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Review Article

Cardiovascular Risk Management Recommendations for Patients with Chronic Myeloid Leukaemia who are Candidates for Ponatinib: Multidisciplinary Delphi Analysis

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Abstract

Progress in the treatment of Chronic Myeloid Leukaemia (CML) has significantly improved the survival rates and prognosis of these patients. As a result, there is a growing awareness of the adverse effects that the treatments used can have on the Cardiovascular (CV) system. A high percentage of patients develop sequential resistance to CML treatments and, in these cases, ponatinib represents a good therapeutic option that has been associated with cardiovascular events. This required the development of recommendations for its management.

A Delphi analysis conducted by a multidisciplinary panel of experts developed and agreed on clinical practice recommendations to optimize cardiovascular risk control in CML patients requiring ponatinib treatment.

Keywords: Chronic myeloid leukaemia; Ponatinib; Recommendations; Cardiovascular risk; Delphi analysis; Multidisciplinary panel

Abbreviations

3D: 3-Dimensional; ASA: Acetylsalicylic Acid; DOACs: Direct-Acting Oral Anticoagulants; CVA: Cerebrovascular Accident; TIA: Transient Ischaemic Attack; ARA-II: Angiotensin II Receptor Antagonists; anti-Xa: Anti-Activated Factor X; GLP-1 RA: GLP-1 Receptor Agonist; VKA: Vitamin K Antagonist; BCG: Bacillus Calmette-Guérin; BCRP: Breast Cancer Resistance Protein; BNP: Brain or B-type Natriuretic Peptide; CHA2DS2-VASc: Ischaemic Stroke Risk Assessment Scale; HDL-c: High Density Lipoprotein Cholesterol; LDL-c: Low Density Lipoprotein Cholesterol; CTRCD: Cancer Therapy-Related Cardiac Dysfunction; CV: Cardiovascular; CVRFs: Cardiovascular Risk Factors; SD: Standard Deviation; DM: Diabetes Mellitus; PAD: Peripheral Arterial Disease; ECG: Electrocardiogram; CVD: Cardiovascular Disease; ELN: European LeukaemiaNet; VTD: Venous Thromboembolic Disease; AF: Atrial Fibrillation; LVEF: Left Ventricular Ejection Fraction; FGFR: Fibroblastic Growth Factor Receptor; GELMC: Spanish Chronic

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Myeloid Leukaemia Group; GLS: Global Longitudinal Strain; HAS-BLED: Bleeding Risk Assessment Scale; HbA1c: Glycosylated Haemoglobin; LMWH: Low Molecular Weight Heparin; AHT: Arterial Hypertension; AMI: Acute Myocardial Infarction; CHF: Congestive Heart Failure; ACEI: Angiotensin-Converting Enzyme Inhibitor; BMI: Body Mass Index; INR: International Normalised Ratio; SGLT-2i: Sodium-Glucose Co-Transporter Type 2 Inhibitor; ABI: Ankle-Brachial Index; TKI: Tyrosine Kinase Inhibitor; CML: Chronic Myeloid Leukaemia; CP-CML: Chronic Phase Chronic Myeloid Leukaemia; NSTEMI: Non-ST Segment Elevation Myocardial Infarction; NT-proBNP: N-terminal pro-brain or B-type Natriuretic Peptide; BP: Blood Pressure; PDGFR: Platelet-Derived Growth Factor Receptor; Pgp: Permeability Glycoprotein; QTc: Corrected QT Interval; CCyR: Complete Cytogenetic Response; MCyR: Major Cytogenetic Response; CVR: Cardiovascular Risk; MMR: Major Molecular Response; RR: Relative Risk; STEMI: ST Elevation Myocardial Infarction; PTE: Pulmonary Thromboembolism; VTE: Venous Thromboembolism; TTE: Transthoracic Echocardiography; DVT: Deep Vein Thrombosis; VEGFR1-3: Vascular Endothelial Growth Factor Receptor

Introduction

The introduction of Tyrosine Kinase Inhibitors (TKIs) targeting the bcr-abl oncoprotein has revolutionized the management of patients with CML. Treatment with imatinib, the first BCR-ABL inhibitor, takes the 10-year survival rate to over 80%, significantly approaching that of the general population. However, the need for continued treatment and the adverse effects associated with the use of TKIs have a significant impact on patient quality of life and health systems [1]. Despite the significant therapeutic advancement provided by imatinib [1,2], a substantial proportion of patients develop resistance or intolerance to imatinib [3] and new TKIs are needed to maintain the therapeutic response [4-8]. New generations of TKIs are associated with an increased risk of cardiovascular complications and require the involvement of multidisciplinary cardio-onco-hematology teams for their early prevention and control [9-12].

Ponatinib is a third generation TKI specifically designed to overcome resistance to other TKIs and is the only one approved with clinical activity against the T315I mutation [13]. The use of ponatinib may be associated with an increased risk of cardiovascular complications, so it is essential to establish prevention strategies and specific management recommendations in patients who are candidates for ponatinib, in order to maximise its therapeutic benefits.

Objectives

The aim of the study was to obtain feedback from members of a multidisciplinary panel of experts on best clinical practices to reduce the risk of cardiovascular events and inappropriate treatment interruptions in patients with CML treated with ponatinib.

Participants and Methodology

This project was carried out by a multidisciplinary panel composed of three coordinators and ten specialist practitioners, using Delphi methodology. Appendix I describe the project phases, the methodology used and the characteristics of the participants.

Results

Section 1: Correlation between clinical trial data and actual practice

The difference between CV events in patients in the PACE study [14] and clinical practice records [15-18] was analyzed. Overall, clinical practice records appear to reflect a lower prevalence of adverse CV events of different grades, which appears to be associated with both younger ages and the more frequent use of ponatinib doses below 45mg. An important conclusion from clinical practice records is that the incidence of Cardiovascular Disease (CVD) increases with a longer follow-up period and in patients who have previously received more than two TKIs [15,18].

Section 2: Medical history and initial clinical evaluation

Initial assessment of the patient with CML makes it possible to establish an adequate CV monitoring and prevention protocol [20,21]. The main points that must be included in the initial medical history and physical examination are summarized in Table 1.

According to the latest recommendations issued by Spanish Chronic Myeloid Leukaemia Group, a multidisciplinary follow-up of patients treated with TKIs makes it possible to optimize prevention strategies. Baseline assessment helps stratify the risk of complications into low, intermediate, high or very high and establish patient-specific management indications [25,26]. In this multidisciplinary team it is essential to have the collaboration of specialists in hematology, cardiology, primary care, cardiovascular risk and clinical pharmacology [27].

Based on the available evidence, the panel makes the recommendations listed in Table 2.

Table 1: Necessary parameters in the patient's medical history and initial physical examination.

Medical history	Chronic illness: DM, AHT, dyslipidaemia [20,21].
	Personal and family history of previous CV diseases [20,21].
	Unhealthy habits: smoking, alcohol, diet, physical activity [20,21].
	Chronic treatments: due to interactions with TKIs [22].
	Haemato-oncological history and treatments received [23].
Physical examination	Height, weight and BMI [24].
	Blood pressure and heart rate [24]
	Determination of ABI [24].
	Cardiopulmonary auscultation [24].
	Peripheral pulses [24].

DM: Diabetes Mellitus; AHT: Arterial Hypertension; BMI: Body Mass Index; ABI: Ankle-Brachial Index.

Table 2: Consensus recommendations for the medical history and initial evaluation of patients who are candidates for ponatinib.

Recommendation	Level of consensus	Level of agreement*
The medical history of patients who are candidates for ponatinib must include the presence of chronic diseases, a personal and family history of cardiovascular disease, unhealthy habits and chronic treatments, in order to discuss possible interactions with ponatinib.	Consensus	Agreement
The essential physical examination must include height, weight, BMI, and cardiopulmonary auscultation.	Consensus	Agreement
The initial patient evaluation must be multidisciplinary, involving the haematologist, the cardiovascular specialist, the hospital pharmacist and the family doctor.	Consensus	Agreement
At the initial patient assessment, the haematologist must be responsible for collecting information from other practitioners and for choosing the most appropriate TKI.	Consensus	Agreement
At the initial patient assessment, the vascular specialist must be responsible for the initial risk assessement.	Consensus	Agreement
In the initial patient assessment, the pharmacist must be responsible for monitoring potential interactions.	No consensus**	Agreement
In the initial patient assessment the family practitioner must be involved because of his/her importance as a more patient accessible practitioner.	Consensus	Agreement
Patients with a history of CV disease, uncontrolled risk factors, or a lower than normal ejection fraction are considered high risk and require cardio-oncology management and follow-up.	Consensus	Agreement

*Based on a Likert scale assessment: disagreement 1 to 3, neither disagreement nor agreement 4 to 6 and agreement 7 to 9. **There is consensus that the panelists disagree.

Table 3: Laboratory and imaging tests recommended in the literature regarding patients who are candidates for TKIs at the initial assessment.

		Recommended in clinical practice	Recommended in selected cases
Laboratory tests	Creatinine and eGFR.	X	
	Blood glucose and HbA_{1c}: [20,28,29].	X	
	Lipid panel (total cholesterol, triglycerides, HDL-c, LDL-c: [9].	X	
	Blood count and clotting tests: [9].	X	
	Determination of electrolytes, liver and pancreatic enzymes [9].	X	
	Determination of BNP: suspected congestive heart failure.		X
Additional tests	Chest X-ray: [2,28,29].		X
	ECG with determination of the QT interval: [27,28].		X
	Baseline echocardiogram: [20,28,29].		X
	ABI: [9,20.27,28].	X	
	Carotid Doppler [23].	X	

BNP: Brain or B-type Natriuretic Peptide; HDL-c: High Density Lipoprotein Cholesterol; LDL-c: Low Density Lipoprotein Cholesterol; ECG: Electrocardiogram.

Table 4: Consensus recommendations on laboratory and imaging tests to be performed on patients who are candidates for ponatinib and for its follow-up.

Recommendation	Level of consensus	Level of agreement*
For patients who are candidates for ponatinib, initial analytical monitoring should include blood count, clotting, liver and pancreatic enzymes, renal function monitoring (creatinine and eGFR), glucose metabolism (glycaemia and HbA_{1c}), electrolytes and cholesterol metabolism (triglycerides, total cholesterol and HDL-c/LDL-c). In addition, BNP/pro-BNP levels will be determined for their prognostic value for congestive heart failure.	Consensus	Agreement
For patients who are candidates for ponatinib, blood pressure levels must first be determined and an ABI, ECG (with determination of the Fridericia QTc interval), echocardiogram and chest X-ray must be performed.	Consensus	Agreement
For moderate, high and very high risk patients** carotid Doppler ultrasound is also recommended and, in moderate CV risk patients, the measurement of coronary Calcium.	Consensus	Agreement
During the follow-up of patients receiving ponatinib, blood pressure and cardiovascular risk monitoring is recommended on a weekly basis during the first month, monthly during the first quarter and quarterly thereafter.	Consensus	Agreement
During the follow-up of patients receiving ponatinib, monitoring of glucose and lipid metabolism and determination of ABI every 3, 6 and 12 months is recommended, reserving echocardiography according to clinical indication.	Consensus	Agreement

*Based on Likert scale assessment: disagreement 1 to 3, neither disagreement nor agreement 4 to 6 and agreement 7 to 9. **See definition of risk in Block 4. QTc: Corrected QT.

Section 3: Laboratory and imaging tests

There is not yet any evidence as to which tests need to be performed in normal clinical practice, since there are no clinical trials that have specifically evaluated this; so the suggestions collected are based on a compilation of retrospective analyses and expert recommendations (Table 3).

With regard to the frequency of the aforementioned tests, a monthly evaluation of Blood Presure (BP) and Cardiovascular Risk (CVR) with an evaluation of glucose and lipid metabolism [28,29] is recommended, in addition to a quarterly evaluation of glucose and lipid metabolism and ABI, and a chest X-ray and ECG if necessary [20,28,29].

Based on the available evidence, the panel makes the recommendations included in Table 4.

Section 4: CVR evaluation and prophylaxis strategies

While there are no validated specific prospective scales to estimate CVD risk in patients with CML who are candidates for ponatinib, the use of available scales makes it possible to optimize control objectives

Table 5: Cardiovascular risk stratification groups established by SCORE.

Risk	Interpretation
Very high	Documented CVD: AMI, ACS, angina, stroke or TIA, peripheral arterial disease, coronary or arterial revascularization.
	DM with target organ damage (e.g. proteinuria), DM with 3 or more associated major CVRFs (smoking, dyslipidaemia and hypertension), or type 1 DM of more than 20 years' duration.
	Stage IV CKD (eGFR< 30mL/min/1.73 m^2).
	SCORE calculated ≥10%.
	Family history of hypercholesterolemia with CVD or 1 major associated CVRF.
High	Very high major CVRF (i.e. marked dyslipidaemia (Total Col >300, LDL >190) or severe hypertension (180/110 mmHg)).
	DM with a major CVRF or of longer than 10 years.
	CKD stage III (eGFR 30–59 mL/min/1.73 m^2).
	SCORE calculated ≥5% and <10%.
	Family history of hypercholesterolemia without CVD or CVRF.
Moderate	SCORE calculated ≥1% and <5%.
Low	SCORE <1%.

TIA: Transient Ischaemic Attack; CVRFs: Cardiovascular Risk Factors.

Table 6: Consensus recommendations for the evaluation of CVR and prophylaxis strategies in the candidate patient for ponatinib or in its follow-up.

Recommendation	Level of consensus	Level of agreement*
Cardiovascular risk must be quantified with SCORE tables in all ponatinib candidates and vascular disease must be actively ruled out.	Consensus	Agreement
High risk patients are those with SCORE >5% or ≥65 years, with DM, moderate or severe chronic kidney disease and/or previous clinical or subclinical cardiovascular disease.	Consensus	Agreement
The administration of ASA 100 mg/day as a primary prophylaxis in low cardiovascular risk patients treated with ponatinib is not recommended as there is no evidence of benefit in this scenario.	Consensus	Agreement

*Based on a Likert scale assessment: disagreement 1 to 3, neither disagreement nor agreement 4 to 6 and agreement 7 to 9.

and to standardize clinical practice in this patient profile.

Specifically, SCORE risk tables make it possible to estimate the risk of cardiovascular mortality at 10 years in patients without known cardiovascular disease, based on various risk factors: age, sex, systolic blood pressure, smoking and total cholesterol [23] (Table 5).

It should be noted that in a small registry (n=85) patient with CML and a SCORE >5% have been observed to be at increased risk of occlusive arterial events during ponatinib treatment [19]. Likewise, real-life studies with ponatinib have shown that patients most likely to develop treatment-derived CV complications are those ≥65 years of age (relative risk (RR): 1.8) and with a history of AHT (RR: 3.2), DM (RR: 2.5) or ischaemic heart disease (RR: 2,6) [30,31], so during treatment these factors must be closely monitored for adequate CVR assessment.

With regard to the prevention of cardiovascular toxicity due to ponatinib, there are currently no published clinical trials supporting the use of any drug as a prophylactic strategy. In the general population without clinical or subclinical cardiovascular disease, the use of Acetylsalicylic Acid (ASA) has not shown any benefit in primary prevention but an increased risk of bleeding [32], although the proportion of patients with CML without prior cardiovascular disease has been shown to be low in patients who are candidates for ponatinib [16]. There is also no data from clinical trials on the control of risk factors during prospective follow-up of the treatment, so the premise that strict control of CVR and adherence to clinical practice guidelines on the management of different heart diseases improves the overall prognosis of patients [33] is extended to patients who are candidates for ponatinib.

Based on the available evidence, the panel makes the recommendations included in Table 6.

Section 5: Cardiovascular therapeutic goals in ponatinib candidates

In general, optimising the control of possible cardiovascular comorbidities must be adapted to clinical practice guidelines, favouring the use of drugs with a better CVR reduction profile.

Regarding AHT control, the latest update of the European guidelines recommends treating patients with BP levels >140/90 mmHg regardless of their cardiovascular risk. Thus, the objective to be achieved will be the reduction of BP <140/90 mmHg for all patients and, if treatment is well tolerated, ≤BP 130/80 mmHg values for the majority of patients [34]. Treatment must be based on lifestyle interventions and pharmacological treatment, and the initiation of treatment with angiotensin-converting enzyme inhibitor/ angiotensin II receptor antagonists (ACEI/ARA-II) and dihydropyridine calcium channel blockers is recommended [35].

Cholesterol target values vary depending on the CVR (Table 7), LDL-c control being the primary objective [36]. Pharmacological guidelines will be the same as in the general population, paying

Table 7: LDL control targets in patients who are candidates for TKIs.

Risk	Lipid Control Objectives (LDL)
Very high risk	<55mg/dL and ↓ 50% from baseline
High Risk	<70mg/dL and ↓ 50% from baseline
Moderate risk	<100mg/dL
Low risk	<116mg/dL

Table 8: Consensus recommendations for the cardiovascular therapeutic objectives in patients who are candidates for ponatinib or for its follow-up.

Recommendation	Level of consensus	Level of agreement
It is recommended that treatment be given to all patients with BP values >140/90mmHg, regardless of their cardiovascular risk, establishing as the first objective of pharmacological treatment the achievement of BP values <140/90mmHg without producing hypotension.	Consensus	Agreement
Antihypertensive treatment must be based on lifestyle interventions and pharmacological treatment, it being advisable to initiate treatment with ACEI/ARA-II and dihydropyridine calcium channel blockers.	Consensus	Agreement
Target cholesterol values vary depending on the patient's cardiovascular risk, (Table 7).	Consensus	Agreement
With regard to lipid-lowering treatment, the same guidelines must be followed as in the general population, taking special care with P450 CYP3A4 drug interactions and binding to Pgp and BCRP transport proteins, so the use of pitavastatin and ezetimibe is recommended due to their lower risk of interactions.	Consensus	Agreement
The overall glycaemic control target in ponatinib candidate patients is HbA_{1c} <7% and may be considered more strictly (HbA_{1c} <6.5%) in a selected population (short-duration or lifestyle treated DM or metformin only, long life expectancy or without significant cardiovascular disease) and less strict (HbA_{1c} <8%) in frail patients.	Consensus	Agreement
A patient-centered approach must be taken to guide the choice of pharmacological agents, the use of SGLT-2i or GLP-1 RA being recommended in patients with DM2 and established cardiovascular disease, due to their demonstrated benefit on cardiovascular function.	Consensus	Agreement

*Based on a Likert scale assessment: disagreement 1 to 3, neither disagreement nor agreement 4 to 6 and agreement 7 to 9.

Table 9: VTD treatment strategies recommended in cancer patients.

Full dose LMWH*	Duration of treatment (long-term treatment phase): LMWH minimum 3 months (6 months desirable for cancer), after which the possibility of extended treatment will be assessed.
	Individualize discontinuation of treatment: maintain LMWH until completion of curative treatment or as long as risk factors for VTD recurrence persist.
	If there is a recurrence of VTD with LMWH: increase the dose and optimize anti-Xa control. Consider an inferior vena cava filter for pulmonary embolism.

*If the patient has platelet levels >50,000 platelets/mm^3, as they have fewer thrombotic relapse rates than vitamin K antagonists. Anti-Xa: Anti-Activated Factor X

Table 10: Consensus recommendations for the prevention of VTD in candidate patients for ponatinib or in its follow-up.

Recommendation	Level of consensus	Level of agreement
Routine prophylaxis with anticoagulant therapy is not recommended in patients treated with ponatinib with no other prothrombotic risk factors susceptible to prophylaxis for associated VTD.	Consensus	Agreement
In case of elective surgery ponatinib should be suspended 7 days before surgery and resumed when no bleeding risk is envisaged (approximately 1-3 days).	Consensus	Agreement
Ponatinib must be suspended in patients with venous thromboembolism until resolution of the event, avoiding the administration of vitamin K antagonists due to the increased risk of interactions, and preferably considering the use of low-molecular-weight heparins or direct-acting oral anticoagulants (rivaroxaban and edoxaban).	Consensus	Agreement
The concomitant use of ASA in patients who are candidates for surgery must be assessed; therefore, in those patients at low/moderate risk, interruption is recommended and ASA must be restricted in high-risk patients to a maximum dose of 100mg/day.	Consensus	Agreement
It is recommended that all patients being considered for ponatinib treatment be assessed by an angiologist/vascular surgeon and an (onco) cardiologist prior to initiation of the treatment.	Consensus	Agreement
During the subsequent follow-up of patients who have previously presented with VTD, it is recommended that limb Doppler scans be performed.	No consensus**	Agreement
During the subsequent follow-up of patients who have previously had VTD, it is recommended that D-dimer levels be determined at the end of treatment to assess the possible risk of recurrence.	No consensus†	Indeterminate

*Based on a Likert scale assessment: disagreement 1 to 3, neither disagreement nor agreement 4 to 6 and agreement 7 to 9. **There is consensus that the panelists disagree. †There was no majority in agreement or disagreement.

particular attention to interactions due to P450 CYP3A4 and binding to Permeability glycoprotein (Pgp) and Breast Cancer Resistance Protein (BCRP) transport proteins [37].

The ADA/EASD consensus advocates an HbA1c target ≤7% except in frail patients or patients with multiple comorbidities where targets may be more lenient (8%) [38]. A patient-centred approach must be employed to guide the choice of pharmacological agents, prioritising the use of Sodium-Glucose Co-Transporter Type 2 inhibitor (SGLT-2) inhibitors or GLP-1 receptor agonist (GLP-1 RA); for patients with established CVD, given their demonstrated cardiovascular benefit [39].

Based on the available evidence, the panel makes the recommendations included in Table 8.

Section 6: Multidisciplinary approach and collaboration with other specialties

Clinical trials with ponatinib followed up over two years have shown a 6% incidence of venous thromboembolic disease (VTD), possibly related to the potent inhibition of tyrosine kinases and vascular endothelial growth factor receptor (VEGFR1-3), fibroblastic growth factor receptor (FGFR) and platelet-derived growth factor receptor (PDGFR) receptors [29], leading to the definition of specific recommendations in this regard in the Summary of Product Characteristics [13].

Regarding the risk of VTD, ponatinib has not been shown to be a risk factor per se and therefore the routine use of antithrombotic prophylaxis is not recommended [40]. However, the association with another risk factor (e.g. hereditary predisposition, comorbidity associated with the tumour process, treatment with immunomodulators, etc.) will make it necessary to consider the benefit/risk ratio of this strategy, following the same guidelines as for any cancer patient [27].

Treatment of any VTD arising during treatment with ponatinib must be associated with an assessment of the possible discontinuation of treatment or dose optimisation to minimise vascular toxicity without compromising efficacy [20,29], as the cardiovascular toxicity of ponatinib has been shown to be dose-dependent [13]. In the event of the onset of VTD during treatment, it is recommended that ponatinib be suspended until resolution of the event and that the indications in Table 9 [27] be followed, prioritising the use of Low Molecular

Table 11: Recommended function monitoring tests.

Laboratory tests	Elevation of BNP may indicate latent cardiac dysfunction, so baseline determination and repeat testing during treatment is recommended [17].
	The role of troponin is not well established, and is not therefore recommended as a routine test [20].
Laboratory tests	A baseline echocardiogram is recommended, and quantification of 3D LVEF whenever this is available. If the LVEF at follow-up falls more than 10% below baseline and below normal values, the study will need to be repeated in 2-3 weeks and, if this is confirmed, the patient must be referred to cardio-oncology [11].
	Left ventricular GLS is a more sensitive and reproducible marker than LVEF for subclinical changes in left ventricular function, so it can be useful in anticipating dysfunction.
	If GLS decreases without changes in the LVEF, it is recommended that the study be repeated at 2-3 weeks [11].
	The use of MRI is only recommended if there is uncertainty in the echocardiographic examination [11].

3D: 3-Dimensional; LVEF: Left Ventricular Ejection Fraction; GLS: Global Longitudinal Strain.

Table 12: Consensus recommendations for the management of pre-existing and emerging cardiovascular problems in patients who are candidates for ponatinib or in its follow-up.

Recommendation	Level of consensus	Level of agreement*
In patients with cardiac dysfunction it is not routinely recommended to perform troponin determination, as its role is not well established in this context.	No consensus	Agreement
Baseline echocardiogram is recommended in all patients. Echocardiogram follow-up at 3 months in high-risk patients and annual follow-up in all patients. If LVEF is below normal, even if the patient is asymptomatic, he/she must be referred to cardio-oncology and heart failure treatment must be initiated. The decision to interrupt ponatinib in the event of a reduction of LVEF must be ndividualised.	Consensus	Agreement
Magnetic resonance imaging is recommended for cardiac function assessment in patients not diagnosed with echocardiography (poor ultrasonic window or clinically inconsistent data).	Consensus	Agreement
The treatment of a patient who develops systolic dysfunction following ponatinib treatment must include the treatment of systolic heart failure, i.e. the administration of ACEI/ARA-II and beta-blockers as soon as practicable. If the patient develops decompensated heart failure, intravenous diuretic therapy (usually furosemide) to control symptoms and acute phase treatment must be initiated, resuming basic treatment as soon as possible.	Consensus	Agreement
In the patient with atrial fibrillation it is recommended that the same risk scores as in the general population be used, i.e. anticoagulate if patients have CHA2DS2-VASc≥1 and consider high bleeding risk if HAS-BLED ≥3.	Consensus	Agreement
Given the risk of thrombocytopenia in cancer patients, anticoagulation is not recommended in patients with less than 50,000 platelets, despite being indicated by CHA2DS2-VASc.	Consensus	Agreement
In patients with atrial fibrillation it is recommended that the same antithrombotic treatment as before be continued; if INR control is difficult or the patient experiences embolic or bleeding events, it is recommended that direct-acting oral anticoagulants be initiated.	Consensus	Agreement
In patients with a history of STEMI, NSTEMI, coronary revascularisation surgery or an ischaemic cerebrovascular event, secondary prophylaxis with antiplatelet agents is recommended in accordance with the recommendations in the available clinical guidelines.	Consensus	Agreement

*Based on Likert scale assessment: disagreement 1 to 3, neither disagreement nor agreement 4 to 6 and agreement 7 to 9. STEMI: ST Elevation Myocardial Infarction; NSTEMI: Non-ST Segment Elevation Myocardial Infarction.

Weight Heparin (LMWH) or Direct-Acting Oral Anticoagulants; (DOACs) over vitamin K antagonists.

Conversely, ponatinib has been shown to act as a platelet antagonist, inducing thrombocytopenia and platelet dysfunction [41]. In a series of 80 patients, an incidence of 11% of bleeding events was reported; however, none of them compromised safety; caution is recommended in the management of patients with antithrombotic therapy or observed thrombocytopenia [42]. Taking these data into account, the concomitant use of ASA should be carefully evaluated, as well as the ponatinib regimen in both elective and emergency surgery, with platelet transfusion being evaluated in the latter case.

Given its increased CVR compared with its analogues, the indication of ponatinib should result in referral to a specialist in Angiology and Vascular Surgery and a Cardiologist or Onco-Cardiologist prior to initiation of treatment. These specialists must perform an adequate assessment of the CVR associated with the drug, as well as its possible management during treatment [9], through an adequate baseline assessment, the establishment of thromboembolic prophylaxis in the indicated cases, treatment for primary prevention in cases of the concurrence of one or more CVRFs and secondary prevention in cases of diagnosis of CV disease and adequate long-term patient follow-up.

Based on the available evidence, the panel makes the recommendations included in Table 10.

Section 7: Management of pre-existing and emerging cardiovascular problems

CML and the Treatments Applied (TKIs) can affect cardiac function [43], so signs and symptoms of CV disease should be monitored and CVRFs actively sought, with a view to emphasising the importance of prevention. For this, in addition to the clinical interview, we have certain diagnostic tests that may be useful in the early identification of patients who will go on to develop cardiac dysfunction [11,20] (Table 11).

The approach with a patient who develops systolic dysfunction following ponatinib treatment is the treatment of systolic heart failure, i.e. initiating ACEI/ARA-II and beta-blockers as soon as possible, as well as the possible addition of potassium-sparing diuretics (e.g. eplerenone, spironolactone). If the patient develops decompensated heart failure, intravenous diuretic therapy should be initiated, resuming background therapy as soon as possible [11,27].

On the other hand, the European Cardio-Oncology guidelines indicate that the thrombotic-haemorrhagic risk balance could be modified in the presence of cancer [11]. However, at the moment there are no specific risk scales for cancer patients, so in practice the risk prediction scales CHA2DS2-VASc and HAS-BLED validated

Table 13: Determining factors in ponatinib dose choice.

Factors associated with a greater likelihood of response	Chronic phase of disease.
	Presence of T315I mutation.
Individual factors associated with increased CVR	Age > 60-65 years.
	History of arterial thrombosis (ischemic heart disease, cerebral vascular disease or peripheral vascular disease).
	Presence of CVRF (AHT, DM, dyslipidaemia, etc.).

Table 14: Consensus recommendations for dose adjustment of ponatinib as approved by regulatory agencies.

Recommendation	Level of consensus	Level of agreement*
When selecting the starting dose for ponatinib, it is necessary to take account of both factors related to an increased likelihood of response and the presence of patient risk factors associated with increased cardiovascular toxicity (e.g. AHT, dyslipidaemia).	Consensus	Agreement
To evaluate treatment response it is recommended that the ELN criteria defining response to second-line TKIs after failure with imatinib be applied; assessments will be performed at 3, 6 and 12 months after the initiation of treatment, bearing in mind that achieving a partial cytogenetic response may be a reasonable objective in some patients in whom there is no other therapeutic alternative.	Consensus	Agreement
In general terms, a dose reduction of 15 mg/day is recommended if an optimal response is obtained, with the aim of reducing cardiovascular toxicity without compromising efficacy; and dose maintenance in cases of concern or failure, if there has been no toxicity.	Consensus	Agreement
In the event of a serious cardiovascular event it is recommended that ponatinib treatment be discontinued indefinitely; however, in this context it is necessary to establish the concept of a serious event in terms of morbidity/mortality in order to adequately assess the drug's benefit/risk ratio.	Consensus	Agreement
In patients with previous vascular events it is necessary to consider the balance of the risk of both the new ischemic event and the mortality associated with the antileukaemic effect of ponatinib.	Consensus	Agreement
In patients who have had a TIA, ponatinib treatment would not be contraindicated.	Consensus	Agreement
In patients who have had ischaemic stroke, ponatinib treatment would be contraindicated.	Consensus	Agreement
In patients who have suffered from non-atherothrombotic AMI, ponatinib treatment would be contraindicated.	Consensus	Agreement
For patients with symptomatic peripheral arterial disease, ponatinib treatment would be contraindicated.	Consensus	Agreement
For patients with asymptomatic peripheral arterial disease, ponatinib treatment would not be contraindicated.	Consensus	Agreement

*Based on a Likert scale assessment: disagreement 1 to 3, neither disagreement nor agreement 4 to 6 and agreement 7 to 9.

for the general population are used [44]. Similarly, the European clinical practice guidelines for the management of Atrial Fibrillation (AF) make no distinction in patients with concomitant oncological pathology, applying the same criteria as in the general population for the use of antithrombotic treatment [45]. As to which anticoagulant drug should be used in patients with AF and CML treated with ponatinib, the recommendations are not yet clear. Vitamin K antagonists do not seem to be an appropriate option, due to a possible alteration of International Normalized Ratio (INR) by interaction with treatment, so the use of LMWH is more frequent. In this regard, it is worth mentioning that in normal practice the use of DOACs is increasing in the general population, although the pivotal trials for their approval have not included patients with these characteristics [46-49]. However, it should be noted that in this last year the first randomised studies in cancer patients have begun to emerge, which will provide new evidence in the choice of treatment.

Also, it should be noted that TKIs produce Peripheral Arterial Disease (PAD) in up to 30% of cases, so it is recommended that determination of ABI and the control of CVRFs at baseline be carried out in all patients, as well as anti-aggregation and revascularisation in symptomatic patients if indicated [20].

Based on the available evidence, the panel makes the recommendations included in Table 12.

Section 8: Dose adjustment as approved by regulatory agencies

In 81% of patients chronic phase CML (CP-CML) included in the PACE trial it was necessary to reduce the dose due to the appearance of toxicity, however, after the dose reduction 96% of patients maintained major cytogenetic response [14]. A predictive model that took into account the influence of dose on the occurrence of thrombotic events demonstrated that every 15 mg/day of ponatinib dose reduction resulted in a 33% decrease in the risk of an arterial occlusive event [50]. These results indicate the need to act to reduce the incidence of thrombosis, especially arterial thrombosis, and several factors are recommended when selecting the starting dose (Table 13).

The European LeukemiaNet. guidelines available at the time of analysis conclude that there is no absolute contraindication to using any particular TKI, indicating that the use of ponatinib is not advisable in patients with any level of PAD and ponatinib should be used with caution in those with ischaemic heart disease or prior cerebral ischaemia, given its increased vascular risk [14]. However, these guidelines do not include the assessment of other specialists.

It must be borne in mind that in the PACE study patients with significant or active CVD were excluded, specifically mentioning congestive heart failure, acute myocardial infarction (AMI) or unstable angina in the previous 3 months. Likewise, 30% of patients with CP-CML developed arterial ischaemia of any type after 5 years, and the history of previous ischaemia was responsible for a 2.65 fold increase in the risk of an arterial event with ponatinib. Additionally, the probability of developing severe cardiac events at 5 years was 12%, and 10% and 11% for cerebral and peripheral events, respectively [14].

However, we do not have the actual mortality data for ponatinib patients treated in the PACE study with previous ischaemic artery disease, which means that we must rely on extrapolations.

Based on the available evidence, the panel makes the recommendations included in Table 14.

Table 15: Main pharmacodynamic interactions reported with ponatinib.

Major pharmacodynamic interactions	Concomitant use of cladribine, deferiprone, dipyrone, clozapine, chlorpromazine or levomepromazine is contraindicated due to the risk of myelosuppression and/or agranulocytosis [53].
	Caution when used at the same time as anticoagulant medicinal products. If association with vitamin K antagonists cannot be avoided, closer monitoring of INR [54] must be carried out.
	The use of intravesical BCG and live virus vaccines must be avoided as the immune response will be limited [54].
	TKIs can produce prolongation of the QT interval. However, cases of severe QTc prolongation are explained by drug interaction or previous heart disease [55,56].
	Carefully assess possible interactions that may aggravate other toxicities (e.g. be cautious when combined with L-asparaginase because of the risk of hepatotoxicity) [54].

BCG: Bacillus Calmette-Guérin.

Table 16: Consensus recommendations for management of drug interactions with ponatinib.

Recommendation	Level of consensus	Level of agreement*
The patient's active medication must be comprehensively recorded in the medical records and periodically updated; and the patient must be educated on the need to consult on the risk of interactions.	Consensus	Agreement
It is recommended that patients with risk factors for potential interactions (e.g. impaired liver function, age, and polymerization) be identified so that these interactions can be minimized.	Consensus	Agreement
In the absence of scientific evidence, theoretical pathways and mechanisms of interaction must be assessed to anticipate possible side effects in the patient, and it is essential that this involve collaboration with the hospital pharmacist.	Consensus	Agreement

*Based on a Likert scale assessment: disagreement 1 to 3, neither disagreement nor agreement 4 to 6 and agreement 7 to 9.

Table 17: Consensus recommendations for lifestyle and communication with patients regarding ponatinib therapy.

Recommendation	Level of consensus	Level of agreement
Interventions aimed at the prevention of cardiotoxicity related to lifestyle modification and health education must be multidisciplinary in nature, including all professionals involved in the patient care circuit.	Consensus	Agreement
Given the relationship between oncology therapy and CVR, lifestyle modification based prevention measures need to be implemented in all ponatinib treated patients, and this is all the more necessary in those at higher risk.	Consensus	Agreement
It is recommended that the lifestyle promoted is one based on a healthy diet in the form of restricting the intake of saturated fatty acids to <10% of the total caloric intake by replacing them with polyunsaturated fatty acids, consuming salt <5g/day and increasing the consumption of fiber and whole meal products; regular exercise, adapted to what is possible for the patient; and smoking cessation.	Consensus	Agreement
Patient counseling must be individualized and decision-making shared between patient and healthcare professional, exploring their knowledge, concerns and expectations in order to achieve adequate engagement and motivation.	Consensus	Agreement

*Based on a Likert scale assessment: disagreement 1 to 3, neither disagreement nor agreement 4 to 6 and agreement 7 to 9.

Section 9: Management of drug-drug interactions

It has been observed that about 20-30% of adverse drug reactions are caused by drug-drug interactions, in addition to other interactions with food, nutritional supplements, medicinal plants, excipients or environmental factors [51]. In addition, although numerous studies reveal the high prescription of TKIs with drugs susceptible to interaction, which can increase toxicity by up to 74%, epidemiological data describing the clinical significance are very limited [52]. Although drug-drug interactions that affect the therapeutic effect of ponatinib are not expected, given the specificity of its binding site, those that affect its safety can be expected, the most relevant being those described in Table 15.

However, it is important to stress that they must be taken as a starting point, since the fact that an interaction is not described does not mean that it can be ruled out [54]. In this sense, oncohaematological pharmacists have the training and experience that allows the early identification of potentially harmful drug-drug interactions, and their inclusion in the clinical team plays a vital role in this field [57].

To reduce the potential for unexpected drug-drug interactions, the patient's medical history must collect comprehensive and interactive information on all medications and supplements the patient receives and must be periodically updated. The patient must also be educated on the need to consult prior to the inclusion of any medicinal product, supplement or alternative therapy, in order not to compromise the efficacy and safety of ponatinib [58].

Based on the available evidence, the panel makes the recommendations included in Table 16.

Section 10: Lifestyle and patient education

As already discussed, TKI therapy leads to an increase in intrinsic CVR, so non-pharmacological cardiotoxicity prevention measures need to be implemented in all patients, regardless of their treatment regimen. These measures must include the promotion of a healthy lifestyle, understood as observance of a balanced diet, regular exercise, adequate body weight control and cessation of smoking, as well as strict identification and control of CVRFs before, during and after treatment [25].

When it comes to dietary patterns, the available European guidelines agree that a Mediterranean diet is the most appropriate in our context [59]. With regard to physical activity, aerobic exercise is recommended, for 150 minutes/week if the exercise is of moderate intensity, or for 75 minutes/week in the case of more vigorous activity. However, shorter exercise sessions may also be appropriate for patients who are unable to meet these requirements [24], as may be the case for patients undergoing oncology therapy.

The timing of oncology diagnosis can be a good opportunity for encouraging patients to change their lifestyle and promote healthier habits, as fear of side effects from therapy or possible relapse greatly increases the patient's willingness to listen to nutrition and lifestyle advice [60].

Based on the available evidence, the panel makes the recommendations included in Table 17.

A summary of CV risk management recommendations in patients

Table 18: CV risk management recommendations in patients with CML before and during ponatinb treatment.

	Patients who are candidates for ponatinib	Patients treated with ponatinib
Medical history and initial clinical evaluation Table 1 and Table 2	• Multidisciplinary evaluation (Table 2). • Detailed clinical history. • Initial physical examination: height, weight, BMI and cardiovascular and pulmonary auscultation.	• Patients with a history of CV disease, uncontrolled risk factors or a lower than normal ejection fraction are considered high risk and require cardio-oncology management and follow-up.
Laboratory and imaging tests Table 3 and Table 4	• Analytical monitoring: blood count, coagulation, liver and pancreatic enzymes, creatinine and eGFR, blood glucose and HbA1c, electrolytes, triglycerides, total cholesterol and HDL-c/LDL-c, BNP/pro-BNP levels. • Blood pressure, ABI, ECG (QTc Fridericia), echocardiogram and chest X-ray. • Carotid Doppler ultrasound in moderate, high and very high risk patients. • Coronary calcium determination in moderate CV risk patients.	• Weekly checking of blood pressure and cardiovascular risk during the first month, monthly during the first quarter and then quarterly. • Monitoring of glucose and lipid metabolism, and determination of ABI every 3, 6 and 12 months. • Echocardiogram follow-up at 3 months of high-risk patients and annual follow-up of all patients.
CVR evaluation and prophylaxis strategies Table 5 and Table 6	• Cardiovascular risk must be quantified with SCORE tables in all ponatinib candidates and vascular disease must be actively ruled out.	• ASA 100 mg/day is not recommended as the primary prophylaxis in low CV risk patients treated with ponatinib.
Cardiovascular treatment objectives Table 7 and Table 8	• Set targets for blood pressure, lipid control and glycaemic control and the treatments necessary to achieve them (Table 8).	• Review of blood pressure, lipid control and glycaemic control objectives and the treatments necessary to achieve them (Table 8).
Prevention of VTD Table 9 and Table 1	• Routine prophylaxis with anticoagulant treatment: not routinely recommended in patients without other risk factors. • Assessment, by an angiologist/vascular surgeon and an (onco)cardiologist, of all patients being considered for ponatinib treatment prior to initiation.	• Elective surgery: suspend ponatinib 7 days before surgery and resume when no bleeding risk is envisaged (approximately 1-3 days). • VTE patients: suspend ponatinib until resolution of the event, avoiding the administration of vitamin K antagonists and considering the use of LMWH and DOACs. • ASA in surgery: in low-/moderate-risk patients interruption is recommended, and ASA restricted in high-risk patients to a maximum dose of 100mg/day.
Management of pre-existing and emerging CV issues Table 11 and Table 12	• Optimization of treatment in accordance with clinical practice guidelines is recommended in patients with a history of CV risk factors or cardiovascular disease.	• If LVEF < normal, refer to cardio-oncology and initiate HF treatment. • The treatment of patients who develop systolic dysfunction following ponatinib treatment must include HF treatment as soon as possible. • If the patient develops severe decompensate HF, ponatinib therapy must be interrupted and the decision on when and whether to resume ponatinib must be agreed by a multidisciplinary team. • In patients with AF, CHA2DS2VASc is recommended for indicating the use of anticoagulation, prioritizing the use of OACs. • Anticoagulation decision in patients with AF or VTD and less than 50,000 platelets must be agreed by the multidisciplinary team.
Adjustment of doses in accordance with approved indications Table 13 and Table 14	• Initial dose of ponatinib: consider factors related to a greater likelihood of response and the presence of CVRFs. • **Patients with previous events:** assess the balance between the possibility of a new event and mortality associated with the antileukaemic effect of ponatinib. • **Ponatinib is indicated in patients** who have had a TIA or have asymptomatic peripheral arterial disease. • **Ponatinib is contraindicated in** patients who have had an ischaemic stroke, non-atherothrombotic AMI or have symptomatic peripheral arterial disease.	• Apply ELN criteria that define the response to second-line TKIs: assessments will be performed at 3, 6 and 12 months after initiation of therapy. • **If an optimal response is achieved:** it is recommended that the ponatinib dose be reduced by 15mg/day to reduce CVR. • **In case of concern or failure**: if there has been no toxicity, dose maintenance is recommended. • **Onset of severe CVD:** suspend treatment indefinitely; assess severity and morbidity/mortality.
Management of drug-drug interactions Table 15 and Table 16	• Recording of patient medication: through the medical history records, with periodic updating. Educate the patient on the need to consult about the risk of interactions.	

with CML before and during treatment with ponatinb is provided in Table 18.

Discussion and Conclusions

The emergence of TKIs, and especially of more recent molecules such as ponatinib, has meant a significant advance in the treatment of CML. However, the cardiovascular complications of these agents remain a clinically relevant concern [61]. In this context, exploratory work has recently begun on what mechanisms underlie this damage, as well as on its proper identification, prevention and management in patients who are candidates for ponatinib [62,63].

As part of this new knowledge, the analysis of the results obtained in this document shows a high degree of agreement among the various specialists who made up the panel of experts, which meets one of the fundamental premises of its approach, i.e. the need

for a multidisciplinary approach to the patient. Thus, for most of the assertions, statistical consensus was reached, and the internal consistency was high in virtually all thematic sections.

Regarding those statements for which statistical consensus were not reached, the experts consider it necessary to make certain clarifications. Regarding the safety of ponatinib in real life, they highlight that the incidence of CVD is indeed lower than that shown in clinical trials [6,9,15-18]; however, more time is needed to confirm this trend. On the other hand, although the oncology pharmacist must monitor analytical data and possible toxicities and interactions, this function must not rest solely with this person, but must be a shared responsibility with the other specialists involved. Regarding the subsequent follow-up of patients who have previously presented Venous Thromboembolism (VTE) once treatment with ponatinib was established, experts recommend performing a limb Doppler scan, in addition to determining D-dimer levels, on conclusion of the procedure, to assess the possible risk of recurrence; however, it is recommended as a suggestion and it remains at the discretion of the clinical judgment of the specialist in charge of the patient's development. Finally, although it is recognised that troponin is a cardiac damage marker with high sensitivity and specificity [64], in the patient with cardiac dysfunction it is not recommended for serial determinations, due to the current lack of clinical evidence in this context. On the other hand, it should be mentioned that a preliminary analysis of the OPTIC study, in which patients were randomized at a starting dose of 45mg versus 30mg (with subsequent reduction to 15 mg in the case of a response) and versus 15mg ponatinib, has shown a higher dose efficacy of 45mg without this resulting in a significant difference in cardiovascular events, even if there is a tendency in the dose dependent reduction of AOEs [65],

Taking into account the evidence described, experts conclude that ponatinib is a valuable drug for combating resistance to all other TKIs and should not be stopped for fear of vascular toxicities. We believe that, based on the best available evidence, applying these recommendations to normal clinical practice supports this as a manageable therapeutic option. We hope that these recommendations, coupled with dose adjustment, such as the one performed in the OPTIC study, will increase the benefit/risk ratio of ponatinib treatment, which will allow a substantial improvement in the approach to the disease and the quality of life of patients with CML.

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Appendix 1 - Supplementary Material

Methodology and participants

The main recommendations and conclusions reached in this work are the result of an analysis conducted in three phases (Table 19), carried out by a multidisciplinary panel composed of three coordinators and ten specialist practitioners.

Table 19: Project Phases.

Phase 1. Definition of the content sections	• Correlation between randomised clinical trials and actual practice. • Medical history and initial clinical evaluation. • Laboratory and imaging tests. • CVR evaluation and prophylaxis strategies. • CV targets in ponatinib candidate patients. • Multidisciplinary approach and collaboration. • Management of CV issues. • Dose adjustment. • Managing Interactions. • Lifestyle and patient education.
Phase 2. Review of the evidence	• Review of the evidence and working meeting: debrief and discussion. • Deriving the main assertions from the evidence.
Phase 3. Consensus	• Drawing up of the Delphi questionnaire by the coordinators. • The panel of experts' validation of the recommendations using the Delphi two-round methodology.

Table 1: Details of the sample of researchers participating in the Delphi questionnaire.

	Mean±SD	Median (p25-p75)	Minimum - maximum
Age (years)	41.9±6.5	44.5(37-47)	30-49
Years of experience	14.5±5.3	17(9-19)	7-20
Autonomous regions			
Andalusia		1	
Castilla y León		1	
Catalonia		1	
Madrid		4	
Valencia		1	
Galicia		1	
Murcia		1	
Specialty			
Cardiology		2	
Hospital Pharmacy		1	
Haematology and Haemotherapy		5	
Internal Medicine		1	
Angiology and Vascular Surgery		1	

SD: Standard Deviation.

The degree of agreement or disagreement was assessed using the Likert 9-point scale (1=Full disagreement, 9=Full agreement) where disagreement is represented by 1 to 3, neither disagreement nor agreement by 4 to 6 and agreement by 7 to 9.

For each item, was studied in which tertile is the median value, and subsequently what percentage of responses is in that tertile. If more than two thirds of the answers are in this tertile, it is considered that there is agreement, and when more than one third is outside this range there is disagreement.

If there is agreement, we mean that there is consensus. If more than two-thirds of the answers are in this tertile, it is considered that there is agreement, and disagreement when more than one third is outside this range.

The internal consistency of the questionnaire was assessed using Cronbach's alpha, both for the overall questionnaire and for each section.

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