



# Cardiovascular risk in chronic myeloid leukaemia: A multidisciplinary consensus on screening and management

Dragana Milojkovic<sup>1</sup>  | Alexander R. Lyon<sup>2</sup> | Priyanka Mehta<sup>3</sup> |  
Evangelia Dimitriadou<sup>4</sup> | Satarupa Choudhuri<sup>5</sup> | Charlotte Manisty<sup>6</sup> |  
Nick Cheshire<sup>2</sup> | Kirsty Crozier<sup>7</sup> | Nanda Basker<sup>8</sup> | Karim Amer<sup>9</sup> |  
Simon Purcell<sup>9</sup> | Susan Tan<sup>10</sup> | Richard E. Clark<sup>11</sup>

<sup>1</sup>Hammersmith Hospital, London, UK

<sup>2</sup>The Royal Brompton Hospital, London, UK

<sup>3</sup>University Hospital Bristol, Bristol, UK

<sup>4</sup>Maidstone & Tunbridge Wells, Tunbridge Wells, UK

<sup>5</sup>Northern Care Alliance, Manchester, UK

<sup>6</sup>Barts Health NHS Trust and University College London, London, UK

<sup>7</sup>Churchill Hospital, Oxford, UK

<sup>8</sup>Southampton General Hospital, Southampton, UK

<sup>9</sup>Pfizer Ltd., London, UK

<sup>10</sup>Envision Pharma Group, Sydney, Australia

<sup>11</sup>Department of Molecular and Clinical Cancer Medicine, University of Liverpool, Liverpool, UK

## Correspondence

Dragana Milojkovic, Hammersmith Hospital, Du Cane Road, London W12 0HS, UK.  
Email: [d.milojkovic@imperial.ac.uk](mailto:d.milojkovic@imperial.ac.uk)

## Abstract

**Introduction:** Tyrosine kinase inhibitors (TKIs) have become the mainstay of treatment for chronic myeloid leukaemia (CML), but cardiovascular (CV) risk and exacerbation of underlying risk factors associated with TKIs have become widely debated. Real-world evidence reveals little application of CV risk factor screening or continued monitoring within UK CML management. This consensus paper presents practical recommendations to assist healthcare professionals in conducting CV screening/comorbidity management for patients receiving TKIs.

**Methods:** We conducted a multidisciplinary panel meeting and two iterative surveys involving 10 CML specialists: five haematologists, two cardio-oncologists, one vascular surgeon, one haemato-oncology pharmacist and one specialist nurse practitioner.

**Results:** The panel recommended that patients commencing second-/third-generation TKIs undergo formal CV risk assessment at baseline, with additional investigations and involvement of cardiologists/vascular surgeons for those with high CV risk. During treatment, patients should undergo CV monitoring, with the nature and frequency of testing dependent on TKI and baseline CV risk. For patients who develop CV adverse events, decision-making around TKI interruption, cessation or change should be multidisciplinary and balance CV and haematological risk.

**Conclusion:** The panel anticipates these recommendations will support healthcare professionals in implementing CV risk screening and monitoring, broadly and consistently, and thereby help optimise TKI treatment for CML.

## KEYWORDS

cardiovascular, chronic myeloid leukaemia, consensus, tyrosine kinase inhibitor



## Novelty Statements

### What is the new aspect of your work?

This nascent multidisciplinary consensus approach utilises leading United Kingdom (UK) expertise from haematology, cardiology, nursing, pharmacy and vascular specialists to provide recommendations on the implementation of cardiovascular (CV) risk screening and monitoring in patients with chronic myeloid leukaemia (CML) receiving tyrosine kinase inhibitor (TKI) therapies.

### What is the central finding of your work?

Upfront formal baseline CV risk screening is initially recommended for all patients with CML receiving TKI therapy, with newly delineated consensus on repeat routine follow-up investigation by a multidisciplinary team (primary care physicians, specialist nurses, pharmacists and haematologists), and specialist referral of patients with high CV risk to cardiology and/or vascular services.

### What is (or could be) the specific clinical relevance of your work?

Real-world studies reveal that CV risk factor screening and monitoring as part of CML management is lacking in the UK; this consensus paper, which provides specific direction to multidisciplinary team members on CV risk factor screening/monitoring and escalation/referral for individual TKI therapies, has the potential to positively impact the treatment outcomes with such therapies.

## 1 | INTRODUCTION

The development of tyrosine kinase inhibitors (TKIs) has enabled most patients with chronic myeloid leukaemia (CML) to experience a life expectancy close to that of the general population.<sup>1</sup> The incidence of CML is highest among people 70–74 years of age, with 56% of newly diagnosed patients having comorbidities, the most common being hypertension, other cardiovascular (CV) disorders and diabetes.<sup>2</sup> There is a strong correlation between comorbidities (including CV comorbidities) at CML diagnosis and worse overall survival.<sup>3</sup> Patients with CML also have an increased risk of CV events compared with the general population.<sup>4–6</sup> For example, a United States (US) real-world analysis of 1639 patients with CML found that the prevalence of CV conditions and CV risk factors 5 years after diagnosis was 33.0% and 77.7%, respectively. Compared with the general US adult population, the standardized prevalence rates at 1 year in patients with CML were significantly higher by factors of 1.3–3.5 times for CV conditions and 20%–40% significantly higher for hypertension, diabetes and obesity ( $p < .001$ ).<sup>4</sup>

The longer life expectancy afforded by the development of TKIs means that screening patients for underlying CV comorbidities is of importance. Moreover, the necessary extended duration of treatment increases the importance of managing treatment-related adverse events (AEs). Each TKI has a distinct AE profile that needs to be considered when deciding which TKI to initiate or when to adjust therapy. Although treatment with the first-generation TKI, imatinib, was associated with a low incidence of CV AEs in 10-year follow-ups of the IRIS trial<sup>7</sup> and the CML study-IV trial,<sup>8</sup> treatment with second-

generation TKIs (dasatinib, nilotinib, bosutinib) or third-generation TKIs (ponatinib) has been associated with an increased risk of CV AEs, including arterial occlusive events (AOEs) and/or peripheral arterial occlusive disease (PAOD).<sup>9</sup> Five-year follow-up data from the DASISION trial showed an increased incidence of pleural effusion (28% vs. 0.8%, respectively) and pulmonary hypertension (5% vs. 0.4%, respectively) with dasatinib versus imatinib.<sup>10</sup> In the ENESTnd trial, 7/556 versus 0/280 patients receiving nilotinib versus imatinib had an AOE according to 3-year follow-up data.<sup>11</sup> Furthermore, 5- and 10-year follow-up data showed numerically more CV events and elevations in blood cholesterol and glucose with nilotinib versus imatinib.<sup>12,13</sup> Five-year analysis showed that CV events, namely ischaemic heart disease, ischaemic cerebrovascular events and/or peripheral artery disease, were reported in 21 (7.5%), 37 (13.4%) and 6 (2.1%) patients in the nilotinib 300 mg twice-daily, nilotinib 400 mg twice-daily and imatinib 400 mg once-daily arms, respectively.<sup>12</sup> In the 10-year analysis, CV events were reported in 46 (16.5%), 65 (23.5%) and 10 (3.6%) patients, respectively, in the nilotinib 300 mg twice-daily, nilotinib 400 mg twice-daily and imatinib 400 mg once-daily arms.<sup>13</sup> After 5 years of follow-up, the BFORE trial showed a marginally higher incidence of CV treatment-emergent AEs in the bosutinib versus imatinib arm (4.9% vs. 0.4%), although this incidence remained low.<sup>14</sup> Finally, 5-year follow-up data from the ponatinib PACE study in previously treated patients with CML showed a 31% cumulative incidence of AOEs, with the exposure-adjusted incidence of new AOEs being 15.8 and 4.9 per 100 patient-years in Years 1 and 5 of the study, respectively.<sup>15</sup> However, it is important to note that, due to the orphan disease status of CML, none of these pivotal trials were

**TABLE 1** Key published recommendations for CV considerations in CML.

| Organisation       | Screening recommendations   | Monitoring/treatment considerations  |
|--------------------|---|--|
| BSH <sup>17</sup>  | All TKIs: <ul style="list-style-type: none"> <li>• Risk assessment algorithm (QRISK3) or equivalent</li> <li>• ECG if clinically indicated</li> <li>• Lipid profile</li> <li>• Fasting glucose and/or HbA1c</li> <li>• Blood pressure</li> <li>• Electrolytes</li> </ul>  | All TKIs: <ul style="list-style-type: none"> <li>• Blood pressure (for imatinib, only if clinically indicated)</li> <li>• Secondary prevention for those with previous CV events</li> <li>• Lipid profile, BNP, HbA1c, echocardiogram, chest X-ray, ECG if clinically indicated</li> </ul> Dasatinib: <ul style="list-style-type: none"> <li>• BNP</li> </ul> Nilotinib and Ponatinib: <ul style="list-style-type: none"> <li>• Lipid profile</li> <li>• HbA1c</li> <li>• BNP</li> </ul>   |
| ELN <sup>18</sup>  | All TKIs: <ul style="list-style-type: none"> <li>• Standard biochemical profile, including cholesterol and HbA1c</li> <li>• ECG</li> </ul> Ponatinib: <ul style="list-style-type: none"> <li>• Control risk factors for arterial occlusive events</li> </ul>  | Nilotinib: <ul style="list-style-type: none"> <li>• Caution needed if dosage &gt;300 mg twice daily</li> </ul> Ponatinib: <ul style="list-style-type: none"> <li>• Consider a starting dose &lt;45 mg daily, except those with T315I mutation, compound mutations or advanced phase CML<sup>a</sup></li> <li>• Control risk factors for arterial occlusive events</li> </ul>   |
| ESMO <sup>19</sup> | All TKIs: <ul style="list-style-type: none"> <li>• Replete potassium and magnesium to appropriate serum levels before starting treatment</li> <li>• Use with caution in patients with heart failure</li> </ul> Nilotinib: <ul style="list-style-type: none"> <li>• Prescribed with caution in patients with CV risk factors</li> <li>• A thorough intervention recommended against CV risk factors</li> </ul>   | All TKIs: <ul style="list-style-type: none"> <li>• Continued clinical monitoring for cardiotoxicity</li> </ul>   |
| NCCN <sup>20</sup> | Dasatinib: <ul style="list-style-type: none"> <li>• Evaluate for cardiopulmonary disease</li> </ul> Nilotinib: <ul style="list-style-type: none"> <li>• ECG</li> <li>• Drugs that prolong QT interval should be avoided</li> <li>• Electrolyte abnormalities should be corrected before starting treatment</li> <li>• Identify and control CV risk factors before starting treatment</li> <li>• Patients with CV risk factors should be referred to a cardiologist</li> <li>• Evaluate for pre-existing PAOD</li> </ul> Ponatinib: <ul style="list-style-type: none"> <li>• Identify and control CV risk factors before starting treatment</li> <li>• Patients with CV risk factors should be referred to a cardiologist</li> </ul> | Dasatinib: <ul style="list-style-type: none"> <li>• Evaluate for cardiopulmonary disease</li> </ul> Nilotinib: <ul style="list-style-type: none"> <li>• ECG for QT interval monitoring, with dose reduction to manage QT prolongation</li> <li>• Electrolytes</li> <li>• CV risk factors</li> <li>• Permanent discontinuation if PAOD is confirmed</li> </ul> Ponatinib: <ul style="list-style-type: none"> <li>• Monitor for high blood pressure, evidence of arterial occlusive or thromboembolic events, and reduced cardiac function</li> <li>• Interrupt or stop ponatinib immediately for vascular occlusion and for new or worsening heart failure</li> </ul> |
| ESC <sup>37b</sup> | Dasatinib, Nilotinib, Bosutinib and Ponatinib: <ul style="list-style-type: none"> <li>• Physical examination</li> <li>• Blood pressure</li> <li>• ECG</li> <li>• Lipid profile</li> <li>• HbA1c</li> </ul> Dasatinib: <ul style="list-style-type: none"> <li>• Echocardiography</li> </ul>  | Dasatinib, Nilotinib, Bosutinib and Ponatinib: <ul style="list-style-type: none"> <li>• Physical examination</li> <li>• Blood pressure</li> </ul> Nilotinib and Ponatinib: <ul style="list-style-type: none"> <li>• ECG</li> <li>• Lipid profile</li> <li>• HbA1c</li> </ul>   |

Abbreviations: BNP, B-type natriuretic peptide; BSH, British Society for Haematology; CML, chronic myeloid leukaemia; CV, cardiovascular; ECG, electrocardiogram; ELN, European LeukemiaNet; ESC, European Society of Cardiology; ESMO, European Society for Medical Oncology; HbA1c, glycated haemoglobin; NCCN, National Comprehensive Cancer Network; PAOD, peripheral occlusive arterial disease.

<sup>a</sup>These lower ponatinib starting doses are currently being evaluated in the ongoing phase 2 OPTIC study.<sup>39</sup>

<sup>b</sup>Class 1 recommendations shown.

powered to collect CV AE data in an impactful way. Thus, while these data are useful for comparison purposes, they should be interpreted with some caution.

It has been reported that CV risk factor screening as part of CML management is poor in the UK. The UK TARGET CML study, a retrospective observational study of 257 patients with chronic phase CML



who had been prescribed a first-line TKI between 2013 and 2017, found 'little evidence that CV risk factors were considered during TKI management'.<sup>16</sup> CV screening, monitoring and comorbidity management have therefore been incorporated into CML treatment guidelines from the British Society for Haematology (BSH), European LeukemiaNet (ELN), European Society for Medical Oncology (ESMO) and National Comprehensive Cancer Network (NCCN, Table 1).<sup>17–20</sup> To assist in managing CV AEs in oncology, the Heart Failure Association of the European Society of Cardiology Cardio-Oncology Study Group, in collaboration with the International Cardio-Oncology Society (HFA-ICOS), released a position statement in 2020 including baseline CV risk proformas for patients commencing cardiotoxic oncology therapies, including TKIs.<sup>21</sup> The group recommends completion of baseline stratification CV risk assessment proformas in all patients scheduled to receive one of seven oncology drug classes with potential cardiotoxicity. The proformas help to stratify the patients into low-, medium- and high-/very high risk categories, with the aim of improving personalised approaches to minimise the risk of cardiovascular toxicity from cancer therapies. It is also recommended that the risk level be recorded in the patient's medical records, reviewed by the treating oncologist or haemato-oncologist, and communicated to the patient and their primary care physician to address modifiable CV risk factors. Although CV comorbidity screening and monitoring are becoming integrated into clinical practice, their implementation has been limited and inconsistent. Multidisciplinary, practical recommendations might therefore be helpful to assist healthcare professionals to consistently implement the recommendations of these major groups.

In order to provide these multidisciplinary recommendations, consensus needs to be generated amongst medical experts across a range of allied health professions. This could be accomplished through face-to-face approaches, such as panel meetings, or the Nominal Group Technique, which involves structured small group discussion followed by voting.<sup>22</sup> Alternatively, iterative surveys can be performed using the Delphi method.<sup>23</sup>

In this study, we used a panel meeting and an iterative survey approach to develop recommendations from clinical experts from the UK around CV risk screening, ongoing assessment and escalation to appropriate allied services in relation to TKI therapies for CML. Based on the clinical experience of this expert group, this consensus paper addresses the considerations needed in a thorough CV assessment, both pre-treatment and throughout TKI therapy. It provides guidance on the undertaking of specialist-recommended tests and referral pathways and, uniquely, recommends a multidisciplinary approach to decision-making for patients with CML in order to provide holistic management.

## 2 | METHODS

We conducted a multidisciplinary expert panel review comprising five haematologists, two cardio-oncologists, one vascular surgeon, one haemato-oncology pharmacist and one specialist nurse

practitioner, from the UK and all with a specialist interest in managing CML.

To establish advice on key CV considerations for different TKIs, the panel reviewed pivotal trial data for all TKIs licensed in the United Kingdom (imatinib, dasatinib, nilotinib, bosutinib and ponatinib) and reviewed current practices on CV comorbidity screening and investigations following CV events. Inspired by the Delphi method,<sup>23</sup> panel members also completed two iterative surveys to assist in achieving group consensus (Figure 1; Data S1 and S2). Here, we report results based on majority viewpoints, defined as  $\geq 70\%$  agreement in these surveys. Additional recommendations based on group discussion have also been included.

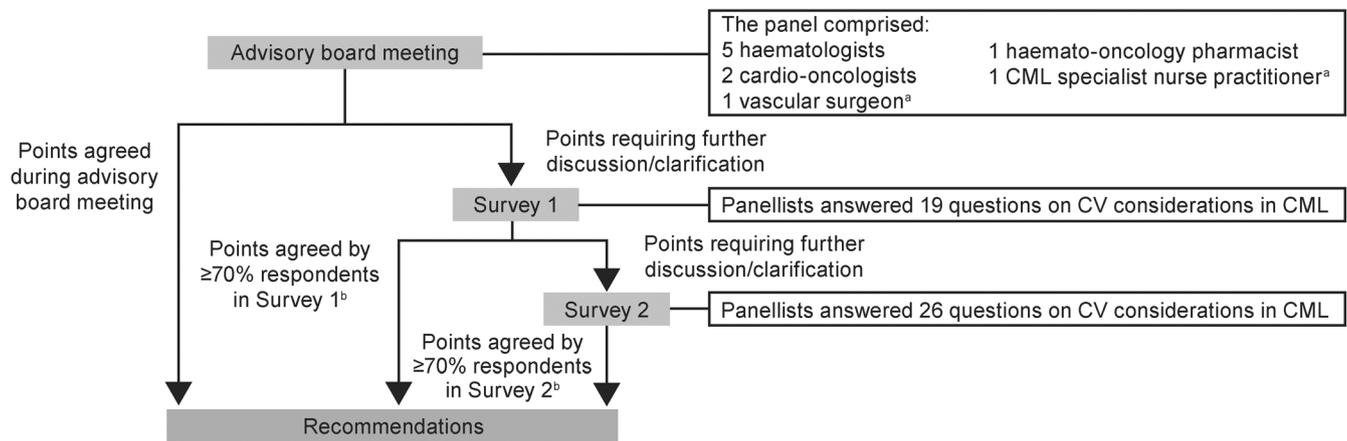
## 3 | RESULTS

### 3.1 | CV screening and risk stratification

*Recommendations: A patient's baseline CV risk should be assessed on the basis of their comorbidities and the safety profile of the selected TKI. For patients determined to be at high risk of CV events with TKI therapy, a multidisciplinary management team is recommended.*

Panel members commented on the importance of considering risk factors in context with each other to define CV risk. For example, age combined with atherogenic risk factors would signal increased CV risk. Irrespective of treatment line, most panellists recommended baseline CV screening before commencing dasatinib, nilotinib, bosutinib or ponatinib, but not necessarily prior to commencing imatinib. The number and types of screening tests depend on the TKI and the patient's baseline CV risk (Table 2). For each TKI, the nature of the screening tests relates to the incidence of AEs associated with each TKI; for example, blood pressure screening is recommended for second- and third-generation TKIs, in line with reported incidences of hypertension (5%, 10.4%, 8.3%, 9.7% and 14% for dasatinib [pulmonary hypertension], nilotinib 300 mg, nilotinib 400 mg, bosutinib and ponatinib, respectively<sup>10,12,14,15</sup>). Panel members agreed that specific tests should be conducted according to clinical symptoms/comorbidities; for example, cardiac biomarkers (B-type natriuretic peptide [BNP], N-terminal pro-BNP [NT-proBNP] and/or troponins) should be checked if there are CV/respiratory symptoms or comorbidities, Doppler ultrasonography if there are CV symptoms or comorbidities, chest X-ray for respiratory symptoms or comorbidities, echocardiography if CV symptoms or comorbidities, or coronary angiography if advised by cardiology.

In the consensus surveys, a combination of past and current medical history and relevant lifestyle risk factors was the most commonly selected method for defining CV risk. Other techniques to define CV risk include QRISK3 risk scoring, measurement of blood metabolic markers and the HFA-ICOS risk proforma (Table 3).<sup>21</sup> The HFA-ICOS risk proforma for patients receiving TKIs was developed using data from patients with CML,<sup>21</sup> who have a higher incidence of CV disease compared with the general population.<sup>4,5</sup> Therefore, for patients with CML, the HFA-ICOS risk proforma may provide an accurate measure of



**FIGURE 1** Method for obtaining recommendations. <sup>a</sup>Although the vascular surgeon and CML specialist nurse practitioner did not attend the initial advisory board meeting, they were fully briefed on meeting outcomes and contributed to the subsequent surveys and review of the recommendations. <sup>b</sup>All 10 panellists responded to Surveys 1 and 2; however, some specific questions were applicable only for certain professions. For these, the 70% threshold was set to 70% of respondents for that question. CML, chronic myeloid leukaemia; CV, cardiovascular.

CV risk. For the HFA-ICOS risk proforma, low CV risk is defined as no medium-high risk parameters or risk score 0–1, moderate CV risk as any medium risk parameters or risk score 2–4 and high CV risk as any high/very high risk parameters or risk score  $\geq 5$ .<sup>21</sup> The HFA-ICOS risk proforma and other risk estimation tools, such as QRISK3, apply a weighting system to help assess combinations of risk factors. Such systems can be beneficial, as multiple moderately elevated risk factors could potentially be worse than one impressively raised risk factor. For QRISK3, most panel members identified low, moderate and high CV risk as being QRISK3  $< 10\%$ ,  $\sim 10\%$ – $20\%$  and  $> 20\%$ , respectively. A benefit of the QRISK3 system is that it was developed using data from a very large population (more than 7 million general practice patients<sup>24</sup>) and is therefore likely to be broadly representative. However, using risk estimation tools for the same population group that the tool was derived from can also improve accuracy. Should a patient have any risk factors not included in the risk estimation tool, it is important to modify their CV risk accordingly. For example, a patient with a family history of early-onset CV disease would likely have an increased risk compared with someone with the same risk factor profile but no such family history. Whichever risk assessment technique is used, the approach should be consistent and reproducible between clinicians.

For patients found to be at high CV risk on dasatinib, nilotinib, bosutinib or ponatinib, the panel recommended multidisciplinary team (MDT) meetings, including the haematologist, cardiologist and vascular surgeon; however, this may be difficult to achieve in practice for all patients.

### 3.2 | CV risk and TKI treatment decisions

*Recommendations: TKI treatment decisions should take account of a patient's CV risk profile, non-CV related comorbidities and mutational status. The potential positive and negative effects of concomitant medications should also be considered.*

Irrespective of treatment line, there is no particular CV condition or CV disease history where the panel would advise against imatinib treatment. This is consistent with the low rate of CV AEs reported with imatinib. For example, in a 10-year follow-up of the IRIS study, 7.1% of patients on imatinib ( $n = 39/551$ ) had a cardiac serious AE (all cause).<sup>7</sup>

For other TKIs, the panel recommended risk/benefit analysis for patients with particular CV conditions or disease history (Table 2), mindful of potential impacts on non-CV comorbidities or other considerations. Examples of such considerations include renal impairment, which would preclude imatinib,<sup>18,25,26</sup> or for women who wish to conceive, a second-generation TKI may be preferred over imatinib to induce a faster and deeper remission and thus potentially allow earlier treatment cessation.<sup>27–29</sup> For patients with high-risk disease (e.g., an additional chromosomal abnormality at diagnosis) or commencing later lines of treatment, the CML disease state may dominate CV risk, altering the risk/benefit analysis. Mutational status in resistance may also limit the treatment options available. For example, ponatinib is the only efficacious TKI for patients with the T315I mutation.<sup>18</sup> Alternatively, if there are no notable mutations, the patient may be treated sequentially as needed with a first-, second- and then a third-generation TKI, with close monitoring for efficacy and safety. Concomitant medications would also need to be considered in case of interaction; it is interesting that TKIs in combination with statin therapy may induce a higher rate of deep molecular response.<sup>30</sup> Conversely, if a patient is on a concomitant drug that inhibits CYP450, the TKI may metabolise more slowly, increasing drug exposure and potentially increasing the likelihood and/or severity of potential side effects.<sup>31</sup> In this situation, alternative treatments may need to be considered.

### 3.3 | CV monitoring

*Recommendations: Depending on the safety profile of the selected TKI, electrocardiograms and a combination of tests for blood pressure,*



**TABLE 2** General recommendations from the majority of panel members for CV screening and monitoring for patients receiving TKIs for CML.

|  | Imatinib               | Dasatinib                             | Nilotinib                           | Bosutinib                           | Ponatinib                           |
|--|------------------------|---------------------------------------|-------------------------------------|-------------------------------------|-------------------------------------|
| <i>Parameters recommended for CV screening prior to commencing treatment</i>                         |                        |                                       |                                     |                                     |                                     |
| Blood pressure   |                        | ✓                                     | ✓                                   | ✓                                   | ✓                                   |
| HbA1c/fasting glucose  |                        |                                       | ✓                                   |                                     | ✓                                   |
| Cholesterol/lipids   |                        | ✓ <sup>a,b</sup>                      | ✓                                   | ✓ <sup>b</sup>                      | ✓                                   |
| Electrolytes   | ✓                      | ✓ <sup>e</sup>                        | ✓                                   | ✓                                   | ✓                                   |
| Electrocardiogram  |                        | ✓                                     | ✓                                   | ✓                                   | ✓                                   |
| <i>Specific CV conditions/disease history requiring risk/benefit analysis and/or monitoring</i>      |                        |                                       |                                     |                                     |                                     |
| Poorly controlled hypertension   |                        |                                       | ✓                                   |                                     | ✓                                   |
| QT prolongation/arrhythmia   |                        | ✓ <sup>a</sup>                        | ✓                                   | ✓ <sup>a</sup>                      | ✓                                   |
| Angina/coronary artery disease   |                        |                                       | ✓                                   |                                     | ✓                                   |
| Arterial thrombotic events, including MI, POAD, stroke/TIA and PCI/stent                             |                        |                                       | ✓                                   |                                     | ✓                                   |
| Heart failure or LV dysfunction  |                        | ✓                                     |                                     |                                     | ✓                                   |
| Pulmonary disease/PAH  |                        | ✓                                     |                                     |                                     | ✓ <sup>a</sup>                      |
| Pleural effusion   |                        | ✓                                     |                                     | ✓ <sup>a</sup>                      |                                     |
| QRISK ≥20%   |                        |                                       | ✓                                   |                                     | ✓                                   |
| QRISK ≥10%   |                        |                                       |                                     |                                     | ✓ <sup>c</sup>                      |
| <i>Parameters and approximate testing frequencies for CV monitoring during treatment<sup>d</sup></i> |                        |                                       |                                     |                                     |                                     |
| Blood pressure   |                        | Monthly to 6-monthly                  | Monthly to quarterly                | Monthly to 6-monthly                | Monthly to quarterly                |
| HbA1c/fasting glucose  |                        |                                       | Monthly to 6-monthly                |                                     | Quarterly to 6-monthly <sup>e</sup> |
| Cholesterol/lipids   |                        | Quarterly to 6-monthly <sup>a,b</sup> | Quarterly to 6-monthly              | Quarterly to 6-monthly <sup>b</sup> | Monthly to 6-monthly                |
| Electrolytes   | Quarterly to 6-monthly | Monthly to 6-monthly                  | Monthly to 6-monthly                | Monthly to 6-monthly                | Monthly to 6-monthly                |
| Electrocardiogram  |                        |                                       | Quarterly to 6-monthly <sup>e</sup> |                                     |                                     |

Note: These general recommendations represent the views of ≥70% or more panel members during the consensus surveys and may need to be adjusted for past medical history.

Abbreviations: CABG, coronary artery bypass graft; CML, chronic myeloid leukaemia; CV, cardiovascular; HbA1c, glycated haemoglobin; LV, left ventricular; MI, myocardial infarction; PAH, pulmonary arterial hypertension; PCI, percutaneous coronary intervention; POAD, peripheral occlusive arterial disease; TIA, transient ischaemic attack; TKI, tyrosine kinase inhibitor.

<sup>a</sup>Although the consensus threshold was not reached during the surveys, the author group agreed to include this based on group discussion.

<sup>b</sup>Only patients with high CV risk.

<sup>c</sup>First-line treatment only.

<sup>d</sup>Frequency dependent on CV risk.

<sup>e</sup>Only patients with medium or high CV risk.

HbA1c/fasting glucose, cholesterol/lipids and electrolytes should be performed prior to commencing treatment and used for CV monitoring. A patient's specific CV conditions and disease history may be used to adjust the frequency of monitoring during treatment.

The panel made general recommendations on screening tests and monitoring timelines with each TKI (Table 2). These monitoring tests and frequencies may need to be adjusted depending on factors such

as personal medical history, CV risk and CV symptoms. Additional testing (including peripheral vascular Doppler ultrasonography) may be needed dependent on the CV risk and drug administration. The impact on patients and on clinics may also be considered, as many screening tests could be burdensome on patients and not cost effective. Other considerations include test availability, waiting and turnaround times and patient compliance. It should be standard practice to

**TABLE 3** Techniques and definitions used by panellists to define CV risk level.

| Low CV risk  | Medium CV risk   | High CV risk  |
|--|--|---|
| No medium-high risk parameters or risk score 0–1 in the HFA-ICOS risk proforma <sup>21</sup> | Any medium risk but no high/very high parameters or risk score 2–4 in the HFA-ICOS risk proforma <sup>21</sup> | Any high/very high risk parameters or risk score 5+ in the HFA-ICOS risk proforma <sup>21</sup>                   |
| QRISK3 score <10%  | QRISK3 score ~10%–20%  | QRISK3 score >20%   |
| No previous CV history   | May have some CV history or family history of CV disease   | Previous CV history   |
| No active atherogenic risk factors   | A single active atherogenic risk factor such as poorly controlled hypertension or diabetes, or smoking         | More than one active atherogenic risk factor such as diabetes (e.g., HbA1c >6%) or poorly controlled hypertension |
| Normal HbA1c (e.g., <4.5%) and normal lipid profile/cholesterol (e.g., Total-C/HDL-C <4)     | Biochemistry results may be normal or moderately elevated (e.g., HbA1c 4.5–6%, Total-C/HDL-C 4–6)              | Abnormal lipid profile/cholesterol (e.g., Total-C/HDL-C >6)   |
| No coronary or peripheral arterial symptoms or abnormalities                                 | May have mild or asymptomatic CV disease or be on primary prevention medication                                | Coronary or peripheral arterial symptoms or abnormalities   |

Note: Each of the above techniques were selected by  $\geq 1$  panellist during the consensus surveys. Panellists considered a patient to have medium or high CV risk if  $\geq 1$  or more of the above risk factors apply.

Abbreviations: CV, cardiovascular; HbA1c, glycated haemoglobin; HDL-C, high-density lipoprotein cholesterol; HFA-ICOS, Heart Failure Association/International Cardio-Oncology Society; QRISK3, QRESEARCH Cardiovascular Risk Algorithm3; Total-C, total cholesterol.

**TABLE 4** Monitoring test results and parameters where TKI dose interruption, discontinuation or switching may be required.

| Monitoring test   | Parameters/outcomes of concern   |
|---|--|
| Cardiac biomarkers, that is, natriuretic peptides and troponins | Any elevation would be of concern, with specific values of NT-proBNP >400 pg/mL, BNP >100 ng/L or troponins >ULN being triggers for TKI dose interruption/discontinuation/switching. If present, a cardiology referral is recommended                      |
| Angiogram   | Significant atheroma/stenosis or symptomatic disease, particularly for dasatinib/nilotinib/ponatinib. If present, cardiology referral is recommended   |
| Doppler imaging   | Interruption/discontinuation/switching if atheroma/stenosis with nilotinib or ponatinib. If carotid stenosis, management is required but not necessarily TKI dose adjustments; vascular surgical opinion is recommended                                    |
| Chest X-ray   | Pleural effusion, especially if the patient is on dasatinib  |
| Echocardiogram  | Any new or significant abnormality, including reduced LV function (for example, LVEF <50% or reduction >10%), PAH (peak systolic TR velocity >2.8 m/s, corresponding to an estimated PASP of 35 mmHg) or cardiomyopathy<br>Cardiology referral recommended |
| ABPI  | Mild <0.9, severe <0.4<br>If present, vascular surgical opinion is recommended   |

Note: These general recommendations represent the views of panel members and are based on consensus survey responses and group discussion.

Abbreviations: ABPI, ankle-brachial pressure index; BNP, B-type natriuretic peptide; LV, left ventricle; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PAH, pulmonary arterial hypertension; PASP, pulmonary artery systolic pressure; TKI, tyrosine kinase inhibitor; TR, tricuspid regurgitation; ULN, upper limit of normal.

have systems in place for structured, regular patient follow-ups, which may assist in maintaining patient compliance. Primary care services should play an important role in the screening and monitoring of patients for CV risks and symptoms. Where CV risk factors such as hypercholesterolaemia, diabetes mellitus or hypertension are identified, optimal control is recommended. For example, the Joint British Societies for the prevention of cardiovascular disease (JBS3) recommends a non-HDL cholesterol target of <2.5 mmol/L for patients with CV disease.<sup>32</sup> For patients on dasatinib, nilotinib, bosutinib or ponatinib, panellists recommended maintaining cholesterol levels as low as possible with a non-HDL cholesterol target of <2.2 mmol/L for patients with CV disease. Targets for blood pressure would be home systolic

<135 mmHg and home diastolic <85 mmHg.<sup>33</sup> Additionally, for patients on statins, care would need to be taken to avoid drug interactions between the statin and the specific TKI regimen.<sup>33</sup>

### 3.4 | CV event management

*Recommendations: Dose interruption, discontinuation or TKI switching should be considered if outcomes of concern are revealed by CV monitoring.*

Certain abnormal test results would prompt panel members to consider TKI dose interruption or discontinuation, including significant



increases in cardiac biomarkers (BNP, NT-proBNP or troponins), significant atheroma progression or new arterial stenosis revealed by angiogram or Doppler ultrasonography (Table 4). The panel recommended cardiology referral for patients with new symptoms, increases in cardiac biomarkers or new electrocardiogram or echocardiographic abnormalities, and a vascular surgery opinion if Doppler ultrasonography is abnormal.

Cardio-oncology services should be available to assist in managing patients with CV comorbidities or who have had a CV event. MDT meetings, including the haematologist, cardiologist and vascular surgeon were recommended for patients who have a CV event. Following a CV AE, the panel commented that decisions on dose modification, interruption or discontinuation should be based on the nature and severity of the event, the specific TKI and the CML disease state. For example, if an AOE occurs during treatment with a pro-atherogenic TKI, it is most likely that an alternative TKI would be sought. Should no other option be available (e.g., for a specific mutational profile), cardiology referral would be required for assessment, risk management and monitoring. Urgent referral to a vascular surgeon is needed if a carotid or lower limb arterial occlusion occurs.

## 4 | DISCUSSION

This consensus paper presents recommendations for CV comorbidity screening, monitoring, and management of patients receiving TKIs for CML from a multidisciplinary panel of clinicians who specialise in managing CML. To the best of our knowledge, this is the first UK multidisciplinary attempt at providing CV-related recommendations in this field. These recommendations may assist healthcare professionals to implement CV risk screening and management broadly and consistently. Although there have been no studies on the effectiveness of CV risk factor management in patients with CML receiving TKIs, patients with CML often have more comorbidities and an increased risk of CV disease compared with the general population.<sup>4,34</sup> Therefore, effective management of CV risk factors and comorbidities could reduce this risk to levels similar to the general population. The consensus of expert opinion is that all patients (exempting those starting imatinib) should undergo formal CV risk assessment at baseline, including specific screening tests and management of any risk factors or abnormalities detected. This is consistent with existing guidelines from BSH, which recommend similar testing parameters and advise using a risk assessment algorithm prior to commencing TKI treatment.<sup>17</sup> For patients at high CV risk or in those with pre-existing CV or peripheral vascular disease, the panel recommended additional investigations and the involvement of cardiologists or vascular surgeons to facilitate clinical decision-making and minimise ongoing risk. This expands upon NCCN guidelines, which recommend cardiology referral for those with CV risk factors commencing nilotinib or ponatinib.<sup>20</sup> Studies have shown the potential for cardiac and/or vascular adverse events during treatment with TKIs.<sup>35,36</sup> Although quantitative evaluation of differences in CV event risk is limited by the heterogeneity of CV event reporting in the relevant clinical trials, additional

monitoring has been recommended for bosutinib, dasatinib, nilotinib and ponatinib.<sup>35,36</sup> Of note, recently published ESC guidelines recommend baseline echocardiography screening for patients commencing dasatinib.<sup>37</sup> Although the majority of panellists did not recommend this, there was a difference of opinion between cardiologists and haematologists, with cardiologists supporting this additional testing. Due to the complexity of these comorbidities and side effects, haematologists may wish to collaborate with allied specialties for the treatment of patients with CML. Furthermore, BSH and ELN guidelines also suggest the inclusion of specialists in the ongoing clinical care of patients with CML, and particularly in relation to the management of side effects arising due to CML treatment.<sup>17,18</sup> The panel also advised that patients receiving second- or third-generation TKIs should undergo intermittent surveillance monitoring, with additional details provided on approximate testing frequencies by TKI and baseline CV risk. The monitoring tests recommended are consistent with those recommended by BSH<sup>17</sup> and include additional parameters and details not included in the recommendations from the NCCN and ESMO.<sup>19,20</sup> The panel recommended that decision-making around TKI interruption, cessation or change in patients who develop CV events should be multidisciplinary and based on the individualised balance of CV and haematological risk. This emphasis on collaborative decision-making differs from society recommendations such as ELN that do not expand upon responsibilities of the different professionals.<sup>18</sup>

Our study combined a panel meeting with an iterative survey technique inspired by the Delphi method. In the Delphi method, multiple surveys are conducted until group consensus is achieved.<sup>23</sup> The definition of consensus is arbitrary and varies between studies, with common definitions being based on percent agreement, or the proportion of ratings within a particular range.<sup>38</sup> Among studies defining consensus by percent agreement, the threshold for consensus varies widely, with one systematic review reporting consensus thresholds ranging from 50% to 97%, with a median of 75%.<sup>38</sup> The surveys conducted in our study are inspired by the Delphi technique in that the second survey is based on responses to the first survey. However, our approach differs in the nature of the questions asked, with our survey comprising a combination of question types, including matrix-style questions, open answer and multiple choice. We selected a threshold of 70% to define consensus to account for the heightened complexity of the questions in our surveys relative to traditional Delphi studies.

This article has strengths and limitations. A limitation of the survey technique used is that some important findings may have fallen just below the (arbitrary) threshold for inclusion. This limitation was addressed by allowing authors to request the inclusion of such items through a panel meeting and group discussion. A strength of this review is the use of a multidisciplinary panel of experts, which helps to ensure the balance and practicality of the recommendations generated. Another strength is using a combination of surveys and a panel discussion, as this enabled panel members to contribute ideas individually as well as being able to build on the ideas of others.

Panel members anticipate that these recommendations will assist in optimising and consistently applying CV screening and AE



management and engaging with CV colleagues so that patients with CML receive the most appropriate TKI therapy for the optimal duration to maintain remission whilst minimising CV toxicity. These recommendations may also be informative for pharmacists and primary care practitioners, who contribute to the review of treatment options for patients with CML and for CV monitoring and risk management.

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## CONFLICT OF INTEREST STATEMENT

DM has received honoraria from Bristol-Myers Squibb, Incyte, Pfizer and Novartis. ARL has received honoraria from Pfizer. PM has received honoraria from Pfizer and Incyte. ED has received honoraria from Pfizer and declares consultancy with Novartis. SC has received honoraria from Pfizer and Bristol-Myers Squibb. CM has received honoraria from Pfizer. NC has no conflicts to declare. KC has received honoraria from Celgene, Pfizer, Incyte and Novartis. NB has received honoraria from Pfizer. KA and SP are employees of and own stock in Pfizer. ST provided medical writing support and was funded by Pfizer. REC has received research funding from Bristol-Myers Squibb, and honoraria from Pfizer, Novartis and Bristol-Myers Squibb in the past 3 years.

## DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

## ORCID

Dragana Milojkovic  <https://orcid.org/0000-0002-0593-8220>

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### SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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