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EMN guideline article

PREVENTION, MONITORING AND TREATMENT OF CARDIOVASCULAR ADVERSE EVENTS IN MYELOMA PATIENTS RECEIVING CARFILZOMIB

A Consensus Paper by the European Myeloma Network and the Italian Society of Arterial
Hypertension

Sara Bringhen, MD,^{1*} Alberto Milan, MD,² Mattia D'Agostino, MD,¹ Claudio Ferri, MD,³ Ralph Wäsch, MD,⁴ Francesca Gay, MD,¹ Alessandra Larocca, MD,¹ Massimo Offidani, MD,⁵ Sonja Zweegman, MD,⁶ Evangelos Terpos, MD,⁷ Hartmut Goldschmidt, MD,⁸ Michele Cavo, MD,⁹ Heinz Ludwig, MD,¹⁰ Christoph Driessen, MD,¹¹ Holger Auner, MD,¹² Jo Caers, MD,¹³ Martin Gramatzki, MD,¹⁴ Meletios A Dimopoulos, MD,⁷ Mario Boccadoro, MD,¹ Hermann Einsele, MD,¹⁵ Pieter Sonneveld, MD,¹⁶ Monika Engelhardt, MD⁴

¹Myeloma Unit, Division of Hematology, University of Torino, Azienda Ospedaliero-Universitaria Città della Salute e della Scienza di Torino, Torino, Italy;

²Dpt of Medical Sciences – Internal Medicine and Hypertension Division - University of Torino - AOU Città della Salute e della Scienza di Torino; Rete Oncologica Piemontese, Torino, Italy;

³University of L'Aquila, MeSVA Department - San Salvatore Hospital, Division of Internal Medicine & Nephrology, Coppito, Italy;

⁴Department of Medicine I, Hematology, Oncology & Stem Cell Transplantation, Medical Center - University of Freiburg, Faculty of Medicine, University of Freiburg, Germany;

⁵Clinica di Ematologia, AOU Ospedali Riuniti di Ancona, Ancona, Italy;

⁶Amsterdam UMC, Vrije Universiteit Amsterdam, VU University Medical Center, Department of Hematology, Cancer Center Amsterdam, Amsterdam

⁷Department of Clinical Therapeutics, National and Kapodostrian University of Athens, School of Medicine, Athens, Greece;

⁸University Clinic Heidelberg, Internal Medicine V and National Center for Tumor Diseases (NCT), Heidelberg, Germany;

⁹"Seràgnoli" Institute of Hematology and Medical Oncology, University of Bologna, Bologna, Italy;

¹⁰1. Medical Department and Oncology, Wilhelminenspital Wien, Vienna, Austria;

¹¹Department of Oncology and Hematology, Kantonsspital St. Gallen, St. Gallen, Switzerland;

¹²Faculty of Medicine, Department of Medicine, Imperial College London, UK;

¹³Department of Hematology, Domane University Liege, Belgium;

¹⁴Division of Stem Cell Transplantation and Immunotherapy, University of Kiel, Kiel, Germany;

¹⁵Department of Internal Medicine II, University Hospital Würzburg, Würzburg, Germany;

¹⁶Department of Hematology, Erasmus Medical Center, Rotterdam, the Netherlands.

***Correspondence:** Dr. Sara Bringhen, MD, PhD, Myeloma Unit, Division of Hematology, University of Torino, Azienda Ospedaliero-Universitaria Città della Salute e della Scienza di Torino, Torino, Italy. Tel.: 0039 0116334260. E-mail: sarabringhen@yahoo.com.

ORCID ID: <https://orcid.org/0000-0003-4539-6363>

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Sara Bringhen has received honoraria from BMS, Celgene, Amgen and Janssen; has served on the advisory boards for Amgen and Janssen; and has undertaken consultancy for Takeda.

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Supervision: Bringhen, Milan, Boccadoro, Einsele, Sonneveld, Engelhardt.

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Running head: CARDIOVASCULAR TOXICITY IN MM

Abstract

The novel proteasome inhibitor carfilzomib alone or in combination with other agents is already one of the standard therapies in relapsed and/or refractory multiple myeloma (MM) patients and produces impressive response rates in newly diagnosed MM as well. However, carfilzomib-related cardiovascular adverse events (CVAEs) – including hypertension (all grades: 12.2%; grade ≥ 3 : 4.3%), heart failure (all grades: 4.1%; grade ≥ 3 : 2.5%) and ischemic heart disease (all grades: 1.8%; grade ≥ 3 : 0.8%) – may lead to treatment suspensions. At present, there are neither prospective studies nor expert consensus on the prevention, monitoring and treatment of CVAEs in myeloma patients treated with carfilzomib.

An expert panel of the European Myeloma Network in collaboration with the Italian Society of Arterial Hypertension and with the endorsement of the European Hematology Association aimed to provide recommendations to support health professionals in selecting the best management strategies for patients, considering the impact on outcome, the risk-benefit ratio of diagnostic and therapeutic tools and thereby to achieve myeloma response with novel combination approaches, while preventing CVAEs.

Patients scheduled to receive carfilzomib need a careful cardiovascular evaluation before treatment and an accurate follow-up during treatment. A detailed clinical assessment before starting carfilzomib treatment is essential to identify patients at risk for CVAEs, and accurate monitoring of blood pressure and of early signs and symptoms suggestive of cardiac dysfunction remains pivotal to safely administer carfilzomib without treatment interruptions or dose reductions.

Keywords: multiple myeloma, cardiovascular toxicity, carfilzomib, adverse events, clinical assessment, blood pressure monitoring

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INTRODUCTION

Carfilzomib (CFZ), a second-generation proteasome inhibitor (PI), is active as a single agent and in combination with other anti-multiple myeloma (MM) agents. CFZ has been approved in Europe for the treatment of relapsed/refractory MM (RRMM), in combination with lenalidomide and/or dexamethasone, based on the randomized trials ASPIRE [1] and ENDEAVOR [2]. In ASPIRE, 792 patients were randomized to receive CFZ with lenalidomide and dexamethasone (KRd group) or lenalidomide and dexamethasone alone (Rd group). In ENDEAVOR, 929 patients were randomized to receive CFZ with dexamethasone (Kd group) or bortezomib with dexamethasone (Vd group). CFZ-based regimens, KRd and Kd, are the first therapy combinations to demonstrate a significant overall survival advantage (21% reduction of risk of death, resulting in nearly eight additional months of overall survival) for relapsed MM patients versus recent standards-of-care (Rd and Vd) [3].

However, in ASPIRE and ENDEAVOR, KRd and Kd treatments were associated with higher than expected rates of hypertension (all grades: 14.3% and 16%; grade ≥ 3 : 4.3% and 9%), heart failure (HF) (all grades: 6.4% and 3%; grade ≥ 3 : 3.8% and 4.8%) and ischemic heart disease (all grades: 5.9% and 0.9%; grade ≥ 3 : 3.3% and 1.7%, respectively) [1,2].

A recent meta-analysis performed on 24 clinical studies with available non-hematological adverse events data associated with CFZ treatment showed that the incidence of all-grade and grades ≥ 3 cardiovascular adverse events (CVAEs) was 18.1% and 8.2%, respectively. In randomized clinical trials, the relative risk (CFZ vs controls) of all-grade and grade ≥ 3 CVAEs were 1.8 and 2.2, respectively [4]. The most frequent CVAEs during treatment with CFZ are hypertension (all grades: 12.2%; grade ≥ 3 : 4.3%), heart failure (all grades: 4.1%; grade ≥ 3 : 2.5%) and ischemic heart disease (all grades: 1.8%; grades ≥ 3 : 0.8%). There is a specific issue with dyspnea, since it is reported in patients treated with CFZ with an incidence of 23.9% (all grades) and 3.2% (grades ≥ 3), although it could be a symptom related to cardiovascular conditions, such as cardiac failure, as well as pulmonary complications. Venous thromboembolic events and thrombotic microangiopathy have also been reported in patients who received CFZ [1,2,11,3–10].

The mechanisms by which CFZ induces CVAEs are poorly understood. However, speculations can be made on its irreversible and highly potent proteasome inhibition activity that could differentiate its safety profile from that of bortezomib [12]. Cardiac stress produces misfolded proteins; proteasome-mediated degradation of these toxic products is pivotal to preserve cellular function in some patients [13]. Moreover, the levels of nitric oxide, an important mediator of endothelial function, could also be modulated by proteasome activity, and decreased nitric oxide levels could impair vasodilatation, inducing hypertension and cardiac dysfunction [14].

Neither prospective studies nor expert consensus have been reported so far on the prevention, monitoring and treatment of CVAEs in MM patients treated with CFZ. Therefore, this European Myeloma Network (EMN) consensus paper, in collaboration with the Italian Society of Arterial Hypertension (SIIA) and the support of the European Hematology Association (EHA), aims to help physicians to prevent and manage CVAEs during CFZ treatment, thereby improving the risk/benefit ratio of this widely used drug.

CURRENTLY AVAILABLE GUIDELINES ON CANCER TREATMENTS AND CARDIOTOXICITY

It is essential to identify patients who are at high risk to develop cardiotoxicity [11,15]. The American Society of Clinical Oncology Clinical Practice Guidelines [15] use treatment-related and patient-related criteria to describe patients at increased risk for cardiac dysfunction (**Table S1**). However, treatment-related criteria are based on cardiotoxicity studies performed in tumor entities other than MM and that interdisciplinary cardiotoxicity expert panels had expertise in medical oncology, cardiology, radiation-oncology, imaging, exercise physiology, cancer prevention, and survivorship, but not in hematology. For instance, trastuzumab-related cardiotoxicity is based on human-epidermal-growth-factor-receptor-2 inhibition, which is not a meaningful target in hematology, while anthracycline and radiotherapy-mediated cardiotoxicity do not represent issues during CFZ treatment, since heart bystander irradiation is rare in MM and CFZ treatment in association with anthracyclines is not an approved regimen in MM [16].

Moreover, these guidelines highlighted the role of left ventricular ejection fraction (LVEF) assessment in preventing and monitoring systolic dysfunction. Regarding CFZ, a sub-analysis of the ENDEAVOR study on 151 patients randomized between Kd vs. Vd failed to demonstrate a lower LVEF in Kd-treated patients through echocardiographic follow-up analyzed by cardiologists in a blinded fashion [6].

The European Society of Cardiology position paper on cancer treatments and cardiotoxicity reviewed the different steps in cardiovascular monitoring and decision-making before, during and after cancer treatment with drugs that can cause potential cardiovascular side effects [11]; however, as in the previously discussed guidelines [15], the study population was represented by patients with breast or other solid cancers. The incidence of CVAEs during treatment with PIs was indeed discussed in these guidelines, even though prevention and monitoring of CVAEs in MM patients were not specifically addressed.

For all these reasons, the following suggestions are based on the American Society of Clinical Oncology Clinical Practice Guidelines [15], the European Society of Cardiology (ESC) position paper

on cancer treatments and cardiotoxicity [11], the ESH (European Society of Hypertension)/ESC guidelines for management of arterial hypertension [17], the American Society of Hypertension and the International Society of Hypertension guidelines [18], and may be considered expert recommendations. The aim of this EMN paper is to assist health professionals in selecting the best management strategies for each single patient. Nevertheless, due to the lack of high quality data on such issues, the final decision concerning each patient must be taken by the responsible health professional, who finally shares the decision with the patient and caregivers.

RISK FACTORS

To identify patients at increased risk for CVAEs, the first step is a careful baseline assessment of risk factors, including cardiovascular risk factors and prior cardiovascular diseases (**Table 1, Figure 1**) as well as prior exposition to cardiotoxic cancer treatments (such as anthracyclines or chest radiotherapy) (**Table S2**) [11]. No data are available on prior exposition to proteasome inhibitors as a risk factor.

Before starting treatment, a detailed clinical assessment is essential to identify patients at risk of cardiovascular side effects. The most frequent CVAE is hypertension, which is itself a trigger event for other CVAEs, such as heart failure and ischemic heart disease. According to the ESH/ESC guidelines for the management of arterial hypertension [17], the estimation of all cardiovascular risks should be performed with a detailed stratification (**Table 1, Figure 1**) or with the handier Systematic Coronary Risk Evaluation (SCORE) model that estimates the risk of dying from cardiovascular disease over 10 years [19].

Arterial hypertension is defined by a systolic blood pressure ≥ 140 mmHg and/or a diastolic blood pressure ≥ 90 mmHg. Methods used to monitor patients' blood pressure are:

1. Office blood pressure monitoring: this is usually higher than out of office blood pressure and home blood pressure and the difference increases as office blood pressure increases.
2. Out-of-office blood pressure monitoring: its major advantage is that it provides many blood pressure measurements away from the medical environment, which correlates better with actual blood pressure than office blood pressure. Out-of-office blood pressure is commonly assessed by ambulatory blood pressure monitoring (ABPM) or home blood pressure monitoring (HBPM) (**Table 2**).

For initial assessment, HBPM may be better suitable in primary care and ABPM in specialist care. However, borderline or abnormal findings on HBPM should be confirmed with ABPM [20], which is

currently considered the reference for out-of-office blood pressure. Furthermore, defining values for arterial hypertension according to HBPM (systolic blood pressure >135 mmHg and/or a diastolic blood pressure >85 mmHg) are slightly lower than the classical definition of arterial hypertension [17]. Patients should be routinely trained for self-measurement of blood pressure to optimize follow-up, for which HBPM is more suitable than ABPM.

Hypertension Mediated Organ Damage (HMOD) (**Figure S1**) predicts cardiovascular death independently of ESH/ESC guidelines and/or SCORE model (<http://www.heartscore.org>), so it should be accurately screened.

ROLE OF BIOMARKERS

Cardiac biomarkers (e.g. cardiac troponins, natriuretic peptides and oxidative stress/inflammatory mediators) are not essential parameters in clinical practice for the early detection of cardiotoxicity, even though they have a role in patients who develop cardiotoxicity. Available data on cardiac biomarkers are described in the **Supplementary Appendix**.

ROLE OF IMAGING

Evaluation of cardiac organ damage represents a pivotal step in cardiovascular risk stratification of general population [21]. Hypertension determines many structural alterations, mainly left ventricular hypertrophy, which has been associated with an increased risk of cardio- and cerebrovascular events [22]. A similar approach to risk stratification could be applied to MM patients candidates for CFZ therapy. A comprehensive assessment requires evaluation of both structural and functional features, with different diagnostic tools.

Standard echocardiography. The most frequently used parameter for routine cardiotoxicity monitoring is LVEF. A LVEF of >52% for men and >54% for women is considered normal [23,24]. A LVEF drop of >10% or >5% with heart failure symptoms is considered diagnostic of cardiotoxicity. LVEF before chemotherapy is considered as a predictor of subsequent cardiotoxicity. Nevertheless, the prognostic value and the timing of serial measurements of LVEF during treatment for cardiotoxicity detection and monitoring are still controversial. In a sub-analysis of the ENDEAVOR study on CFZ treated patients, serial screening with echocardiography in unselected patients was not helpful to mitigate the risk of CVAEs [6]. However, echocardiography assessment can be helpful to obtain a baseline evaluation of LVEF in patients before treatment and in case of established CVAEs for diagnostic purposes.

Advanced echocardiographic evaluation. Myocardial deformations can be studied using different ultrasound techniques as Tissue Doppler and 2D and 3D speckle-tracking echocardiography [25]. Tissue Doppler is more sensitive than LVEF assessments in recognizing chemo- and/or radiotherapy-induced left ventricle systolic dysfunction, early cardiotoxicity even for low-dose chemotherapy, and differences in regional myocardial function secondary to localized drug damage (i.e., the interventricular septum) [26]. However, Tissue Doppler has several limitations, such as a low reproducibility with angle dependency, a limited spatial resolution, a high sensitivity to signal noise and a high inter-observer variability.

Global Longitudinal Strain (GLS) assessed using automated speckle-tracking echocardiography is an emerging technique for detecting and quantifying subtle disturbances in LV systolic function. GLS reflects the longitudinal contraction of the myocardium and its accuracy has been validated against tagged magnetic resonance imaging [27]. GLS provides more consistent results than radial and circumferential myocardial deformation analyses in the early recognition of myocardial damage, the prediction of late cardiotoxicity onset, and the planning of cardio-protection strategies. There is evidence that GLS is the most sensitive and specific measurement for the early detection of subclinical myocardial injury [28]. The American Society of Echocardiography (ASE) and the European Association of Cardiovascular Imaging (EACVI) consensus [29] suggested a practical approach for GLS use in patients undergoing chemotherapy. More precisely, a GLS reduction <8% from baseline is not meaningful, but >15% from baseline is very likely abnormal.

In our experience, 28 consecutive relapsed/refractory MM (RRMM) patients treated with bortezomib (BTZ) and CFZ were compared with a population of 22 non-MM control subjects, matched for age, sex and mean 24h blood pressure [30]. All patients underwent trans-thoracic echocardiography, ABPM and a pulse-wave velocity study, to assess cardiac morphology and function, blood pressure load and arterial stiffness. Pulse wave velocity was similar between PI-treated patients and controls. GLS was the only echocardiographic parameter significantly decreased in PI-treated ($p=0.02$) and in CFZ-treated patients ($p=0.002$), even after correction for the main cardiac function parameters ($p=0.01$ and $p=0.036$, respectively). Among CFZ patients, we also found increased values of LV mass indexed by Body Surface Area ($p=0.047$). Moreover, in this cohort, the cumulative dose of CFZ was associated with a more prominent modification of GLS and LV mass indexed by Body Surface Area [30].

Cardiac magnetic resonance. Cardiac magnetic resonance is the reference standard in assessing LV and right ventricle volumes and function, and it is now extensively used to detect acute and chronic cardiac chemotherapy complications [31]. Cardiac magnetic resonance is superior to echocardiography for many reasons (wide field of view, flexible scanning planes, no ionizing

radiation), but it has several limitations (low availability, high costs, contraindication to ferromagnetic devices).

Radionuclide angiography (multigated angiography-MUGA). Multigated angiography has been the 'gold standard' imaging technique to evaluate LV systolic function in patients undergoing chemotherapy for many years [32]. The main limit of MUGA is radiation exposure, which reduces its use after increasing availability of other imaging techniques. Multigated angiography also does not provide comprehensive information on right ventricle function, left and right atrial size, and presence or absence of valvular or pericardial disease.

The ASE and EACVI positions on the role of imaging techniques in cardiotoxicity management are summarized in **Table 3** [29].

PREVENTION OF CHEMOTHERAPY-INDUCED CARDIOTOXICITY IN CANCER PATIENTS

β -blockers. It is well known that chronic activation of the sympathetic nervous system plays an important role in heart failure pathogenesis; therefore, β -blockers should be used in all patients with reduced LVEF to prevent heart failure-related hospitalization and mortality. However, the use of β -blockers in oncologic patients undergoing chemotherapy, with asymptomatic LV dysfunction, is as yet not well established [33].

Renin-angiotensin-aldosterone system: angiotensin-converting-enzyme inhibitors (ACE-i) and angiotensin II receptor blockers (ARB). The activation of renin-angiotensin-aldosterone system is one of the potential mechanisms involved in chemotherapy-induced cardiotoxicity. Angiotensin-converting-enzyme inhibitors attenuate oxidative stress, reduce interstitial fibrosis, and improve intracellular calcium handling, cardiomyocyte metabolism and mitochondrial function, and there is good evidence on their efficacy in anthracycline-induced cardiotoxicity [33,34]. The efficacy of a combined therapy with ACE-i and β -blockers in preventing cardiotoxicity has been demonstrated in the OVERCOME trial [35]. This study evaluated the efficacy of enalapril and carvedilol in preventing chemotherapy-induced LV systolic dysfunction in patients with hematologic diseases treated with conventional chemotherapy. Results showed a lower reduction in LV function and a lower incidence of heart failure in patients treated with this combination treatment compared to placebo. As a consequence, ACE-i and β -blockers proved beneficial in conventional-chemotherapy induced cardiotoxicity. The PRADA trial demonstrated that in patients treated for early breast cancer with anthracycline-containing regimens with or without trastuzumab and radiation, the treatment with the ARB candesartan provided protection against early decline in global left ventricular function, while no short-term beneficial effect was observed for the β -blocker metoprolol alone [36].

Nutritional supplementation and exercise training. Non-pharmacologic strategies to reduce chemotherapy-induced cardiotoxicity include lifestyle interventions and a preventive exercise rehabilitation. The mechanisms responsible for the positive effects of aerobic exercise include reduced reactive oxygen species production, negative modulation of pro-apoptotic signaling, improved calcium handling and activation of the AMP-kinase pathway, with ameliorated myocardial energetics [33,37]. In addition, and possibly most importantly, exercise improves many cardiovascular risk factors, such as hypertension, dyslipidemia, overweight, obesity, insulin-resistance, and diabetes. Food supplements can increase antioxidants levels and there is some evidence of the cardio-protective effect of antioxidants (such as Vitamin A and Vitamin E) in animal models. At present, no evidence is available in the clinical setting [33,38,39].

SUGGESTIONS FOR WORK-UP IN MM PATIENTS CANDIDATE TO CFZ THERAPY

In general, no differences in CVAEs were observed between RRMM and newly diagnosed MM patients, nor among different treatment combinations [4]. According to these data, an appropriate cardiovascular assessment is recommended for all patients receiving CFZ (**Figure 2**). Patients with no cardiovascular risks and normal blood pressure can start treatment with CFZ immediately. According to ESC/ESH guidelines (**Figure 1**), in low-moderate risk patients, correction of modifiable risk factors and hypertension should be started as well. In high-risk patients, a case by case evaluation considering the risk/benefit ratio should be performed before starting CFZ. Finally, there are no data on CFZ treatment in very high-risk patients. Given that most risk factors in those very patients are not modifiable, MM treatment options other than CFZ should be considered.

A slightly higher incidence of CVAEs was reported in patients receiving higher doses of CFZ ($\geq 45\text{mg/m}^2$) [4] and in elderly patients (≥ 75 years): thus, these subgroups should be more strictly monitored. No suggestions could be done for amyloidosis patients because few data are available and FDA or EMA have not approved CFZ use in clinical practice for these patients. The use of CFZ in this setting is not suggested outside clinical trials.

Before starting therapy

Clinicians should perform a comprehensive assessment of oncologic patients, including:

- Medical history: to determine previous cardiovascular events and risk factors (hypertension, diabetes, dyslipidemia, obesity, smoking, etc.) as well as prior exposition to cardiotoxic cancer treatments (**Table S2**);
- Physical examination:

- Blood pressure (hypertension is a potent and modifiable risk factor for cardiac dysfunction onset, and should be assessed before starting treatment);
- Heart auscultation to identify murmurs (significant valvular heart disease is a risk factor for cardiac dysfunction);
- Signs of heart failure (elevated venous pressure, lung crackles or pedal edema);
- 12-lead electrocardiogram (ECG) to detect possible markers of structural heart disease, including LV damage/dysfunction, arrhythmias (atrial fibrillation, atrial flutter, heart block), evidence of previous myocardial infarction (Q-waves, left bundle branch block), and evidence of LV hypertrophy;
- LVEF measurement using echocardiography, cardiac magnetic resonance or MUGA to assess asymptomatic cardiac organ damage and to have a baseline evaluation useful as a reference in case of CVAEs;
- ABPM/HBPM (**Table 2**) to detect unknown, borderline or uncontrolled hypertension.

Patients with home blood pressure >135/85mmHg should be treated; those already receiving hypertensive medication may need adjustments in their medication to manage their blood pressure before the start of CFZ treatment.

During therapy

- Clinicians should screen and manage modifiable cardiovascular risk factors (smoking, hypertension, diabetes, dyslipidemia, obesity) in all patients.
- In general, an aggressive hydration should be avoided and patients should be monitored for signs and symptoms of fluid overload, including weight gain. In the majority of patients, 250 mL hydration before CFZ infusion in cycle 1 is sufficient. Any additional hydration is based on physician discretion according to the risk of lysis syndrome.
- In case of severe dyspnea, CFZ should be temporarily discontinued until symptoms disappear or return to baseline levels. There are concerns that dyspnea may be caused by fluid overload rather than drug toxicity. Hydration has been previously recommended in CFZ treatment to prevent or reduce any acute renal function impairment. However, if aggressive hydration is not expected to be tolerated by the patient, serum creatinine may be monitored and, if stable, hydration may be decreased or discontinued. Most patients with dyspnea as primary manifestation of a potential cardiac disease do not typically show an EF impairment or other evidence of myocardial dysfunction. In these patients, CFZ could be restarted as soon as symptoms improve.

- Home blood pressure monitoring is recommended during treatment: if home blood pressure values exceed >135/85 mmHg in at least 2 measurements, CFZ should be temporarily held and hypertensive therapy should be adjusted until blood pressure target levels are reached (\leq 135/85 mmHg) (**Figure 2, Table S3**). Careful evaluation of patients' blood pressure and appropriate management of anti-hypertensive therapy are important measures for reducing the risk of CVAEs in patients receiving chemotherapeutic medication. Recent recommendations for managing hypertension with anti-angiogenic drugs have been published [33,40]. No clear recommendation for an antihypertensive agent can be made in this context, due to the lack of controlled studies focused on this issue. The most commonly prescribed antihypertensive agents are ACE-I and ARBs, dihydropyridine calcium channel blockers, β -blockers and diuretics [41].
- In patients with clinical signs or symptoms suggestive for grade \geq 2 cardiac dysfunction, CFZ should be temporarily discontinued until recovery and the following strategy is recommended:
 - ECG and echocardiogram for diagnostic workup;
 - Cardiac magnetic resonance or MUGA if echocardiogram is not available or technically feasible (e.g., poor image quality). Cardiac magnetic resonance should be preferred;
 - Serum cardiac biomarkers (cardiac troponin, brain natriuretic peptides) or echocardiography-derived strain imaging together with routine diagnostic imaging;
 - Referral to a cardiologist depending on findings.

No recommendations can be made regarding further continuation or discontinuation of cancer therapy in patients with evidence of cardiac dysfunction during treatment, as long as cardiac function has recovered to grade 1 or baseline. This decision should be taken by the hematologist in close collaboration with the cardiologist, evaluating both the clinical circumstances and the risks/benefits of continuation of therapy responsible for the cardiac dysfunction. CFZ relationship with the emerging CVAE should be assessed. If grade 3/4 CVAEs are related to CFZ use, dose reductions or definitive discontinuation may be needed. CFZ treatment could be restarted at the dose used before the event, or at a reduced dose if the CVAE was not related to CFZ.

According to the type of therapy and the individual risk of patients, specific thromboprophylaxis strategies are recommended regardless of CFZ treatment and have been discussed elsewhere [42].

CONCLUSIONS

With the use of cardiotoxic drugs, hematologists need to develop strategies to identify and manage cardiovascular risk in clinical investigations and in general practice. The highly effective agent CFZ is associated with CVAEs risk. Since this agent has shown to improve both progression-free survival and

overall survival compared to standard treatment in RRMM patients, avoiding dangerous toxicities that may prevent patient access to CFZ has become a priority. However, the risk-benefit ratio for an agent should be interpreted depending on the nature and severity of the disease, and restrictive approaches can potentially delay or prevent the access to innovative treatments. This consensus paper considers the best available present evidence and the application of data from large trials and provide clinically useful recommendation and treatment algorithms for its safe use (**Figures 1-2**). Future studies should prospectively analyze the mechanism of cardiovascular damage, the risk factors of developing CVAEs (including new techniques such as global longitudinal strain) and the potential role of cardio-protective drugs.

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Table 1. Factors influencing the stratification of total cardiovascular risk [43]

Demographic characteristics and laboratory parameters
Sex ^a (men >women)
Age ^a
Smoking (current or past history) ^a
Total cholesterol ^a and HDL-C
Uric acid
Diabetes ^a
Overweight or obesity
Family history of premature CVD (men aged <55 years and women aged <65 years)
Family or parental history of early-onset hypertension
Early-onset menopause
Sedentary lifestyle
Psychosocial and socioeconomic factors
Heart rate (resting values >80 beats/min)
Asymptomatic HMOD
Arterial stiffening: Pulse pressure (in older people) >_60 mmHg Carotid–femoral PWV >10 m/s
ECG LVH (Sokolow–Lyon index >35 mm, or R in aVL >_11 mm; Cornell voltage duration product >2440 mm.ms, or Cornell voltage >28 mm in men or >20 mm in women)
Echocardiographic LVH [LV mass index: men >50 g/m ^{2.7} ; women >47 g/m ^{2.7} (height in m ^{2.7}); indexation for BSA may be used in normal-weight patients; LV mass/BSA g/m ² >115 (men) and >95 (women)]
Microalbuminuria (30–300 mg/24 h), or elevated albumin–creatinine ratio (30–300 mg/g; 3.4–34 mg/mmol) (preferentially on morning spot urine) ^b
Moderate CKD with eGFR >30–59 mL/min/1.73 m ² (BSA) or severe CKD eGFR <30 mL/min/1.73 m ² ^b
Ankle-brachial index <0.9
Advanced retinopathy: haemorrhages or exudates, papilloedema
Established CV or renal disease
Cerebrovascular disease: ischaemic stroke, cerebral haemorrhage, TIA
CAD: myocardial infarction, angina, myocardial revascularization
Presence of atheromatous plaque on imaging
Heart failure, including HFpEF
Peripheral artery disease
Atrial fibrillation

BSA = body surface area; CAD = coronary artery disease; CKD = chronic kidney disease; CV = cardiovascular; CVD = cardiovascular disease; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; HDL-C = HDL cholesterol; HFpEF = heart failure with preserved ejection fraction; HMOD = hypertension-mediated organ damage; LV = left ventricular; LVH = left ventricular hypertrophy; PWV = pulse wave velocity; SCORE = Systematic COronary Risk Evaluation; TIA = transient ischaemic attack.

^aCV risk factors included in the SCORE system.

^bProteinuria and reduced eGFR are independent risk factors.

Source: Williams B, Mancia G, Spiering W, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. *Eur Heart J* 2018; 39: 3021–104; Table 4, p. 3031. Publisher: Oxford University Press. DOI: 10.1093/eurheartj/ehy339.

<https://academic.oup.com/eurheartj/article/39/33/3021/5079119> (Last accessed: Sept 21, 2018).

Table 2. Main features of ambulatory blood pressure monitoring and home blood pressure monitoring

	ABPM	HBPM
Brief description	Blood pressure measurement with a portable blood pressure measuring device for a 24 hours period.	Blood pressure self-measurements daily for at least 3–4 days and preferably for 7 consecutive days.
Primary care	-	+
Specialist care	+	-
Cheap	-	++
24 hour	++	-
Daily activity	++	-
Sleep	++	-
Long period (at least 7 days)	-	++

ABPM= ambulatory blood pressure monitoring; HBPM= home blood pressure monitoring

Table 3. The role of imaging in the management of CVAEs

Echocardiography is the first-choice method for evaluating patients before, during and after chemotherapy, and Left Ventricular Ejection Fraction (LVEF) is the primary technique.
Cardiotoxicity cannot be predicted by LVEF alone but an accurate echocardiographic investigation is strongly recommended, if available, to integrate the standard examination with data from different imaging techniques (Tissue Doppler Imaging and speckle-tracking echocardiography).
Diastolic indices are not useful for early detection of cardiotoxicity because of their inability to predict heart failure.
Global Longitudinal Strain (GLS) should be performed only by speckle-tracking echocardiography for a sensitive diagnosis of chemotherapy-induced cardiac damage, and the same ultrasound equipment should be used for serial examinations.
Cardiac magnetic resonance is recommended for LVEF quantification when the quality of echocardiogram is suboptimal. Furthermore, cardiac magnetic resonance is suggested for confirming a LVEF <53%.
Multigated angiography provides a highly reproducible quantification of LVEF during cancer therapy, but radiation exposure remains its main limitation. Therefore, this technique should be considered only when first line echocardiography and second line cardiac magnetic resonance are unavailable.

Main figures: titles and legends

Figure 1. Classification of hypertension stages according to blood pressure levels, presence of cardiovascular risk factors, hypertension-mediated organ damage, or comorbidities, defined by the 2018 ESC/ESH Guidelines

Legend:

CV risk is illustrated for a middle-aged male. The CV risk does not necessarily correspond to the actual risk at different ages. The use of the SCORE system is recommended for formal estimation of CV risk for treatment decisions. BP = blood pressure; CKD = chronic kidney disease; CV = cardiovascular; DBP = diastolic blood pressure; HMOD = hypertension-mediated organ damage; SBP = systolic blood pressure; SCORE = Systematic COronary Risk Evaluation.

Source: Williams B, Mancia G, Spiering W, *et al.* 2018 ESC/ESH Guidelines for the management of arterial hypertension. *Eur Heart J* 2018; **39**: 3021–104; Figure 1, p. 3034. Publisher: Oxford University Press. DOI: 10.1093/eurheartj/ehy339.

<https://academic.oup.com/eurheartj/article/39/33/3021/5079119> (Last accessed: Sept 21, 2018).

Figure 2. Flowchart for patient selection and evaluation before and during treatment with CFZ

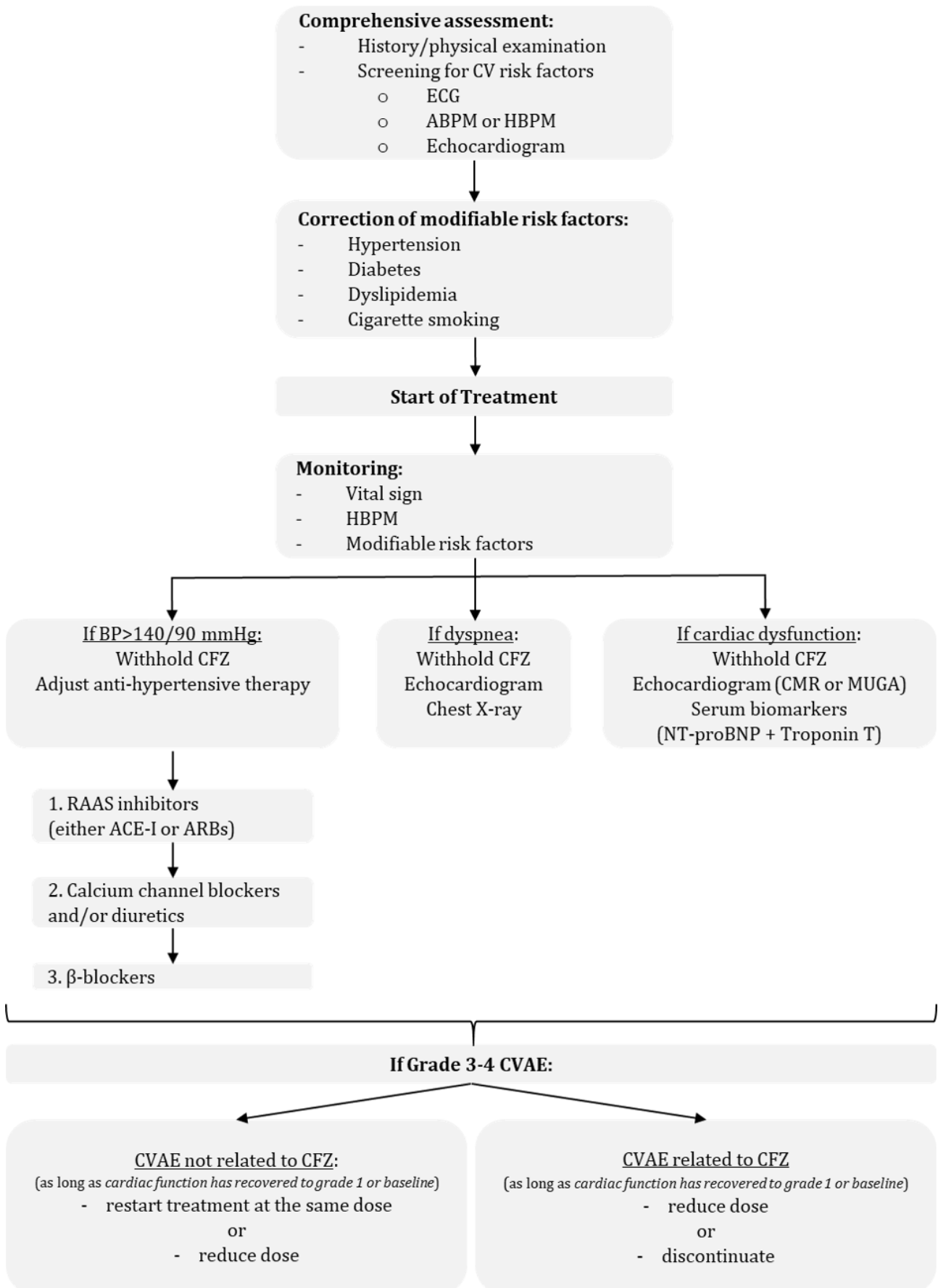
Legend:

CV = cardiovascular; ECG = electrocardiogram; ABPM = ambulatory blood pressure monitoring; HBPM = home blood pressure monitoring; BP = blood pressure; CFZ = carfilzomib; CMR = cardiac magnetic resonance; MUGA = multigated angiography; RAAS = Renin-angiotensin-aldosterone system; ACE-I = angiotensin-converting-enzyme inhibitors; ARB = angiotensin II receptor blockers.

Figure 1

Hypertension disease staging	Other risk factors, HMOD, or disease	BP (mmHg) grading			
		High normal SBP 130-139 DBP 85-89	Grade 1 SBP 140-159 DBP 90-99	Grade 2 SBP 160-179 DBP 100-109	Grade 3 SBP \geq 180 or DBP \geq 110
Stage 1 (uncomplicated)	No other risk factors	Low risk	Low risk	Moderate risk	High risk
	1 or 2 risk factors	Low risk	Moderate risk	Moderate to high risk	High risk
	\geq 3 risk factors	Low to Moderate risk	Moderate to high risk	High Risk	High risk
Stage 2 (asymptomatic disease)	HMOD, CKD grade 3, or diabetes mellitus without organ damage	Moderate to high risk	High risk	High risk	High to very high risk
Stage 3 (established disease)	Established CVD, CKD grade \geq 4, or diabetes mellitus with organ damage	Very high risk	Very high risk	Very high risk	Very high risk

Figure 2



EMN guideline article

PREVENTION, MONITORING AND TREATMENT OF CARDIOVASCULAR ADVERSE EVENTS IN MYELOMA PATIENTS RECEIVING CARFILZOMIB

A Consensus Paper by the European Myeloma Network
and
the Italian Society of Arterial Hypertension

Supplementary Appendix

- ❖ **Role of Biomarkers**
- ❖ **Table S1.** Patients who are at increased risk for cardiac dysfunction according to the American Society of Clinical Oncology Clinical Practice Guidelines
- ❖ **Table S2.** Baseline risk factors for cardiotoxicity
- ❖ **Table S3.** Office blood pressure treatment target range
- ❖ **Figure S1.** Target organ damage in hypertension

Role of Biomarkers

Cardiac biomarkers (e.g. cardiac troponins, natriuretic peptides and oxidative stress/inflammatory mediators) are not essential parameters in clinical practice for the early detection of cardiotoxicity; however, they may have a role to stratificate patients regarding the risk to develop cardiotoxicity [1–4].

Cardiac troponin. Cardiac troponin is a complex of three units (Tn I, T, and c) involved in myocardium contraction [5]. Units I and T are sensitive and they are specific biomarkers of myocardial damage and of cardiovascular adverse events (CVAEs) [6–8]. Their role has become pivotal because their elevation may precede myocardial impairment. The increase in cardiac troponin may help to stratificate patients regarding the risk of developing cardiotoxicity [9]. Cardiac troponin is easy to use, widely available and less expensive than imaging, but its main limit is that most data on its role in cardiotoxicity are derived from anthracyclines-based treatment. In patients treated with trastuzumab and tyrosine kinase inhibitors (TKIs), cardiac troponin has anticipated the onset of a clinically significant left ventricle (LV) dysfunction [5]. Nevertheless, the timing and frequency of cardiac troponin evaluations, the cut-off point for positivity and the comparison of different troponin assays are still unsolved. Thus, serial cardiac troponin measurements are not recommended by the European society of medical oncology guidelines for the early detection of cardiotoxicity in clinical practice [10].

Natriuretic peptides. Increased levels of wall stress determine a release of natriuretic peptides from atrial and ventricular myocardium. Brain natriuretic peptides and their N-terminal fragment (NT-proBNP) are involved in vasodilation, inhibition of the renin-angiotensin-aldosterone system and sympathetic tone, natriuresis and kaliuresis. NT-proBNP is used in the diagnosis and prognostic stratification of patients with HF and as a screening test for asymptomatic LV dysfunction [5,11,12]. Brain natriuretic peptides and NT-proBNP have been used as early biomarkers for chemotherapy-induced cardiotoxicity with conflicting results. In some studies, plasma levels of NT-proBNP that had persistently increased during chemotherapy were associated with the onset of cardiac impairment [5,13].

Oxidative stress and inflammatory parameters. Although cardiac troponin I and brain natriuretic peptides have a predictive value for cardiotoxicity in high-dose anthracycline-based therapies, they are not able to depict the early stages of cardiac impairment or cardiotoxicity induced by new therapeutic agents. Cytokines and parameters of oxidative stress have been considered as circulating biomarkers for cardiotoxicity, because their elevation during chemotherapy could detect indirect mechanisms inducing initial cardiac impairment. Increased

circulating levels of interleukin 6 and its soluble receptor, as well as TNF α and its receptor, were found to be correlated with cardiomyocyte apoptosis. Other potential markers might be the C-reactive protein, heart-type fatty acid-binding protein, glycogen phosphorylase BB, and circulating microRNAs, but – especially in MM settings – they may not reflect drug-induced cardiotoxicity, but most likely be an expression of inflammation and tumor burden [5].

Table S1. Patients who are at increased risk for cardiac dysfunction according to the American Society of Clinical Oncology Clinical Practice Guidelines [14].

High-dose anthracycline (i.e., doxorubicin $\geq 250\text{mg}/\text{m}^2$, epirubicin $\geq 600\text{mg}/\text{m}^2$)	
High-dose radiotherapy (RT) (≥ 30 Gy) focused on fields including the heart	
Lower-dose anthracycline (i.e., doxorubicin $< 250\text{mg}/\text{m}^2$, epirubicin $< 600\text{mg}/\text{m}^2$) in combination with lower-dose RT (< 30 Gy) focused on fields including the heart	
Treatment with lower-dose anthracycline (i.e., doxorubicin $< 250\text{mg}/\text{m}^2$, epirubicin $< 600\text{mg}/\text{m}^2$) or trastuzumab alone, associated with the presence of any of the following risks:	More than 2 cardiovascular risk factors, including smoking, hypertension, diabetes, dyslipidemia, and obesity, during or after treatment
	Older age (≥ 60 years) at the beginning of treatment
	Impaired cardiac function (i.e., borderline low left ventricular ejection fraction (LVEF) [50% to 55%], history of myocardial infarction, mild to severe valvular heart disease) before or during treatment
Lower-dose anthracycline (i.e., doxorubicin $< 250\text{mg}/\text{m}^2$, epirubicin $< 600\text{mg}/\text{m}^2$) followed by trastuzumab.	

Table S2. Baseline risk factors for cardiotoxicity

CV risk factors
NON MODIFIABLE
Age
Gender
Genetic factors
Race
MODIFIABLE
Hypertension
Smoking
Diabetes Mellitus
Physical inactivity
Obesity
Dyslipidaemia
Asymptomatic or established organ damage
Hypertension-mediated organ damage (HMOD)
Pulse pressure ≥ 60 mmHg
Electrocardiographic or Echocardiographic LVH
Carotid wall thickening (IMT >0.9 mm) or plaque
Ankle Brachial Index (ABI) <0.9
CKD stage III
Microalbuminuria (30-300 mg/24 h), or albumin-creatinine ratio (30-300 mg/g; 3.4-34 mg/mmol)
Advanced retinopathy: haemorrhages or exudates, papilloedema
ESTABLISHED DISEASE
Cerebrovascular disease: ischaemic stroke; cerebral haemorrhage; transient ischaemic attack
CHD: myocardial infarction; angina; myocardial revascularization
Heart failure, including heart failure with preserved EF
Symptomatic lower extremities peripheral artery disease
CKD stage IV-V; proteinuria (>300 mg/24 h)
Atrial Fibrillation
Previous cardiotoxic treatments
Anthracyclines
Radiotherapy (chest, mediastinum)

CHD, coronary heart disease; CKD, chronic kidney disease; EF, ejection fraction; IMT, intima-media thickness; LVH, left ventricular hypertrophy; PWV, pulse wave velocity.

Table S3. Office blood pressure treatment target range [15]

Age group	Office SBP treatment target ranges (mmHg)					Office DBP treatment target range (mmHg)
	Hypertension	+ Diabetes	+ CKD	+ CAD	+Stroke ^a /TIA	
18-65 years	Target to 130 <i>or lower if tolerated</i> Not <120	Target to 130 <i>or lower if tolerated</i> Not <120	Target to <140 to 130 <i>if tolerated</i>	Target to 130 <i>or lower if tolerated</i> Not <120	Target to 130 <i>or lower if tolerated</i> Not <120	70-79
65-79 years ^b	Target to 130-139 <i>if tolerated</i>	Target to 130-139 <i>if tolerated</i>	Target to 130-139 <i>if tolerated</i>	Target to 130-139 <i>if tolerated</i>	Target to 130-139 <i>if tolerated</i>	70-79
≥80 years ^b	Target to 130-139 <i>if tolerated</i>	Target to 130-139 <i>if tolerated</i>	Target to 130-139 <i>if tolerated</i>	Target to 130-139 <i>if tolerated</i>	Target to 130-139 <i>if tolerated</i>	70-79
Office DBP treatment target range (mmHg)	70-79	70-79	70-79	70-79	70-79	

CAD = coronary artery disease; CKD = chronic kidney disease (includes diabetic and non-diabetic CKD); DBP = diastolic blood pressure; SBP = systolic blood pressure; TIA = transient ischaemic attack.

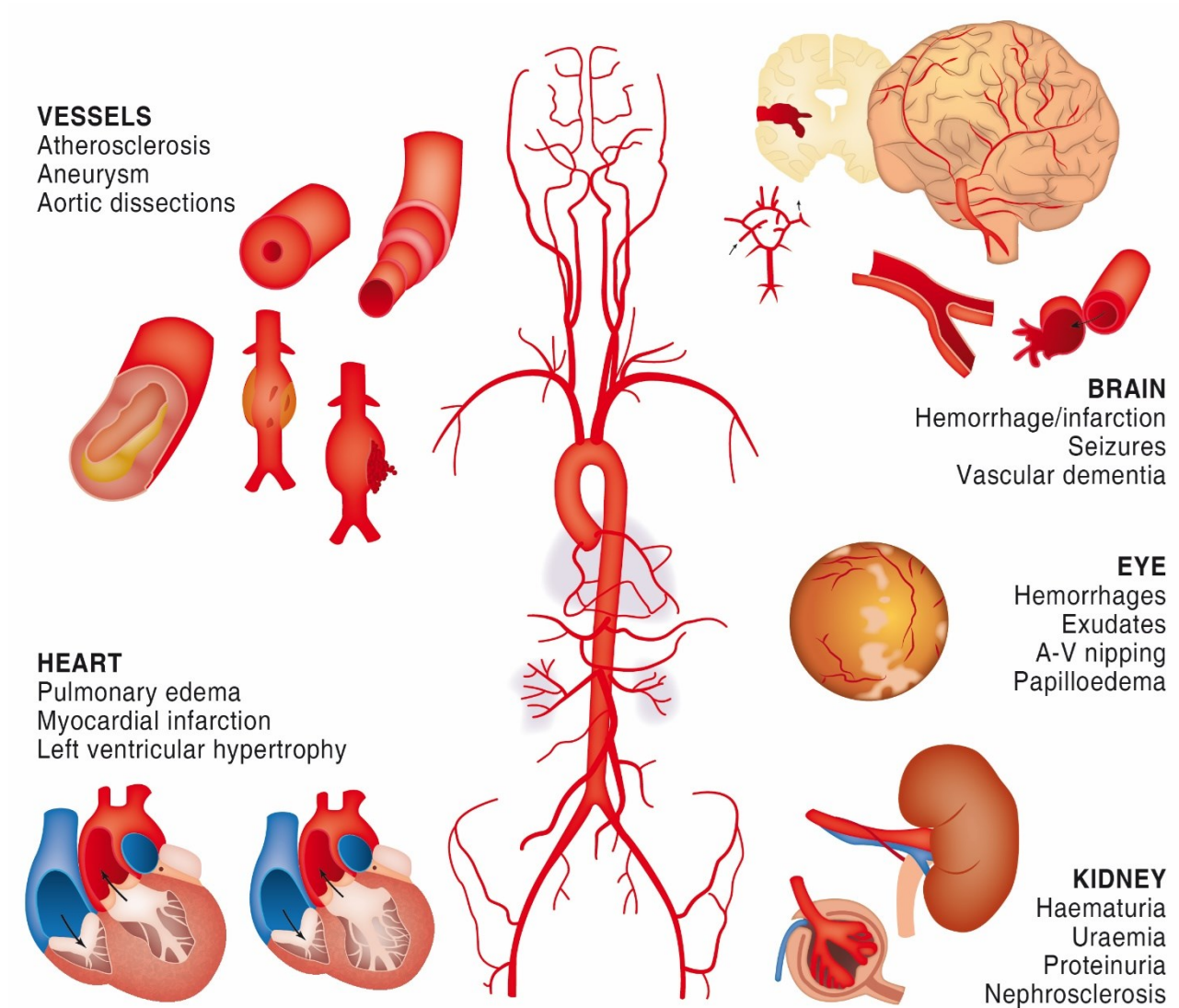
^aRefers to patients with previous stroke and does not refer to blood pressure targets immediately after acute stroke.

^bTreatment decisions and blood pressure targets may need to be modified in older patients who are frail and independent.

Source: Williams B, Mancia G, Spiering W, *et al.* 2018 ESC/ESH Guidelines for the management of arterial hypertension. *Eur Heart J* 2018; **39**: 3021-104; Table 23, p. 3066. Publisher: Oxford University Press. DOI: 10.1093/eurheartj/ehy339.

<https://academic.oup.com/eurheartj/article/39/33/3021/5079119> (Last accessed: Sept 21, 2018).

Figure S1. Target organ damage in hypertension



A-V = arteriovenous.

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