Monitoring Cardiovascular Health in CML Patients Receiving TKI Therapy

CML HORIZONS
HYBRID MEETING 2024
Vilnius, Lithuania
24–26 May 2024

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Charity fund of patients «DROP OF BLOOD», Ukraine
Simulation Training Platform for continuous medical education "ClinCaseQuest"

CML Treatment Journey and Cardiovascular Complications

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"I have suffered from chronic myeloid leukemia since 2008. Initially I was treated with imatinib at 800 mg daily, but even at such dose there was no adequate response. Consequently, imatinib was replaced with nilotinib at a dose of 800 mg daily. A response was achieved after three months of administration.

However, I was unaware of this drug's potential side effects on blood vessels.

Starting in October 2020, I began experiencing severe leg pain. My family doctor could not provide effective help. By 2023, I underwent amputation of my left leg and received invasive vascular stenting in my right leg. Since 2023, I have been treated with bosutinib, but I continue to experience persistent pain in my right leg and problems with blood circulation".

Letter from a CML Patient (Dnipro Region, Ukraine) to Professor Iryna Dyagil, November 2023

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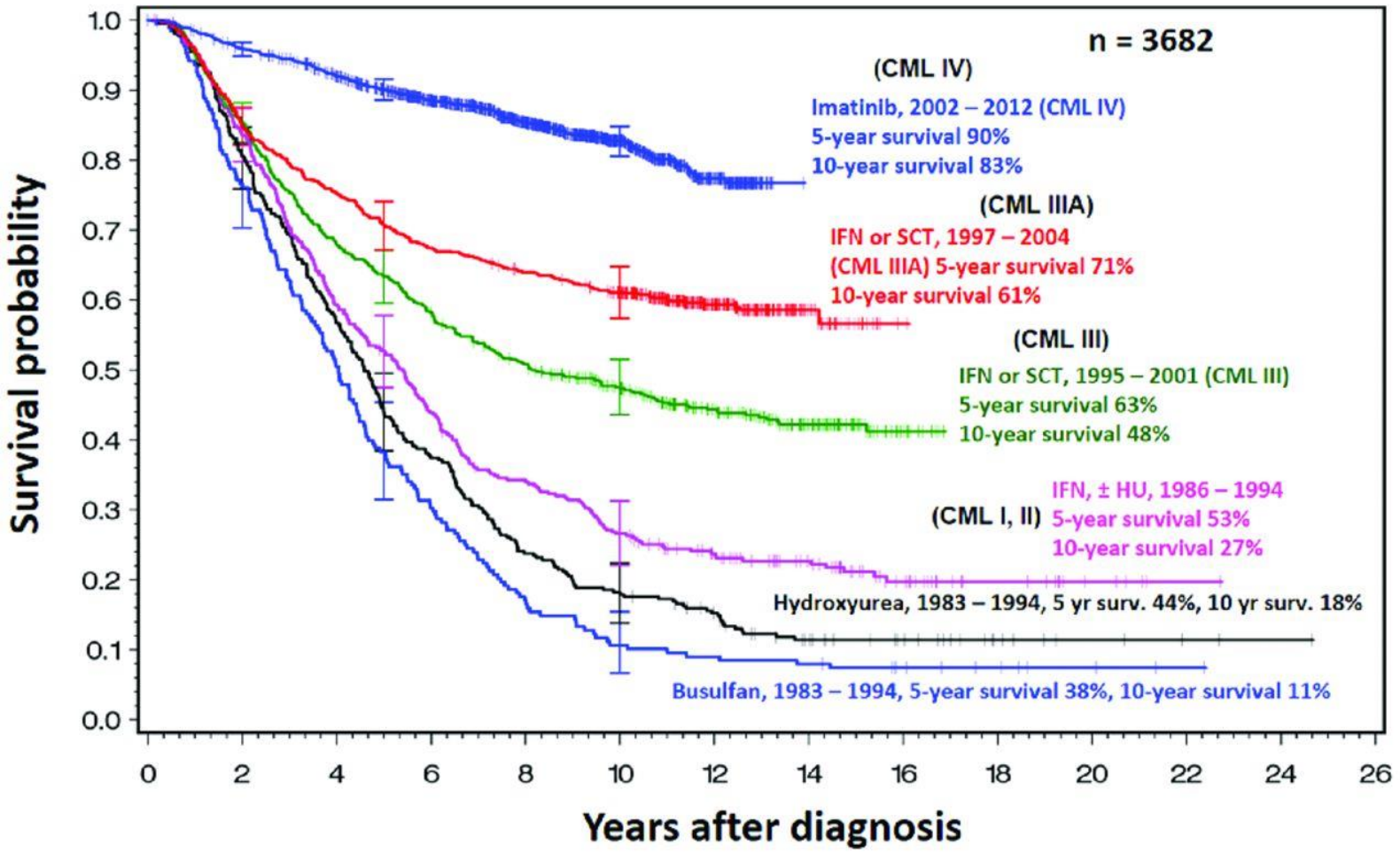
Cardiovascular risk in patients with CML

Survival rates in Chronic Myeloid Leukemia



Rüdiger Hehlmann. Innovation in hematology. Perspectives: CML 2016. Vol. 101 No. 6 (2016): June, 2016. https://doi.org/10.3324/haematol.2016.142877

Survival Rates in Chronic Myelogenous Leukemia: Does a Patient with CML Face Different Cardiovascular Risks Compared to the General Population?

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Cardiovascular risk is higher in patients with CML than in the general population

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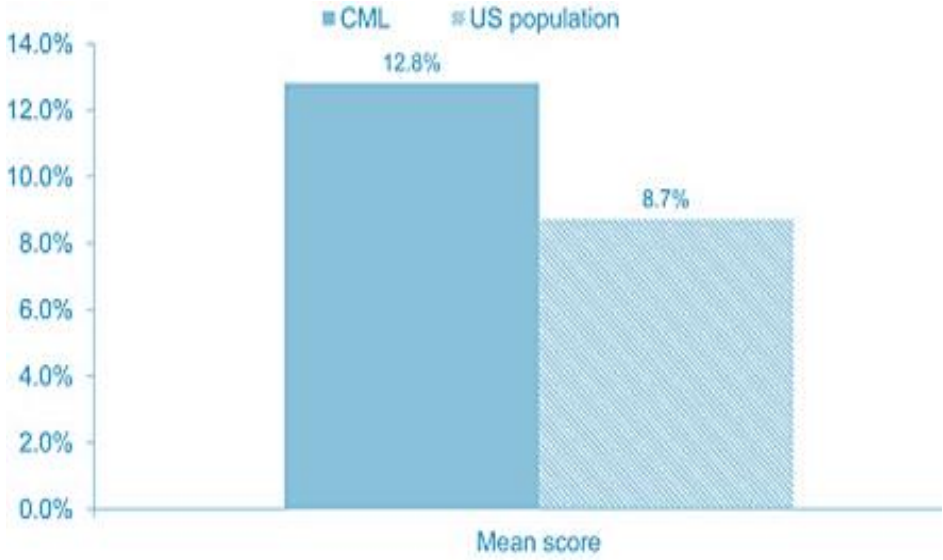
- A population-based study assessed the prevalence of cardiovascular disease (CVD) and CVD risk factors among 1,639 patients with CML in the United States.
- During the 5-year follow-up, the prevalence of cardiovascular diseases was 33.0%, and the prevalence of risk factors for cardiovascular diseases was 77.7%.
- Compared with the general US adult population, standardized prevalence rates at 1 year in CML patients were significantly higher, ranging from 1.3- to 3.5-fold for cardiovascular disease and 20-40% higher for hypertension, diabetes, and obesity ($p < 0.001$).



Coutinho AD, Makenbaeva D, Farrelly E, Landsman-BlumbergPB, Lenihan D. Elevated cardiovascular disease risk in patients with chronic myelogenous leukemia seen incommunity-based oncology practices in the United States.Clin Lymphoma Myeloma Leuk. 2017;17(10):676–83.

Increased risk of cardiovascular disease in patients with CML

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Basic State of the Cardiovascular System

Traditional Risk Factors + **Tyrosine Kinase Inhibitors** = **Cardiovascular Risk, Prognosis, and Complications**

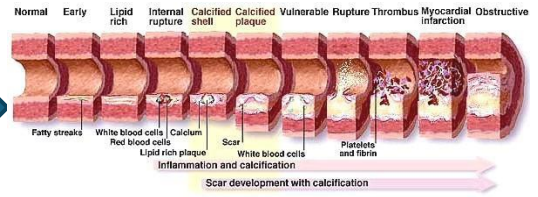
Non-Modifiable Risk Factors

- Individual history of CHD
- Family history of CHD
- Age
- Gender

Modifiable Risk Factors

- Smoking, Dyslipidemia, Increased LDL-C (Low-Density Lipoprotein Cholesterol), Decreased HDL-C (High-Density Lipoprotein Cholesterol), Increased TG (Triglycerides), Increased BP (Blood Pressure), Diabetes, Obesity, Low physical activity, Alcohol consumption

Acceleration of Vascular Aging



Lopina N, Dmytrenko I, Hamov D, Lopin D, Dyagil I. A New Paradigm of Cardio-Hematological Monitoring in Chronic Myeloid Leukemia Patients Treated With Tyrosine Kinase Inhibitors. Cureus. 2022 Jun 8;14(6):e25766. doi: 10.7759/cureus.25766. PMID: 35812557; PMCID: PMC9270100.

Framingham Heart Study: Relative Risk of Developing Coronary Heart Disease

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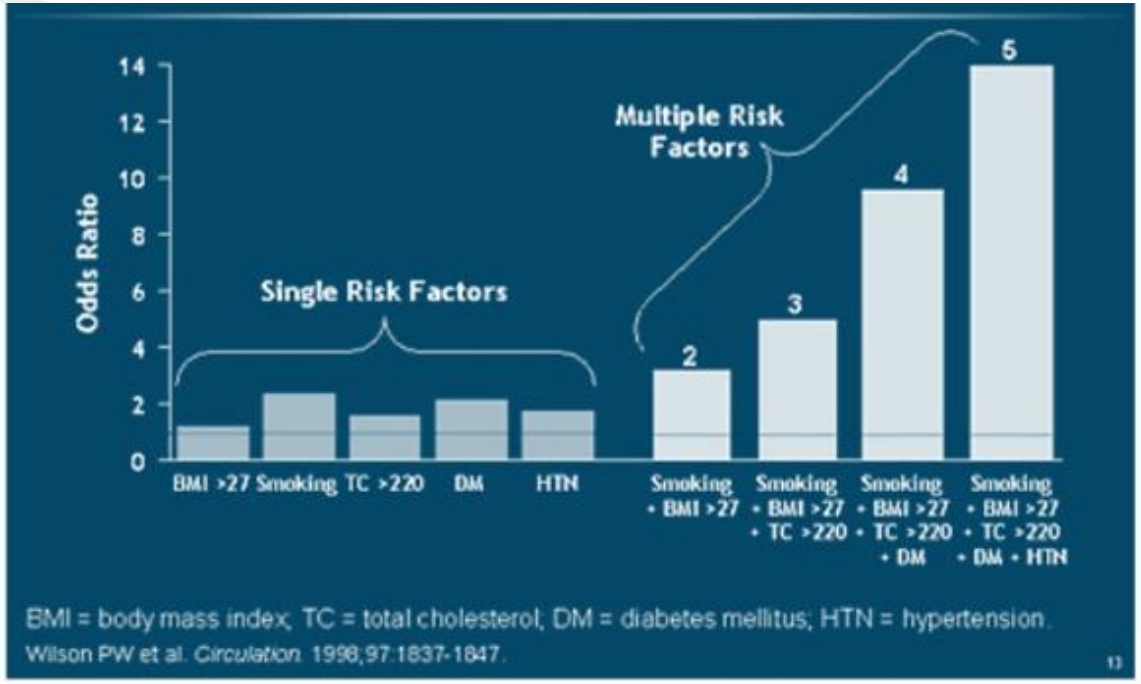

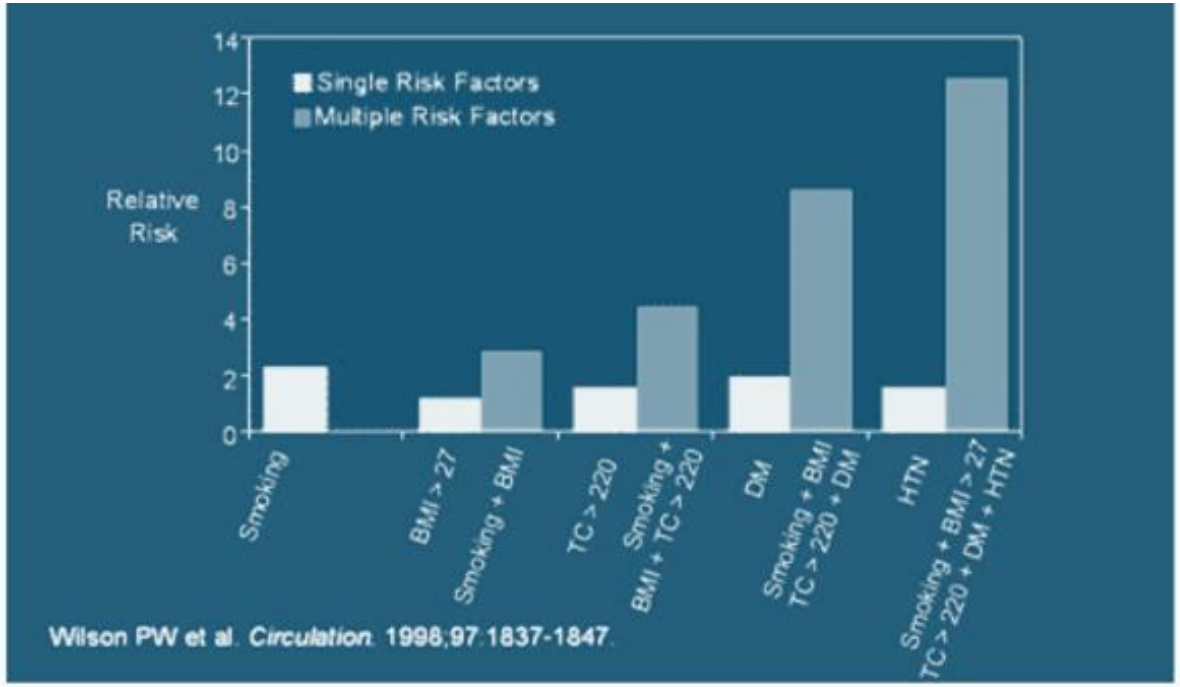

The combination of risk factors increases the risk of developing coronary heart disease

Do all tyrosine kinase inhibitors have the same level of cardiovascular toxicity?

Cardiovascular events over a 5-year follow-up (ENESTnd study) in patients with CML who received nilotinib as first-line therapy

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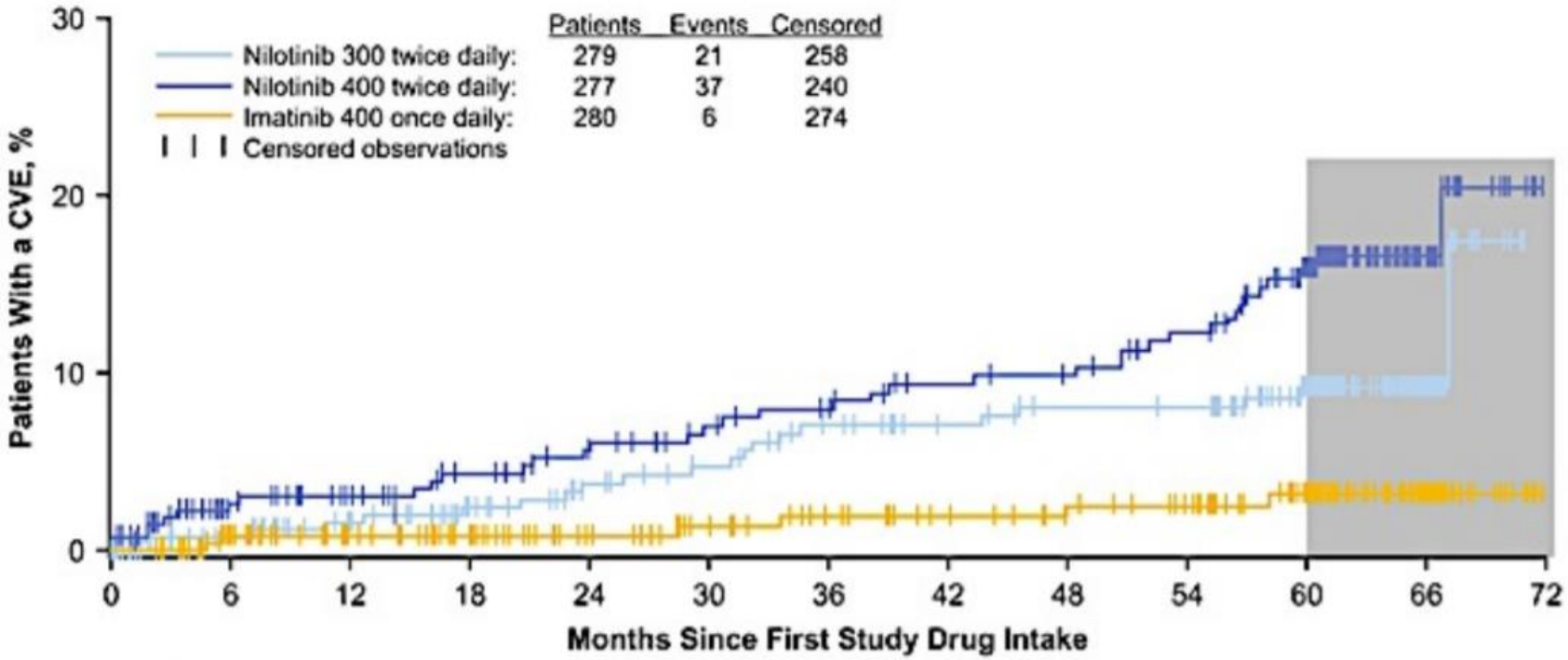

At-risk : Events

Nilotinib 300 mg twice daily	279 : 0	254 : 2	240 : 4	223 : 6	209 : 9	202 : 11	192 : 16	185 : 16	179 : 18	178 : 18	151 : 20	43 : 20	0 : 21
Nilotinib 400 mg twice daily	277 : 0	243 : 7	233 : 8	222 : 11	211 : 14	202 : 17	197 : 19	189 : 22	186 : 23	176 : 28	148 : 35	46 : 36	0 : 37
Imatinib 400 mg once daily	280 : 0	248 : 2	227 : 2	213 : 2	196 : 2	183 : 3	173 : 4	166 : 4	159 : 5	153 : 5	133 : 6	46 : 6	0 : 6

Larson RA, et al. J Clin Oncol. 2014;32:5s (suppl; abstr 7073).

Peripheral artery disease associated with nilotinib: Biochemical changes and alterations in the ankle-brachial index

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Table 4. Biochemial risk factors for PAOD in patients under tyrosine kinase inhibitor therapy

	All	*First-line imatinib*	*First-line nilotinib*	*Second-line nilotinib*	*Post-nilotinib*	*Nilotinib-naive*
N	159	54	33	33	25	14
Cholesterol (mg/dl, range)	194 (104–310)	164 (104–258)	209* (142–306)	222* (146–310)	193** (110–306)	194 (136–218)
LDL (mg/dl, range)	116 (33–234)	95 (47–152)	135*** (33–215)	139* (77–210)	117** (56–234)	124** (56–160)
HDL (mg/dl, range)	56.5 (15–111)	48 (16–107)	62.5 (30–111)	58 (15–90)	48.5 (31–74)	52.2 (28–109)
Trigylcerides (mg/dl, range)	106 (37–500)	101,5 (50–407)	98 (37–500)	108 (44–290)	129.5 (75–280)	119 (59–246)
Blood glucose (mg/dl, range)	88 (43–285)	90 (74–279)	89.5 (68–178)	84 (57–285)	94.5 (66–152)	80 (43–102)
HbA1c (%, range)	5.55 (4.0–8.6)	5.4 (4.5–8)	5.7 (4.5–7.7)	5.7 (4.8–8.6)	5.7 (4.9–6.9)	5.4 (4.0–6.5)

Abbreviations: HbA1c, glycated hemoglobin; HDL; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TG, trigylcerides. *$P<0.0001$. **$P<0.05$. ***$P<0.0003$ for comparison vs first-line imatinib group.

Table 5. Screening for PAOD in patients under tyrosine kinase inhibitor

	All	*First-line imatinib*	*First-line nilotinib*	P[a]	*Second-line nilotinib*	P[a]	*Post-nilotinib*	P[a]	*Nilotinib-naive*	P[a]
Pathological ABI (%)	31/129 (24)	3/48 (6.3)	7/27 (26)	0.0297	10/28 (35.7)	0.0029	3/18 (16.6)	ND	1/8 (12.5)	ND
Pathological duplex sonography (%)	8/30 (26.7)	1	2		2		3		0	
SAE (%)	5/159 (3.1)	0/54 (0)	1/33 (3)		3/33 (9.1)		1/25 (4)		0/14 (0)	
Pathological duplex sonography or SAE (%)	13/159 (8.2)	1/54 (1.9)	3/33 (9.1)	0.1507	5/33 (15.2)	0.0276	4/25 (16)	0.0327	0/14 (0)	ND

Abbreviations: ABI, ankle-brachial index, ND, not determined; SAE, severe adverse event. [a]For comparison vs first-line imatinib group.

Kim TD et al. Leukemia 2013; 27:1316-21.

Peripheral artery disease associated with nilotinib: Understanding its clinical significance

Table 6. Clinical characteristics of patients with PAOD under tyrosine kinase inhibitor therapy

Median duration of CML (months, range)	84 (12-240)
Median nilotinib exposure (months, range)	36 (6–72)
Median age at PAOD event (years, range)	68 (38–87)
Treatment at PAOD event	
First-line Imatinib (%)	1 (3.7)
First-line Nilotinib (%)	9 (33.3)
Second-line Nilotinib (%)	11 (40.7)
Third-line Nilotinib (%)	1 (3.7)
Post-nilotinib (%)[a]	5 (18.5)
Number of risk factors for PAOD[b]	
0	0
1–2	8 (29.6)
3–4	15 (55.6)
>4	4 (14.8)
Involved arteries (%)	
Tibial artery	10 (37)
Femoral artery	12 (44.4)
Iliacal artery	4 (14.8)
Popliteal artery	2 (7.4)
Ischemic neuropathy	1 (3.7)
Type of intervention (%)	
PTA	9 (33.3)
Stent (%)	6 (22.2)
Amputation	6 (22.2)
Surgery	5 (18.5)
No invasive intervention	11 (40.7)

Abbreviations: ABI, ankle-brachial index; CML, chronic myeloid leukemia; PAOD, peripheral artery occlusive disease PTA, percutaneous transluminal angioplasty. [a]Patients in the post-nilotinib cohort were already on alternative TKIs. [b]Only age >60, hypertension, diabetes, male gender, nicotine abuse and CHD.

Kim TD et al. Leukemia 2013; 27:1316-21

Arterial occlusive event (AOE) rates with ponatinib PACE study

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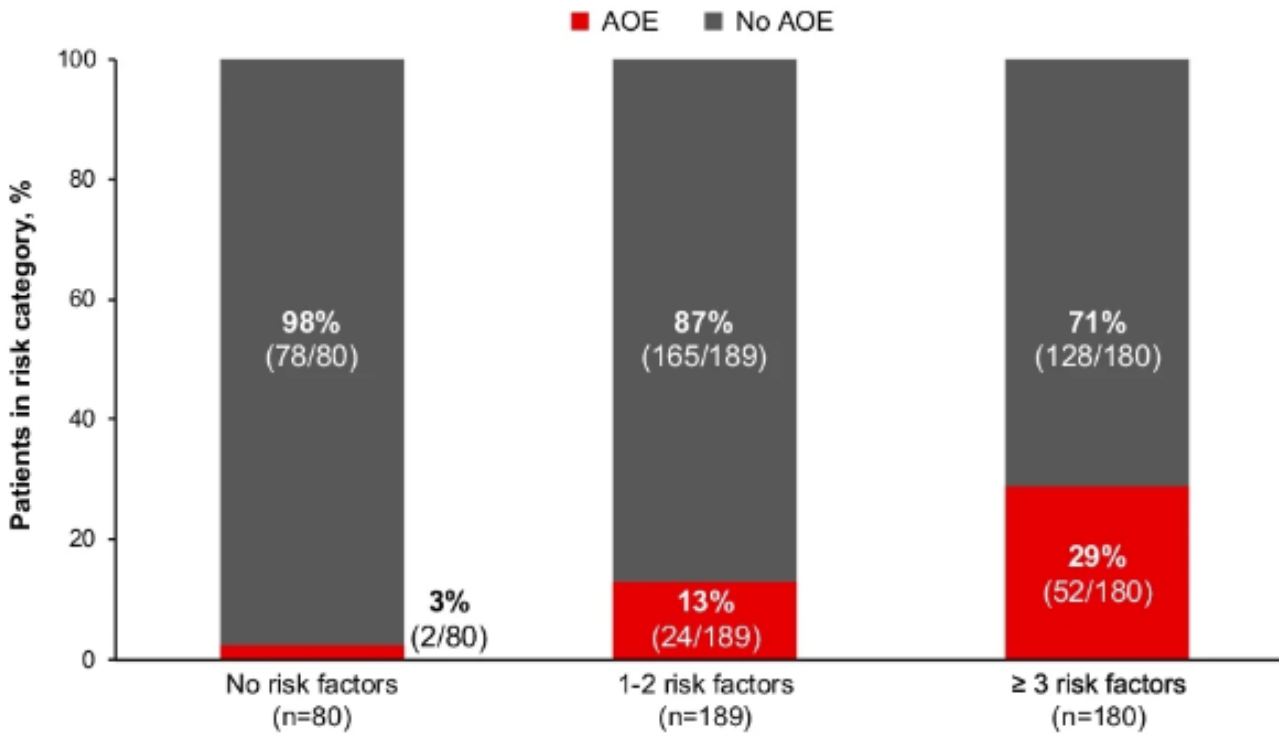
Arterial occlusive event (AOE) rates with ponatinib



Januzzi, J.L., Garasic, J.M., Kasner, S.E. et al. Retrospective analysis of arterial occlusive events in the PACE trial by an independent adjudication committee. J Hematol Oncol 15, 1 (2022). https://doi.org/10.1186/s13045-021-01221-z

Comparative studies on cardiovascular complications in CML patients treated with TKIs

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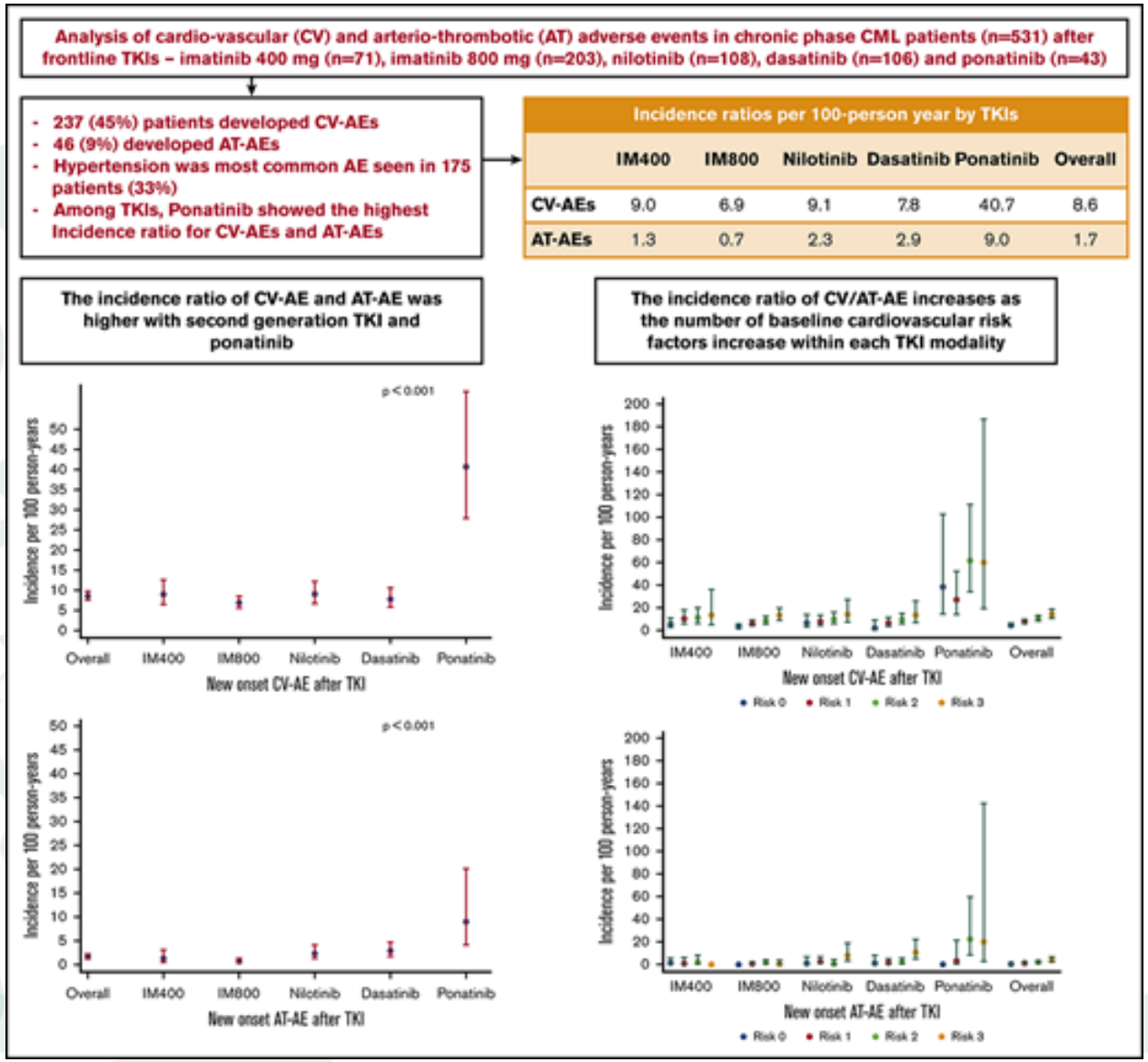

Comparative analysis of **imatinib 400, imatinib 800 mg, nilotinib, dasatinib** and **ponatinib**

- Ponatinib therapy was associated with an increased incidence rate for CV adverse events (4.62; 95% CI, 2.7-7.7; P <.0001) and atherothrombotic adverse events (6.38; 95% CI, 1 .8-21.8; P<.0001) compared to imatinib 400 mg.
- There is an increased risk of cardiovascular events and adverse events (except for hypertension) and atherothrombotic adverse events in CML patients treated with new TKIs, especially ponatinib

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Jorge E. Cortes et al. Analysis of cardiovascular and arteriothrombotic adverse events in chronic-phase CML patients after frontline TKIs. Clinical Trials & Observations. Blood Adv (2019) 3 (6): 851–861. https://doi.org/10.1182/bloodadvances.2018025874

The First Year of Therapy

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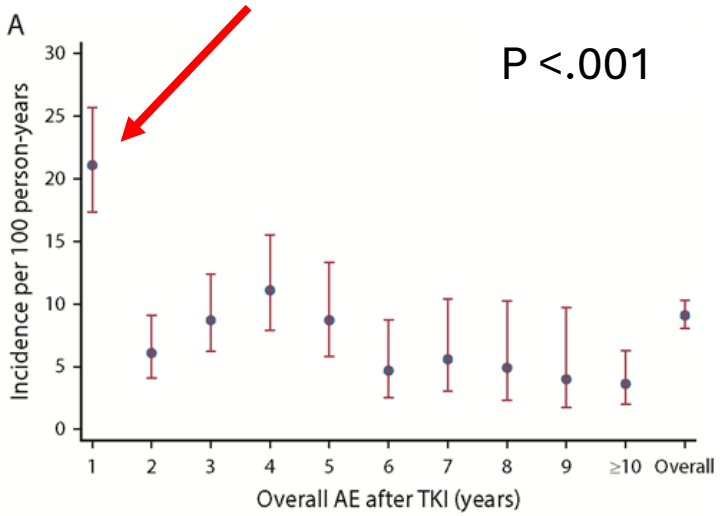
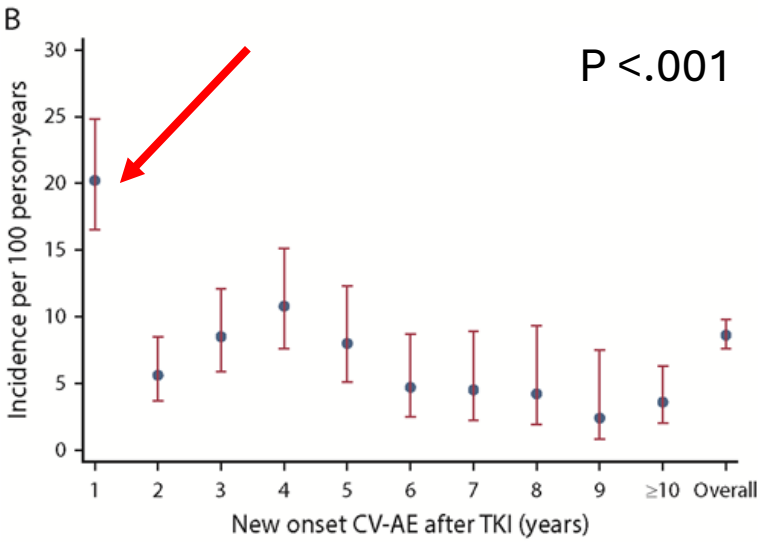
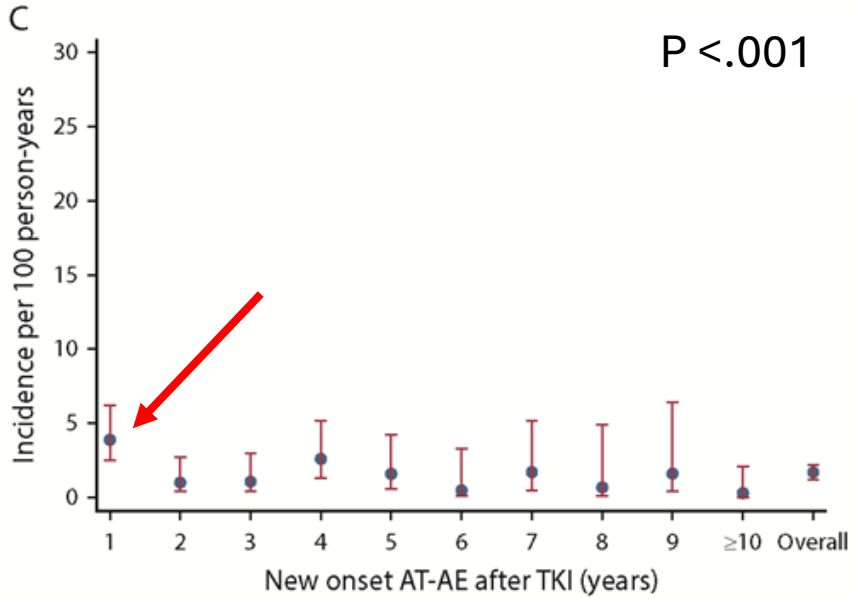
The highest rates for ponatinib



The frequency of all cardiovascular adverse events was highest in the first year of TKI therapy.



The incidence of new cardiovascular adverse events peaked during the first year of TKI therapy



New adverse atherothrombotic complications were most prevalent in the first year after starting TKI therapy and continued to occur in subsequent years

E. Cortes et al. Analysis of cardiovascular and arteriothrombotic adverse events in chronic-phase CML patients after frontline TKIs. Clinical Trials & Observations. Blood Adv (2019) 3 (6): 851–861. https://doi.org/10.1182/bloodadvances.2018025874

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Population-Based Study: Cardiovascular Events in CML Patients Receiving TKIs

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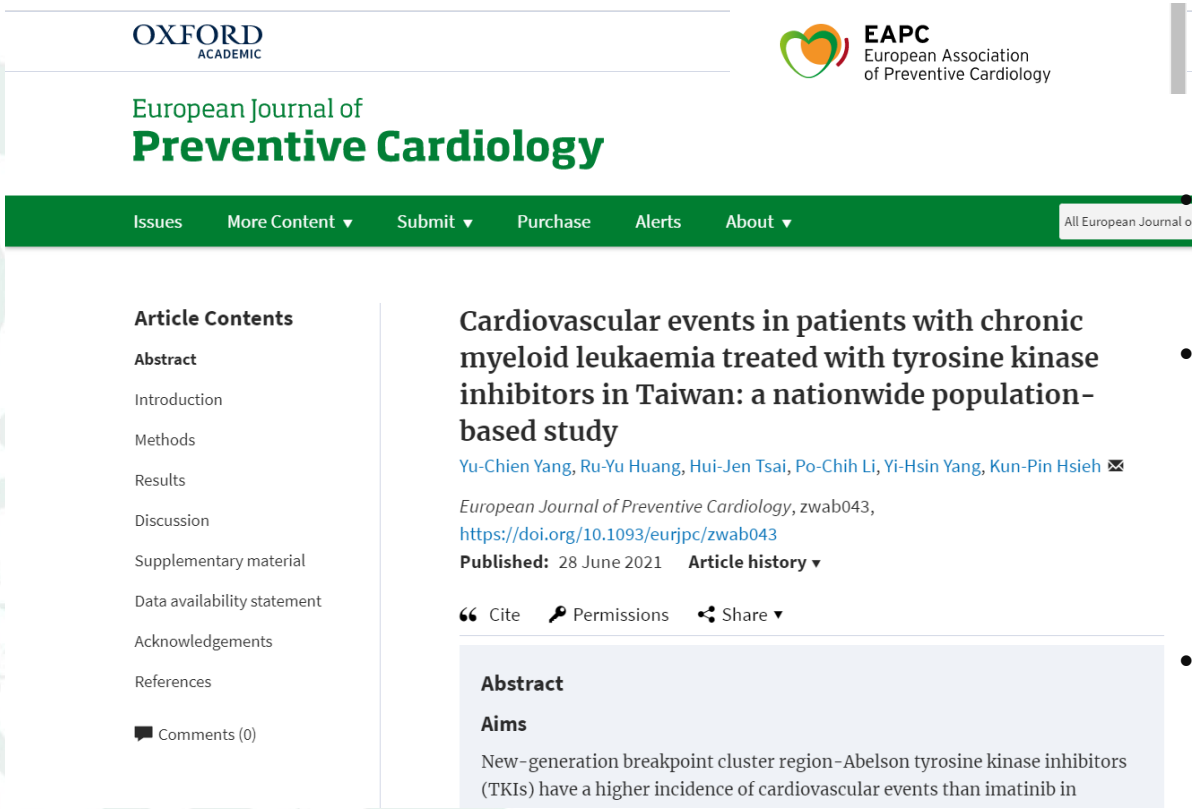

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Comments (0)

Cardiovascular events in patients with chronic myeloid leukaemia treated with tyrosine kinase inhibitors in Taiwan: a nationwide population-based study

Yu-Chien Yang, Ru-Yu Huang, Hui-Jen Tsai, Po-Chih Li, Yi-Hsin Yang, Kun-Pin Hsieh

European Journal of Preventive Cardiology, zwab043,
https://doi.org/10.1093/eurjpc/zwab043
Published: 28 June 2021 **Article history** ▾

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Abstract

Aims

New-generation breakpoint cluster region-Abelson tyrosine kinase inhibitors (TKIs) have a higher incidence of cardiovascular events than imatinib in

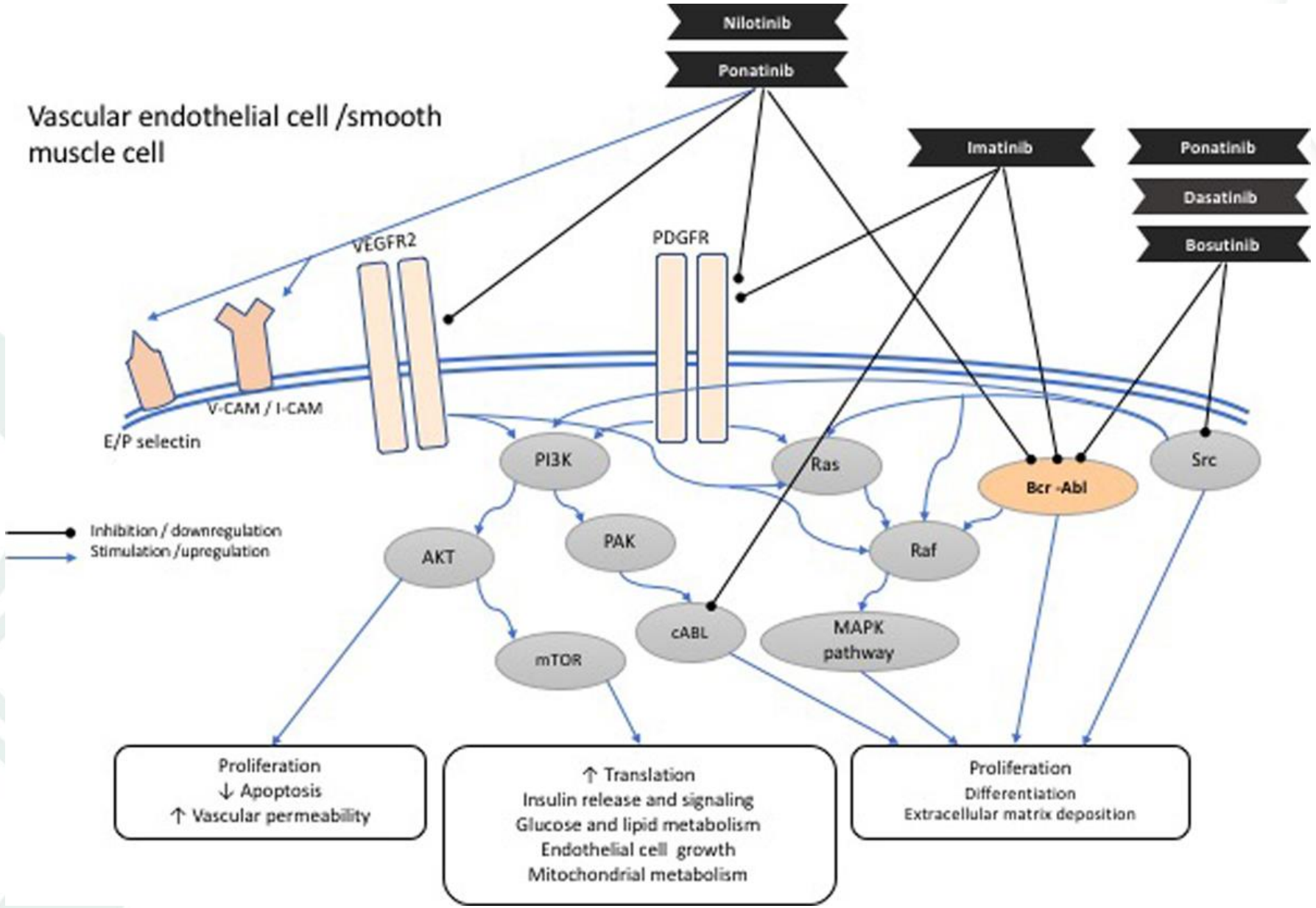
- A retrospective population-based cohort study included patients receiving first-line imatinib, dasatinib, and nilotinib between January 1, 2007, and December 31, 2016, with a total of 1,207 patients included.

- New-generation TKIs have a higher incidence of cardiovascular events than imatinib in patients with CML

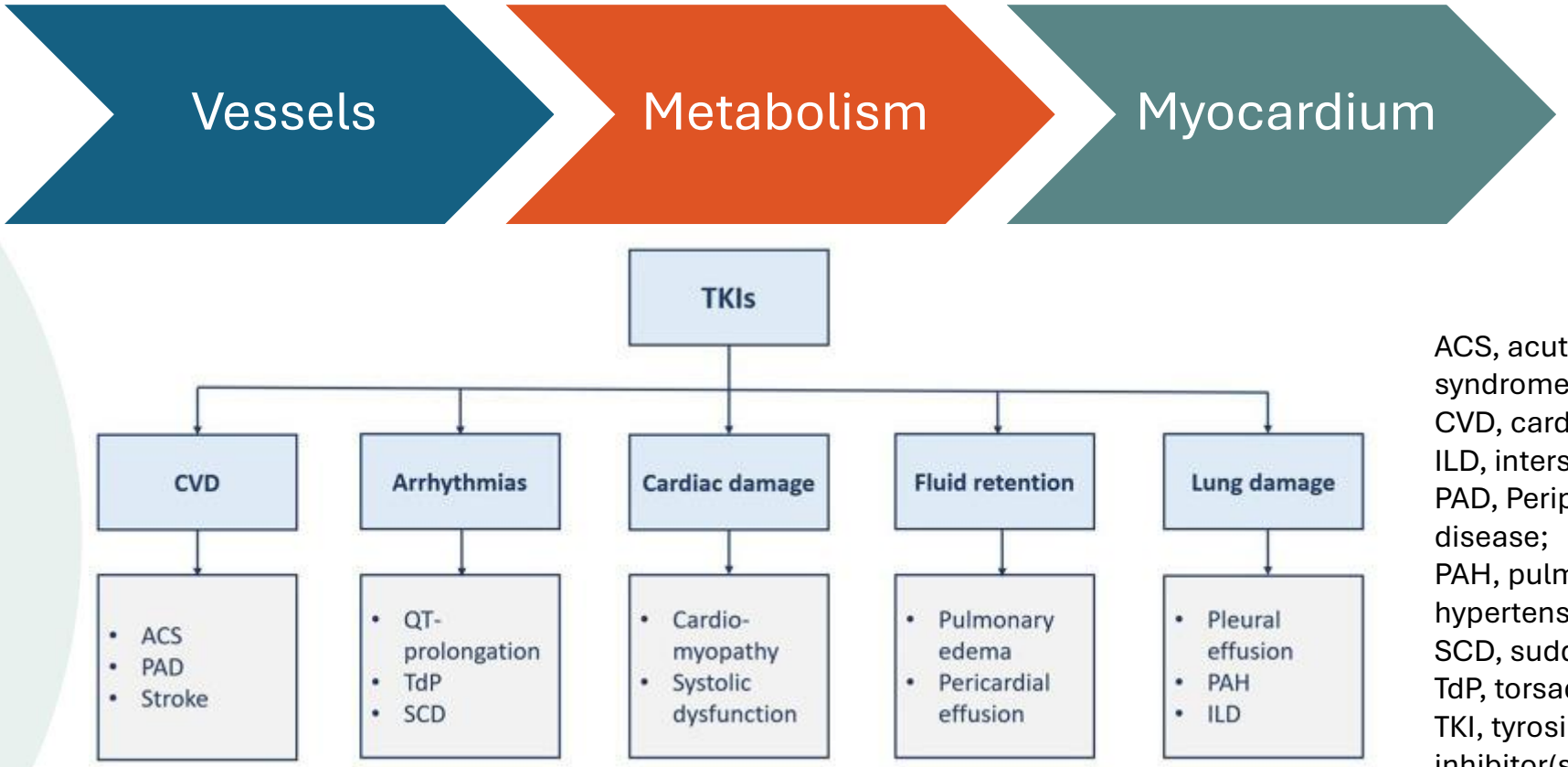
- Atherothromboembolic events were the primary outcome, while other cardiovascular events were considered secondary. Nilotinib was associated with a significantly higher risk of atherothromboembolic events (adjusted HR = 4.92, 95% CI = 1.68–14.36) compared to imatinib.

- The risks of atherothromboembolic and other cardiovascular events were similar between dasatinib and imatinib, and between nilotinib and dasatinib. Patients treated with nilotinib, however, faced a significantly higher risk of developing atherothromboembolic events than those treated with imatinib, but no significant differences were found between dasatinib and imatinib in the risk of these events.

Yu-Chien Yang, Ru-Yu Huang, Hui-Jen Tsai, Po-Chih Li, Yi-Hsin Yang, Kun-Pin Hsieh, Cardiovascular events in patients with chronic myeloid leukaemia treated with tyrosine kinase inhibitors in Taiwan: a nationwide population-based study, European Journal of Preventive Cardiology, 2021; zwab043, https://doi.org/10.1093/eurjpc/zwab043


Nilotinib
Ponatinib
Vascular endothelial cell /smooth muscle cell
Imatinib
Ponatinib
Dasatinib
Bosutinib
VEGFR2
PDGFR
V-CAM / I-CAM
E/P selectin
PI3K
Ras
Bcr-Abl
Src
Inhibition / downregulation
Stimulation /upregulation
AKT
PAK
Raf
cABL
MAPK pathway
mTOR
Proliferation
↓ Apoptosis
↑ Vascular permeability
↑ Translation
Insulin release and signaling
Glucose and lipid metabolism
Endothelial cell growth
Mitochondrial metabolism
Proliferation
Differentiation
Extracellular matrix deposition

Effects of Tyrosine Kinase Inhibitors on the Cardiovascular System



ACS, acute coronary syndrome;
CVD, cardiovascular disease;
ILD, interstitial lung disease;
PAD, Peripheral arterial disease;
PAH, pulmonary arterial hypertension;
SCD, sudden cardiac death;
TdP, torsade de pointes;
TKI, tyrosine kinase inhibitor(s).

Kaddoura R, Dabdoob WA, Ahmed K, Yassin MA. A practical guide to managing cardiopulmonary toxicities of tyrosine kinase inhibitors in chronic myeloid leukemia. Front Med (Lausanne). 2023 May 5;10:1163137. doi: 10.3389/fmed.2023.1163137. PMID: 37358999; PMCID: PMC10286131.

Tyrosine Kinase Inhibitors for the Treatment of CML: Molecular Targets and Cardiovascular Effects

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Tyrosine kinase inhibitor	Year of implementation	Molecular target	Vascular effect
Imatinib	2001	PDGFR-α (0.1), KIT (0.1), **ABL1** (0.6)	Positive metabolic profile for blood glucose and lipid profile
Bozutinib	2014	**ABL1** (4.4), FGFR 2, VEGFR 2, PDGFRβ, SRC (1.2)	Hypertension
Dasatinib	2006	**ABL1** (0.27), KIT (79.0), PDGFR-α, PDGFR-β, SRC (0.8)	Platelet dysfunction, pulmonary hypertension, and the appearance of exudate in the pleural cavity
Nilotinib	2007	**ABL1** (18.5), KIT, PDGFR-α	Peripheral artery disease, Chronic Heart Disease, Acute Cerebrovascular Accident (Stroke), Hyperglycemia, Dyslipidemia, Prolongation of the QT interval
Ponatinib	2012	**ABL1** (3.7), FGFR 1 (2.2), FGFR 2 and 3, VEGFR 1, 2, and 3, PDGFR-α (1.1), PDGFR-β, KIT, SRC (5.4), TIE2	Peripheral artery disease, Hypertension, Coronary Heart Disease / Acute cerebrovascular accident (Stroke), Venous Thromboembolism, Hyperglycemia

Barber M.C., Mauro M.J., Moslehi J. Cardiovascular care of patients with chronic myeloid leukemia (CML) on tyrosine kinase inhibitor (TKI) therapy. American Society of Hematology. Hematology. 2017:110-114. Moslehi JJ, Deininger M. Tyrosine kinase inhibitor-associated cardiovascular toxicity in chronic myeloid leukemia. J Clin Oncol. 2015; 33(35):4210-4218.

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The Problem of Routine Clinical Practice

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Managing toxicity in the treatment of CML often resembles a football game between different doctors, where, unfortunately, it is the patient who frequently losing

- **Toxicity as a Diagnosis of Exclusion:** Toxicity is often diagnosed by exclusion, complicating effective management.
- **Shortage of Specialists:** There are few specialists in cardio-oncology.
- **Low Awareness of TKI Toxicity Profiles:** Awareness of the toxicity profiles of drugs is low.
- **Underuse of Cardiovascular Prevention Strategies:** There is a low level of use of cardiovascular prevention strategies in patients with hematological diseases.
- **Unreasonable Restrictions:** Hematology oncology patients face unreasonable restrictions on access to cardiovascular prevention strategies available to the general population.
- **Insufficient Monitoring Time:** There is insufficient time to monitor toxicities effectively.
- **Limitations in Clinical Guidelines:** There are significant limitations in clinical recommendations for cardiovascular prevention in patients with CML.
- **Unresolved Issues in Cardiovascular Prevention:** Many issues in cardiovascular prevention remain unresolved.

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Reduction of Cardiovascular Risk in Patients with CML

Cardiovascular risk reduction strategy

We should play as one team to reduce cardiovascular risk in CML patients

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Cardiohematological guidelines and publications

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bjh guidelines

A British Society for Haematology Guideline on the diagnosis and management of chronic myeloid leukaemia

Graeme Smith,[1] Jane Apperley,[2] Dragana Milojkovic,[2] Nicholas C. P. Cross,[3] Letizia Foroni,[2] Jenny Byrne,[4] Andy Goringe,[5] Anupama Rao,[6] Jamshid Khorashad,[2] Hugues de Lavallade,[7] Adam J. Mead,[8] Wendy Osborn Chris Plummer,[9] Gail Jones,[9,10] Mhairi Copland[11] and behalf of British Society for Haematology

[1]St James's University Hospital, Leeds, [2]Imperial College, London, [3]University of Southampton, Southampton, [4]Univers Nottingham, [5]University Hospital of Wales, Cardiff, [6]Great Ormond Street Hospital, London, [7]King's College Hospital tion Trust, London, [8]MRC Molecular Haematology Unit, MRC Weatherall Institute of Molecular Medicine, Radcliffe L Medicine, University of Oxford, Oxford, [9]Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle, UK, [10]BS Oncology Task Force representative, and [11]University of Glasgow, Glasgow, Scotland

Keywords: BCR-ABL, CML, tyrosine kinases, imatinib.

The management of chronic myeloid leukaemia (CML) has seen considerable change in the last several years. The objective of this guideline is to provide healthcare professionals with clear guidance on the investigation and management of CML in adults and children.

Methodology

This guideline was compiled according to the British Society for Haematology (BSH) process described at http://www.b-s-h.org.uk/guidelines. The Grading of Recommendations Assessment (GRADE) nomenclature was used to evaluate levels of evidence and to assess the strength of recommendations. The GRADE criteria can be found at http://www.gradeworkinggroup.org.

publications written in English and studies humans.

Review of the manuscript

Review of the manuscript was performed by th lines Committee Haemato-oncology Task Fo Guidelines Committee and the haemato-once board of the BSH. It was also posted on the m of the BSH website for comment. This guic been reviewed by patient representatives from (http://www.cmlsupport.org). These organisa necessarily endorse the contents.

Diagnostic criteria and essential inve

Although CML can be diagnosed from periphe

2020

Cardiovascular care of patients with chronic myeloid leukemia (CML) on tyrosine kinase inhibitor (TKI) therapy

Mary C. Barber,[1,2,3] Michael J. Mauro,[4] and Javid Moslehi[1,2,3]

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Cardiovascular (CV) health has emerged as an important consideration in patients with chronic myeloid leukemia (CML) hibitors (TKIs) has increased the is population include CV disease ABL1 TKIs represented a unique ee remission." Importantly, later- as been associated with pleural/ e been linked to the development echanisms of drug toxicities, the mplications in patients with CML. tenet of patient care in CML. We CV health of patients with CML.

2017

Review article

Recommendations for the management of cardiovascular risk in patients with chronic myeloid leukemia on tyrosine kinase inhibitors: risk assessment, stratification, treatment and monitoring

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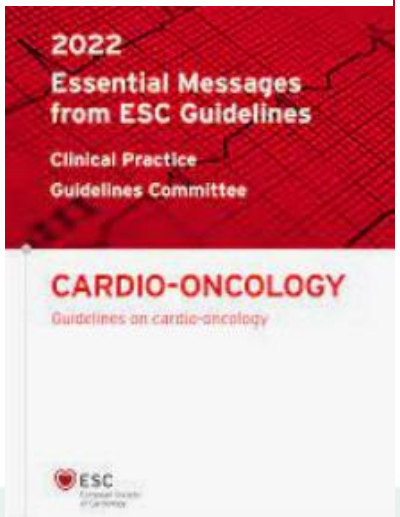
ABSTRACT

This manuscript summarizes the results of the consensus meeting composed of hematologists and cardiologists to establish recommendations for the prevention and follow-up of cardiovascular (CV) risk in patients with chronic myeloid leukemia (CML) treated with BCR-ABL tyrosine kinase inhibitors (TKIs) from the point of view of clinical practice and from the perspective of hematology consultation.

In the first medical appointment, the CV risk factors should be identified to perform the baseline risk stratification, based on the Brazilian Guideline of Dyslipidemia and Atherosclerosis Prevention Update (risk levels: very high, high, intermediate and low).

2020

2022 ESC Guidelines on cardio-oncology



2020

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24–26 May 2024

A new paradigm in the treatment of CML patients is cardiohematological monitoring

Risk stratification in chronic myeloid leukemia patients

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AMERICAN SOCIETY OF HEMATOLOGY ®

"We also need to get better at patient risk stratification: a personalized approach is needed for toxicity assessment"

Conferences ASH: American Society of Hematology, 2020

Risk assessment considering the geographical region of residence

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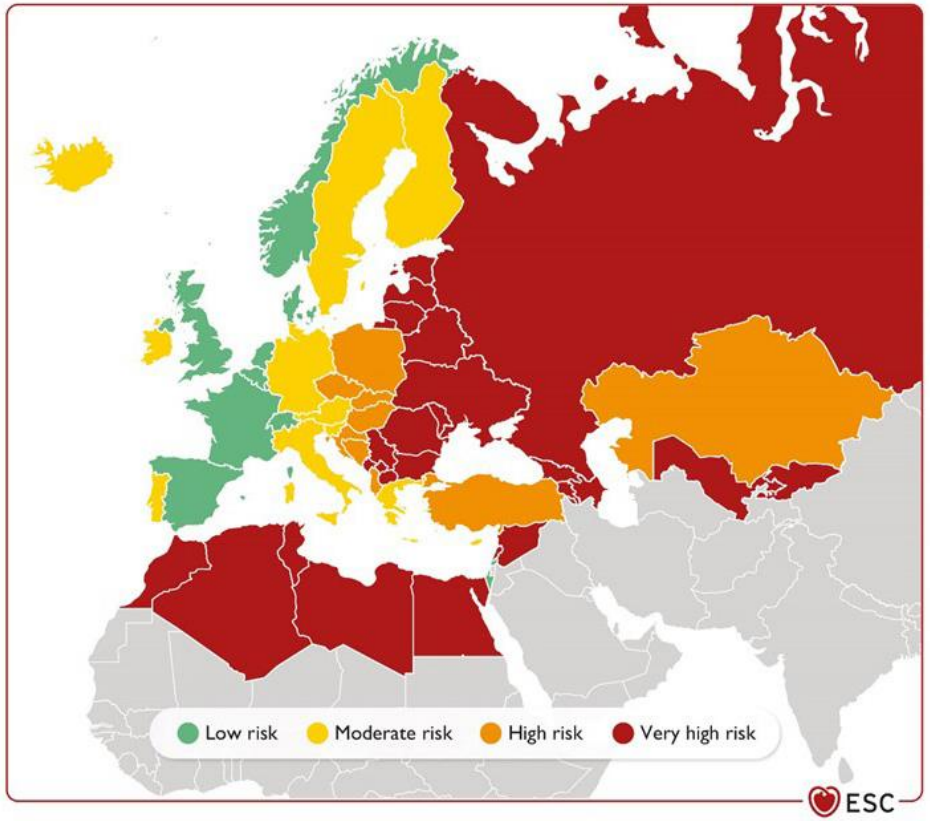

Risk regions based on World Health Organization cardiovascular mortality rates

Low-risk countries: Belgium, Denmark, France, Israel, Luxembourg, Norway, Spain, Switzerland, the Netherlands, and the United Kingdom.

Moderate-risk countries: Austria, Cyprus, Finland, Germany, Greece, Iceland, Ireland, Italy, Malta, Portugal, San Marino, Slovenia, and Sweden.

High-risk countries: Albania, Bosnia and Herzegovina, Croatia, Czech Republic, Estonia, Hungary, Kazakhstan, Poland, Slovakia, and Turkey.

Very-high-risk countries: Algeria, Armenia, Azerbaijan, Belarus, Bulgaria, Egypt, Georgia, Kyrgyzstan, Latvia, Lebanon, Libya, Lithuania, Montenegro, Morocco, Republic of Moldova, Romania, Serbia, Syria, The Former Yugoslav Republic (Macedonia), Tunisia, Ukraine, and Uzbekistan.

Frank L. et al. ESC Scientific Document Group, 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice: Developed by the Task Force for cardiovascular disease prevention in clinical practice with representatives of the European Society of Cardiology and 12 medical societies With the special contribution of the European Association of Preventive Cardiology (EAPC), European Heart Journal, Volume 42, Issue 34, 7 September 2021, Pages 3227–3337, https://doi.org/10.1093/eurheartj/ehab484

SCORE2 and SCORE2-OP scales for assessing cardiovascular risk

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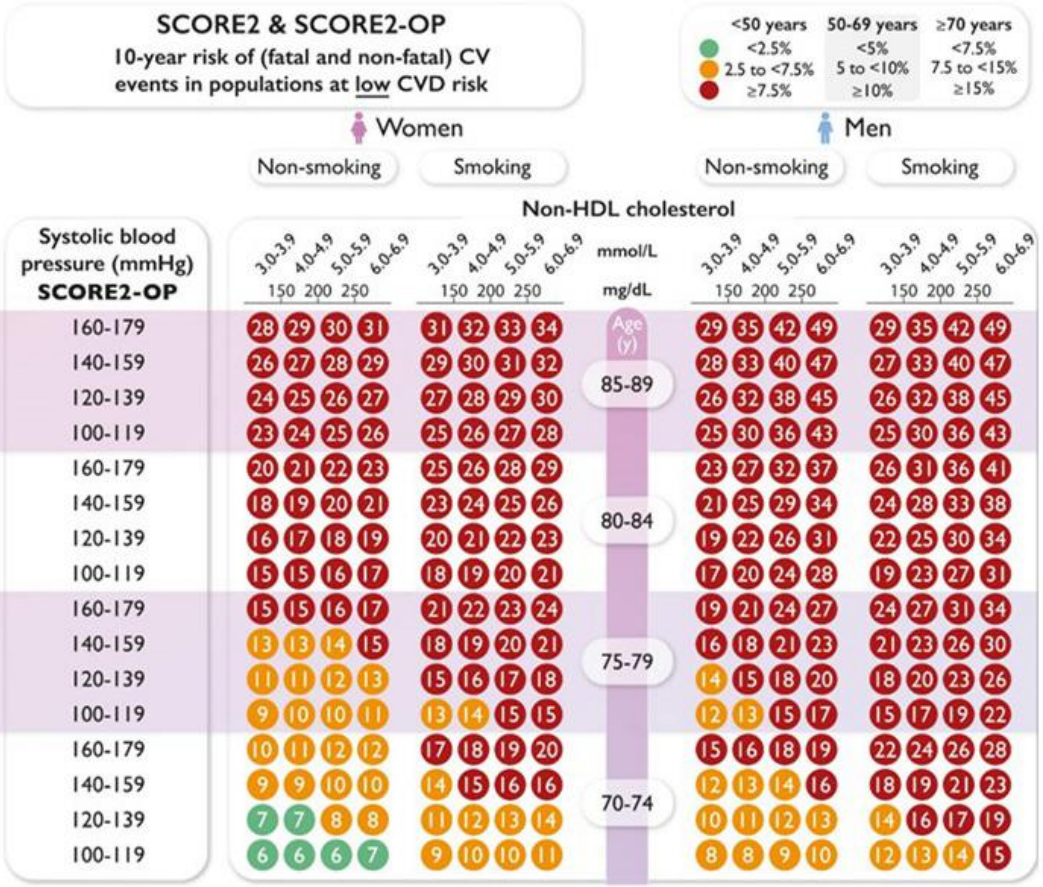

SCORE2 and SCORE2-OP risk chart for fatal and non-fatal (MI, stroke) ASCVD

Low CVD Risk (1)

NB!

The SCORE2 charts do not apply to persons with documented CVD or other high-risk conditions such as diabetes mellitus, family hypercholesterolemia, or other genetic or rare lipid or BP disorders, CKD, and in pregnant women.

The updated SCORE algorithm – SCORE2 – estimates an individual's 10-year risk of *fatal and non-fatal* CVD events (myocardial infarction, stroke) in apparently healthy people aged up 40 years with risk factors that are untreated or have been stable for several years.

Frank L. et al. ESC Scientific Document Group, 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice: Developed by the Task Force for cardiovascular disease prevention in clinical practice with representatives of the European Society of Cardiology and 12 medical societies With the special contribution of the European Association of Preventive Cardiology (EAPC), European Heart Journal, Volume 42, Issue 34, 7 September 2021, Pages 3227–3337, https://doi.org/10.1093/eurheartj/ehab484

Cardiovascular disease risk categories based on SCORE2 and SCORE2-OP assessments in generally healthy individuals, categorized by age

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	< 50 years	50-69 years	≥ 70 years[a]
Low or moderate risk of cardiovascular disease: treatment of risk factors is generally not recommended	< 2.5%	< 5%	< 7.5%
High risk of cardiovascular disease: treatment of risk factors should be considered	2.5 to < 7.5%	5 to < 10%	7.5 to < 15%
Very high risk of cardiovascular disease: Treatment of risk factors is usually recommended[a]	≥ 7.5%	≥ 10%	≥ 15%

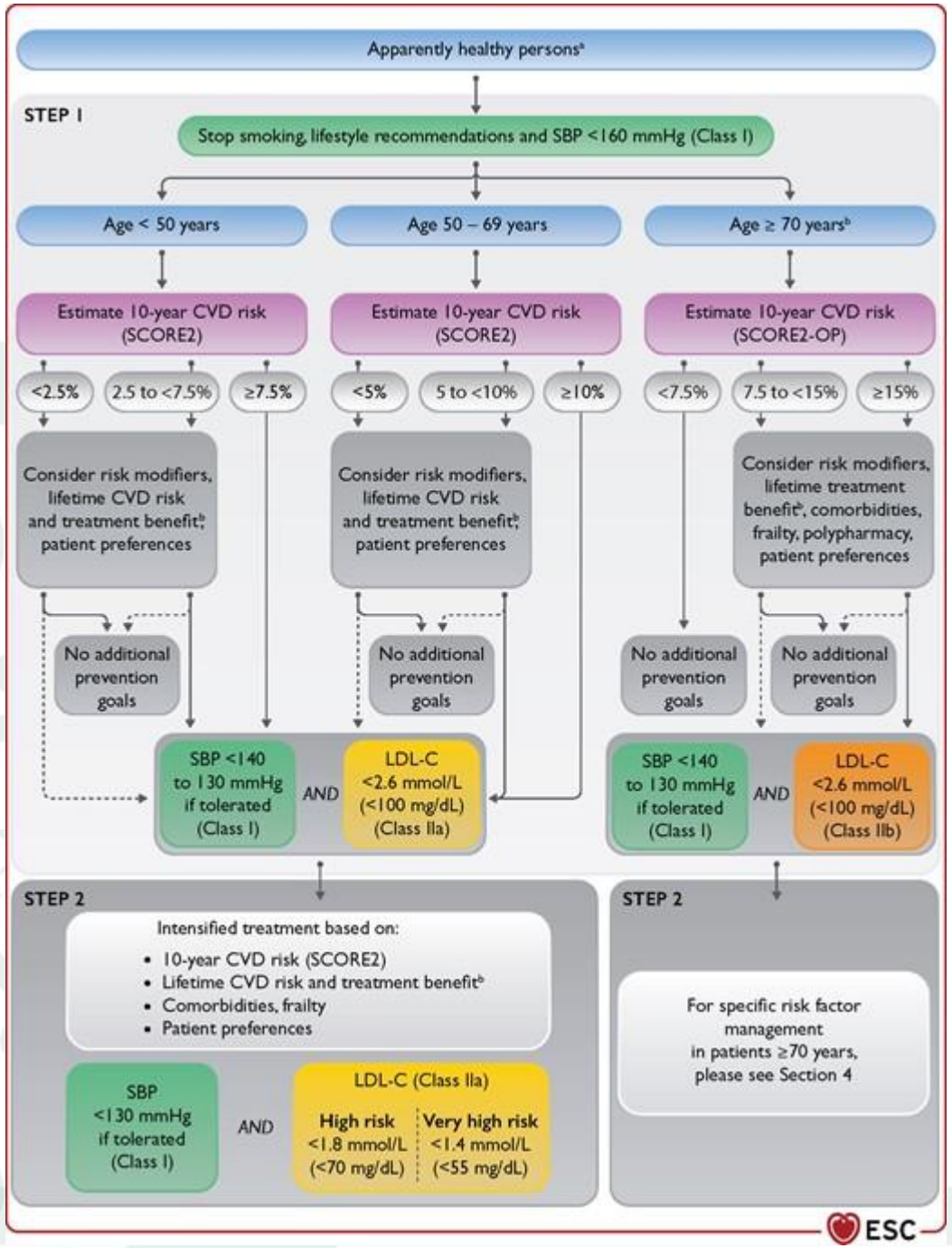
a *– In apparently healthy individuals aged over 70 years, the recommendation for lipid-lowering drug treatment is Class IIb ('may be considered')*

Frank L. et al. ESC Scientific Document Group, 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice: Developed by the Task Force for cardiovascular disease prevention in clinical practice with representatives of the European Society of Cardiology and 12 medical societies With the special contribution of the European Association of Preventive Cardiology (EAPC), European Heart Journal, Volume 42, Issue 34, 7 September 2021, Pages 3227–3337, https://doi.org/10.1093/eurheartj/ehab484

Very high CV risk	• Documented ASCVD, clinical or unequivocal on imaging. Documented clinical ASCVD includes previous AMI, ACS, coronary revascularization and other arterial revascularization procedures, stroke and TIA, aortic aneurysm, and PAD. Unequivocally documented ASCVD on imaging includes plaque on coronary angiography, carotid ultrasound, or CTA. It does NOT include some increase in continuous imaging parameters such as intima-media thickness of the carotid artery • Familial hypercholesterolemia with confirmed CAD of the atherosclerotic origin or another major risk factor • Severe chronic kidney disease without diabetes or ASCVD (eGFR<30 mL/minute/1.73 m2 or eGFR 30–44 mL/minute/1.73 m2 and ACR >30) • SCORE ≥10% • Score on SCORE2 and SCORE2-OP (<50 years: ≥7.5%; 50–69 years: ≥10%; ≥70 years: ≥15%) • Patients with DM with established ASCVD and/or severe TOD: eGFR <45 mL/minute/1.73 m2 irrespective of albuminuria; eGFR 45–59 mL/min/1.73 m2 and microalbuminuria (ACR 30–300 mg/g); Proteinuria (ACR >300 mg/g); presence of microvascular disease in at least three different sites (e.g., microalbuminuria plus retinopathy plus neuropathy)
High CV risk	• Significant increase in one of these risk factors (total cholesterol >8 mmol/l or LDL cholesterol >4.9 mmol/L or blood pressure ≥180/110 mmHg) • Familial hypercholesterolemia without additional risk factors • DM without TOD or diabetes mellitus lasting >10 years or another additional risk factor. • Moderate CKD without diabetes or ASCVD (eGFR 30–44 mL/minute/1.73 m2 and ACR <30 or eGFR 45–59 mL/minute/1.73 m2 and ACR 30–300 or eGFR ≥60 mL/minute/1.73 m2 and ACR >300) • Patients with DM without ASCVD and/or severe TOD, and not fulfilling the moderate risk criteria • SCORE 5-9%, Score on SCORE2 and SCORE2-OP (<50 years: 2.5 to <7.5%; 50–69 years: 5 to <10%; ≥70 years: 7.5 to <15%)
Moderate CV risk	• Young patients (for type 1 diabetes <35 years; for type 2 diabetes <50 years) with diabetes <10 years without other additional risk factors • Patients with well-controlled short-standing DM (e.g., <10 years), no evidence of TOD, and no additional ASCVD risk factors • SCORE 1–4% • Score on SCORE2 and SCORE2-OP (<50 years: <2.5%; 50–69 years: <5%, ≥70 years: <7.5%)
Low risk	SCORE score <1% Score on SCORE2 and SCORE2-OP (<50 years: <2.5%; 50–69 years: <5%, ≥70 years: <7.5%)

ASCVD: atherosclerotic cardiovascular disease; AMI: acute myocardial infarction; ACS: acute coronary syndromes; ACR: albumin-to-creatinine ratio: (to convert mg/g to mg/mmol: divide by 10); CKD: chronic kidney disease; CTA: computed tomography angiography; DM: diabetes mellitus; eGFR: estimated glomerular filtration rate; TIA: transient ischaemic attack; TOD: target organ damage; PAD: peripheral artery disease; SCORE: Systematic COronary Risk Evaluation; SCORE2: Systematic COronary Risk Evaluation 2; SCORE2-OP: Systematic COronary Risk Evaluation Older Persons

Mach F., Baigent C., Catapano A.L. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk: The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS). European Heart Journal, Volume 41, Issue 1, 1 January 2020, Pages 111–188.



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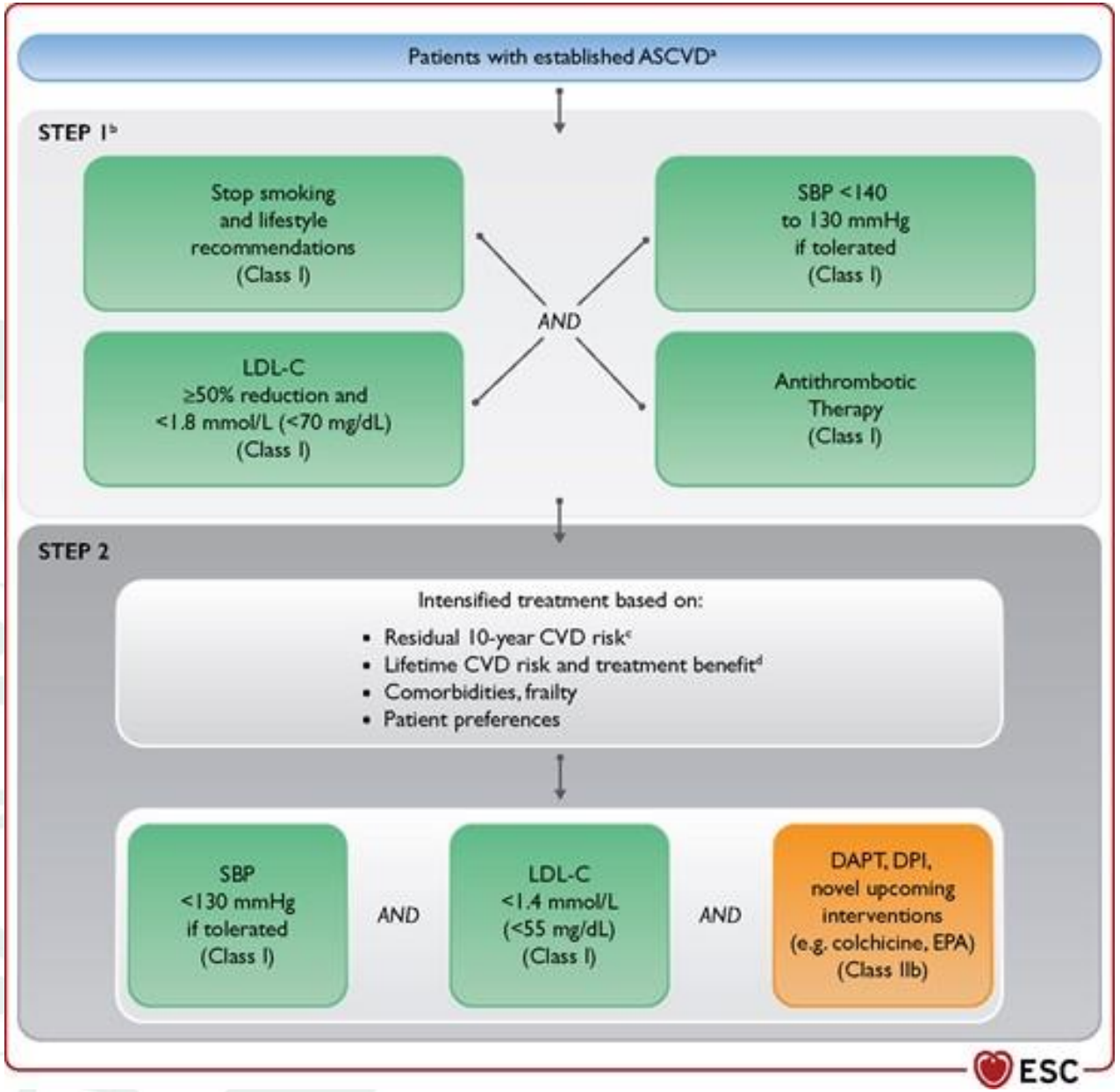
Cardiovascular risk reduction strategy based on risk assessment and low-density lipoprotein (LDL-C) levels

In patients with CML, it is important to consider both the risk assessment based on the general population algorithm and the specific target therapy drug prescribed for the patient.

Frank L. et al. ESC Scientific Document Group, 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice: Developed by the Task Force for cardiovascular disease prevention in clinical practice with representatives of the European Society of Cardiology and 12 medical societies With the special contribution of the European Association of Preventive Cardiology (EAPC), European Heart Journal, Volume 42, Issue 34, 7 September 2021, Pages 3227–3337, https://doi.org/10.1093/eurheartj/ehab484



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Assessment and management of risk factors in patients with established atherosclerotic cardiovascular disease

Frank L. et al. ESC Scientific Document Group, 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice: Developed by the Task Force for cardiovascular disease prevention in clinical practice with representatives of the European Society of Cardiology and 12 medical societies With the special contribution of the European Association of Preventive Cardiology (EAPC), European Heart Journal, Volume 42, Issue 34, 7 September 2021, Pages 3227–3337, https://doi.org/10.1093/eurheartj/ehab484

Key aspects of cardiovascular risk reduction in patients with CML include two stages:

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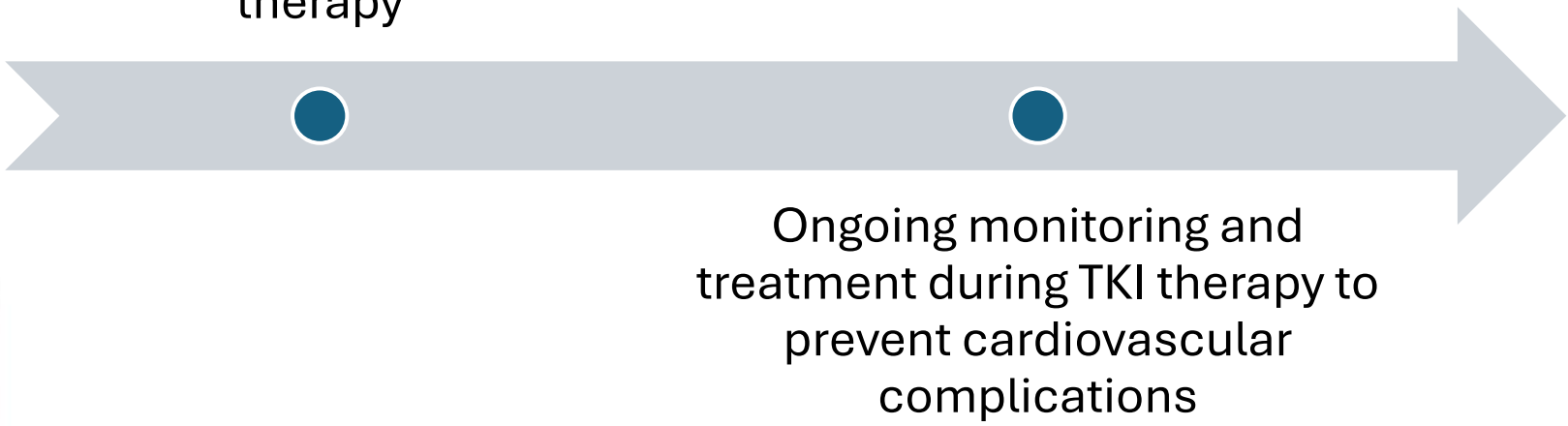

British Society of Hematology guidelines for the diagnosis and management of CML patients

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- All patients should undergo cardiovascular risk assessment
- An electrocardiogram (ECG) should be performed.
- Baseline lipid profile, fasting glucose, and/or HbA1c levels should be obtained.
- Evaluation of concomitant diseases is essential for the choice of TKI.

Graeme Smith et al. on behalf of British Society for Haematology A British Society for Haematology Guideline on the diagnosis and management of chronic myeloid leukaemia. doi: 10.1111/bjh.16971

Guidelines for first-line TKI choice by pre-existing medical condition

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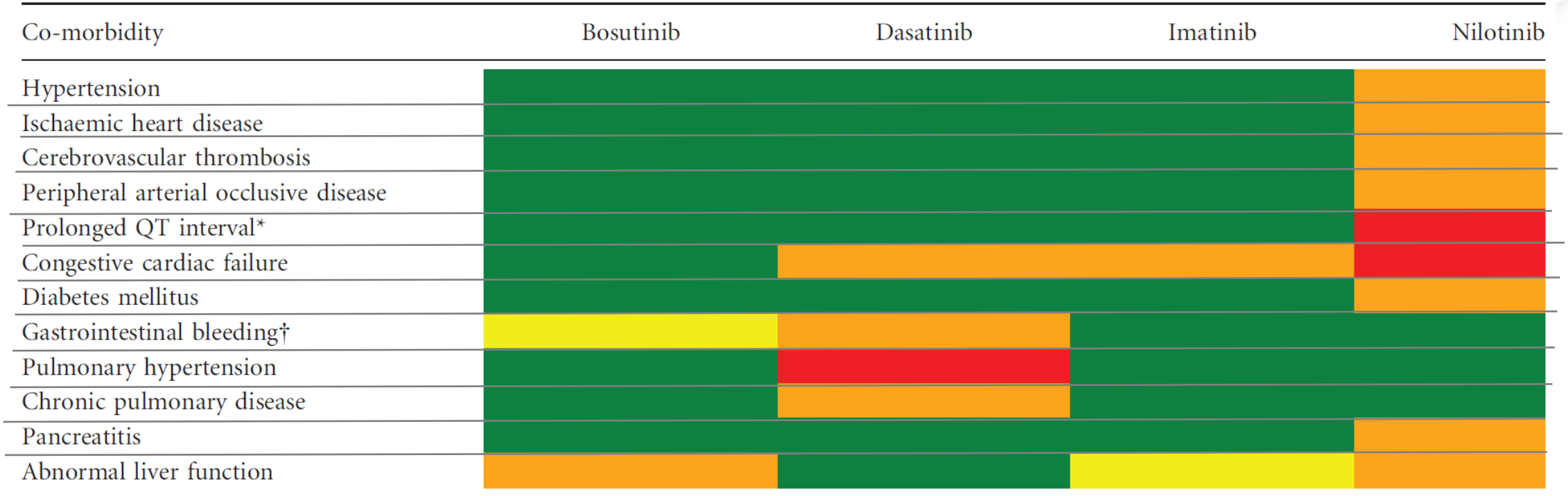

■, no contra-indication; ■, low risk of exacerbation of pre-existing condition; ■, intermediate risk of exacerbation of pre-existing condition; ■, avoid if possible.

*Some evidence that all 2GTKI prolong QT.

†Imatinib has been associated with the development of gastric antral vascular ectasia (GAVE).

adapted from Michael Deininger

Graeme Smith et al. on behalf of British Society for Haematology A British Society for Haematology Guideline on the diagnosis and management of chronic myeloid leukaemia. doi: 10.1111/bjh.16971

Algorithm for the management of low- and high-risk chronic myeloid leukemia (CML) patients receiving TKI therapy

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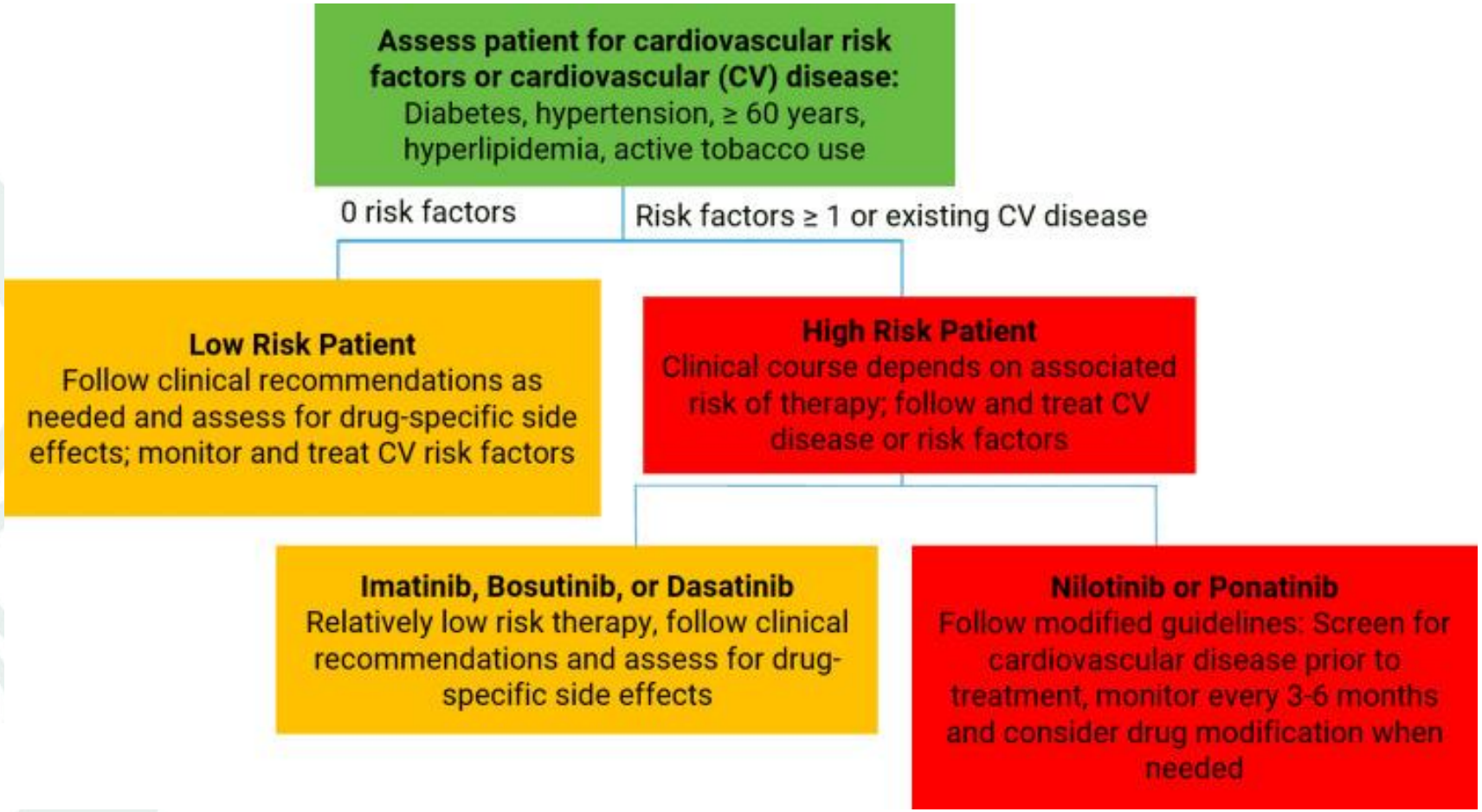

Mary C. Barber, Michael J. Mauro, and Javid Moslehi. Cardiovascular care of patients with chronic myeloid leukemia (CML) on tyrosine kinase inhibitor (TKI) therapy. American Society of Hematology. Hematology 2017.

Понатиніб – не зареєстровано на території України

Cardiovascular monitoring in CML patients during TKI therapy (initially, every 3 to 6 months)

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	Imatinib	Bosutinib	Dasatinib	Nilotinib	Ponatinib
Blood pressure control	Recommended	Recommended	Recommended	Recommended	Recommended
Ankle-brachial index	If clinically indicated	If clinically indicated	If clinically indicated	Recommended	Recommended
Lipid profile	If clinically indicated	If clinically indicated	If clinically indicated	Recommended	Recommended
Fasting glucose/HbA1C	If clinically indicated	If clinically indicated	If clinically indicated	Recommended	Recommended
ECG	If clinically indicated	If clinically indicated	Recommended	Recommended	Recommended
Echocardiography	If clinically indicated	If clinically indicated	If clinically indicated	If clinically indicated	If clinically indicated

Barber M, Mauro M and Moslehi J, Blood 2017

Cardiovascular assessment in CML patients receiving TKIs

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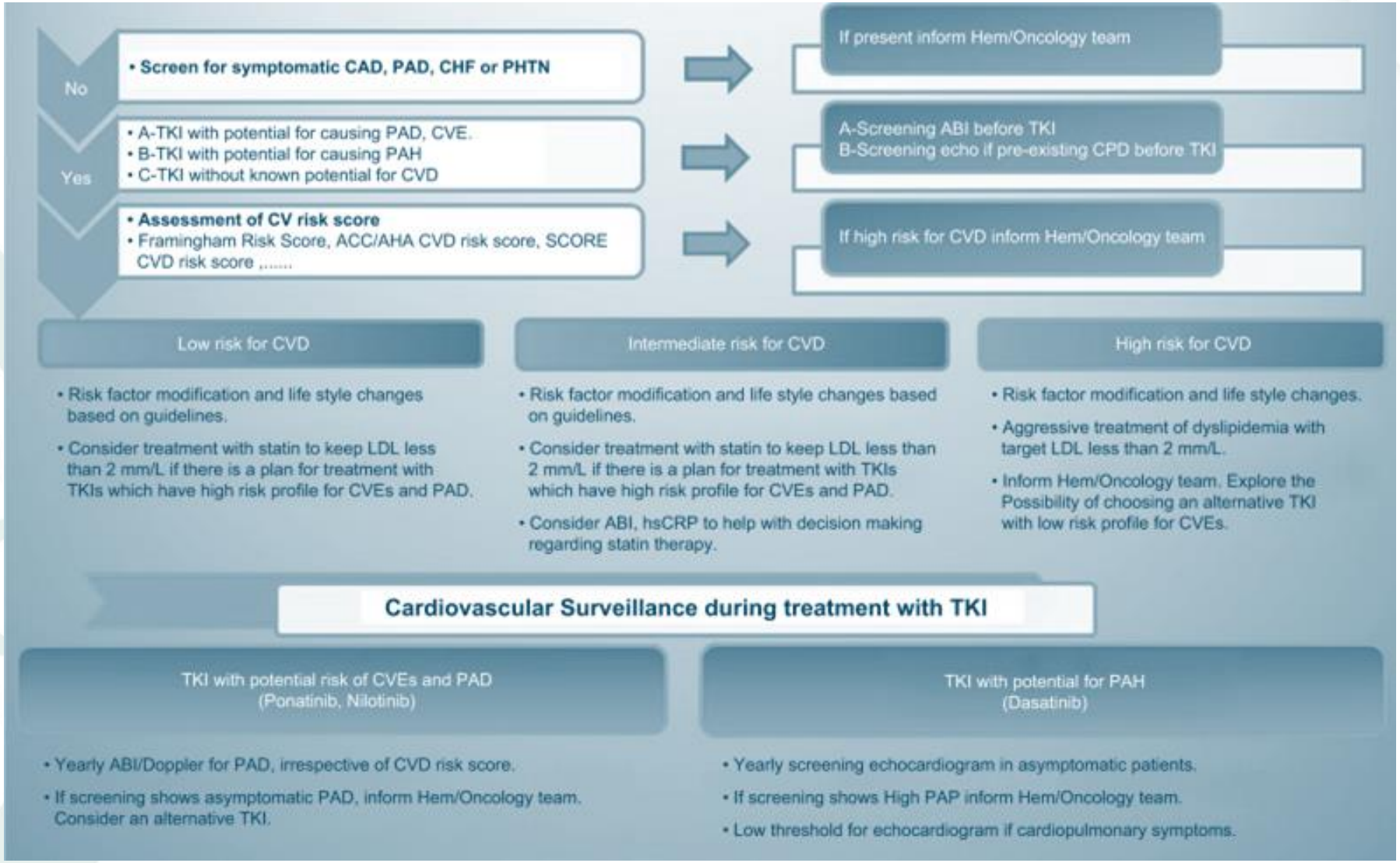

Aghel N, Delgado DH, Lipton JH Cardiovascular toxicities of BCR-ABL tyrosine kinase inhibitors in chronic myeloid leukemia: preventive strategies and cardiovascular surveillance. 2017 Volume 2017:13 Pages 293—303.DOI https://doi.org/10.2147/VHRM.S108874

British Society of Hematology Guidelines for the diagnosis and management of patients with CML: Key concepts relevant to the prevention of cardiovascular events

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- If cardiovascular (CV) risk is high, very high (> 10%), atorvastatin 20 mg daily should be considered.
- Aspirin should not be prescribed for primary prophylaxis in asymptomatic patients, except in patients with known carotid stenosis > 50%.
- Hypertension is common with TKIs (more than 10% with some TKIs), but the risk of life-threatening CV events is low.
- Blood pressure (BP) should be measured before and during TKI treatment, and hypertension should be managed in collaboration with a general practitioner according to current guidelines.
- TKI treatment should be stopped if blood pressure is higher than 180/110 mm Hg.
- QT prolongation is rare: an ECG should be performed at the start of treatment for patients starting bosutinib and nilotinib or as clinically indicated.
- Electrolytes should be measured, and specialist advice should be obtained in patients with a Fridericia QTc interval (QTcF) > 450 ms (men) or > 460 ms (women).
- Venous thromboembolic disease is uncommon but has been reported frequently in patients treated with nilotinib and ponatinib.

Graeme Smith et al. on behalf of British Society for Haematology A British Society for Haematology Guideline on the diagnosis and management of chronic myeloid leukaemia. doi: 10.1111/bjh.16971

Practical ABCDE steps to reduce cardiovascular risk in patients with CML receiving therapy with TKIs

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ABCDE Steps of prevention	Actions/measures
A	**A**wareness of CV disease signs and symptoms **A**spirin in select patients **A**nkle–brachial index measurement to monitor for peripheral artery disease
B	**B**lood pressure control
C	**C**igarette and tobacco cessation **C**holesterol level, including regular monitoring and treatment, if needed
D	**D**iabetes mellitus regular monitoring and treatment, if needed **D**iet and weight management
E	**E**xercise **E**CG **E**chocardiography

Tyrosine Kinase Inhibitors in Leukemia and Cardiovascular Events. From Mechanism to Patient Care. Ali Manouchehri, Elishama Kanu, Michael J. Mauro, Aaron W. Aday, Jonathan R. Lindner, and Javid Moslehi. Arteriosclerosis, Thrombosis, and Vascular BiologyVolume 40, Issue 2, February 2020; Pages 301-308

Statins

and

CML

To Prescribe or Not?

- For whom?
- When?
- How long?
- What goals will be achieved?
- If yes, which statin?

Statins

and

CML

- Is it safe to combine statins with targeted therapy drugs?
- Who should prescribe and monitor therapy: a hematologist, a cardiologist, or a family physician?
- Which clinical recommendations to prioritize, given the lack of consensus on the issue?

The first experimental data indicating an increase in the antileukemic activity of imatinib against the background of combined therapy with a statin

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MALIGNANT HEMATOPOIESIS | VOLUME 42, ISSUE 6, P439-447, JUNE 01, 2014

Statins inhibit *ABCB1* and *ABCG2* drug transporter activity in chronic myeloid leukemia cells and potentiate antileukemic effects of imatinib

Eliza Glodkowska-Mrowka • Piotr Mrowka • Grzegorz W. Basak • ... Pawel Krzysztof Wlodarski • Marek Jakobisiak • Tomasz Stoklosa • Show all authors

Published: March 24, 2014 • DOI: https://doi.org/10.1016/j.exphem.2014.02.006 • Check for updates

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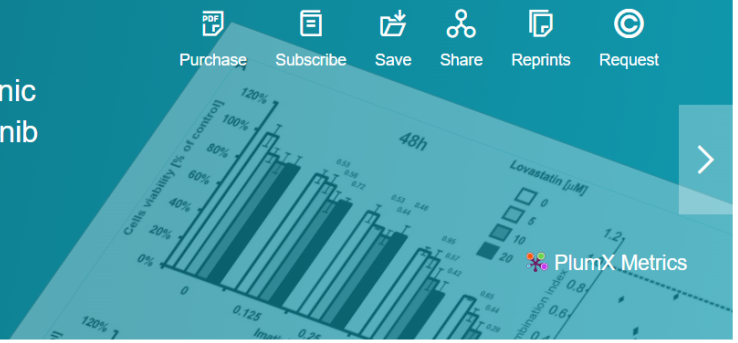

References
Article Info
Related Articles

Despite undisputed success of tyrosine kinase inhibitors in the therapy of chronic myeloid leukemia (CML), development of drug resistance and inability to cure the disease challenge clinicians and researchers. Additionally, recent reports regarding cardiovascular toxicities of second and third generation tyrosine kinase inhibitors prove that there is still a place for novel therapeutic combinations in CML. We have previously shown that statins are able to modulate activity of chemotherapeutics or antibodies used in oncology. Therefore, we decided to verify that statins are able to potentiate antileukemic activity of imatinib, still a frontline treatment of CML. Lovastatin, a cholesterol lowering drug, synergistically potentiates antileukemic activity of imatinib in cell lines and in primary CD34+ CML cells from patients in different phases of the disease, including patients resistant to imatinib with no detectable mutations. This effect is related to increased intracellular concentration of imatinib in CD34+ CML cells and cell lines measured using uptake of ^{14}C-labeled imatinib. Lovastatin does not influence influx but significantly inhibits efflux of imatinib mediated by ATP-binding cassette (ABC) transporters: ABCB1 and ABCG2. The addition of cholesterol completely reverses these effects. Statins do not affect expression of *ABCB1* and *ABCG2* genes. The effects are drug-class specific, as observed with other statins. Our results suggest that statins may offer a valuable

2014

Glodkowska-Mrowka E, Mrowka P, Basak GW, Niesiobedzka-Krezel J, Seferynska I, Wlodarski PK, Jakobisiak M, Stoklosa T. Statins inhibit ABCB1 and ABCG2 drug transporter activity in chronic myeloid leukemia cells and potentiate antileukemic effects of imatinib. Exp Hematol. 2014 Jun;42(6):439-47. doi: 10.1016/j.exphem.2014.02.006. Epub 2014 Mar 22. PMID: 24667683.

cancers

MDPI

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Article

Statins Enhance the Molecular Response in Chronic Myeloid Leukemia when Combined with Tyrosine Kinase Inhibitors

Hyeok-Jae Jang [1,†], Young-Min Woo [1,†], Kazuhito Naka [2,†], Jong-Ho Park [3], Ho-Jae Han [1], Hee-Jin Kim [4], Sun-Hee Kim [4], Jae-Sook Ahn [5], Taehyung Kim [6,7], Shinya Kimura [8], Sarah Zarabi [9], Jeffrey H. Lipton [9], Mark D. Minden [9,10], Chul-Won Jung [11], Hyeoung-Joon Kim [5], Jong-Won Kim [1,4,*] and Dennis Dong Hwan Kim [9,*]

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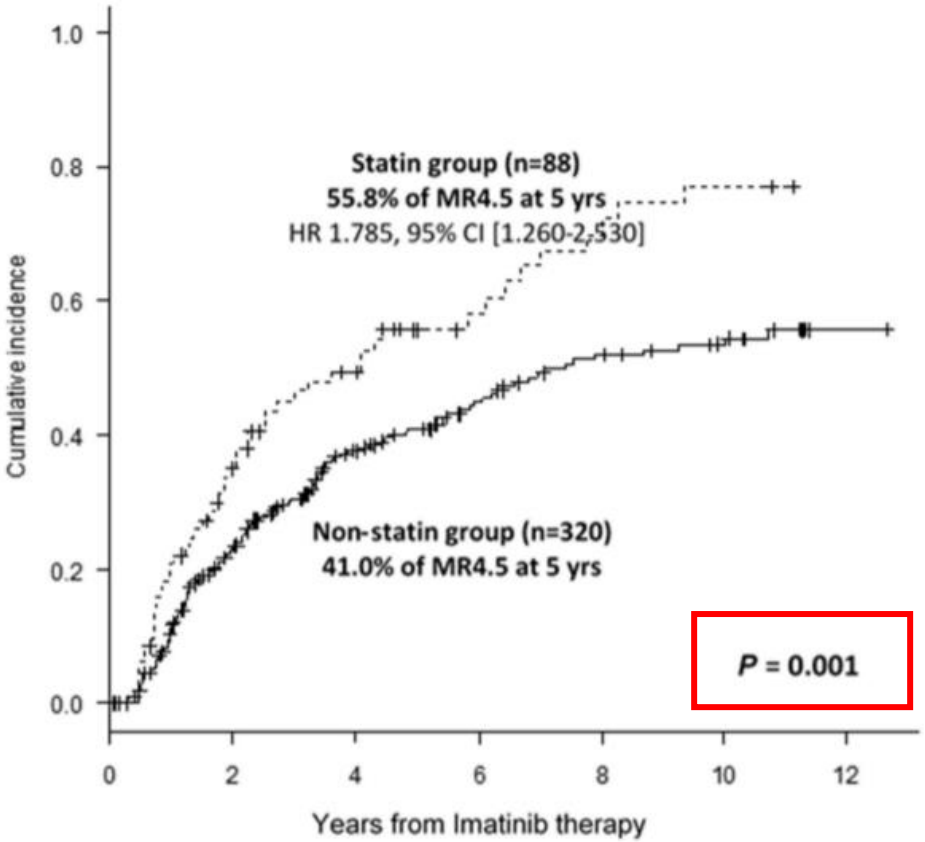
Citation: Jang, H.-J.; Woo, Y.-M.; Naka, K.; Park, J.-H.; Han, H.-J.; Kim, H.-J.; Kim, S.-H.; Ahn, J.-S.; Kim, T.; Kimura, S.; et al. Statins Enhance the Molecular Response in Chronic Myeloid Leukemia when Combined with Tyrosine Kinase Inhibitors. *Cancers* **2021**, *13*, 5543. https://

- Worldwide, statins are commonly prescribed to CML patients receiving second-generation TKI therapy to mitigate cardiovascular risk factors such as hyperlipidemia.
- The study results confirm the therapeutic benefit of concurrent statin use in TKI therapy for patients with CML.
- The combined effects of **statins and TKIs increase the likelihood of achieving a deep molecular response**

2021

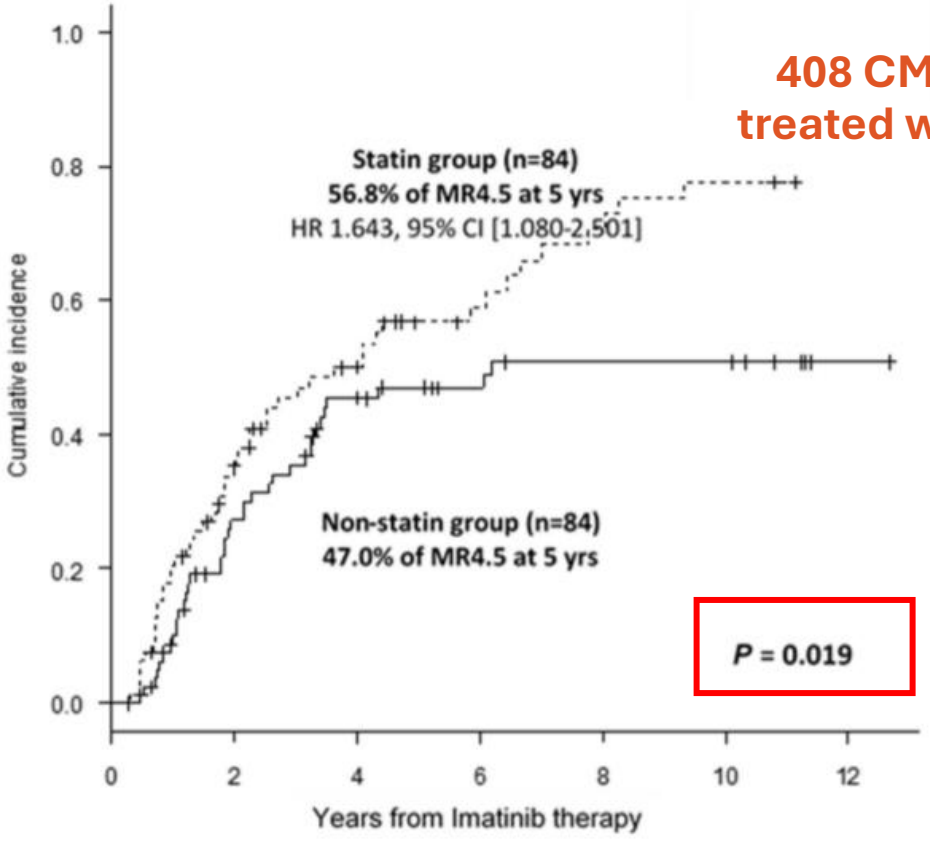
Statins enhance the rate of deep molecular response in CML patients undergoing imatinib therapy

- The rates of deep molecular response were significantly higher in patients receiving a statin/TKI combination compared to those receiving a TKI alone (p = 0.0016).



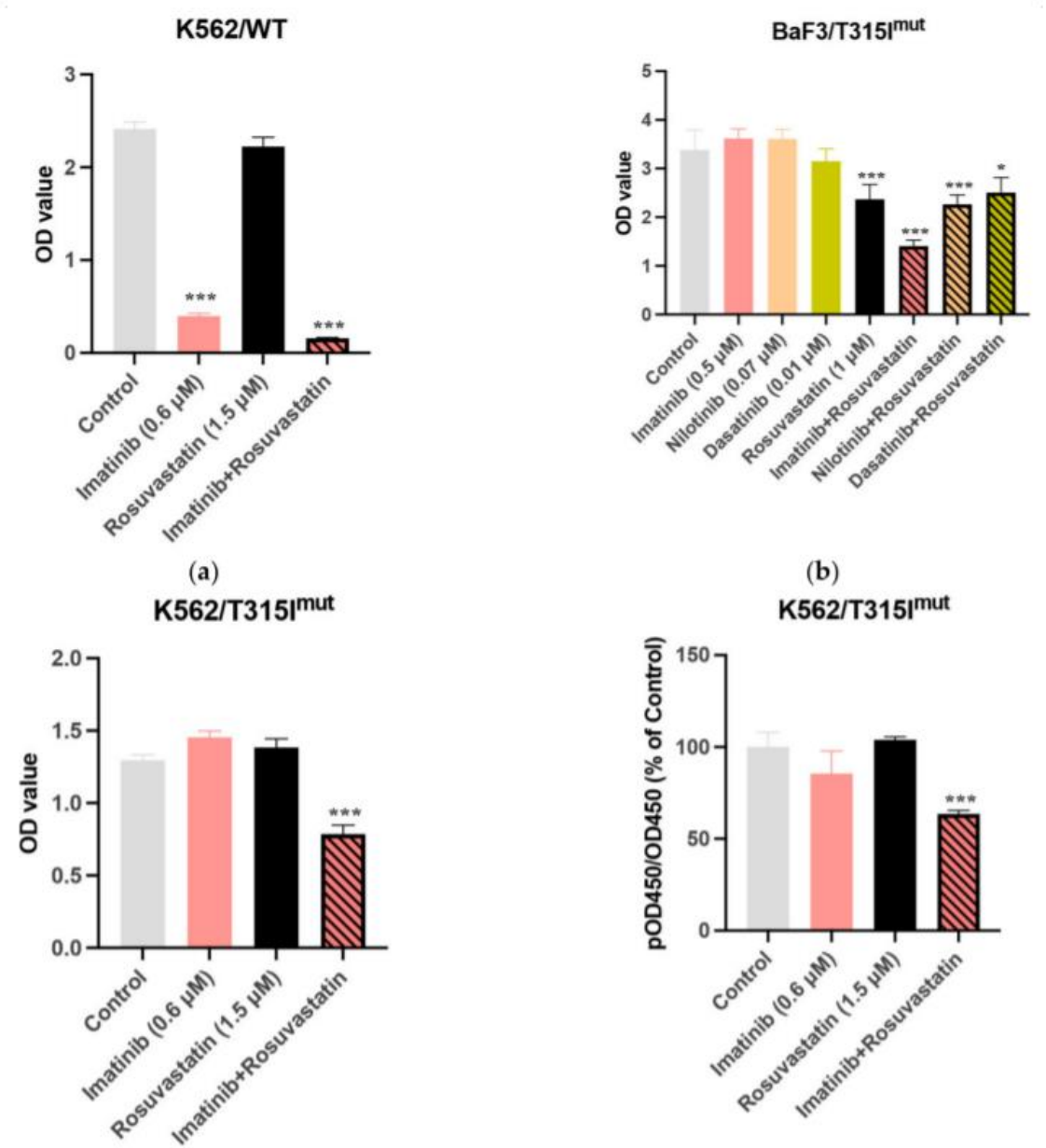
Comparison of the cumulative rate of deep molecular response between patients treated with statin/TKI combination therapy versus TKI monotherapy

408 CML patients treated with imatinib



The comparison of the cumulative rate of deep molecular response between patients treated with statin/TKI combination therapy versus TKI monotherapy after propensity score matching (PSM) is a common method used in clinical trials to achieve balanced covariate allocation between treatment and control groups

Jang, H.-J.; Woo, Y.-M.; Naka, K.; Park, J.-H.; Han, H.-J.; Kim, H.-J.; Kim, S.-H.; Ahn, J.-S.; Kim, T.;Kimura, S.; et al. Statins Enhance the Molecular Response in Chronic Myeloid Leukemia when Combined with Tyrosine Kinase Inhibitors. Cancers 2021, 13, 5543. https://doi.org/10.3390/cancers13215543



- The statin/TKI combination showed a potent cytotoxic effect against CML in both 'wild-type' and mutant ABL1, BaF3, and K562/T315I mutant cells

Jang, H.-J.; Woo, Y.-M.; Naka, K.; Park, J.-H.; Han, H.-J.; Kim, H.-J.; Kim, S.-H.; Ahn, J.-S.; Kim, T.;Kimura, S.; et al. Statins Enhance the Molecular Response in Chronic Myeloid Leukemia when Combined with Tyrosine Kinase Inhibitors. Cancers 2021, 13, 5543. https://doi.org/10.3390/cancers13215543

Statins inhibit the colony-forming ability of mouse CML-KLS+ cells in vitro

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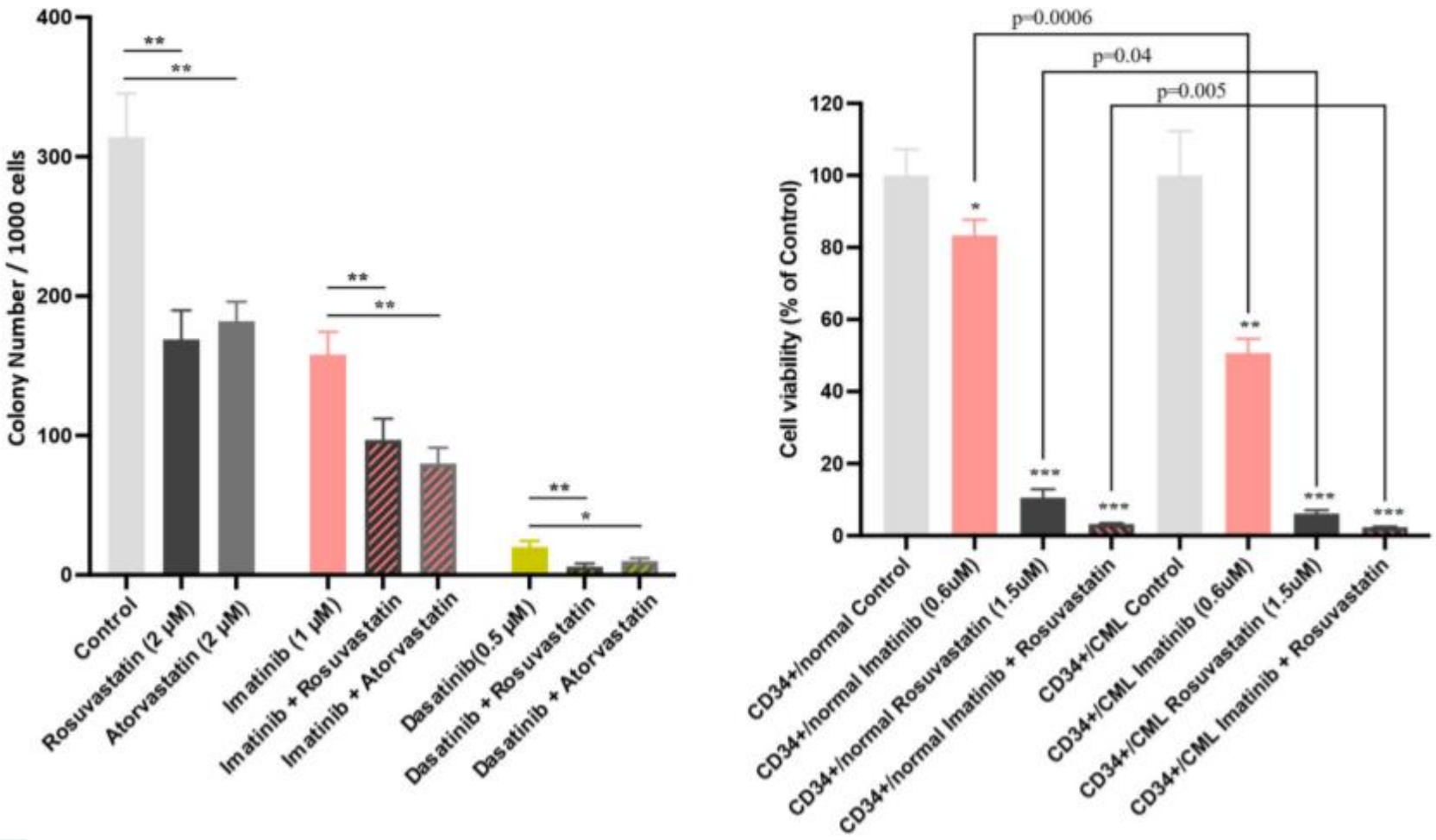
- Statins may potentially inhibit or destroy leukemia progenitor cells in CML patients



Jang, H.-J.; Woo, Y.-M.; Naka, K.; Park, J.-H.; Han, H.-J.; Kim, H.-J.; Kim, S.-H.; Ahn, J.-S.; Kim, T.;Kimura, S.; et al. Statins Enhance the Molecular Response in Chronic Myeloid Leukemia when Combined with Tyrosine Kinase Inhibitors. Cancers 2021, 13, 5543. https://doi.org/10.3390/cancers13215543

The combination of rosuvastatin and TKI therapy downregulates c-Myc and hematopoietic stem cell differentiation pathways

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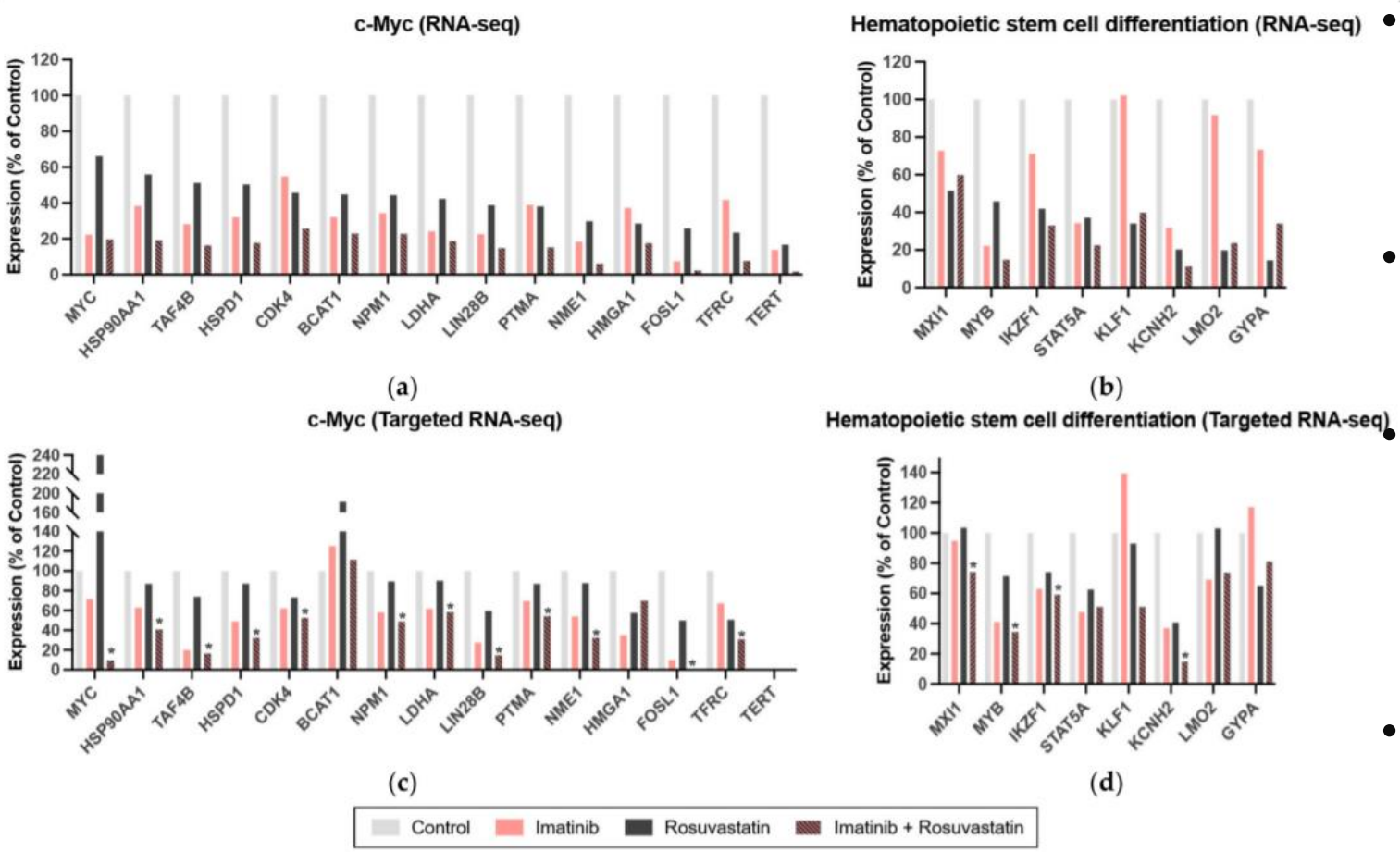

- In addition, RNA-seq data showed that the statin/TKI combination downregulated the c-Myc and hematopoietic stem cell differentiation pathways.
- These pathways are potential therapeutic targets for eliminating leukemia progenitor cells in CML patients.
- Quiescent leukemic stem cells are often resistant to both conventional chemotherapy and targeted therapies, persisting after therapy is discontinued and promoting relapse.
- Thus, it is crucial to determine the percentage of stem cells and monitor their entry and exit from quiescence.

Jang, H.-J.; Woo, Y.-M.; Naka, K.; Park, J.-H.; Han, H.-J.; Kim, H.-J.; Kim, S.-H.; Ahn, J.-S.; Kim, T.;Kimura, S.; et al. Statins Enhance the Molecular Response in Chronic Myeloid Leukemia when Combined with Tyrosine Kinase Inhibitors. Cancers 2021, 13, 5543. https://doi.org/10.3390/cancers13215543

Cytochromes involved in the process of the liver tyrosine kinase inhibitors biotransformation

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Tyrosine kinase inhibitor	Cytochromes involved in the process of biotransformation in the liver
Imatinib	CYP3A4, CYP3A5
Dasatinib	CYP3A4 (preferably), CYP3A5, UGT
Nilotinib	CYP3A4, CYP2C8
Ponatinib	CYP3A4, (CYP2C8, 2D6,3A5 to a lesser extent)
Bosutinib	CYP3A4

CYP: cytochrome P-450 enzymes

Imatinib, dasatinib, nilotinib, ponatinib, and bosutinib are metabolized by enzymes in the cytochrome P450 system. Concomitant use of drugs that inhibit the CYP3A4 and CYP3A5 enzymes may affect their therapeutic effects.

NCCN Guidelines version 1.2022 Chronic Myeloid Leukemia

Понатиніб – не зареєстровано на території України

Drug interactions between statins and imatinib, dasatinib, nilotinib

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HMG-CoA reductase inhibitors			
Simvastatin	• **Inhibition of CYP 3A4 by imatinib:** ↑ **simvastatin exposure**[9,18,19,48] • **Inhibition of Pgp by simvastatin:** ↑ **imatinib exposure**[9,23,24,55,69-72]	• **Inhibition of CYP 3A4 by dasatinib:** ↑ **simvastatin exposure**[9,18,19,48] • Inhibition of Pgp by simvastatin: ↑ dasatinib exposure[9,10,52,67,68]	• Inhibition of CYP 3A4 by nilotinib: ↑ simvastatin exposure[9,18,19]
Pravastatin	—	—	—
Atorvastatin	• **Inhibition of CYP 3A4 by imatinib:** ↑ **atorvastatin exposure**[9,18,19] • Inhibition of Pgp by atorvastatin: ↑ imatinib exposure[9,23,24,55,69-72]	• Inhibition of CYP 3A4 by dasatinib: ↑ atorvastatin exposure[9,18,19] • Inhibition of Pgp by atorvastatin: ↑ dasatinib exposure[9,10,67,68]	• Inhibition of CYP 3A4 by nilotinib: ↑ atorvastatin exposure[9,18,19]
Rosuvastatin	—	—	—

Haouala A., Widmer N., Duchosal M.A., Montemurro M., Buclin T., Decosterd L. A. Drug interactions with the tyrosine kinase inhibitors imatinib, dasatinib, and nilotinib. Blood. 2011;117(8):e75-e87.

What should be done if the desired LDL-cholesterol goal is not achieved?

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Expected reduction in low-density lipoprotein-cholesterol for combination therapy

Treatment	The average decrease in LDL-cholesterol
Moderate-intensity statin	~30%
High-intensity statin	~50%
High-intensity statin + ezetimibe	~65%
PCSK9 inhibitor	~60%
PCSK9 inhibitor plus high-intensity statin	~75%
PCSK9 inhibitor plus high-intensity statin plus ezetimibe	~85%

PCSK9: proprotein convertase subtilisin/Kexin type 9

Frank L. et al. ESC Scientific Document Group, 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice: Developed by the Task Force for cardiovascular disease prevention in clinical practice with representatives of the European Society of Cardiology and 12 medical societies With the special contribution of the European Association of Preventive Cardiology (EAPC), European Heart Journal, Volume 42, Issue 34, 7 September 2021, Pages 3227–3337, https://doi.org/10.1093/eurheartj/ehab484

Factors should be considered to reduce cardiovascular risk in CML patients

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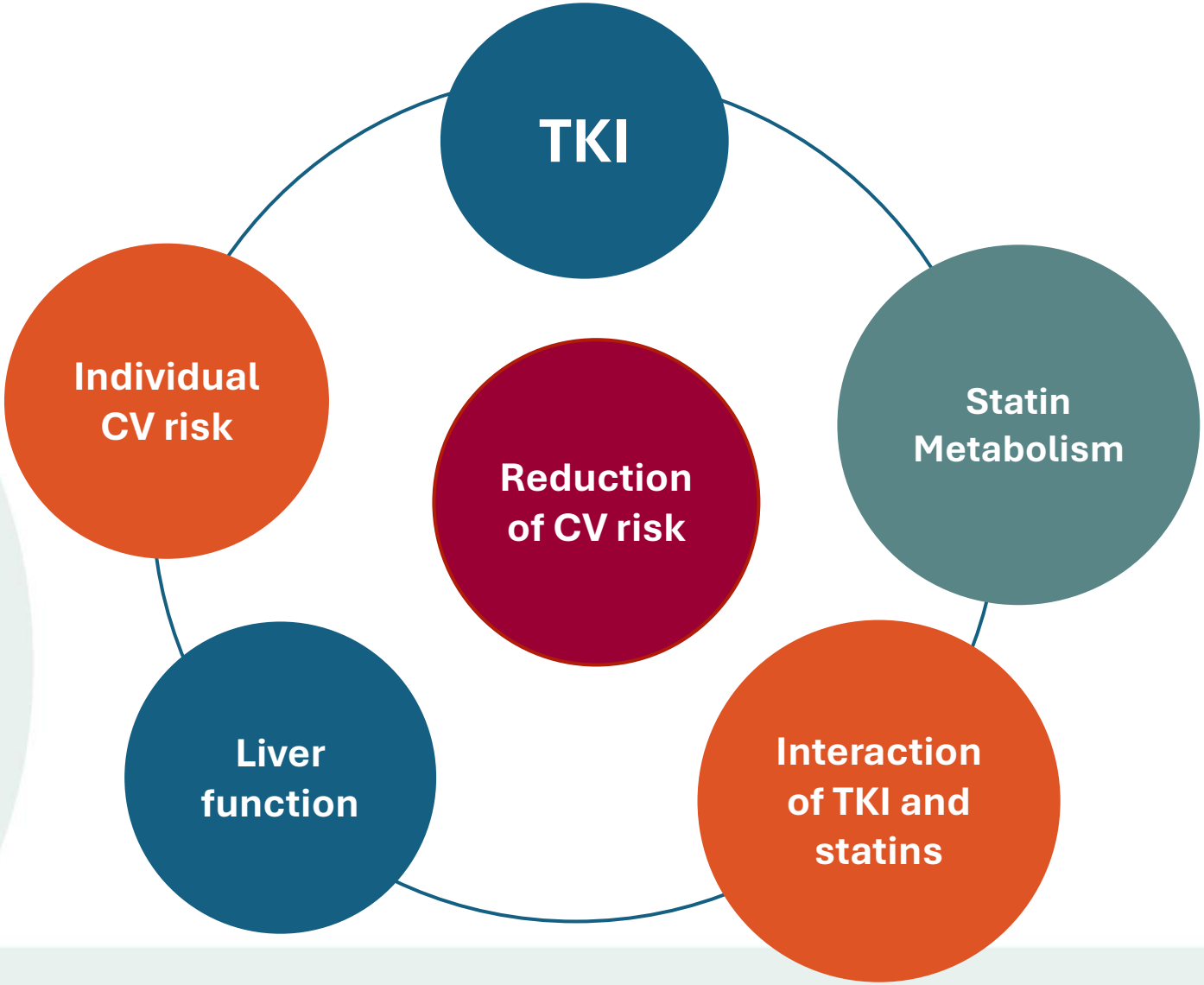

General approach to cardiovascular toxicity

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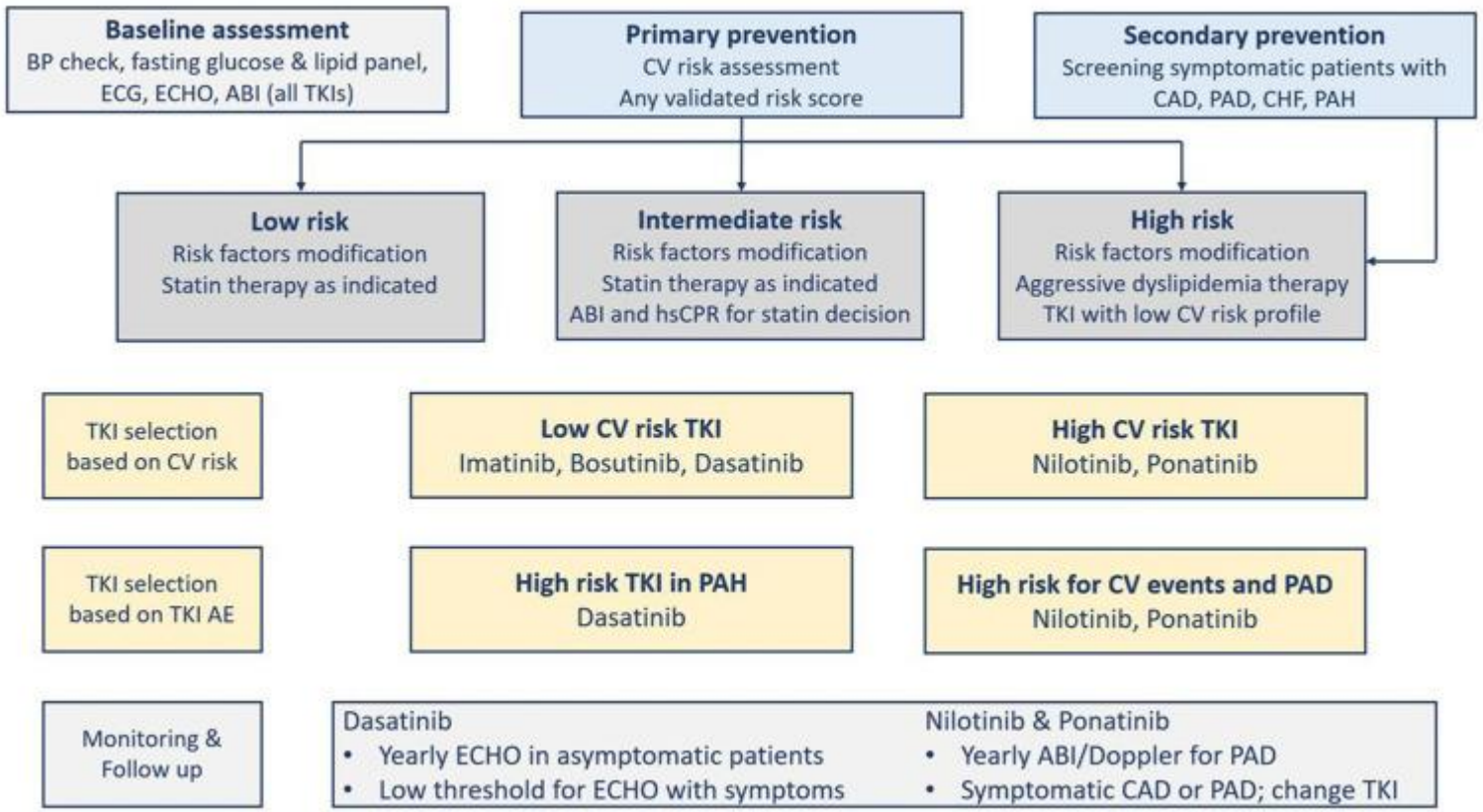

ABI, Ankle-brachial index; AE, Adverse Events; BP, blood pressure; CAD, coronary artery disease; CHF, congestive heart failure; CV, cardiovascular; ECG, electrocardiogram; ECHO, echocardiography; PAD, Peripheral arterial disease; PAH, pulmonary arterial hypertension; TKI, tyrosine kinase inhibitor(s).

Kaddoura R, Dabdoob WA, Ahmed K, Yassin MA. A practical guide to managing cardiopulmonary toxicities of tyrosine kinase inhibitors in chronic myeloid leukemia. Front Med (Lausanne). 2023 May 5;10:1163137. doi: 10.3389/fmed.2023.1163137. PMID: 37358999; PMCID: PMC10286131.

Assessment of QTc prolongation before and during tyrosine kinase inhibitor therapy

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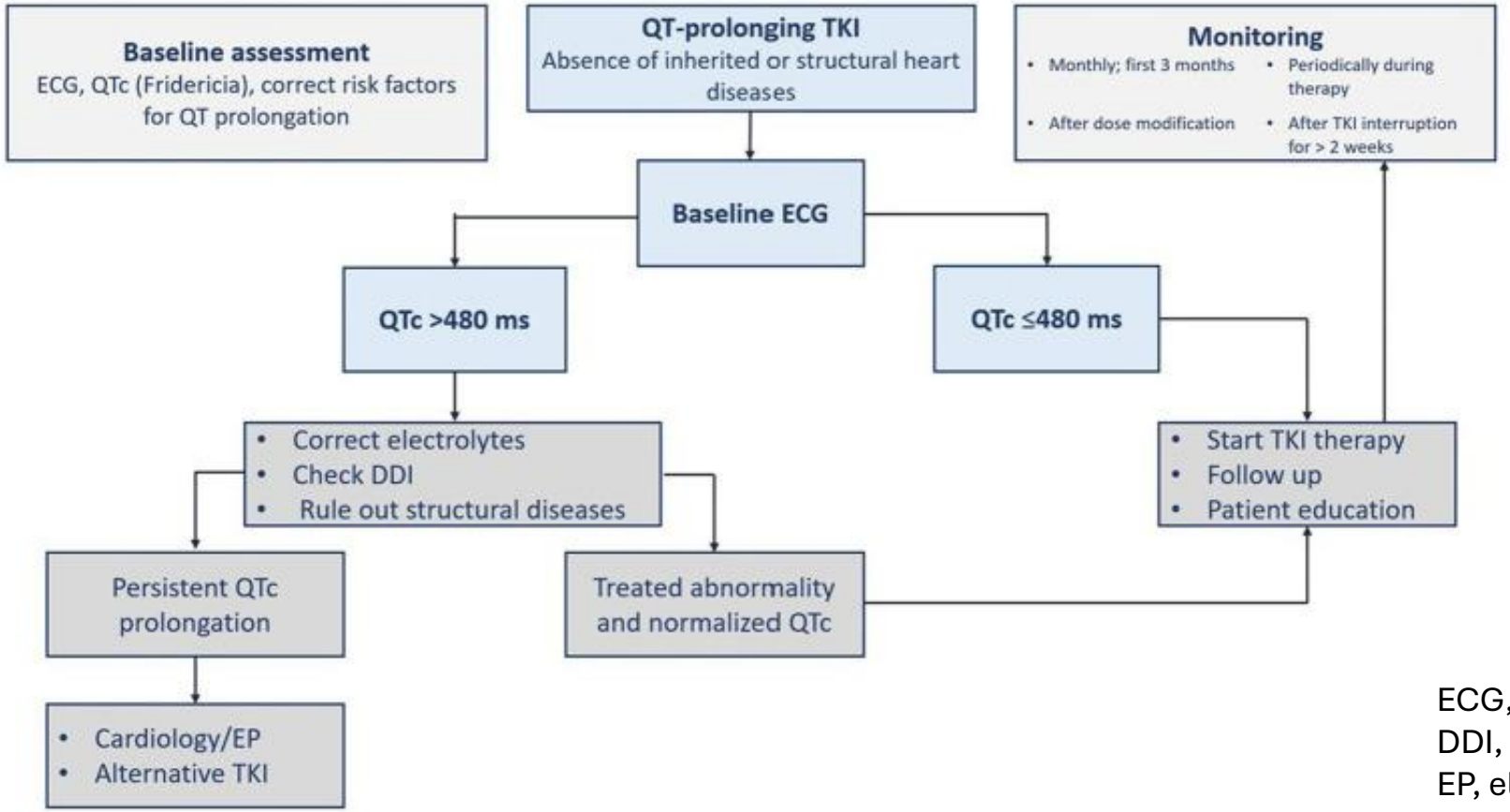

ECG, electrocardiogram;
DDI, drug-drug interaction;
EP, electrophysiology;
TKI, tyrosine kinase inhibitor(s);
QTc, corrected QT interval.

Kaddoura R, Dabdoob WA, Ahmed K, Yassin MA. A practical guide to managing cardiopulmonary toxicities of tyrosine kinase inhibitors in chronic myeloid leukemia. Front Med (Lausanne). 2023 May 5;10:1163137. doi: 10.3389/fmed.2023.1163137. PMID: 37358999; PMCID: PMC10286131.

Management of heart failure and fluid retention

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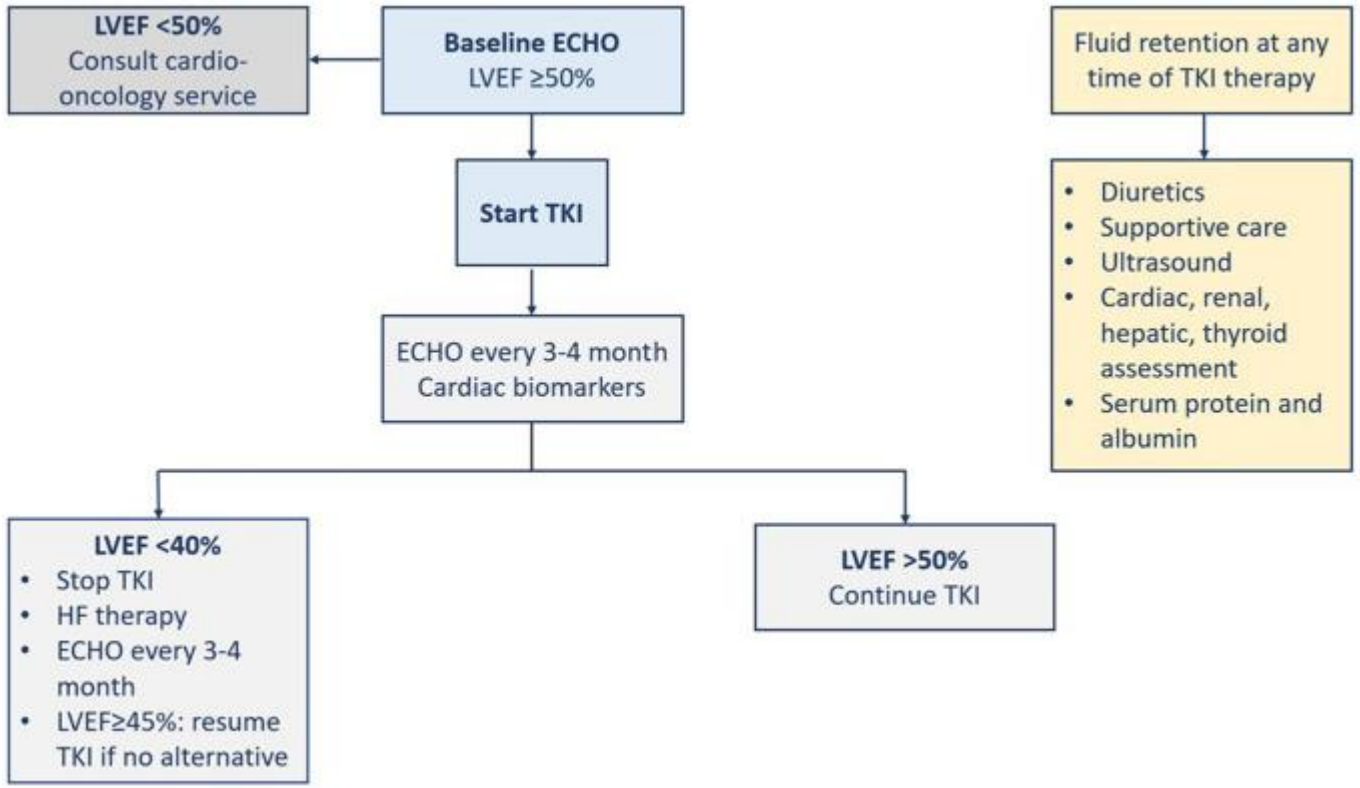

ECHO, echocardiography;
LVEF, left ventricular ejection fraction;
TKI, tyrosine kinase inhibitor.

Kaddoura R, Dabdoob WA, Ahmed K, Yassin MA. A practical guide to managing cardiopulmonary toxicities of tyrosine kinase inhibitors in chronic myeloid leukemia. Front Med (Lausanne). 2023 May 5;10:1163137. doi: 10.3389/fmed.2023.1163137. PMID: 37358999; PMCID: PMC10286131.

Management and monitoring of pleural effusion

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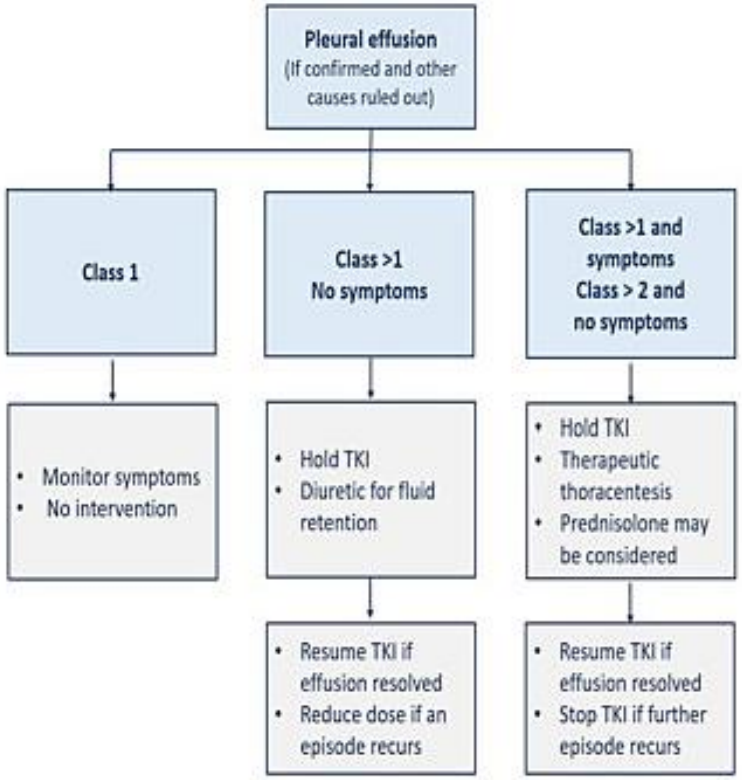

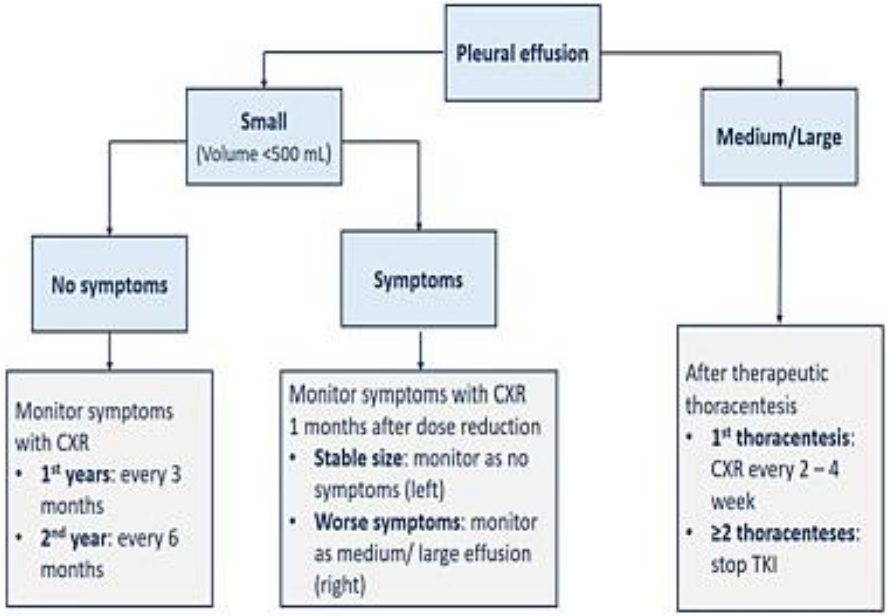

CXR, chest x-ray;
TKI, tyrosine kinase inhibitor

Kaddoura R, Dabdoob WA, Ahmed K, Yassin MA. A practical guide to managing cardiopulmonary toxicities of tyrosine kinase inhibitors in chronic myeloid leukemia. Front Med (Lausanne). 2023 May 5;10:1163137. doi: 10.3389/fmed.2023.1163137. PMID: 37358999; PMCID: PMC10286131.

Diagnosis and management of TKI-induced pulmonary artery hypertension

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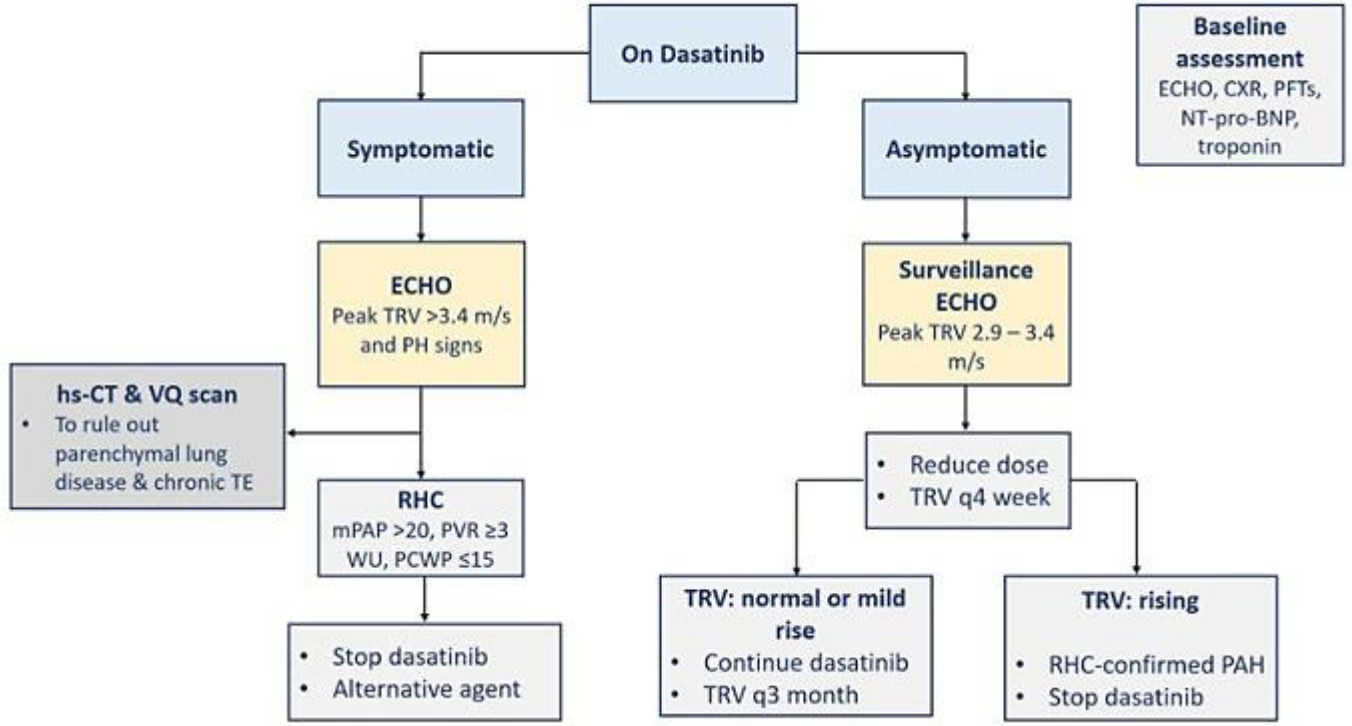

BNP, B-type natriuretic peptide;
CXR, chest x-ray;
ECHO, echocardiography;
hs-CT, high resolution computed tomography;
mPAP, mean pulmonary arterial pressure;
PAH, pulmonary arterial hypertension;
PCWP, pulmonary artery wedge pressure;
PFTs, pulmonary function tests;
PH, pulmonary hypertension;
PVR, pulmonary vascular resistance;
RHC, right heart catheterization;
TE, thromboembolism;
TKI, tyrosine kinase inhibitor;
TRV, tricuspid regurgitation velocity;
VQ, ventilation perfusion; WU, Wood units.

Kaddoura R, Dabdoob WA, Ahmed K, Yassin MA. A practical guide to managing cardiopulmonary toxicities of tyrosine kinase inhibitors in chronic myeloid leukemia. Front Med (Lausanne). 2023 May 5;10:1163137. doi: 10.3389/fmed.2023.1163137. PMID: 37358999; PMCID: PMC10286131.

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Cureus
Publishing Beyond Open Access

Cureus. 2022 Jun; 14(6): e25766.
Published online 2022 Jun 8. doi: 10.7759/cureus.25766
PMCID: PMC9270100
PMID: 35812557

A New Paradigm of Cardio-Hematological Monitoring in Chronic Myeloid Leukemia Patients Treated With Tyrosine Kinase Inhibitors

Monitoring Editor: Alexander Muacevic and John R Adler

Nataliia Lopina,[✉1] Iryna Dmytrenko,[2] Dmytro Hamov,[3] Dmytro Lopin,[4] and Iryna Dyagil[2]

▸ Author information ▸ Article notes ▸ Copyright and License information Disclaimer

Lopina N, Dmytrenko I, Hamov D, Lopin D, Dyagil I. A New Paradigm of Cardio-Hematological Monitoring in Chronic Myeloid Leukemia Patients Treated With Tyrosine Kinase Inhibitors. Cureus. 2022 Jun 8;14(6):e25766. doi: 10.7759/cureus.25766. PMID: 35812557; PMCID: PMC9270100.
Лопіна Н.А., Дягіль І.С., Дмитренко І.В., Гамов Д.С., Лопін Д.О. Нова парадигма кардіогематологічного моніторингу у хворих на хронічну мієлоїдну лейкемію, які приймають інгібітори тирозинкіназ
Український кардіологічний журнал, том 29, № 1–2, 2022, С. 72–86
DOI: http://doi.org/10.31928/1608-635X-2022.1-2.7286

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9270100/

Low cardiovascular risk

Low-risk cardiovascular toxicity TKIs: imatinib, bosutinib, dasatinib;

**High-risk cardiovascular toxicity TKIs: nilotinib, ponatinib

	Low-risk cardiovascular toxicity TKIs*	High-risk cardiovascular toxicity TKIs**
	Repeated risk stratification in a half of year	Repeated risk stratification in a half of year
	Lifestyle modification	Lifestyle modification
	Diet	Diet
	Physical activity	Physical activity
	Blood pressure control and treatment if needed	Blood pressure control and treatment if needed
	TKI treatment adverse effects monitoring	TKI treatment adverse effects monitoring
		Low doses of statin (target LDL-cholesterol level less than 3.0 mmol/L)
	Lifestyle modification	Lifestyle modification
	Diet	Diet
	Physical activity	Physical activity
	Blood pressure control and treatment if needed	Blood pressure control and treatment if needed

Lopina N, Dmytrenko I, Hamov D, Lopin D, Dyagil I. A New Paradigm of Cardio-Hematological Monitoring in Chronic Myeloid Leukemia Patients Treated With Tyrosine Kinase Inhibitors. Cureus. 2022 Jun 8;14(6):e25766. doi: 10.7759/cureus.25766. PMID: 35812557; PMCID: PMC9270100.

	Low-risk cardiovascular toxicity TKIs*	High-risk cardiovascular toxicity TKIs**
Moderate cardiovascular risk	Repeated risk stratification in a half of year	Repeated risk stratification in a half of year
	Lifestyle modification	Lifestyle modification
	Diet	Diet
	Physical activity	Physical activity
	Blood pressure control and treatment if needed	Blood pressure control and treatment if needed
	TKI treatment adverse effects monitoring	TKI treatment adverse effects monitoring
	Statin (target LDL-cholesterol level less than 2.6 mmol/L)	Statin (target LDL-cholesterol level less than 2.6 mmol/L)

Lopina N, Dmytrenko I, Hamov D, Lopin D, Dyagil I. A New Paradigm of Cardio-Hematological Monitoring in Chronic Myeloid Leukemia Patients Treated With Tyrosine Kinase Inhibitors. Cureus. 2022 Jun 8;14(6):e25766. doi: 10.7759/cureus.25766. PMID: 35812557; PMCID: PMC9270100.

High cardiovascular risk

	Low-risk cardiovascular toxicity TKIs*	High-risk cardiovascular toxicity TKIs**
	Repeated risk stratification in a half of year	Repeated risk stratification in a half of year
	Lifestyle modification	Lifestyle modification
	Diet	Diet
	Physical activity	Physical activity
	Blood pressure control and treatment if needed	Blood pressure control and treatment if needed
	TKI treatment adverse effects monitoring	TKI treatment adverse effects monitoring
	High-intensity statin therapy or hypolipidemic combination (target LDL-cholesterol level less than 1.8 mmol/L)	High-intensity statin therapy or hypolipidemic combination (target LDL-cholesterol level less than 1.8 mmol/L)

Lopina N, Dmytrenko I, Hamov D, Lopin D, Dyagil I. A New Paradigm of Cardio-Hematological Monitoring in Chronic Myeloid Leukemia Patients Treated With Tyrosine Kinase Inhibitors. Cureus. 2022 Jun 8;14(6):e25766. doi: 10.7759/cureus.25766. PMID: 35812557; PMCID: PMC9270100.

Very cardiovascular high risk

	Low-risk cardiovascular toxicity TKIs*	High-risk cardiovascular toxicity TKIs**
	Lifestyle modification	Lifestyle modification
	Diet	Diet
	Physical activity	Physical activity
	Blood pressure control and treatment if needed	Blood pressure control and treatment if needed
	TKI treatment adverse effects monitoring	TKI treatment adverse effects monitoring
	High-intensity statin therapy or hypolipidemic combination (target LDL-cholesterol level less than 1.4 mmol/L)	High-intensity statin therapy or hypolipidemic combination (target LDL-cholesterol level less than 1.4 mmol/L)

Lopina N, Dmytrenko I, Hamov D, Lopin D, Dyagil I. A New Paradigm of Cardio-Hematological Monitoring in Chronic Myeloid Leukemia Patients Treated With Tyrosine Kinase Inhibitors. Cureus. 2022 Jun 8;14(6):e25766. doi: 10.7759/cureus.25766. PMID: 35812557; PMCID: PMC9270100.

What should be done to reduce cardiovascular risk in patients with CML taking tyrosine kinase inhibitors?

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- ✓ **Baseline Assessment of Cardiovascular Disease Risk Factors**
- ✓ **Basic Assessment of the Cardiovascular System's State**
- ✓ **Individual Approach: Patient risk stratification and selection of a personalized prevention strategy to reduce cardiovascular risk.**
- ✓ **Adherence to ABCDE Guidelines: Patients should follow the ABCDE guidelines for cardiovascular health.**
- ✓ **Regular Cardiovascular Monitoring**

Strategy for Reducing Cardiovascular Risk in Patients with CML

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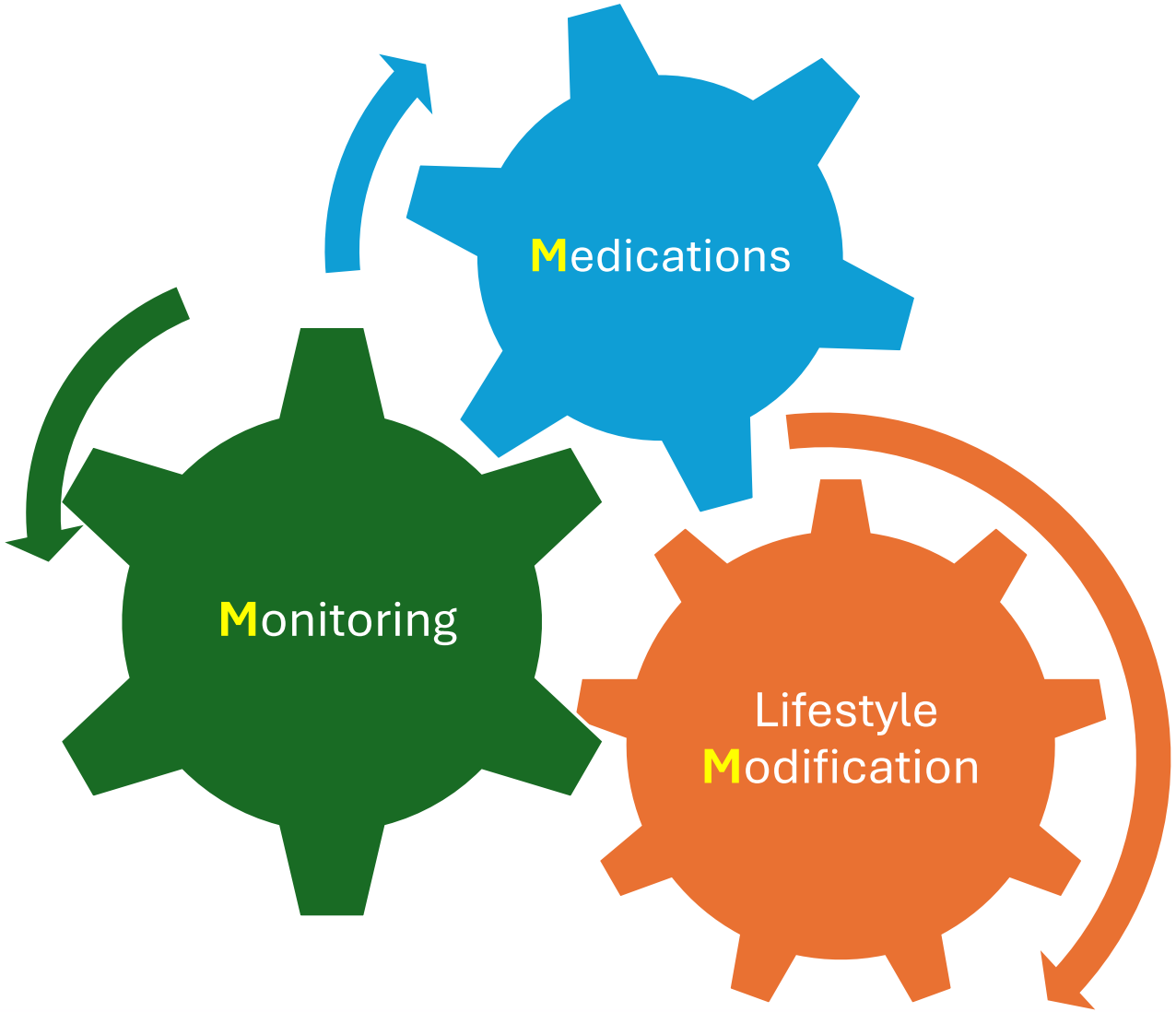

Unresolved issues in clinical guidelines devoted to cardiovascular prevention

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- target levels of LDL-cholesterol in patients with CML and the comparability of target levels for CML patients with the general population or the necessity to achieve LDL-cholesterol levels following the recommendations for people at high and very high cardiovascular risk for all CML patients, especially who are treated with high CV toxicity TKIs;
- which statin is more recommended in the CML patient population;
- should statins be prescribed to CML patients with low and moderate cardiovascular risk as adjunctive therapy to accelerate the achievement of a deep molecular response?
- should statins be prescribed to patients receiving TKIs of low and moderate cardiovascular toxicity and at low and moderate cardiovascular risk;
- who should prescribe and monitor the therapy (hematologists, cardiologists, or family physicians);
- how the cardio-hematological team of specialists should be formed.

Lopina N, Dmytrenko I, Hamov D, Lopin D, Dyagil I. A New Paradigm of Cardio-Hematological Monitoring in Chronic Myeloid Leukemia Patients Treated With Tyrosine Kinase Inhibitors. Cureus. 2022 Jun 8;14(6):e25766. doi: 10.7759/cureus.25766. PMID: 35812557; PMCID: PMC9270100.

Cardio-hematological monitoring is the basis of success in the treatment strategy for patients with CML

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Thank you for your attention!

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