

Cardiovascular risk factors in MPN patients

Marko Lucijanic, MD PhD

University hospital Dubrava, Zagreb
University of Zagreb School of Medicine

KLINIČKA
BOLNICA
DUBRAVA



Dominant disease related risks in MPN patients

- All MPN patients are burdened with high thrombotic risk ¹
- High prevalence of modifiable CV risk factors in MPN patients ²

1. Barbui T, Thiele J, Gisslinger H, et al. The 2016 WHO classification and diagnostic criteria for myeloproliferative neoplasms: document summary and in-depth discussion. *Blood Cancer J.* 2018;8(2):15. doi:10.1038/s41408-018-0054-y

2. Krecak I, Verstovsek S, Lucijanic M. Optimization of cardiovascular risk factor management in patients with BCR::ABL1 negative chronic myeloproliferative neoplasms, current knowledge, and perspectives. *Ann Hematol.* 2023 Sep 4. doi:10.1007/s00277-023-05426-9.

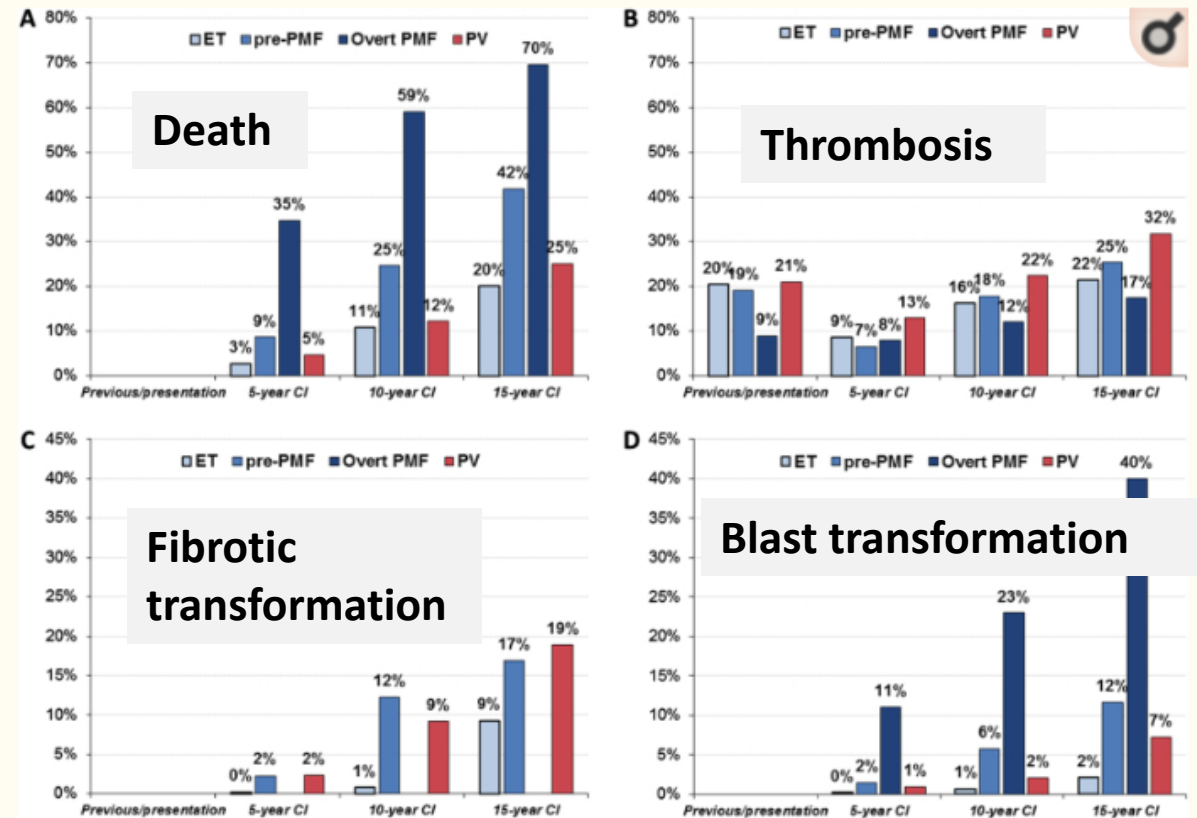


Fig. 1

Mortality **a**, major arterial and venous thrombotic complications **b**, myelofibrosis **c**, and Blast transformation **d** in ET, Pre-PMF, overt PMF and PV cohorts. Prevalence of previous events and cumulative incidence (CI) during follow-up calculated at 5, 10, and 15 years from diagnosis. For PMF, two different data sets were considered: $n = 707$ for panel **a**, ¹⁸ and $n = 383$ for panel **d**¹⁴ and regarding PV for all panels¹¹⁰

Do CV risk factors prognostically matter?

- Inconsistent results in the literature regarding CV risk factors prognostic importance ³
- Prognostic contribution of classic CV risk factors is often **masked** and overshadowed by MPN disease features due to overlap in their biology ³
- CV risk factors are **not directly considered** in the thrombotic risk stratification in the **contemporary MPN thrombotic risk scores**



3. Krecak I, Verstovsek S, Lucijanic M. Reappraisal of Cardiovascular Risk Factors in Patients With Chronic Myeloproliferative Neoplasms. Clin Adv Hematol Oncol. 2023;21(10):541-548.

Classic CV risk factors may have their own specific features in MPN patients

...and most importantly – they are modifiable



Smoking
Impairs treatment responses



Diabetes mellitus
Optimal target levels of glycated hemoglobin in MPNs are unknown



Arterial hypertension
Can diminish in polycythemic patients after the start of phlebotomies



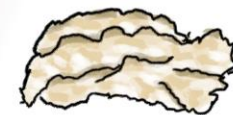
Hyperuricemia
Promotes endothelial dysfunction and cardiovascular events



Hyperlipidemia
MPNs may be considered high-risk regarding the control of blood lipids



MPN-related glomerulopathy
Promotes thrombosis and impairs survival



Obesity and cachexia
A U-shaped association between body mass index and disease-related symptoms

2. Krecak I, Verstovsek S, Lucijanac M. Optimization of cardiovascular risk factor management in patients with BCR::ABL1 negative chronic myeloproliferative neoplasms, current knowledge, and perspectives. Ann Hematol. 2023 Sep 4. doi: 10.1007/s00277-023-05426-9.

Arterial hypertension



- The most common CV comorbidity in MPN patients (40-90%)²
- AH in MPN patients has less variation during blood pressure measurements, higher occurrence of **non-dipper phenotype** and **lower sympathetic nervous system activity**^{4,5}
- AH may diminish after start of **phlebotomies**, even among non-MPN patients^{6,7}

2. Krecak I, Verstovsek S, Lucijanic M. Optimization of cardiovascular risk factor management in patients with BCR::ABL1 negative chronic myeloproliferative neoplasms, current knowledge, and perspectives. *Ann Hematol.* 2023 Sep 4. doi: 10.1007/s00277-023-05426-9

4. Akdi A, Özeke Ö, Karanfil M, Ertem AG, Yayla Ç, Demirtaş K, Güney T, Ünal S, Selçuk MT. Diurnal rhythm of blood pressure in patients with polycythemia vera. *Blood Press Monit.* 2020 Apr;25(2):69-74. doi: 10.1097/MBP.0000000000000427.

5. Józwiak-Plebanek K, Dobrowolski P, Lewandowski J, Narkiewicz K, Sikorska A, Siński M, Eisenhofer G, Schmieider RE, Januszewicz M, Windyga J, Prejbisz A, Januszewicz A. Blood pressure profile, sympathetic nervous system activity, and subclinical target organ damage in patients with polycythemia vera. *Pol Arch Intern Med.* 2020 Aug 27;130(7-8):607-614. doi: 10.20452/pamw.15473.

6. Zidek W, Tenschert W, Karoff C, Vetter H. Treatment of resistant hypertension by phlebotomy. *Klin Wochenschr.* 1985 Aug 16;63(16):762-4. doi: 10.1007/BF01733828.

7. Xiong XJ, Wang PQ, Li SJ. Blood-Letting Therapy for Hypertension: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Chin J Integr Med.* 2019 Feb;25(2):139-146. doi: 10.1007/s11655-018-3009-2.

Diabetes mellitus



- Insufficiently recognized or is a less common CV comorbidity in MPNs (5-17%) ²
- Novel therapies like **SGLT-2 inhibitors** may promote erythrocytosis – of unclear significance regarding thrombotic risk ⁸
- Optimal levels of **glycated hemoglobin (HbA1c)** for the diagnosis and treatment of DM in MPN patients are still not established – HbA1c values may be affected by high cellular turnover, and other MPN specific features and therapies ^{9, 10}

2. Krecak I, Verstovsek S, Lucijanac M. Optimization of cardiovascular risk factor management in patients with BCR::ABL1 negative chronic myeloproliferative neoplasms, current knowledge, and perspectives. *Ann Hematol.* 2023 Sep 4. doi: 10.1007/s00277-023-05426-9

8. Gangat N, Abdallah M, Szuber N, Saliba A, Alkhateeb H, Al-Kali A, Begna KH, Pardanani A, Tefferi A. Sodium-glucose co-transporter-2 inhibitor use and JAK2 unmutated erythrocytosis in 100 consecutive cases. *Am J Hematol.* 2023 Jul;98(7):E165-E167. doi: 10.1002/ajh.26933.

9. Karsegard J, Wicky J, Mensi N, Caulfield A, Philippe J. Spurious glycohemoglobin values associated with hydroxyurea treatment. *Diabetes Care.* 1997 Jul;20(7):1211-2. doi: 10.2337/diacare.20.7.1211.

10. Ren Q, Lv X, Yang L, Yue J, Luo Y, Zhou L, Meng S, Yang S, Puchi B, Zhou X, Ji L. Erythrocytosis and Performance of HbA1c in Detecting Diabetes on an Oxygen-Deficient Plateau: A Population-based Study. *J Clin Endocrinol Metab.* 2020 Apr 1;105(4):dgaa001. doi: 10.1210/clinem/dgaa001.

Smoking



- Smoking-induced inflammation and its carcinogenic potential may promote the development of MPNs ^{11, 12}, **impair treatment responses (interferons) ¹³**, and **negatively affect thrombotic risk and survival ^{13, 14}**
- Causality with MPNs may be confounded by referral bias (smoking is a well-known cause of peripheral blood cytoses) ¹²

11. Lindholm Sørensen A, Hasselbalch HC. Smoking and philadelphia-negative chronic myeloproliferative neoplasms. *Eur J Haematol*. 2016 Jul;97(1):63-9. doi: 10.1111/ejh.12684.

12. Duncombe AS, Anderson LA, James G, de Vocht F, Fritschi L, Mesa R, Clarke M, McMullin MF. Modifiable Lifestyle and Medical Risk Factors Associated With Myeloproliferative Neoplasms. *Hemasphere*. 2020 Jan 3;4(1):e327. doi: 10.1097/HS9.0000000000000327.

13. Sørensen AL, Knudsen TA, Skov V, Kjaer L, Holm N, Ellervik C, Hasselbalch HC. Smoking impairs molecular response, and reduces overall survival in patients with chronic myeloproliferative neoplasms: A retrospective cohort study. *Br J Haematol*. 2021 Apr;193(1):83-92. doi: 10.1111/bjh.17130.

14. Furuya C, Hashimoto Y, Morishita S, Inano T, Ochiai T, Shirane S, Edahiro Y, Araki M, Ando M, Komatsu N. Reevaluation of cardiovascular risk factors for thrombotic events in 580 Japanese patients with essential thrombocythemia. *J Thromb Thrombolysis*. 2023 Feb;55(2):263-272. doi: 10.1007/s11239-022-02751-0.

Hyperlipidemia



- Many MPN patients have **hypocholesterolemia**, which is hypothesized to be a consequence of high lipid membrane utilization in the proliferating cells ¹⁵
- Low-density lipoprotein (LDL) values of **<1.8 mmol/L (<70 mg/dl)** are associated with lower incidence of thrombotic events and may have the strongest discriminatory properties regarding thrombotic risk in PV and ET patients ¹⁶
 - this **cut-off** value corresponds to that of target LDL levels for the treatment of **high-risk persons in the general population** ¹⁷

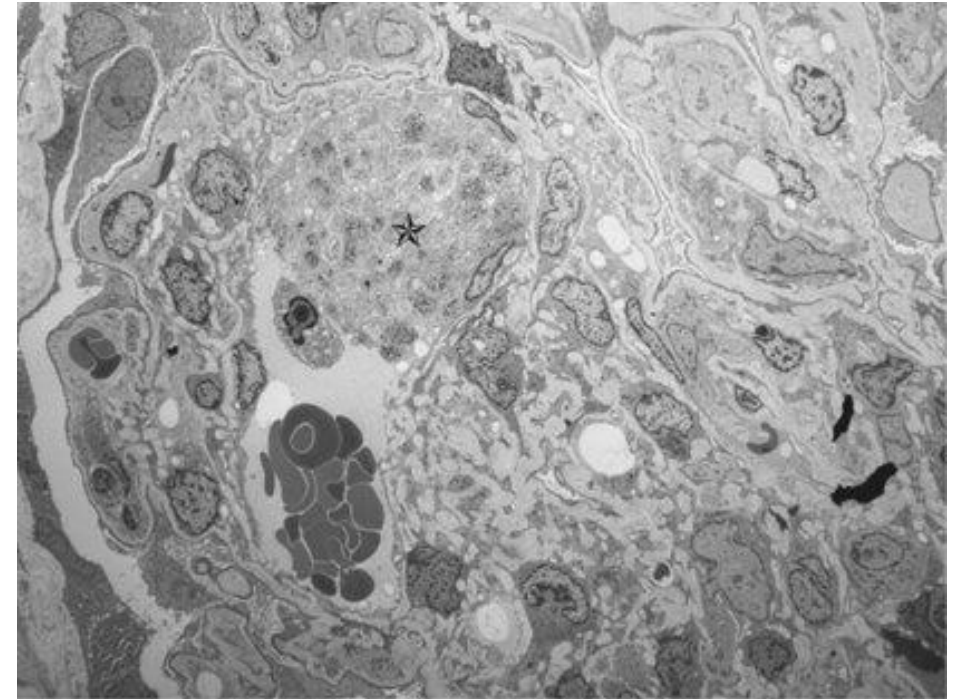
15. Fujita H, Hamaki T, Handa N, Ohwada A, Tomiyama J, Nishimura S. Hypocholesterolemia in patients with polycythemia vera. *J Clin Exp Hematop.* 2012;52(2):85-9. doi: 10.3960/jslrt.52.85.

16. Krečak I, Holik H, Coha B, Perić MM, Zekanović I, Krečak MV, Gverić-Krečak V, Lucijanić M. Low-density lipoprotein (LDL) and the risk of thrombotic events in essential thrombocythemia and polycythemia vera. *Ann Hematol.* 2021 May;100(5):1335-1336. doi: 10.1007/s00277-021-04431-0.

17. Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L, Chapman MJ, De Backer GG, Delgado V, Ference BA, Graham IM, Halliday A, Landmesser U, Mihaylova B, Pedersen TR, Riccardi G, Richter DJ, Sabatine MS, Taskinen MR, Tokgozoglul L, Wiklund O; ESC Scientific Document Group. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. *Eur Heart J.* 2020 Jan 1;41(1):111-188. doi: 10.1093/eurheartj/ehz455.

Chronic kidney disease and MPN-related glomerulopathy

- CKD is highly **prevalent among MPN** patients (up to 1/3 patients) ¹⁸ and was shown to bear **high thrombotic risk** for both arterial and venous thrombotic events in MPNs ^{19, 20}
- This is of particular interest due to its possible association with **MPN-related glomerulopathy**, the MPN manifestation at the level of glomeruli ^{18, 21}



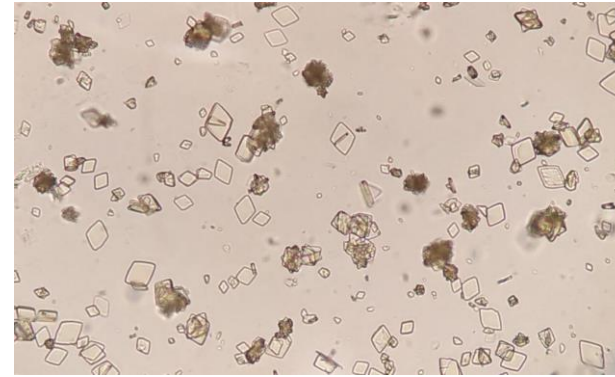
18. Lucijanac M, Krecak I, Kusec R. Renal disease associated with chronic myeloproliferative neoplasms. *Expert Rev Hematol.* 2022 Feb;15(2):93-96. doi: 10.1080/17474086.2022.2039117.

19. Krečak I, Holik H, Martina MP, Zekanović I, Coha B, Gverić-Krečak V. Chronic kidney disease could be a risk factor for thrombosis in essential thrombocythemia and polycythemia vera. *Int J Hematol.* 2020 Sep;112(3):377-384. doi: 10.1007/s12185-020-02898-7.

20. Lucijanac M, Galusic D, Krecak I, Sedinic M, Holik H, Perisa V, Moric Peric M, Zekanovic I, Stoos-Veic T, Kusec R. Reduced renal function strongly affects survival and thrombosis in patients with myelofibrosis. *Ann Hematol.* 2020 Dec;99(12):2779-2785. doi: 10.1007/s00277-020-04239-4.

21. Said SM, Leung N, Sethi S, Cornell LD, Fidler ME, Grande JP, Herrmann S, Tefferi A, D'Agati VD, Nasr SH. Myeloproliferative neoplasms cause glomerulopathy. *Kidney Int.* 2011 Oct;80(7):753-9. doi: 10.1038/ki.2011.147.

Hyperuricemia



- **Undisclosed role of serum uric acid control** considering thrombotic risk reduction in the general population ²²
- Hyperuricemia reflects higher cellular turnover, nutritional habits and kidney function, and is associated with the **occurrence of gout and increased CV risk among MPN patients** ^{23, 24, 25}
- Due to lack of recognition by current treatment guidelines and the unknown optimal treatment target levels, urate-lowering therapies are usually prescribed to MPN patients on an individual basis

22. Mackenzie IS, Hawkey CJ, Ford I, Greenlaw N, Pigazzani F, Rogers A, Struthers AD, Begg AG, Wei L, Avery AJ, Taggar JS, Walker A, Duce SL, Barr RJ, Dumbleton JS, Rooke ED, Townend JN, Ritchie LD, MacDonald TM; ALL-HEART Study Group. Allopurinol versus usual care in UK patients with ischaemic heart disease (ALL-HEART): a multicentre, prospective, randomised, open-label, blinded-endpoint trial. *Lancet*. 2022 Oct 8;400(10359):1195-1205. doi: 10.1016/S0140-6736(22)01657-9.

23. Yu T, Weinreb N, Wittman R, Wasserman LR. Secondary gout associated with chronic myeloproliferative disorders. *Semin Arthritis Rheum*. 1976 Feb;5(3):247-56. doi: 10.1016/0049-0172(76)90026-3.

24. Krečak I, Lucijanić M, Gverić-Krečak V, Duraković N. Hyperuricemia might promote thrombosis in essential thrombocythemia and polycythemia vera. *Leuk Lymphoma*. 2020 Jul;61(7):1744-1747. doi: 10.1080/10428194.2020.1731503.

25. Lucijanic M, Krecak I, Galusic D, Sedinic M, Holik H, Perisa V, Moric Peric M, Zekanovic I, Stoos-Veic T, Pejisa V, Kusec R. Higher serum uric acid is associated with higher risks of thrombosis and death in patients with primary myelofibrosis. *Wien Klin Wochenschr*. 2022 Feb;134(3-4):97-103. doi: 10.1007/s00508-020-01802-x.

Obesity and cachexia



- **Obesity and cachexia**, on the different sides of body mass index (BMI) spectrum, bear **specific risks in MPN patients** ²⁶
- It is unclear whether more favorable outcomes associated with higher BMI may reflect the **absence of cachexia** or the so called “**obesity paradox**” ²⁷
- Obesity induces inflammation and may promote carcinogenesis. Biomarkers associated with **cachexia** reflect **negatively on outcomes** of MPN patients and can be reverted with specific therapies ^{28, 29}

15. Christensen SF, Scherber RM, Brochmann N, Goros M, Gelfond J, Andersen CL, Flachs EM, Mesa R. Body Mass Index and Total Symptom Burden in Myeloproliferative Neoplasms Discovery of a U-shaped Association. *Cancers (Basel)*. 2020 Aug 6;12(8):2202. doi: 10.3390/cancers12082202.

16. Benevolo G, Elli EM, Bartoletti D, Latagliata R, Tiribelli M, Heidel FH, Cavazzini F, Bonifacio M, Crugnola M, Binotto G, D'Addio A, Tieghi A, Bergamaschi M, Caocci G, Polverelli N, Bossi E, Auteri G, Carosino I, Catani L, Cuneo A, Krampera M, Lanza F, Lemoli RM, Vianelli N, Breccia M, Palumbo GA, Cavo M, Palandri F. Impact of comorbidities and body mass index on the outcome of polycythemia vera patients. *Hematol Oncol*. 2021 Aug;39(3):409-418. doi: 10.1002/hon.2843.

17. Lucijanac M, Veletic I, Rahelic D, Pejisa V, Cicic D, Skelin M, Livun A, Tupek KM, Stoos-Veic T, Lucijanac T, Maglicic A, Kusec R. Assessing serum albumin concentration, lymphocyte count and prognostic nutritional index might improve prognostication in patients with myelofibrosis. *Wien Klin Wochenschr*. 2018 Feb;130(3-4):126-133. doi: 10.1007/s00508-018-1318-z.

18. Tefferi A, Nicolosi M, Penna D, Mudireddy M, Szuber N, Lasho TL, Hanson CA, Ketterling RP, Gangat N, Pardanani AD. Development of a prognostically relevant cachexia index in primary myelofibrosis using serum albumin and cholesterol levels. *Blood Adv*. 2018 Aug 14;2(15):1980-1984. doi: 10.1182/bloodadvances.2018018051.

Some additional peculiarities

- MPN disease clone may produce both **proatherogenic** and **cardioprotective** cytokines ^{2, 24}
- Classic CV risk scores used in the general population might **sub-optimally perform in MPN patients** (CHA₂DS₂-VASc, sPESI) ^{25, 26}
- MPN patients may have **improved prognosis at the time of acute thrombotic event** compared to patients from the general population (as shown for CVI and MI) ^{27, 28}
- **Changing role** of aspirin for the **primary prevention of thrombotic events** in the general population has not yet reached MPN patients ^{3, 29, 30}

2. Krecak I, Verstovsek S, Lucijanic M. Optimization of cardiovascular risk factor management in patients with BCR::ABL1 negative chronic myeloproliferative neoplasms, current knowledge, and perspectives. *Ann Hematol.* 2023 Sep 4. doi: 10.1007/s00277-023-05426-9.

3. Krecak I, Verstovsek S, Lucijanic M. Reappraisal of Cardiovascular Risk Factors in Patients With Chronic Myeloproliferative Neoplasms. *Clin Adv Hematol Oncol.* 2023;21(10):541-548.

24. Lucijanic M, Livun A, Tupek KM, et al. Heat shock protein 27 (HSP27/HSPB1) expression is increased in patients with primary and secondary myelofibrosis and may be affecting their survival. *Leuk Lymphoma.* 2017;58(10):2497-2500.

25. Leiva O, Jenkins A, Rosovsky RP, Leaf RK, Goodarzi K, Hobbs G. Predictors of increased risk of adverse cardiovascular outcomes among patients with myeloproliferative neoplasms and atrial fibrillation. *J Cardiol.* 2023;81(3):260-267.

26. Krečak I, Grohovac D, Vučenović Bašić N et al. Clinical presentation, treatment patterns, and outcomes of pulmonary embolism in patients with chronic myeloproliferative neoplasms. *Thromb Res* 2023.

27. Leiva O, Xia Y, Siddiqui E, Hobbs G, Bangalore S. Outcomes of Patients With Myeloproliferative Neoplasms Admitted With Myocardial Infarction. *JACC: CardioOncology* 2023;5:457-468.

28. De Stefano V, Carobbio A, Di Lazzaro V et al. Benefit-risk profile of cytoreductive drugs along with antiplatelet and antithrombotic therapy after transient ischemic attack or ischemic stroke in myeloproliferative neoplasms. *Blood Cancer J* 2018;8:25.

29. Berger JS. Aspirin for Primary Prevention-Time to Rethink Our Approach. *JAMA Netw Open.* 2022;5(4):e2210144.

30. Lucijanic M, Skelin M, Kusec R. Second primary malignancies in myeloproliferative neoplasms and the role of aspirin. *Leukemia.* 2019;33(10):2554.

Conclusions

- CV comorbidities may share **common pathophysiological mechanisms** with MPNs and require simultaneous and focused medical care
- **MPN-specific risk scores** for particular CV comorbidities and **optimal target values of different metabolic parameters for MPN patients** (i.e., LDL, HbA1c, or serum uric acid) are needed
- **RCTs** in MPN patients using contemporary and potent medications (i.e., statins, PCSK9 inhibitors, ACE inhibitors, SGLT2 inhibitors and others) for the treatment of different CV comorbidities (**on top of MPN-specific treatments**) may be needed to establish new standards of care



Smoking

Impairs treatment responses



Diabetes mellitus

Optimal target levels of glycated hemoglobin in MPNs are unknown



Arterial hypertension

Can diminish in polycythemic patients after the start of phlebotomies



Hyperuricemia

Promotes endothelial dysfunction and cardiovascular events



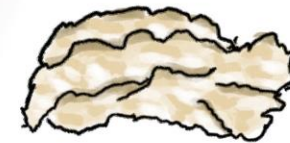
Hyperlipidemia

MPNs may be considered high-risk regarding the control of blood lipids



MPN-related glomerulopathy

Promotes thrombosis and impairs survival



Obesity and cachexia

A U-shaped association between body mass index and disease-related symptoms