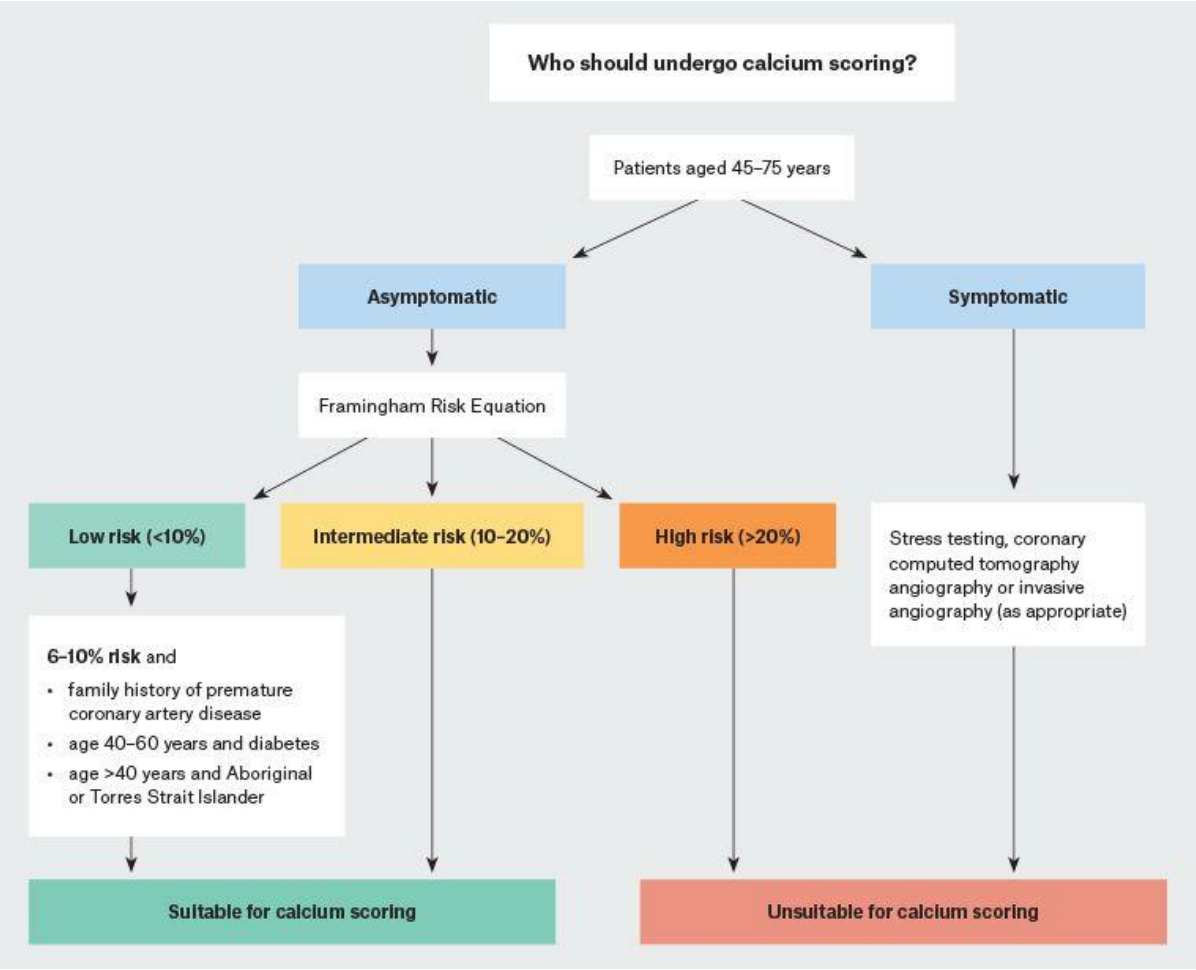
Muscle strengthening activities x2/wk

- Weights, push-ups, pull-ups etc



JUST MOVE – IT IS ALL BENEFICIAL

SCREENING FOR CORONARY ARTERY DISEASE



Framingham Risk Score

- Estimates 10-year risk of developing clinical cardiovascular disease (heart attack, stroke etc)
- Variables include:
  - Age
  - Sex
  - Smoker
  - Cholesterol
  - HDL
  - Systolic BP
  - Medication for hypertension

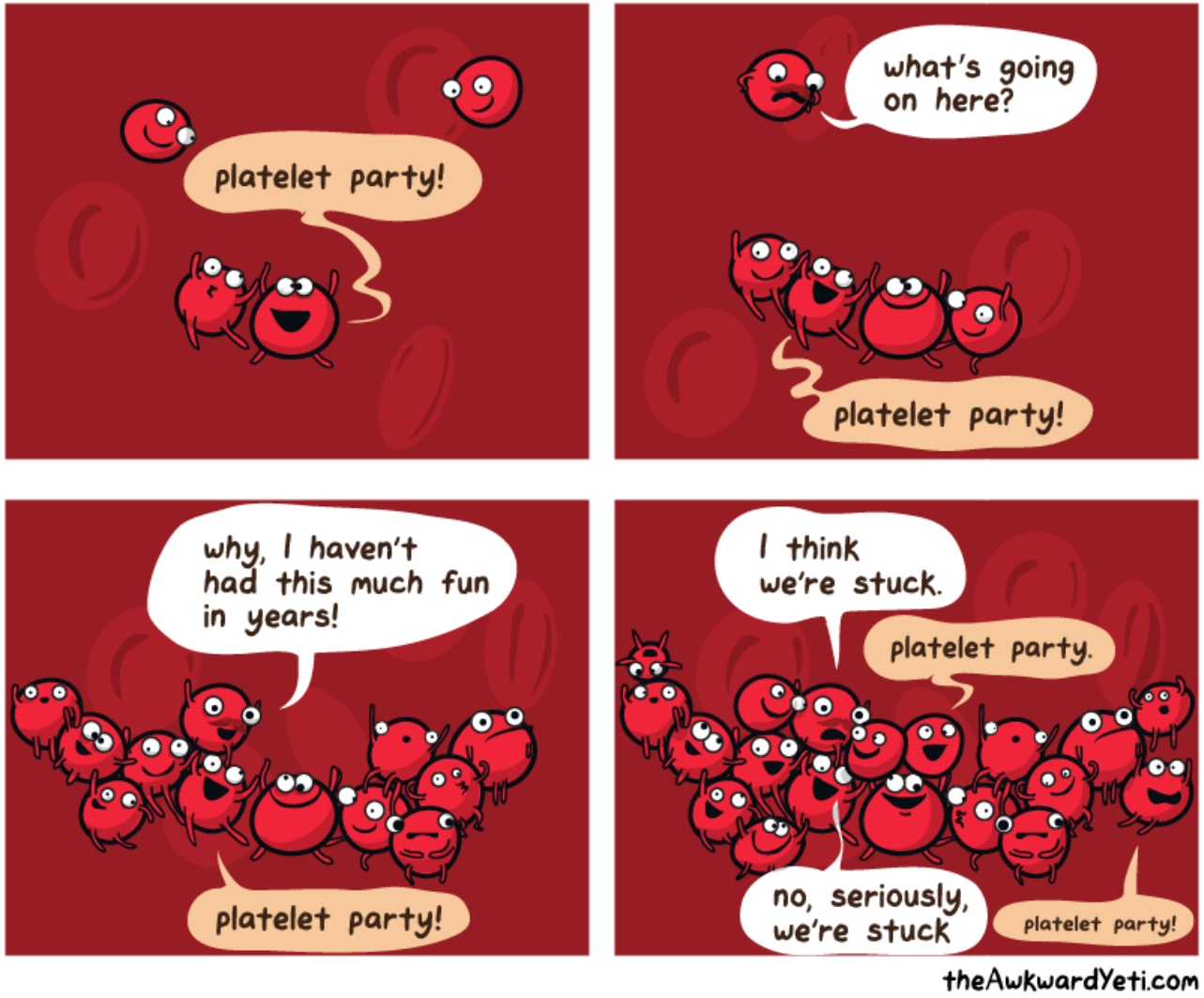
CT CORONARY CALCIUM SCORE

Table 1. Interpretation of coronary calcium score[3]		
Calcium score	Interpretation	Risk of myocardial infarction/stroke at 10 years
0	Very low risk	<1%
1–100	Low risk	<10%
101–400	Moderate risk	10–20%
101–400 and >75th percentile	Moderately high risk	15–20%
>400	High risk	>20%

- Calcium score predicts important cardiovascular outcomes, including cardiac events and all-cause mortality
- Pts with CAC >100
  - Statin, lifestyle management and risk factor control

Chua AJGP. 2020; 49(8)"464-469

QUESTIONS?


platelet party!
what's going on here?
platelet party!
why, I haven't had this much fun in years!
platelet party!
I think we're stuck.
platelet party.
no, seriously, we're stuck
platelet party!
theAwkwardYeti.com

MPNS AND OTHER HEALTH ISSUES

MPNS AND OTHER HEALTH ISSUES

Other cancers

Skin cancers

Others

Autoimmune

CKD

Liver disease

Gut health

Dementia

SECOND MALIGNANCIES

Early studies suggest MPN pts have a higher risk of

- Non-haematologic malignancies
- Lymphomas
- Aggressive myeloid malignancies

Several recent studies but largest from Sweden (nationwide cancer registry)

- Increased risk (x2) compared to matched controls seen in:
  - Non melanoma and melanoma skin cancer
  - Kidney cancer
  - Brain cancer
  - Endocrine cancers
  - Lymphoma

Landtblom. Leukemia. 2018;32(10):2203-2210

SKIN CANCERS

Increased risk in all MPN patients, particularly those on:

- Hydroxycarbamide, ruxolitinib, momelotinib

Increased risk of recurrence & metatastic spread reported

Reducing risk

- Sun protection
- Counsel patients on risk
- Close dermatological monitoring
- Seek early assessment of skin lesions
- Consider alternate to hydroxycarbamide

For patients on a JAKi the risks & benefits of each treatment option need to be carefully considered & discussed as not clear that switching to an alternate JAKi impacts outcomes

Landtblom. Leukemia. 2018;32(10):2203-2210
Rampotas. Blood. 2024;143((2):178-182

DEMENTIA

Several recognised risk factors:

- Age, sex, lifestyle (obesity, diabetes, hypertension, smoking), genetic factors, head injuries

MPNS chronic inflammatory & thrombogenic

- May lead to reductions in cerebral blood flow at a microvascular level
- Could contribute to cognitive impairment, memory loss, and dementia development

Danish study

- MPN pts have elevated dementia risk
- Stronger association with PV and men

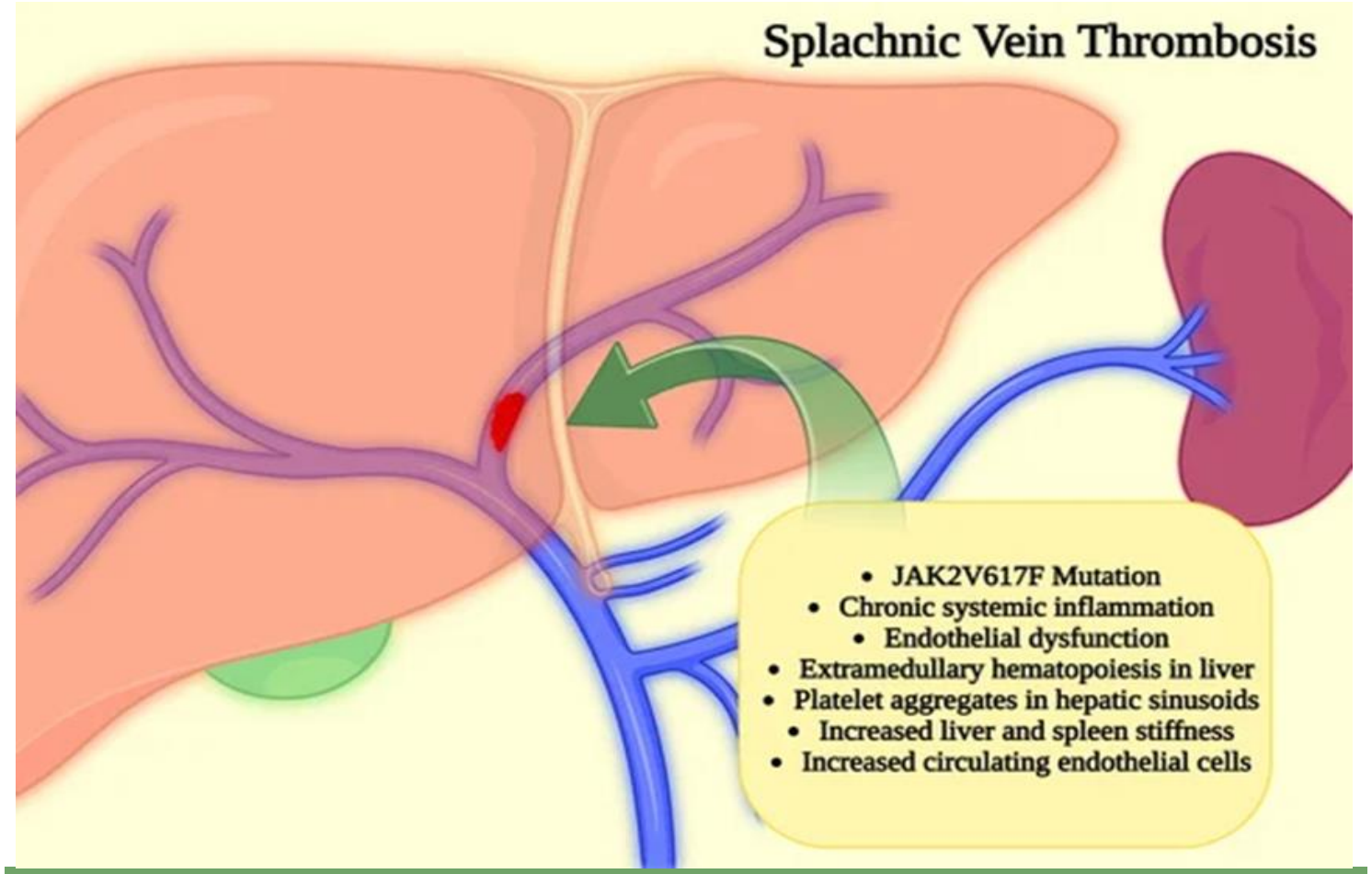
Sun. European Journal of Haematology2025;114:45-56
Alzheimers New Zealand

AUTOIMMUNE DISEASE

Studies suggest higher prevalence of autoimmune or inflammatory diseases (AID) in patients with MPNs

Italian-Mayo collaboration

- Most prevalent diagnoses included
  - Organ-specific AID (e.g. thyroid disorders)
  - Inflammatory arthritis (e.g. rheumatoid arthritis)
  - Inflammatory dermatosis (e.g. psoriasis)
- AID developing after dx with MPN more likely in
  - Females
  - Patients with prior history of AID
- AID diagnosed prior to MPN
  - Does not affect overall, myelofibrosis-free, or leukaemia-free survival
  - Increases risk of venous thrombosis at time of MPN diagnosis
    - Confirms that tumor-extrinsic inflammation may exacerbate MPN-related thrombosis tendance



LIVER DYSFUNCTION IN MPN

May be due to

- Splanchnic vein (upper gut) thrombosis
  - *JAK2* mutation promotes thrombosis (endothelial dysfunction and inflammation)
- Hepatic microthromboses
  - Thrombosis in hepatic sinusoids (small blood vessels in liver)
- Blood cell production (extramedullary haematopoiesis) in liver (in MF)
- Platelet aggregates/clumps seen in liver biopsies
- MPN therapy

Mihaila. Livers. 2025, 5(3), 29

CKD IN MPN

Chronic kidney disease increasingly recognised in MPN pts

- May occur in up to 15.4% of pts
- (In Australia 11% of adults have CKD although many undiagnosed)

Risk factors

- Age ≥65 yrs
- TET2, ASXL1 variants
- Cardiovascular events
- Hypertension
- Diabetes

CKD adversely impacts on survival especially if

- Males
- PMF
- Age ≥65 yr

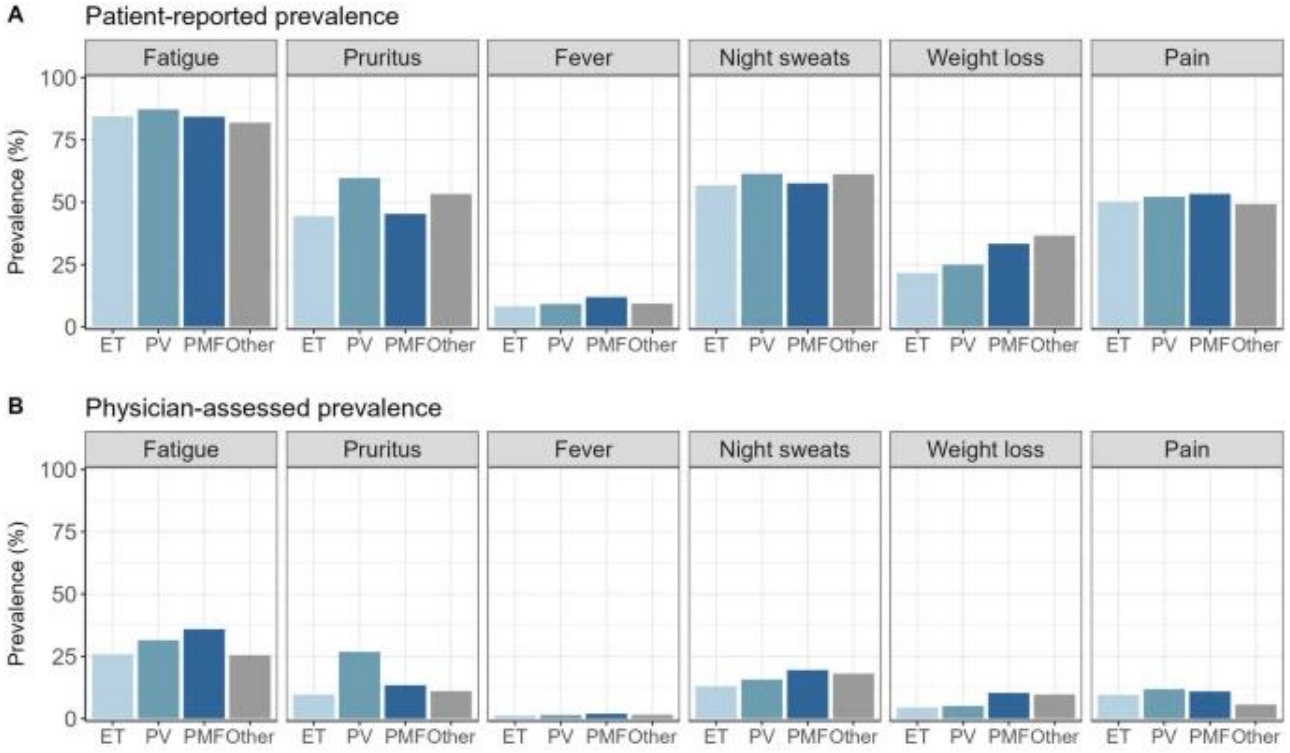
Gao Blood. 2024;144(S1):6643

MPN SYMPTOM BURDEN

Symptoms impact on pts QoL and ADLs

3979 German MPN pts compared physician and pt reported symptoms collected at same time

- Significant discrepancies in symptom recognition between pt-reported and physician-reported data
- Physicians reported much lower symptom presence



Manz. Leukemia. 2025;39:864-875

MPN SYMPTOM BURDEN

3979 German MPN pts

- 93% of pts were symptomatic at baseline
- Severe symptom burden in 38% of pts
  - Score of 7–10 in at least one symptom
- Reported symptoms
  - Fatigue – most common reported by physicians and pts
  - Night sweats, pain, pruritus, weight loss, fever
- Pts receiving cytoreductive therapy
  - Similar symptom burden to those not on cytoreductive therapy
- PMF pts did not exhibit an increased burden compared to ET, PV & MPN-U
  - Aligns with previous studies

Manz. Leukemia. 2025;39:864-875

MPN SYMPTOM BURDEN

Integrative oncology

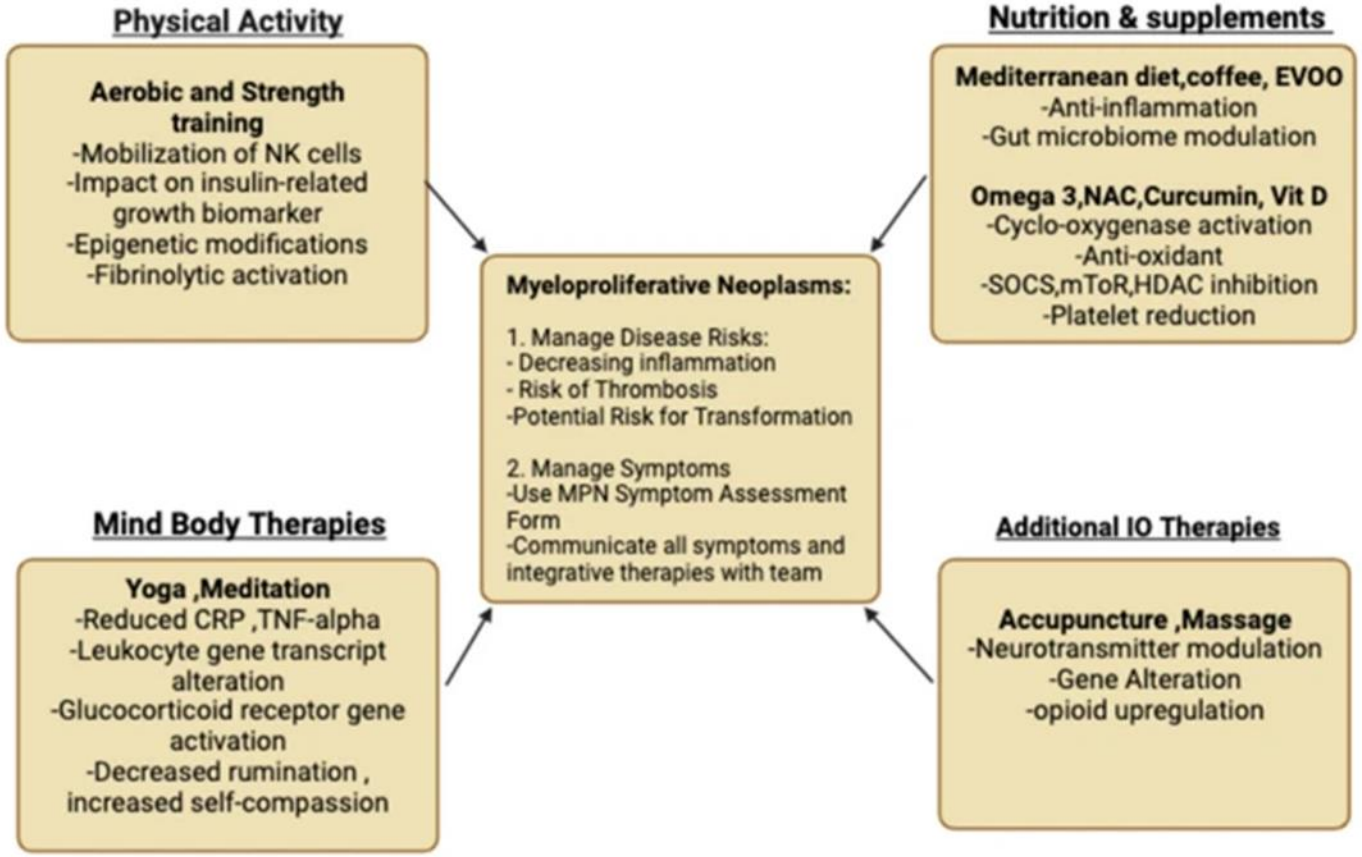
- Targeting mind, body, nutrition, supplements, and other supportive care therapies

Studies suggest benefit of IO in MPN

Benefits due to

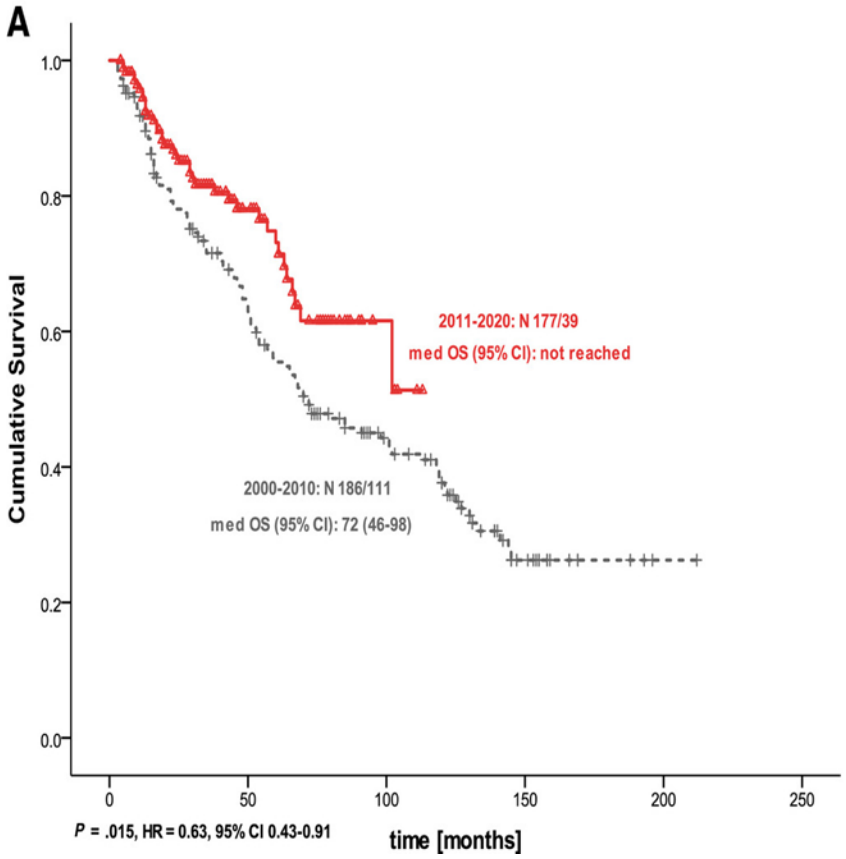
- Enhanced physical capacity
- Reduced disease-related inflammation
- Subconscious mind training
- Gut microbiome modulation

Combine IO with evidence-based pharmacological treatments to enhance QoL and clinical outcomes for MPN pts

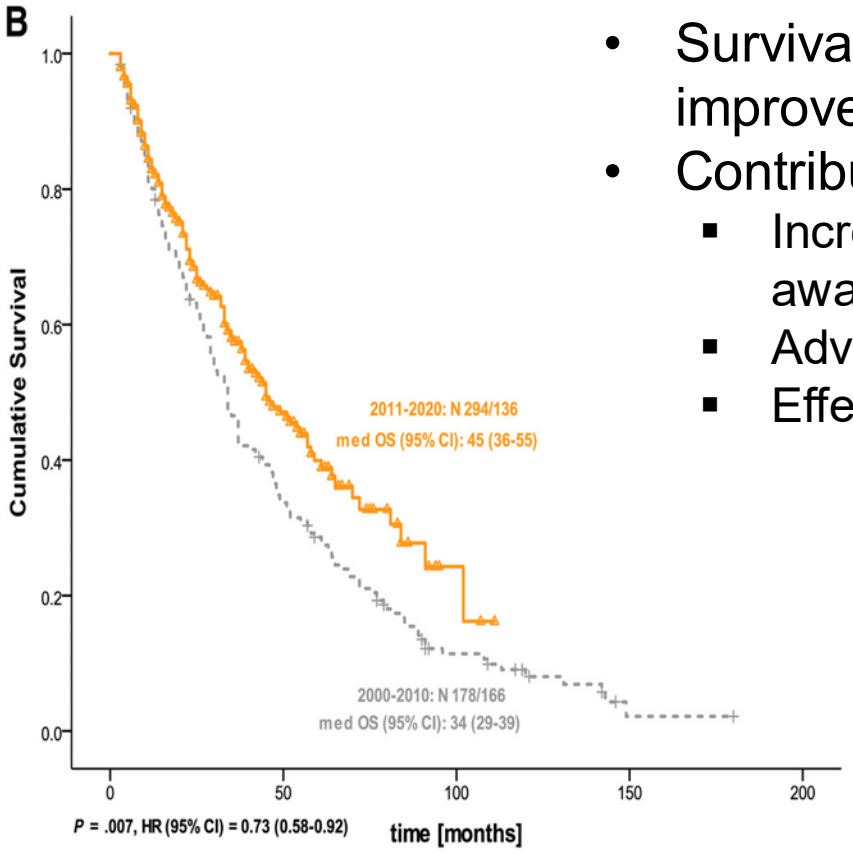


Singh. Curr Oncol Rep.2024;26(10):1135-1145

MF SURVIVAL



A: Pts <65 yrs



B: Pts ≥65 yrs

- Survival of pts with MF has improved over last decade
- Contributing factors:
  - Increased disease awareness
  - Advances in supportive care
  - Effective treatments

Masarova Cancer 2022;128(8):1658-1665

MPNS

“MPN patient quality of life is central to everything we do. We aim to assist pts and families to find support and relevant up to date information related to MPN.”

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