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CHRONIC MYELOID LEUKAEMIA AND TYROSINE KINASE INHIBITOR THERAPY:

ASSESSMENT AND MANAGEMENT OF CARDIOVASCULAR RISK FACTORS

Ross, David M¹; Arthur, Chris²; Burbury, Kate³, Ko, Brian S.⁴; Mills, Anthony K.⁵;
Shortt, Jake^{6,7}, Kostner, Karam⁸

¹Royal Adelaide Hospital and Flinders Medical Centre, Adelaide, South Australia, Australia; ²Royal North Shore Hospital, New South Wales, Australia; ³Peter MacCallum Cancer Centre, Victoria, Australia; ⁴ MonashHeart, Monash Health, Melbourne, Victoria, Australia; ⁵Princess Alexandra Hospital, Queensland, Australia; ⁶Monash Haematology, Monash Health, Clayton, Victoria, Australia; ⁷ School of Clinical Sciences at Monash Health, Faculty of Medicine, Nursing and Health Sciences, Monash University, Clayton, Victoria, Australia; ⁸Mater Hospital and University of Queensland, Queensland, Australia.

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Corresponding author:

Dr David Ross

Royal Adelaide Hospital

Port Rd

Adelaide

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SA 5000

Australia

david.ross@sa.gov.au

+61 8 7074 2429

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Abstract

Several BCR-ABL1 tyrosine kinase inhibitors (TKIs) are approved for the first-line treatment of chronic phase chronic myeloid leukaemia (CML). Disease control is achieved in the vast majority of patients and disease-specific survival is excellent. Consequently, there is now emphasis on managing comorbidities and minimising treatment-related toxicity. Second-generation TKIs have cardiovascular risks that are greater than with imatinib treatment, but these risks must be balanced against the superior CML responses encountered with more potent TKIs. Cardiovascular risk should be assessed at baseline using a locally validated model based on the Framingham risk equation. Clinicians involved in the care of CML patients should be aware of the vascular complications of TKIs and manage cardiovascular risk factors early to mitigate treatment-related risks. Reversible risk factors, such as dyslipidaemia, smoking, diabetes, and hypertension, should be addressed. We summarise the available data on cardiovascular complications in CML patients treated with TKIs. Using the latest evidence and collective expert opinion, we provide practical advice for clinicians to assess, stratify, and manage cardiovascular risk in people with CML receiving TKI therapy.

Keywords:

chronic myeloid leukaemia; tyrosine kinase inhibitors; cardiovascular risk

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Introduction

BCR-ABL Tyrosine Kinase Inhibitors (TKIs) are highly effective treatments for chronic myeloid leukaemia (CML). Imatinib and the second generation TKIs, nilotinib and dasatinib, are available for use in any line of therapy for chronic phase CML in Australia. Ponatinib is available for patients who are resistant to or intolerant of both nilotinib and dasatinib or who are expressing the T315I kinase domain mutation that confers resistance to most ATP-competitive TKIs. Bosutinib is approved by the Therapeutic Goods Administration (TGA) for the second or third-line treatment of CML, but is not publicly funded, and therefore not widely used in Australia.¹

Approximately 330 people are diagnosed with CML each year in Australia and the median age at diagnosis is 55 years.² With eight-year overall survival (OS) rates of more than 88% with TKI therapy, most people with CML have close to normal life expectancy.³ The newer, more potent TKIs have shown higher molecular response rates and lower rates of progression to accelerated or blast phase than standard dose imatinib. Progression (transformation) to accelerated phase / blast crisis (AP/BC) was reported in 4.6% of patients treated with dasatinib versus 7.3% of patients on imatinib in the 5-year follow-up of DASISION, while in ENESTnd AP/BC occurred in 3.5% of patients on nilotinib 300 mg twice daily and 7.4% of patients on imatinib with a similar duration of follow-up.^{4, 5}

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There is, however, no significant difference in OS between imatinib and newer TKIs at the standard doses approved for first-line treatment.^{4,5} Estimated 5-year OS on the ENESTnd study was similar with nilotinib 300 mg twice daily and imatinib 400 mg daily, at 93.7% and 96.2% respectively.⁴ Similarly, 5-year OS for patients on dasatinib 100 mg daily was 91% versus 90% for imatinib 400 mg daily in the DASISION study.⁵ The absence of a survival advantage with more potent TKIs may be explained by studies being under-powered to detect a small difference in survival, or by a small increase in deaths unrelated to CML. In addition, patients who develop imatinib intolerance or failure may be 'rescued' by second-line treatment with a more potent TKI.

In the first one to two years of TKI treatment there is a major focus on maximising treatment response to reduce the risk of progression. Most progression events occur during the first few years of treatment, and very few people who have shown a good response to TKIs after two to three years will subsequently die from CML-related events. Consequently, for the large number of people living for many years with long-term TKI treatment for CML the focus of CML management shifts toward preventing or minimising these important side-effects to maximise quality of life.

Vascular adverse events are an emerging issue, particularly among CML patients receiving second generation TKIs. Of particular relevance are the venous and arterial events reported during ponatinib, nilotinib, and dasatinib

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therapy and pulmonary hypertension and pleural effusion in patients receiving dasatinib. It can be difficult to determine whether vascular events during TKI therapy are related to treatment. The prevalence of cardiovascular disease (CVD) in the general population aged 55 to 64 years in Australia is approximately 35%, and 64% of this age group have three or more modifiable CVD risk factors.^{6 7} We aim to provide practical advice to clinicians regarding assessment, stratification, and management of CVD risk in people with CML.

Methods

We conducted a search of the Cochrane library, Embase, Medline, Medline Daily and In-Process, and PreMedline for publications up to 31 July 2017. The search focused on tyrosine kinase inhibitors, chronic myeloid leukaemia and the following search terms: cardiovascular, vascular, cardiac and pulmonary events; cardiovascular and cardiac safety; coronary risk; peripheral vascular disease; ischaemic heart disease; venous thromboembolism and cerebrovascular events; hypertension and pulmonary hypertension; and hyperglycaemia, hyperlipidaemia and hypercholesterolaemia. Since bosutinib is not widely used in Australia it was excluded from this review. On 17 August 2017 a group of haematologists and cardiologists from around Australia met to review the key evidence generated from this literature

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search and to develop consensus recommendations for the assessment and management of cardiovascular risk in people with CML receiving TKI therapy.

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Molecular responses on first-line TKI treatment

The BCR-ABL gene is present in all CML patients, and the measurement of molecular response (based on BCR-ABL quantification by reverse-transcriptase PCR standardised to the International Scale) is routinely used to assess response and guide treatment decisions. The second generation TKIs, nilotinib and dasatinib show faster and deeper levels of molecular response than standard dose imatinib in first-line treatment.^{4, 5} The ENESTnd study compared nilotinib 300 mg twice daily (n=282) or nilotinib 400 mg twice daily (n=281) to imatinib 400 mg once daily (n=283).^{4, 8} Similar molecular responses were seen with nilotinib 300 mg twice daily and nilotinib 400 mg twice daily. The 300 mg twice daily dose is now the recommended nilotinib dose for *de novo* patients in clinical practice. By 12 months the cumulative incidence of major molecular response (MMR; BCR-ABL $\leq 0.1\%$) was significantly higher in patients receiving nilotinib 300 mg twice daily (51%) than in those receiving imatinib (27%; $P < 0.001$), with these figures rising to 77% and 60% after five years. After five years the cumulative incidence of a deep molecular response (MR^{4.5}; BCR-ABL^{IS} $\leq 0.0032\%$), was 53.5% in patients receiving nilotinib 300 mg twice daily compared to 31.4% in those receiving imatinib. In the DASISION study comparing dasatinib 100 mg daily (n=259) with imatinib 400 mg daily (n=260) the cumulative incidence of MMR by 12 months was significantly higher with dasatinib (46%) than with imatinib (28%).^{5, 9} By five

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years of follow-up 76% and 64% of patients, respectively, had achieved MMR (p=0.0022). The cumulative incidence of MR^{4.5} by 5 years was 42% for dasatinib and 33% for imatinib (p=0.025).

The phase 3 EPIC study comparing ponatinib with imatinib for the treatment of newly-diagnosed CML was stopped early due to treatment-emergent cardiovascular adverse events and too few patients were treated for a meaningful comparison of efficacy.¹⁰ In the phase 2 PACE study of ponatinib in 267 heavily pre-treated patients with chronic-phase CML significant anti-leukaemic activity was demonstrated: 34% of patients achieved MMR (56% of those with the T315I mutation).¹¹ MR^{4.5} was observed in 15% of patients with chronic-phase CML (23% of those with T315I mutation).

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CV Ischaemic Events with TKI therapy

The exact incidence of CV ischaemic events during TKI therapy remains unclear as many of the earlier studies did not routinely report CV events. In addition, variable definitions for CV endpoints and CV exclusion criteria were used in the different studies.

An epidemiological study reported that the incidence of a composite endpoint of major arterial events (PAOD, IHD, and CVA or transient ischaemic attack (TIA)) in people with CML was 0.8 per 100 patient-years (95% CI 0 to 1.8) with non-TKI therapy, with imatinib 0.1 (95% CI 0 to 0.1), dasatinib 1.1 (95% CI 0.8 to 1.4), nilotinib 2.8 (95% CI 2.0 to 3.6), and ponatinib 10.6 (4.6 to 46.5) per 100 patient-years.¹²

Dose-dependent treatment-emergent CV events have been seen with nilotinib (7.5% with 300 mg dose and 13.4% with the 400 mg dose) and at a higher rate than with imatinib (2.1%).⁴ In the DASISION study arterial ischaemic events occurred in 5% of dasatinib-treated patients and in 2% of patients on imatinib.⁵ The third generation TKI, ponatinib, has the highest reported incidence of CV events. In the EPIC study, arterial occlusive events, serious arterial occlusive events, and serious grade 3 or 4 ischaemic events were reported in 7.1% of patients treated with ponatinib versus 2.0% with imatinib.¹⁰ A single-centre study from MD Anderson confirmed that rates of CV events

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and arterio-thrombotic events were higher with ponatinib than with second generation TKIs.¹³

Pulmonary hypertension is more commonly observed with dasatinib compared with other TKIs, with an incidence of approximately 5%

In DASISION, pulmonary arterial hypertension (PAH) was reported in 5.4% of patients receiving treatment with dasatinib compared 0.4% of those receiving imatinib (0.4%).⁵ Nine of the 14 patients with PAH also had a pleural effusion. Routine surveillance with echocardiography was not conducted, so most cases that were identified were likely to have had symptomatic disease, and 5.4% possibly under-estimates the true incidence. It is unclear whether the apparent association with pleural effusion reflects ascertainment bias due to a higher rate of echocardiography in patients with effusions, or whether the two conditions may have shared risk factors. PAH has rarely been reported in patients receiving imatinib, nilotinib, and ponatinib.

Reported rates of PAH during dasatinib treatment vary between 0.45% in a French registry up to 25% in a small retrospective study.^{14, 15} These cases of PAH were clinically significant events, requiring medical intervention and cessation of dasatinib. Clinical and haemodynamic improvement was seen in most patients within nine months of discontinuing dasatinib in the registry data.

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Peripheral arterial occlusive disease is more common with nilotinib and ponatinib

In a meta-analysis the pooled rate of PAOD events was 0.3 per 100 patient years among CML patients. The event rates for individual TKIs were 0.1 for imatinib, 0.2 for dasatinib, 1.3 for nilotinib, and 3.9 per 100 patient-years for ponatinib.¹² In the ENESTnd study the incidence of PAOD was the same in each of the nilotinib dose arms at 2.5%, suggesting that the dose-dependent effect seen with overall CV events may not occur for PAOD.⁴ Two imatinib-treated patients in DASISION had PAOD events compared to no patients receiving dasatinib.¹⁰

Rates of venous thrombotic events are low during CML treatment with an incidence of <1% for all TKIs.

A population-based registry reported that patients with CML are twice as likely to develop venous thromboembolic events as the general population (incidence rate ratio (IRR): 2.0 (95% CI 1.2 to 3.3)).¹⁶ A meta-analysis of 12 randomised clinical trials showed a similar odds ratio for the risk of venous occlusive events comparing newer TKIs with imatinib, but this did not reach statistical significance (OR 2.17, 95% CI 0.90 to 5.25).¹⁷ In this meta-analysis

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venous occlusive events were reported in 0.27% of imatinib-treated patients, 0.65% of patients receiving ponatinib, 0.79% with nilotinib, and 0.86% with dasatinib.

Ischaemic heart disease is more common with dasatinib, nilotinib, and ponatinib (in order of increasing risk) than with imatinib.

The incidence of MI was higher with nilotinib (2.9 per 100 patient-years; 95% CI 0.6 to 5.8) than with dasatinib (1.9; 95% CI 0.4 to 3.7) or imatinib (0.8; 95% CI 0.4 to 1.0).¹⁶ In this population-based study the number of patients on newer TKIs was smaller, and with the emerging recognition of CV AEs with nilotinib, clinicians may have preferentially used imatinib or dasatinib in patients with increased CV risk. A meta-analysis of 29 clinical trials (some non-randomised) reported a rate of ischaemic heart disease (IHD) of 0.1 per 100 patient-years for imatinib, 0.6 for dasatinib, 1.4 for nilotinib, and 6.0 for ponatinib.¹²

The rate of IHD during nilotinib treatment appears to be dose-dependent with an incidence of 3.9% (n=11) at a dose of 300 mg twice daily and 8.7% (n=24) with 400 mg twice daily, compared to 1.8% (n=5) of patients receiving imatinib.⁴

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**The incidence of cerebrovascular complications is around 1% or less for all
first-line TKIs**

The overall rate of cerebrovascular events in the CML population is similar to that in the general population (IRR 0.9; 95% CI 0.5 to 1.5). Population-based registry data have shown a cerebrovascular event rate of 0.4 per 100 person-years with imatinib (95% CI, 0.1 to 0.5); 0.4 (95% CI, 0 to 1.2) with dasatinib, and 1.1 (95% CI, 0 to 3.0) with nilotinib.¹⁶ In a meta-analysis of clinical trials the cerebrovascular event rates were <0.1 per 100 patient-years for imatinib (95%CI 0-0.1), 0.3 for nilotinib (95%CI 0.1-0.4), 0.7 for dasatinib (95%CI 0.4-1.0), and 2.9 for ponatinib (95%CI 0-6.1).

In the ENESTnd study more patients receiving nilotinib than imatinib experienced ischaemic cerebrovascular events: four (1.4%) patients with nilotinib 300 mg, nine (3.2%) patients with nilotinib 400 mg and one (0.4%) patient with imatinib.⁴ These data again suggest a dose-dependent risk with nilotinib. In DASISION, two dasatinib-treated patients had a transient ischaemic attack compared to no imatinib-treated patients.⁵

Cerebrovascular events were reported in 3.6% of ponatinib-treated patients in PACE and in 2% of patients in EPIC with a median follow-up of 15 months (range 0.1 to 25) and 5.1 months (range 3.2 to 7.1), respectively.^{10, 11}

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Possible mechanisms for CV effects of TKIs

CV effects of TKIs may be considered in three broad categories: 1) exacerbating conventional CV risk factors, such as hypertension, hyperlipidaemia and impaired glucose tolerance; 2) increased endothelial reactivity; 3) increased or decreased platelet reactivity. Glycaemic control may be improved with imatinib and dasatinib, but worsened by nilotinib.¹⁸⁻²⁰ Nilotinib can increase LDL-cholesterol levels.⁴ Triglycerides are either unaffected or reduced by all three first-line TKIs.²⁰ Systemic hypertension is more common with ponatinib.²¹ A study assessing the impact of imatinib, dasatinib and nilotinib on thrombus generation on immobilised collagen demonstrated accelerated thrombus formation after exposure to nilotinib *in vitro* and *ex vivo*.²² Nilotinib and ponatinib are reported to inhibit endothelial proliferation and survival *in vitro*, which may affect vascular regeneration, repair and re-perfusion.^{23, 24} Nilotinib induces increased platelet adhesion and activation, whereas dasatinib inhibits platelet aggregation and is associated with a small increase in clinically significant bleeding.^{22, 25} More work is needed to understand better the impact of TKIs on vascular risk.

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Assessing Cardiovascular Risk Factors

Most CV ischaemic events during TKI treatment of CML emerge in those patients with pre-existing CV disease and/or risk factors.^{4, 10} In the ENESTnd study an exploratory analysis using the Framingham risk score for baseline CVD risk demonstrated that 32% of patients in the study were in the intermediate or high risk Framingham groups, but that these patients accounted for 70% of the reported CV events.⁴ In the EPIC study one or more cardiovascular risk factors, or a history of CVD, was present in 10 out of 11 patients who developed arterial occlusive events on ponatinib and in 2 out of 3 patients who had events on imatinib.¹⁰ The assessment of CV risk and modification of treatable risk factors is therefore recommended in all TKI-treated CML patients. The National Vascular Disease Prevention Alliance (NVDPA) and the New Zealand Ministry of Health provide comprehensive guidelines for the assessment of absolute CVD risk based on the Framingham Risk Equation, and each provides an online CV disease risk calculator. The NVDPA risk calculator can be used in adults aged 35-74. The New Zealand Society for the Study of Diabetes (NZSSD) risk calculator can be used in adults with type 2 diabetes mellitus.

Cardiovascular risk status should be assessed prior to commencing TKI treatment and periodically re-evaluated using an online calculator (<http://www.cvdcheck.org.au> or <http://www.nzssd.org.nz/cvd/>)

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Additional Assessments

Echocardiography

Echocardiography may be valuable for monitoring TKI-treated patients who may be at risk of, or with elevated pulmonary artery pressures, or additional risk factors for heart disease. We therefore recommend an early baseline echocardiogram before starting dasatinib or ponatinib treatment, and in patients on any TKI if there is a prior history of cardiac or ischaemic vascular complications. Considering the waiting times for cardiac investigations in some healthcare settings we do not recommend routinely delaying TKI treatment until a test is performed. However, since CV events have been reported as early as four weeks after starting treatment, we recommend testing as soon as possible after diagnosis. The early stages of pulmonary vascular disease may not be detected by routine echocardiography, which relies on an accurate tricuspid valve Doppler signal at rest,²⁶ and formal cardiac catheterisation studies may be required if there is a high clinical suspicion of symptomatic PAH.

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Recommendation for Echocardiography

Baseline echocardiography should be considered for all patients receiving dasatinib or ponatinib and in high CV risk patients receiving other TKIs.

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Cardiac CT and Coronary Artery Calcium Scoring

In asymptomatic individuals, coronary artery calcium scoring (CAC) is a technique for measuring the amount of calcium in the coronary arteries using an ECG-gated non-contrast CT scan of the heart. In the setting of primary prevention CAC can predict the risk of a future cardiac adverse event. CAC is a surrogate marker for total atherosclerotic plaque burden derived from 3 mm reconstructions of ECG gated non contrast CT (Agatson Score). The radiation dose is approximately 1 mSv (similar to breast mammography). The Cardiac Society of Australia and New Zealand (CSANZ) recommend the use of CAC scoring for patients with intermediate CV Risk (absolute 10-year CV risk of 10-20%) in whom CAC is considered cost-effective.²⁷ The score is not recommended for patients at low risk (<5%) or for those with high risk (>20%) as it is unlikely to change management in these patients. A CAC score greater than 400, or greater than 100 and above the 75th percentile for age, usually identifies patients who may benefit from aspirin and statin therapy to reduce cardiovascular risk, in addition to dietary and lifestyle interventions.²⁸⁻³⁰ Calcium scoring is not currently reimbursed in Australia and New Zealand and costs between 100 and 200 dollars.

Recommendation for Coronary Artery Calcium Scoring

CAC Scoring should be considered for patients with intermediate risk of a cardiovascular event (10-20% over the next 5 years).

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Ankle-Brachial Index

The ankle-brachial index (ABI) is the ratio of the systolic blood pressure in the lower limb to that in the upper limb, and is used as a non-invasive indicator of significant atherosclerosis. The ABI is reported to have high sensitivity for the detection of significant atherosclerosis in the arteries of the lower limbs in symptomatic patients presenting with claudication.³¹ In asymptomatic individuals an abnormal ABI is associated with increased all-cause mortality (HR 2.99; 95% CI 2.16 to 4.12) and increased cardiovascular mortality (HR 2.35; 95% CI 1.91 to 2.89).³² The probability of finding an abnormal ABI is related to the prevalence of vascular risk factors, e.g. in one study 34% of hospitalised patients with diabetes had an abnormal ABI.³³ Consequently, ABI screening identifies very few patients who are not already identified as being at high CV risk, and therefore we do not recommend its routine use in asymptomatic individuals.

Recommendation for Ankle-Brachial Index

ABI testing should be considered for symptomatic patients with claudication in the lower limbs.

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Choice of TKI

The choice of TKI treatment for CML requires a balance between the level of CV risk and CML risk. For example, a patient with high CML risk and low CV risk may be a more suitable candidate for a second generation TKI, whereas a patient with high CV risk and low CML risk may be considered appropriate for imatinib treatment. Furthermore, additional goals of treatment should also play a role in the choice of TKI. These may include the minimisation of common TKI side effects that affect quality of life, and the emerging goal of treatment-free remission (TFR).³⁴

Treatment-free remission

Patients who achieve a deep molecular response (typically MR^{4.5}) on TKI treatment and sustain this response for at least two years may have around a 50% chance of remaining in MMR if the TKI is discontinued.³⁴ During the first five years of treatment the chances of being eligible for a discontinuation attempt are higher among patients on second-generation TKIs. The ENESTfreedom study of nilotinib discontinuation reported that the prevalence of CVD risk factors (e.g. hyperlipidaemia) reduced during TFR.³⁵ The number of vascular events was lower in the second year of TFR than during the first year of TFR or during nilotinib treatment. There are currently no data on CVD risk after stopping dasatinib or ponatinib treatment. The achievement of TFR

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might be an important step to minimise the long-term risk of TKI-related adverse effects.

Managing risk factors

Patients should be stratified by CV risk level to determine the need for appropriate therapies to reduce CV risk factors (Figure 1). All patients should be given general advice about lifestyle factors.

Low Cardiovascular Risk (<10% risk over next 5 years)

For low risk patients the cardiovascular risk score should be reviewed every two years (Figure 1).

Intermediate Cardiovascular Risk (10-20% over next 5 years)

For patients in the intermediate risk group, treatment of modifiable risk factors is indicated if lifestyle intervention for three to six months has not reduced the individual's risk factors.⁶ More aggressive risk factor modification is also indicated for Aboriginal and Torres Strait Islander people, patients with an early family history of CVD, familial hyperlipidaemia, and those with persistently high blood pressure.^{6, 36} Patients with intermediate CV risk should be re-assessed every 6 to 12 months (Figure 1). Specific areas in which CV risk can be reduced include diabetes, hyperlipidaemia, and hypertension.

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Impaired glucose tolerance and diabetes mellitus

Measurement of the fasting plasma glucose is recommended to screen for diabetes.⁶ A value of ≤ 5.4 mmol/L is considered normal. A result between 5.5 mmol/L and 6.0 mmol/L may be normal but some people will show diabetes or impaired glucose tolerance in an oral glucose tolerance test (OGTT). A value of ≥ 6.1 mmol/L but ≤ 6.9 mmol/L is diagnostic of impaired fasting glucose and requires an OGTT to confirm diabetes or impaired glucose tolerance. A value of ≥ 7.0 mmol/L on two separate occasions is diagnostic of diabetes and does not require an OGTT.

Patients with diabetes should be treated following recommended guidelines for the initiation of metformin or a sulphonylurea.³⁷ The target for HbA_{1c} is shown in Table 1. Patients whose glycaemic control is sub-optimal should be referred to an endocrinologist for specialist input.

Hyperlipidaemia

Statins are very effective for the lowering of LDL-cholesterol and are widely used for the treatment of hyperlipidaemia to reach recommended targets (Table 1). Many drugs, including TKIs are metabolised by CYP3A4, and the statins least likely to affect CYP3A4 are pravastatin and rosuvastatin.^{6, 38, 39}

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Hypertension

Patients with persistently high blood pressure $\geq 160/100$ mmHg should start treatment with either an angiotensin converting enzyme (ACE) inhibitor, an angiotensin receptor blocker (ARB), a calcium channel blocker, or low-dose thiazide or thiazide-like diuretic. Blood pressure targets for treatment are shown in Table 1.

High Cardiovascular Risk (>20% over next 5 years)

All of the measures recommended for lower risk patients should be undertaken. In addition to a calculated high absolute risk for a CV event, patients with known risk factors, such as diabetes and aged over 60 years or with microalbuminuria, those with stage III or more kidney disease, genetic dyslipidaemias, severe hypertension or with established vascular disease, need more rigorous management of risk factors. Therefore, liaison with a cardiologist (or other vascular specialist) is recommended (Figure 1).

Need for a team approach to optimise and personalise management

An important practical question is who should be responsible for assessing and managing vascular risk factors in an asymptomatic CML patient. In Australia and New Zealand conditions such as hyperlipidaemia or hypertension will commonly be managed by the general practitioner (GP). However, GPs with limited familiarity with TKIs may be reluctant to intervene

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without the advice of the treating haematologist. Conversely, the haematologist may be reluctant to take on the management of such conditions. A team approach is needed with good communication regarding shared treatment goals. In the tertiary hospital setting, where many CML patients are managed, some centres have cardio-oncology clinics or cancer survivorship clinics that focus on the late effects of cancer treatments. Such clinics may provide a useful platform for the multi-disciplinary management of CML patients with additional CV risk factors.

Limitations

The data that we have reviewed regarding vascular risk in TKI-treated CML have some important limitations. Clinical trials may have had differing inclusion and exclusion criteria, differing definitions for vascular events, and commonly did not report pre-treatment vascular risk factors. Clinical trials compared second generation TKIs to imatinib only, rendering direct comparison between newer TKIs more difficult. Attention to cardiovascular outcomes has been greater in more recent trials. Registry data may help to provide a real world picture of CV risk in CML, but are generally less complete and systematic than prospective data collection in clinical trials. Lastly, no interventional studies have been undertaken in CML to demonstrate whether the treatment of CV risk factors reverses the excess risk related to TKIs.

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Conclusions

With optimal TKI selection and adherence very few chronic phase CML patients will die from their leukaemia. Comorbid conditions now have a greater impact on overall survival than do conventional CML-specific factors, such as Sokal score.⁴⁰ CVD remains common in the general population, including CML patients, with substantial clinical consequences. Furthermore, CVD is potentially exacerbated by TKI therapy and is therefore an increasingly important focus in the management of CML. Most CV events occur in older patients and in those with additional risk factors. These risk factors should be considered at the time of TKI selection and periodic sequential risk re-assessment of vascular risk factors should be undertaken in a team approach so that any correctable risk factors are treated appropriately. In this review, we have tried to provide recommendations for the assessment and management of CV risk and complications during TKI treatment. The recommendations are currently based on expert opinion derived from currently available clinical data and experimental data proposing the pathophysiological mechanisms of action. With a growing awareness of cardiovascular disease in CML new studies may provide the data for evidence-based recommendations in the future.

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Table 1 Targets for CV Risk Factors in Primary Prevention

Risk factor	Treatment Target
Diabetes	

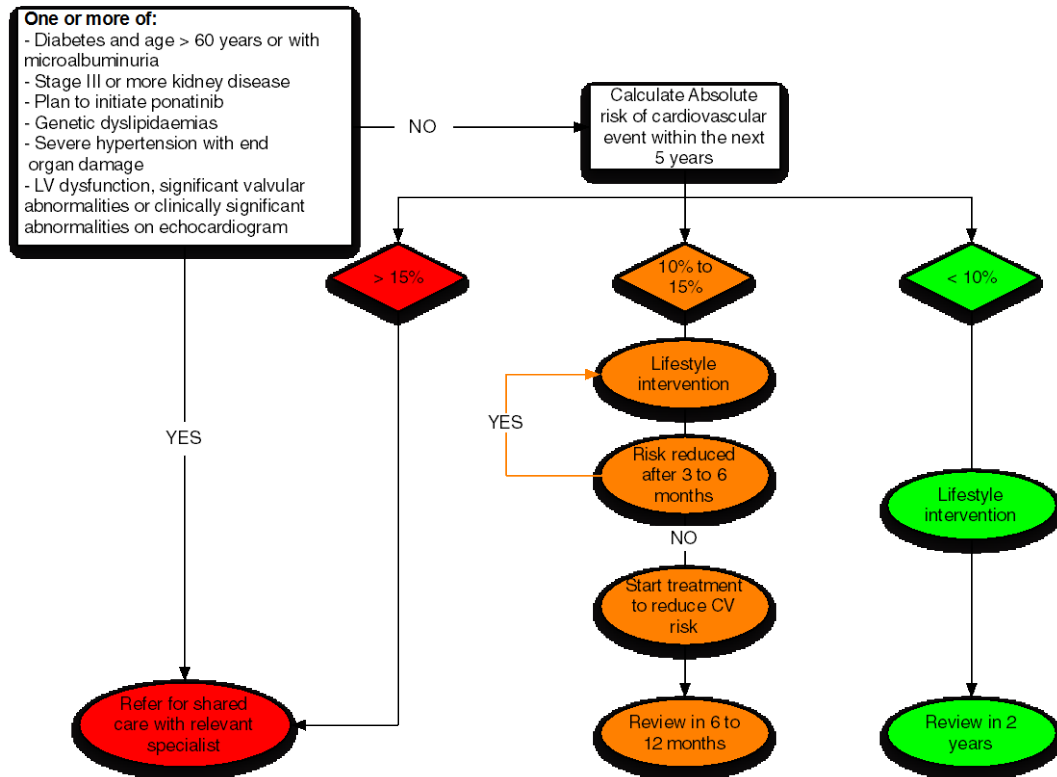
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HbA1c	≤ 7%
Lipids	
Total Cholesterol	< 4.0mmol/L
HDL-C	≥ 1.0 mmol/L
LDL-C	< 2.0 mmol/L
Non HDL-C	< 2.5 mmol/L
Triglycerides	< 2.0 mmol/L
Blood pressure	<140/90 mmHg ≤ 130/80 mm/Hg (in people with diabetes)

Adapted from the NVDPA Guidelines for the Management of Absolute Cardiovascular Risk Factors⁶

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Figure 1: Assessing Cardiovascular Risk in Patients with CML



Adapted from the NVDPA Guidelines for the Management of Absolute Cardiovascular Risk Factors⁶

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