Il paziente Cardiopatico

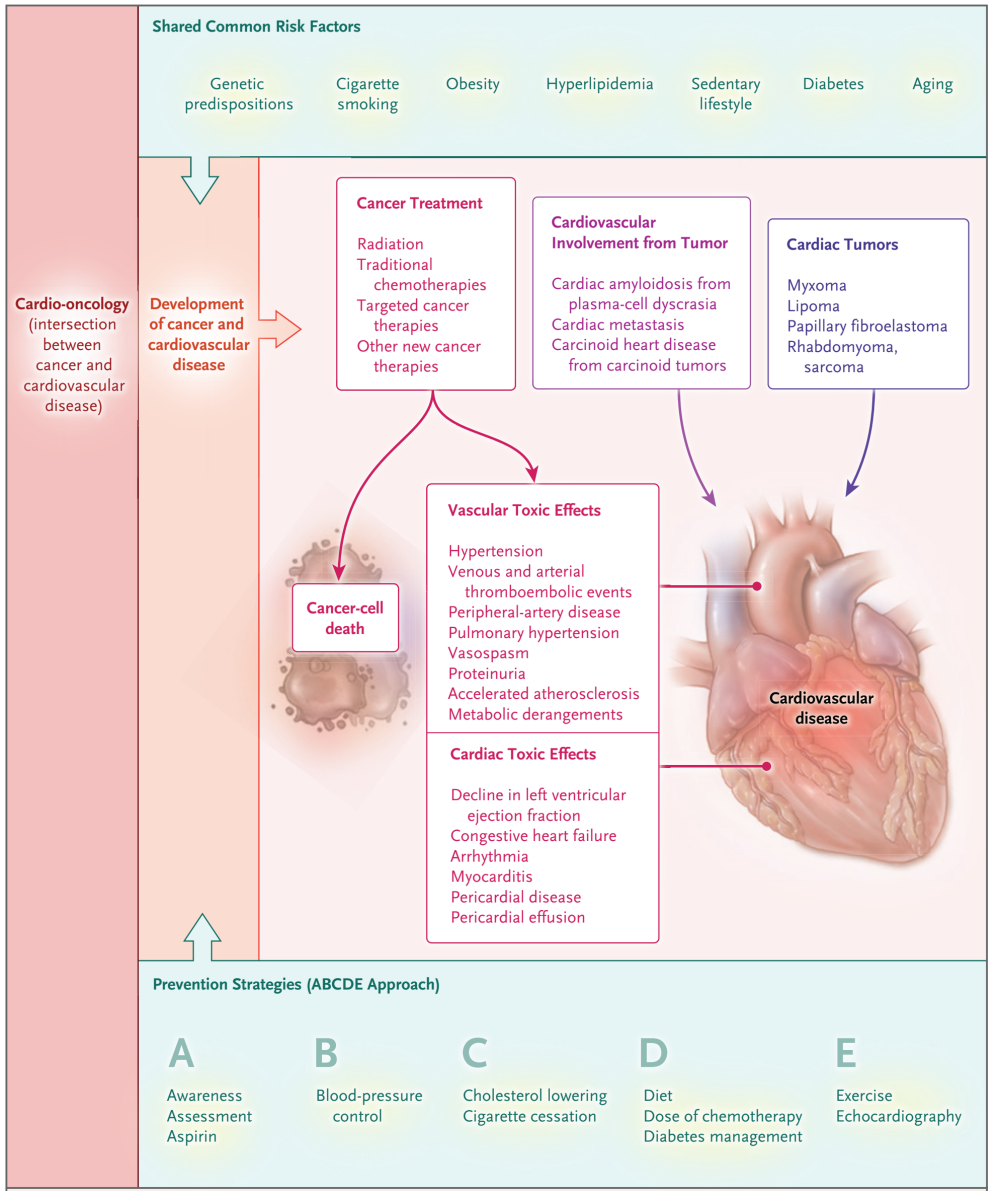
Ilaria Rizzello
Istituto di Ematologia «Seragnoli», IRCCS, Azienda Ospedaliero-Universitaria di Bologna, Italy

HIGHLIGHTS IN EMATOLOGIA
TREVISO, 1-2 DICEMBRE 2023

Disclosures of Ilaria Rizzello

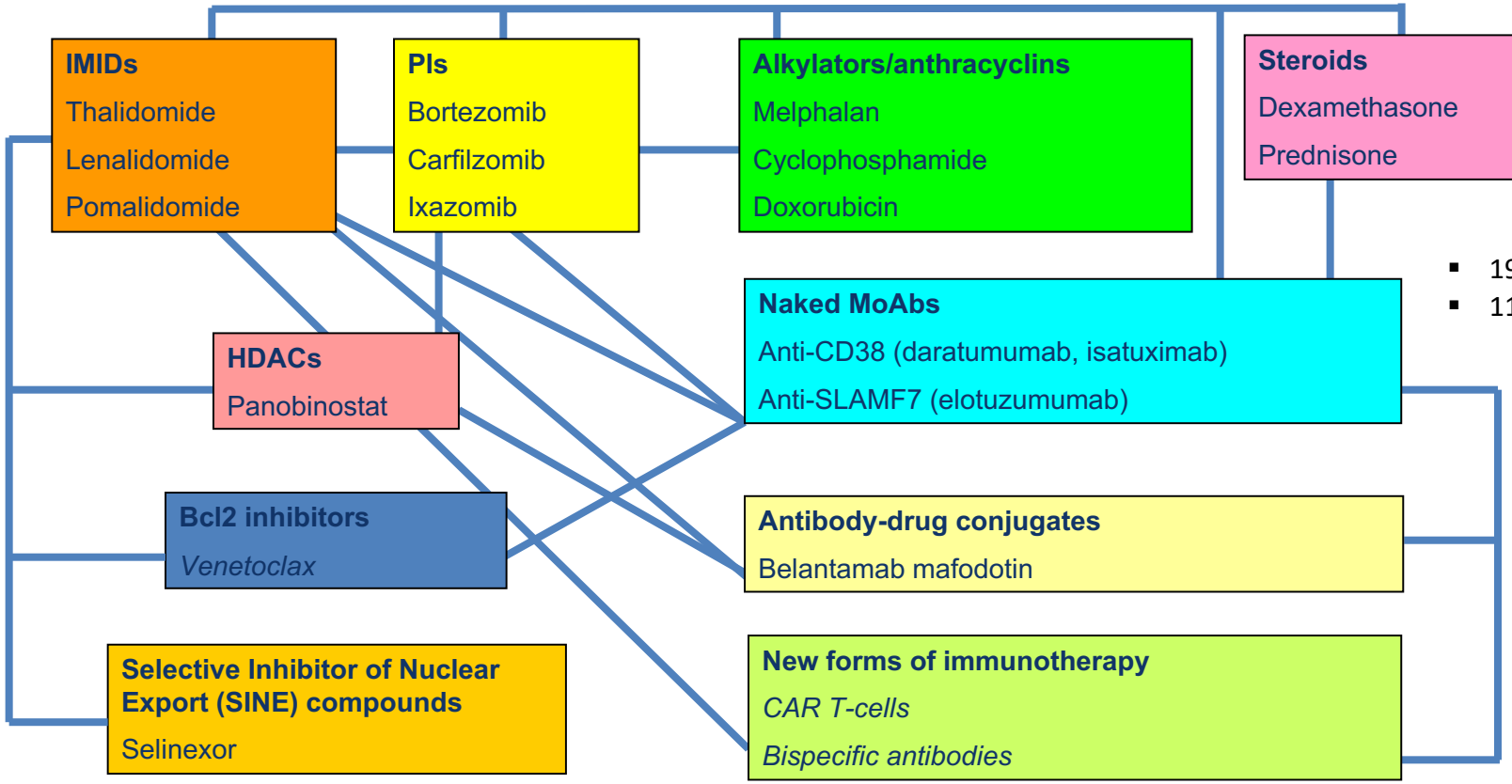
Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
GSK						X	X
Amgen							X
Sanofi							X
BMS							X

Cardiovascular Toxic Effects of Targeted Cancer Therapies



Moslehi JJ, NEJM 2016

Anti-MM agents: 2023



- 190 different doublets
- 1140 different triplets

Van De Donk, Hematology Am Soc Hematol Educ Program 2020

Examples of Antimyeloma Therapy and Cardiac AEs

	Drug Class/Name	Reported Cardiac AEs
Chemotherapy[1]	**Anthracyclines** (e.g. doxorubicin, PLD)	Systolic left ventricular dysfunction, heart failure
	Alkylating agents (e.g. cyclophosphamide)	Systolic left ventricular dysfunction, heart failure, pericardial effusion, myopericarditis
IMiDs	**Thalidomide**	Thromboembolism, bradycardia Thalidomide + dexamethasone vs placebo + dexamethasone in NDMM[8] •Grade 3/4 atrial fibrillation: 5% vs 3% •Grade 3/4 myocardial ischemia: 3% vs 1%
	Lenalidomide	Thromboembolism, bradycardia Rd vs placebo + dexamethasone in relapsed MM[7] •Grade 3/4 cardiac failure congestive*: 1.4% vs 0.3% •Grade 3/4 atrial fibrillation*: 3.7% vs 1.1%
	Pomalidomide	Thromboembolism POM + LoDex vs POM alone in RRMM[6] •Cardiac failure congestive* SAE: 3% vs 0% •Atrial fibrillation* SAE: 3% vs 2%
Proteasome Inhibitors	**Bortezomib**	Hypotension Grade ≥3 heart failure*: •Ranged from <1.0% - 4.7% with BTZ-based regimens across NDMM & RRMM[2] •Ranged from <1.0% - 3.9% with non-BTZ-based regimens across NDMM & RRMM[2]
	Carfilzomib	Hypertension, cardiac failure, dyspnea Grade ≥3 cardiac failure†: •ASPIRE: 3.8% (KRd) vs 1.8% (Rd) in RRMM[3] •ENDEAVOR: 4.8% (Kd) vs 1.8% (Vd) in RRMM[4]
	Ixazomib	Heart failure† (Grades 3/4): •TOURMALINE-MM1: 2.5% (IRd) vs 1.7% (Rd) in RRMM[5]

Cardiovascular toxicity

Cardiac side effects:

- Congestive heart failure (CHF)
- Acute coronary syndrome (ACS)
- Arrhythmias
- Cardiomyopathy

Vascular side effects:

- Hypertension
- Venous thromboembolic events
- Arterial thromboembolic events

Proteasome Inhibitors

IMIDs

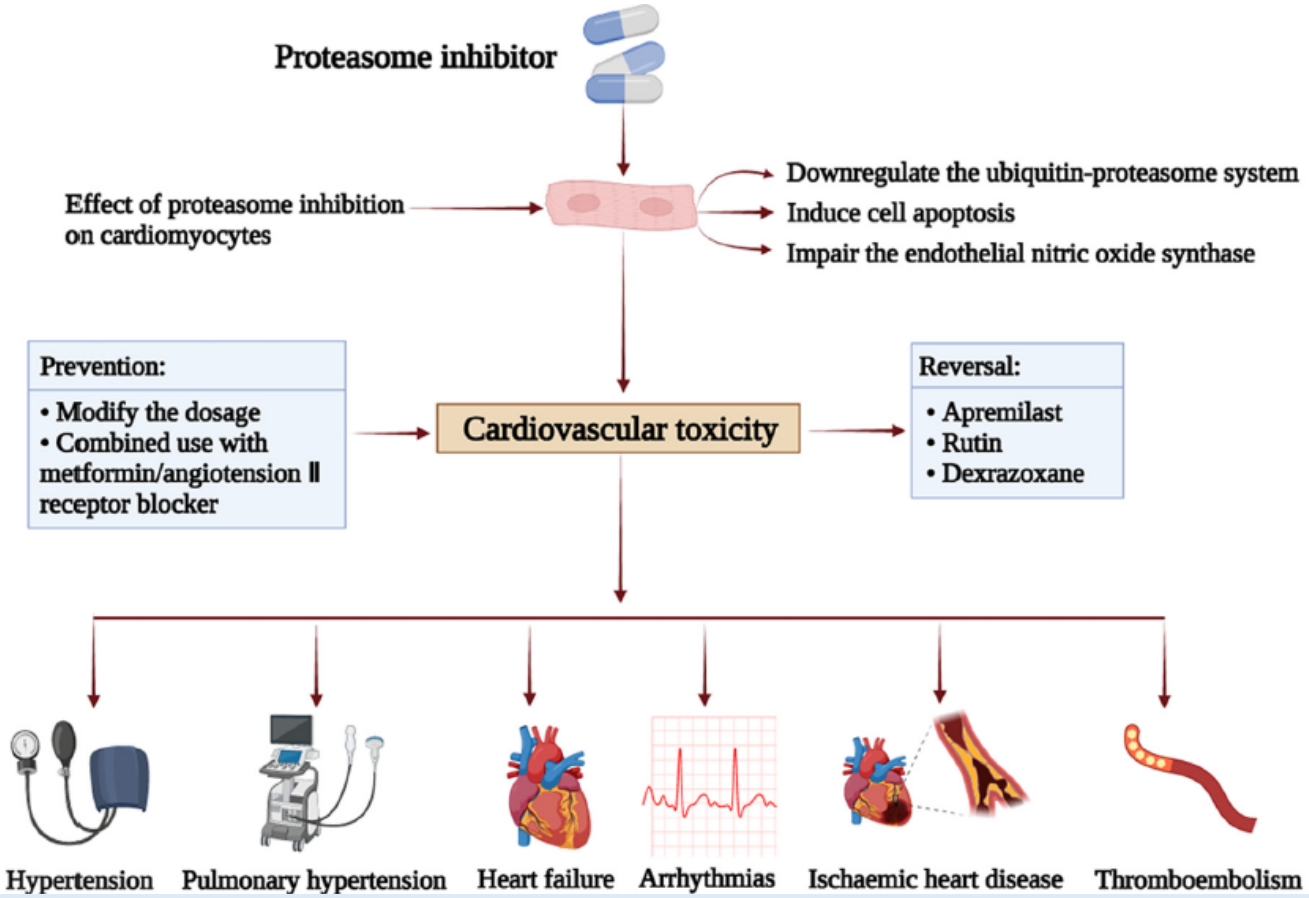
Cardiovascular toxicity with PIs

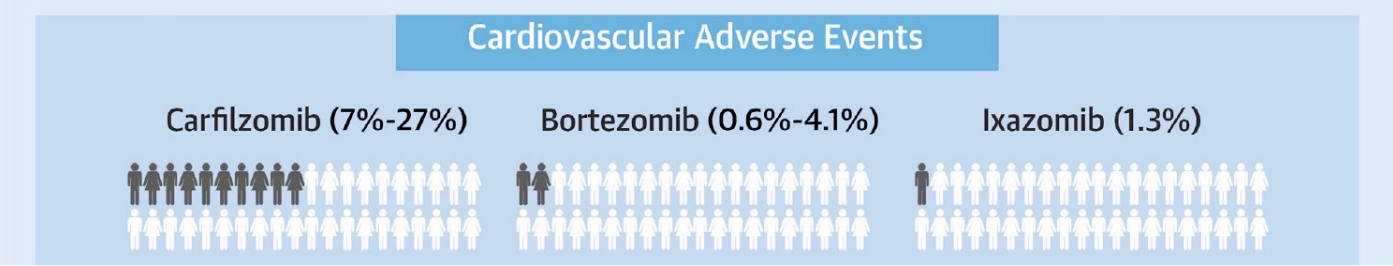
Pre-treatment Risk Stratification

- ✓ Prior cardiac dysfunction
- ✓ Conventional cardiac risk factors
- ✓ Prior anthracycline-based treatment
- ✓ Prior mediastinal or chest radiotherapy

High risk → Monitoring

- ✓ Periodic cardiac physical examination
- ✓ Serial BP monitoring
- ✓ Cardiac biomarkers
- ✓ Cardiac imaging





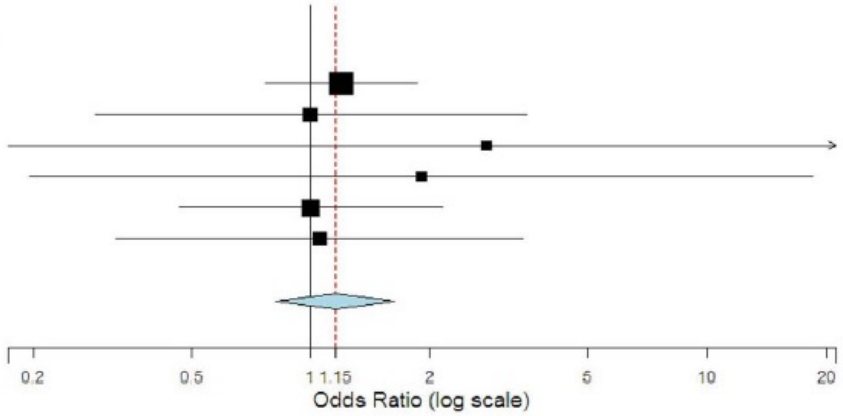
Zheng Y et al, Curr Probl Cardiol 2023;48:101536

Georgiopoulos G, et al. J Am Coll Cardiol CardioOnc. 2023;5(1):1–21

Cardiotoxicity associated with bortezomib vs. control

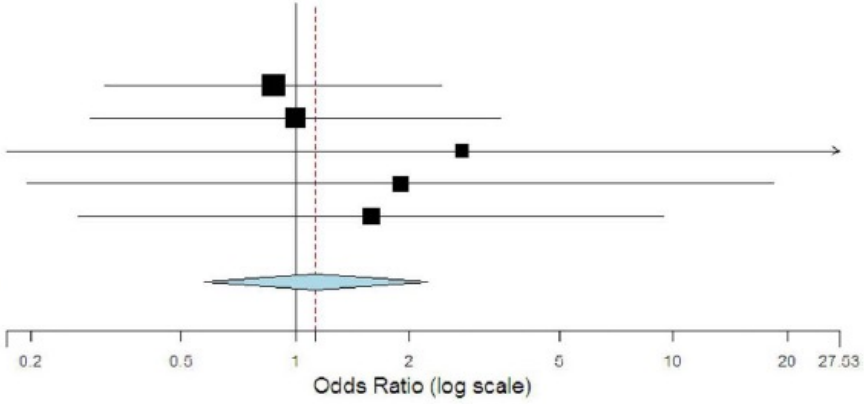
all-grade

Studies	Estimate (95% C.I.)	Ev/Trt	Ev/Ctrl
Richardson P.G. et al/2005/III	1.195 (0.771, 1.852)	50/331	43/332
Cavo M. et al/2010/ III	1.000 (0.286, 3.496)	5/236	5/236
Coiffier B. et al/2011/ III	2.763 (0.172, 44.271)	1/334	0/339
Garderet L. et al/2012/ III	1.899 (0.196, 18.418)	2/133	1/129
Harousseau J. L. et al/2010/ III	1.000 (0.466, 2.144)	14/239	14/239
Hjorth M. et al/2012/ III	1.051 (0.322, 3.432)	6/64	6/67
Overall (I^2=0% , P=0.977)	**1.154 (0.819, 1.624)**	**78/1337**	**69/1342**



high-grade

Studies	Estimate (95% C.I.)	Ev/Trt	Ev/Ctrl
Richardson P.G. et al/2005/III	0.875 (0.315, 2.435)	7/331	8/332
Cavo M. et al/2010/ III	1.000 (0.286, 3.496)	5/236	5/236
Coiffier B. et al/2011/ III	2.763 (0.172, 44.271)	1/334	0/339
Garderet L. et al/2012/ III	1.899 (0.196, 18.418)	2/133	1/129
Hjorth M. et al/2012/ III	1.584 (0.267, 9.406)	3/64	2/67
Overall (I^2=0% , P=0.908)	**1.134 (0.575, 2.237)**	**18/1098**	**16/1103**



Yi Xiao YI, et al. PLoS One 2014

Cardiovascular toxicity with Carfilzomib

Table 1. Incidence (in %) of cardiovascular events in patients with relapsed/refractory multiple myeloma treated with carfilzomib in phase 2 and 3 studies

	Hypertension		Cardiac failure		Ischemic heart disease		Dyspnea	
	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3
Phase 3 studies								
ASPIRE[37 #]								
KRd group (n=392)	14.3	4.3	6.4	3.8	5.9	3.3	19.4	2.8
Rd group (n=389)	6.9	1.8	4.1	1.8	4.6	2.1	14.9	1.8
ENDEAVOR[31 §]								
Kd group (n=463)	25	9	<9	<6	<3	<2	28	5
Vd group (n=456)	9	3	<4	<3	<4	<3	13	2
FOCUS[40]								
Carfilzomib group (n=157)	15	3	5	2			15	1
CS±cyclophosphamide group (n=158)	6	0	1	1			9	0
Phase 2 studies[38 *]								
Carfilzomib (n=526)			7.2	5.7	3.4	1.3		
IKEMA								
IsaKd group (n=179)	37	20	7	4	5	1	28	5
Kd group (n=123)	31	20	7	4	4	2	21	1
CANDOR								
DaraKd group (n=308)	31	18	7	5	4	3	20	4
Kd group (n=153)	27	13	10	9	3	3	22	3

Bringhen, Milan, Ferri EMN&SIIA et al. Haematologica 2018
Moreau P et al, Lancet, 2021
Dimopoulos M, et al, Lancet, 2020

Carfilzomib: cardiovascular AEs

subgroup analysis

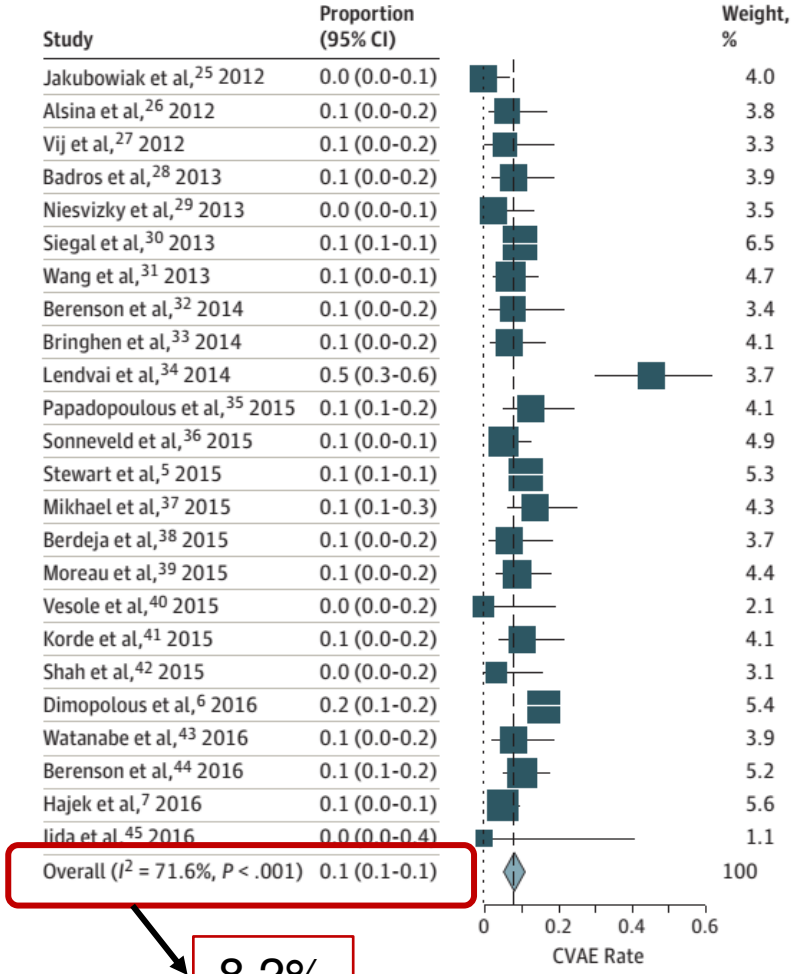
	All patients All grades heart failure n/N (%)	**< 65 years** All grades heart failure n/N (%)	**65-74 years** All grades heart failure n/N (%)	**≥ 75 years** All grades heart failure n/N (%)
ASPIRE[1]				
KRd	27/392 (6.9)	7/207 (3.4)	7/142 (4.9)	**11/43 (25.6)**
Rd	16/389 (4.1)	6/184 (3.3)	7/155 (4.5)	3/50 (6)
ENDEAVOR[2]				
Kd	38/463 (8.2)	10/223 (4.5)	12/163 (7.4)	**16/77 (20.8)**
Vd	13/456 (2.9)	5/208 (2.4)	5/183 (2.7)	3/65 (4.6)
FORTE[3]				
KCyd	(3)	(3)	-	-
KRd	(5)	(5)	-	-
POOLED ANALYSIS[4]				
KCyd	17/154 (11)	-	9/117 (7.7)	**8/37 (21.6)**

1.Dimopoulos M, et al; Lancet 2015. 2.Stewart K, et al; NEJM 2015. 3.Gay F, et al. ASCO 2017. 4.Mina R, at al. IMW 2017

Carfilzomib-Associated Cardiovascular Adverse Events
A Systematic Review and Meta-analysis

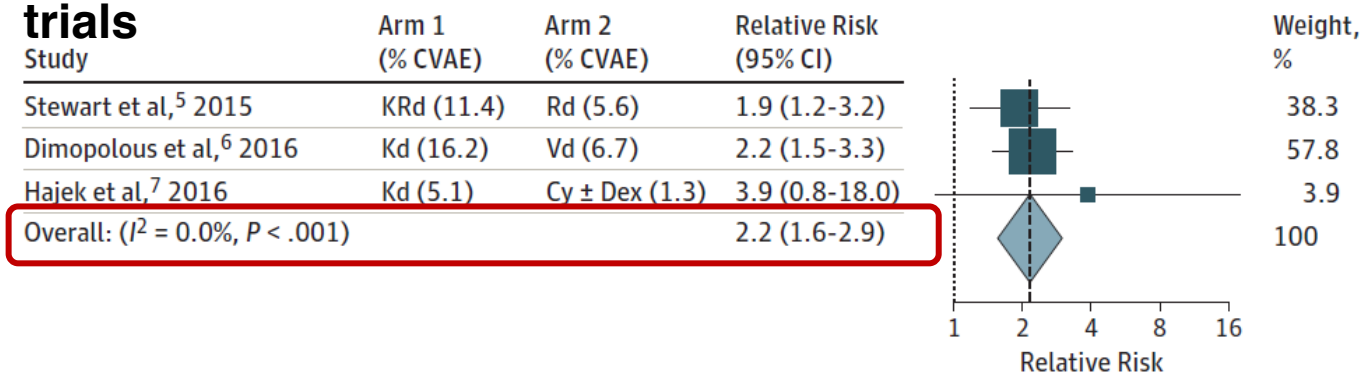
24 studies including 2594 patients

Rate of grade ≥3 CVAE



8.2%

Relative risk of CVAE in randomized clinical trials



Waxman AJ, et al. Jama Oncology 2018

Carfilzomib-Associated Cardiovascular Adverse Events
A Systematic Review and Meta-analysis

	All-Grade Adverse Events					Grade ≥3 Adverse Events				
Outcome	No. of Studies	% (95% CI)	*P* Value	I^2	I^2 *P* Value	No. of Studies	% (95% CI)	*P* Value	I^2	I^2 *P* Value
All events	22	18.1 (13.5-23.3)	<.001	87.4	<.001	24	8.2 (5.9-10.7)	<.001	71.6	<.001
Congestive heart failure	17	4.1 (2.3-6.2)	<.001	65.2	<.001	23	2.5 (1.5-3.8)	<.001	49.2	.004
Hypertension	16	12.2 (9.8-14.9)	<.001	54.1	.004	17	4.3 (2.6-6.4)	<.001	60.3	.001
Arrhythmia	13	2.4 (0.4-5.6)	.004	84.4	<.001	17	0.8 (0.3-1.4)	<.001	0	.86
Ischemia	13	1.8 (0.8-3.0)	<.001	38.0	.08	18	0.8 (0.4-1.4)	<.001	0	.78
Cardiac arrest		NA	NA	NA	NA	24	0.0 (0.0-0.1)	>.99	0	.98
Dyspnea	17	23.9 (18.4-29.9)	<.001	88.4	<.001	18	3.2 (2.2-4.3)	<.001	29.5	.11
Edema	12	24.7 (21.0-28.6)	<.001	64.2	.001	12	0.4 (0.1-0.9)	<.001	0	.61

Abbreviation: NA, not applicable.

Waxman AJ, et al. Jama Oncology 2018

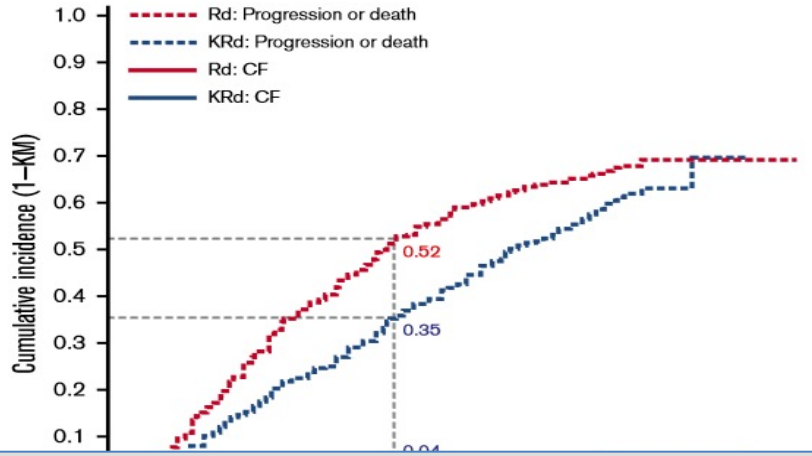
Subgroup Analysis of High-Grade Cardiovascular Adverse Events by Study Characteristics

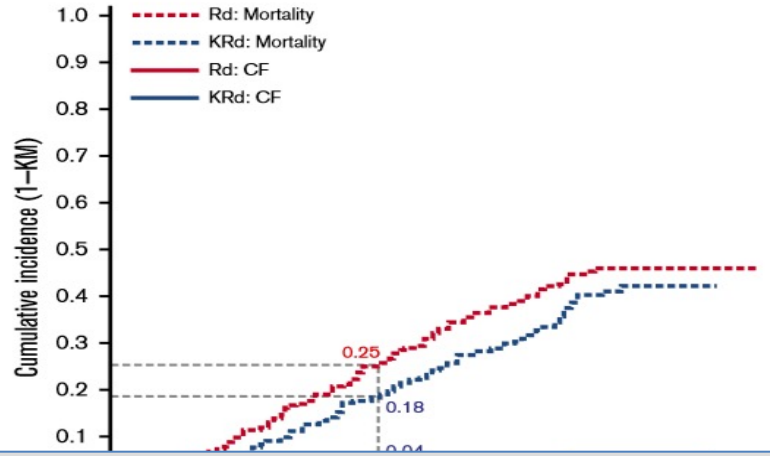
Study Characteristic	Estimate, % (95% CI)		*P* Value
	No	Yes	
Median age >65 years	8.1 (5.4-11.2)	8.5 (5.6-11.9)	.95
Phase 1 trial	9.5 (6.9-12.3)	2.3 (0.1-6.2)	.02[a]
Randomized trial	7.7 (5.2-10.5)	10.8 (5.8-17.0)	.48
Newly diagnosed MM	8.7 (6.1-11.8)	6.7 (2.9-11.8)	.38
≥3 Prior therapies	8.4 (5.4-12.0)	8.2 (4.6-12.5)	.87
≥6 Months carfilzomib[b]	9.9 (5.7-15.0)	7.1 (4.2-10.7)	.26
Dose ≥45 mg/m^2	6.4 (3.3-8.6)	11.9 (7.25-17.49)	.02[a]
30-Minute infusion	6.7 (4.9-8.8)	11.0 (6.4-16.5)	.06
Combination regimen	10.6 (6.6-15.2)	6.5 (4.1-9.2)	.08

Waxman AJ, et al. Jama Oncology 2018

Benefit-risk analysis in the ASPIRE and ENDEAVOR trials

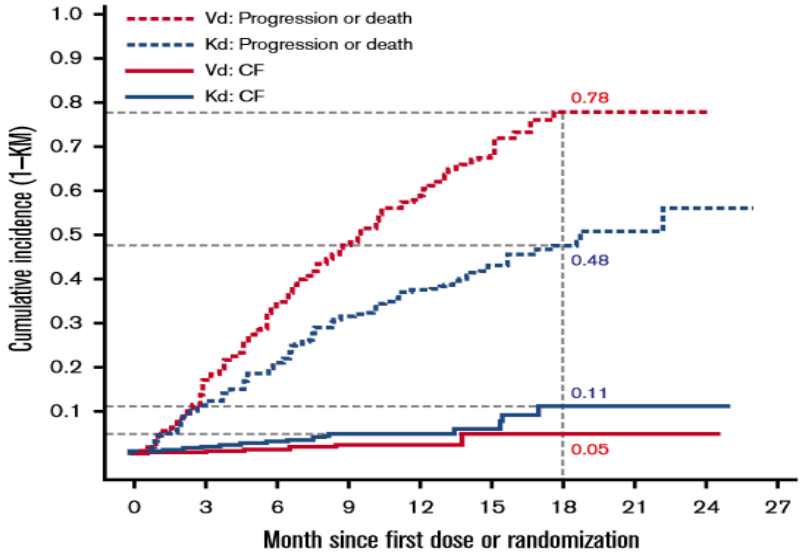
ASPIRE

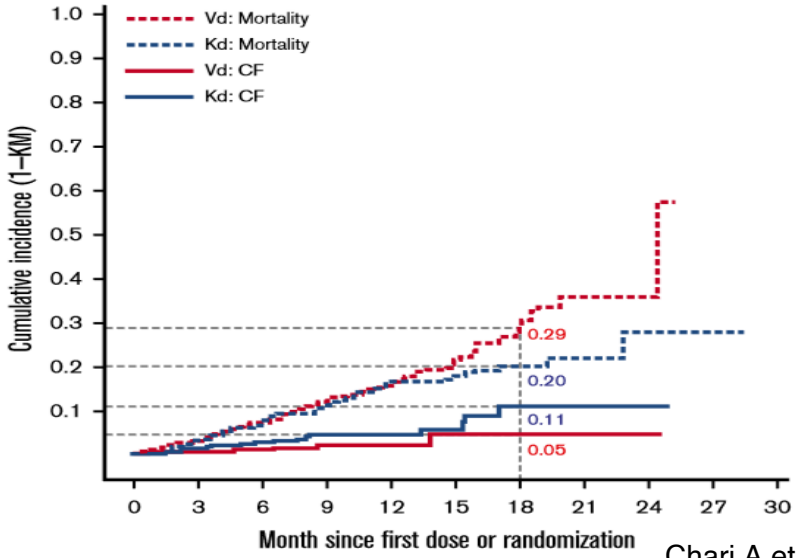




The results suggest that **the benefit of carfilzomib** treatment in reducing disease progression, and even death, **outweighs CV risks for most patients**.

ENDEAVOR





Chari A et, Blood Advance 2018 Jul 10

Carfilzomib-based regimens in real life

Table 4. Main studies conducted on real-life patients treated with carfilzomib-based regimens.

Study	Type of study	N. of patients	Rate of pre-existing CV history	Rate of CVAE
Atrash[56]	R	130	54%	11.5% hospitalized for heart failure
Chari[64]	R	498	84% of non-hospitalized; 92% of hospitalized patients	22% had ≥1 CVAE; 5% had ≥1 hospitalization for
Rosenthal[65]	P	62	20% baseline hypertension	8% had cardiac SAE; 32% had hypertension
Dimopoulos[66]	P	60	28%	11.6% had a CVAE

R: retrospective; P: prospective; N.: number; CV: cardiovascular; CVAE: cardiovascular adverse event(s); SAE: serious adverse event(s).

Bringhen, Milan, Ferri EMN&SIIA et al. Haematologica 2018

Carfilzomib-based regimen in real life (KRd)

Patients (no. = 197)

Male: 58%
Age <75 y: 97%

Cardiac risk factors recorded in 99 pts (**50%**):

- Hypertension (40%)
- Elevated NT-proBNP (>322 pg/ml) (8%)
- Left ventricular disfuncion (EF<55%) (6%)
- Coronary artery disease (4%)
- AL amyloidosis without cardiac involvement (1%)

TABLE 2 Adverse events (all grades and grade ≥ 3)

Adverse event	No. of patients (%)	
	All grades	≥ grade 3
Hematological		
Anemia	131 (66)	14 (7)
Thrombocytopenia	124 (63)	36 (18)
Neutropenia	98 (50)	41 (21)
Non hematological		
Thrombotic events	22 (11)	7 (4)
Gastrointestinal toxicities	33 (17)	3 (1)
Elevated liver function tests	26 (13)	5 (2)
Infections	72 (36)	21 (11)
Skin rash	19 (10)	5 (3)
Of specific interest (cardio-vascular)		
Hypertension	31 (16)	12 (6)
Arrhythmia	12 (6)	1 (0.5)
Heart failure	7 (3)	2 (1)

Abbreviation: no, number.

Rocchi S, et al, Hematol Oncol. 2021

Risk factors for cardiovascular disease

Current myocardial disease	*Demographic and other CV risk factors*
• Heart failure (with either preserved or reduced ejection fraction) • Asymptomatic LV dysfunction (LVEF <50% or high natriuretic peptide[a]) • Evidence of CAD (previous myocardial infarction, angina, PCI or CABG, myocardial ischaemia) • Moderate and severe VHD with LVH or LV impairment • Hypertensive heart disease with LV hypertrophy • Hypertrophic cardiomyopathy • Dilated cardiomyopathy • Restrictive cardiomyopathy • Cardiac sarcoidosis with myocardial involvement • Significant cardiac arrhythmias (e.g. AF, ventricular tachyarrhythmias)	• Age (paediatric population <18 years; >50 years for trastuzumab; >65 years for anthracyclines) • Family history of premature CV disease (<50 years) • Arterial hypertension • Diabetes mellitus • Hypercholesterolaemia
Previous cardiotoxic cancer treatment	***Lifestyle risk factors***
• Prior anthracycline use • Prior radiotherapy to chest or mediastinum	• Smoking • High alcohol intake • Obesity • Sedentary habit

Zamorano et al Eur Heart J 2016

Risk factors for cardiovascular disease

Blood pressure evaluation

Hypertension is defined as a SBP ≥140 mmHg and/or a DBP ≥90 mmHg on **at least two** BP measurements and should be confirmed with ABPM or HBPM:

- Ambulatory Blood Pressure Monitoring (ABPM):
  - portable blood pressure measuring device
  - for a 24 hours period
  - information on blood pressure
    - during daily activities
    - sleep
- Home Blood Pressure Monitoring (HBPM):
  - blood pressure self-measurements
  - daily for at least 3–4 d or preferably for 7 consecutive days

Risk factors for cardiovascular disease

Blood pressure evaluation

	ABPM	HBPM
Primary care	-	+
Specialist care	+	-
Cost	++	-
24 hours	++	-
Daily activity	++	-
Sleep	++	-
Long period (at least 7 days)	-	++

For initial assessment → HBPM may be more suitable.
For borderline or abnormal findings on HBPM → should be confirmed with ABPM

Risk stratification

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 ≥180 or DBP ≥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
	≥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 ≥4, or diabetes mellitus with organ damage	Very high risk	Very high risk	Very high risk	Very high risk

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.

Williams et al. ESC/ESH 2018

Risk stratification in Multiple Myeloma
2022 Update

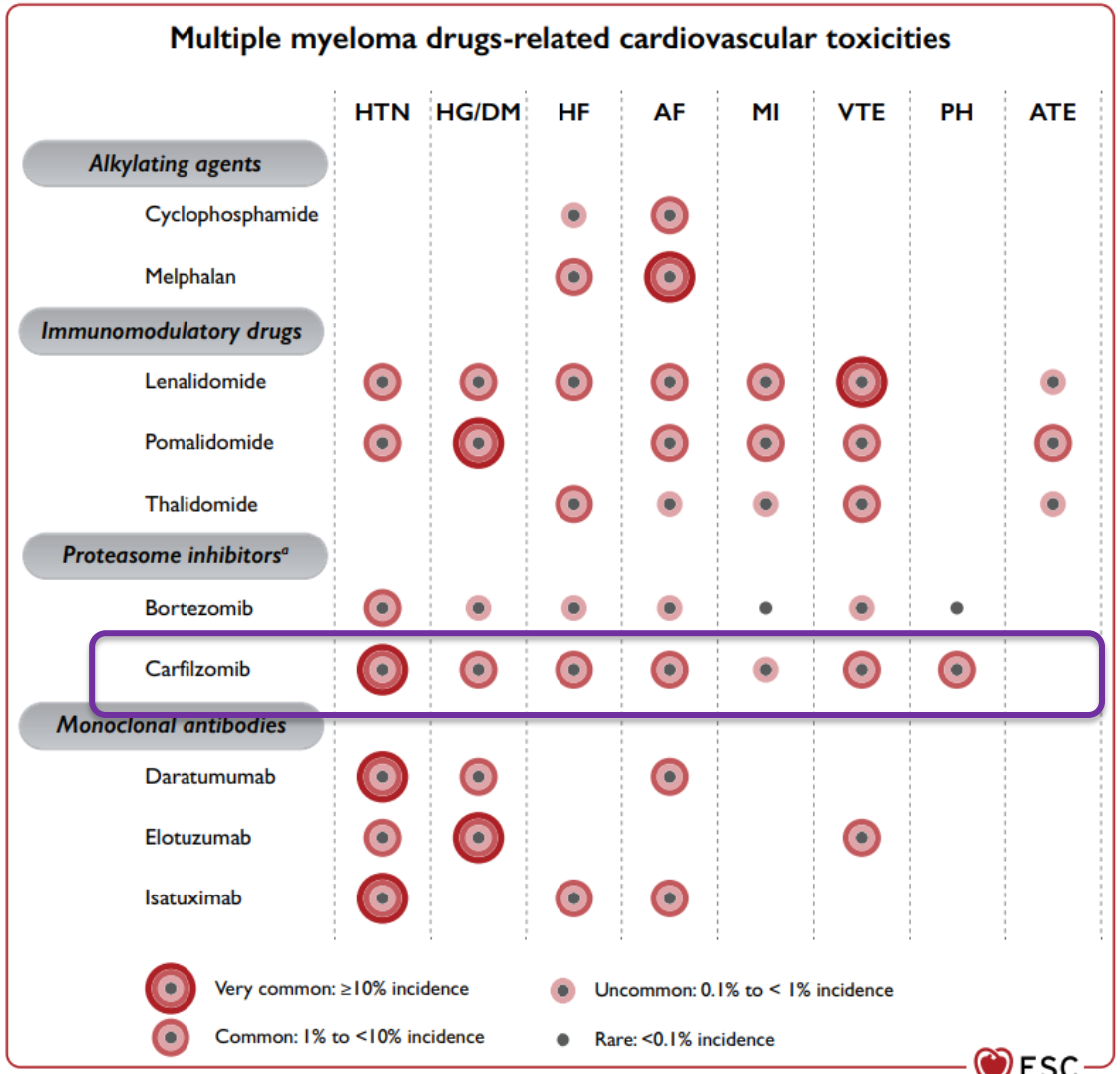
Risk factor	Score	Level of evidence
Previous CVD		
HF or cardiomyopathy	Very high	C
Prior PI cardiotoxicity	Very high	C
Venous thrombosis (DVT or PE)	Very high	C
Cardiac amyloidosis	Very high	C
Arterial vascular disease (IHD, PCI, CABG, stable angina, TIA, stroke, PVD)	Very high	C
Prior IMiD CV toxicity	High	B
Arrhythmia[a]	Medium2	C
Cardiac imaging		
Baseline LVEF < 50%	High	C
Borderline LVEF 50–54%	Medium2	C
LV hypertrophy[b]	Medium1	C
Cardiac biomarkers (where available)		
Elevated baseline troponin[c]	Medium2	C
Elevated baseline BNP or NT-proBNP[c]	High	B

Risk factor	Score	Level of evidence
Demographic and CVRF		
Age ≥ 75 years	High	C
Age 65–74 years	Medium1	C
Hypertension[d]	Medium1	C
DM[e]	Medium1	C
Hyperlipidaemia[f]	Medium1	C
Chronic kidney disease[g]	Medium1	C
Family history of thrombophilia	Medium1	C
Previous cardiotoxic cancer treatment		
Prior anthracycline exposure	High	C
Prior thoracic spine RT	Medium1	C
Current myeloma treatment		
High-dose dexamethasone > 160 mg/month	Medium1	C
Lifestyle risk factors		
Current smoker or significant smoking history	Medium1	C
Obesity (BMI > 30 kg/m^2)	Medium1	C

- Low risk: no risk factors OR one medium1 risk factor;
- Medium risk: medium risk factors with a total of 2–4 points;
- High risk: medium risk factors with a total of ≥5 points OR any high-risk factor;
- Very high risk: any very high-risk factor.

Medium1 = 1 point. Medium2 = 2 points.

Alexander R. Lyon et al, European Heart Journal - Cardiovascular Imaging (2022) 00, 1–133

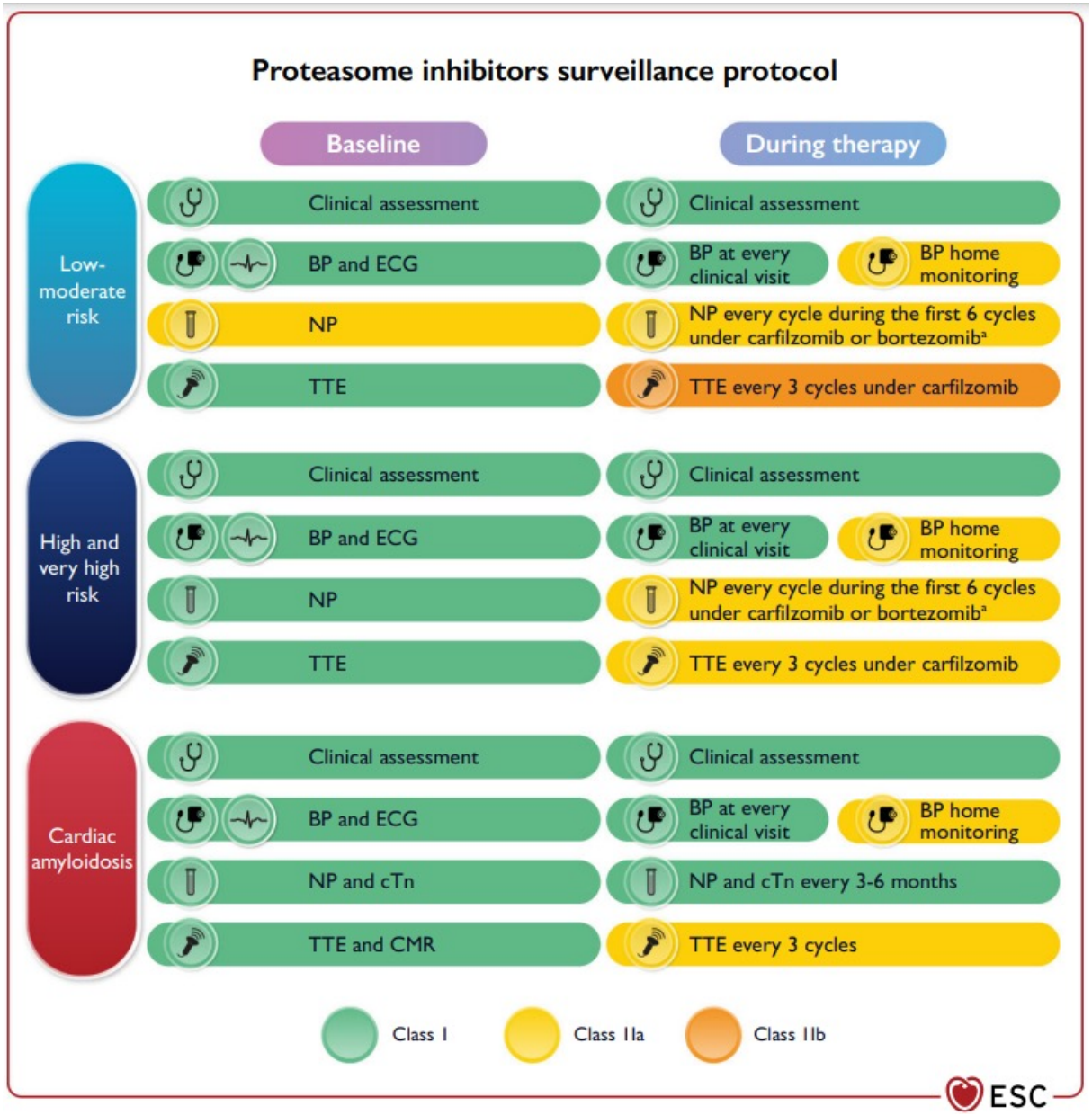


AF, atrial fibrillation; ATE, arterial thromboembolism; DM, diabetes mellitus; EMA, European Medicines Agency; FDA, Food and Drug Administration; HF, heart failure; HG, hyperglycaemia; HTN, hypertension; MedDRA, medical dictionary for regulatory activities; MI, myocardial infarction; PH, pulmonary hypertension; VTE, venous thromboembolism. Adverse reactions reported in multiple clinical trials or during post-marketing use are listed by system organ class (in MedDRA) and frequency. If the frequency is unknown or cannot be estimated from the available data, a blank space has been left. A Ixazomib produces peripheral oedema in up to 18% of patients and hyperglycaemia in combination with lenalidomide or pomalidomide and dexamethasone. Figure developed from EMA prescribing information, FDA prescribing information.

Alexander R. Lyon et al, European Heart Journal - Cardiovascular Imaging (2022) 00, 1–133

Management according to the risk

- No-risk patients → start treatment with CFZ immediately.
- Low moderate risk patients →
  - Treatment of hypertension
  - Correction of modifiable risk factors
- High-risk patients → case by case evaluation considering the risk/benefit ratio should be performed
- Very high-risk patients →
  - no data on CFZ treatment
  - most risk factors are not modifiable
  - other MM treatments should be preferred



Alexander R. Lyon et al, European Heart Journal - Cardiovascular Imaging (2022) 00, 1–133

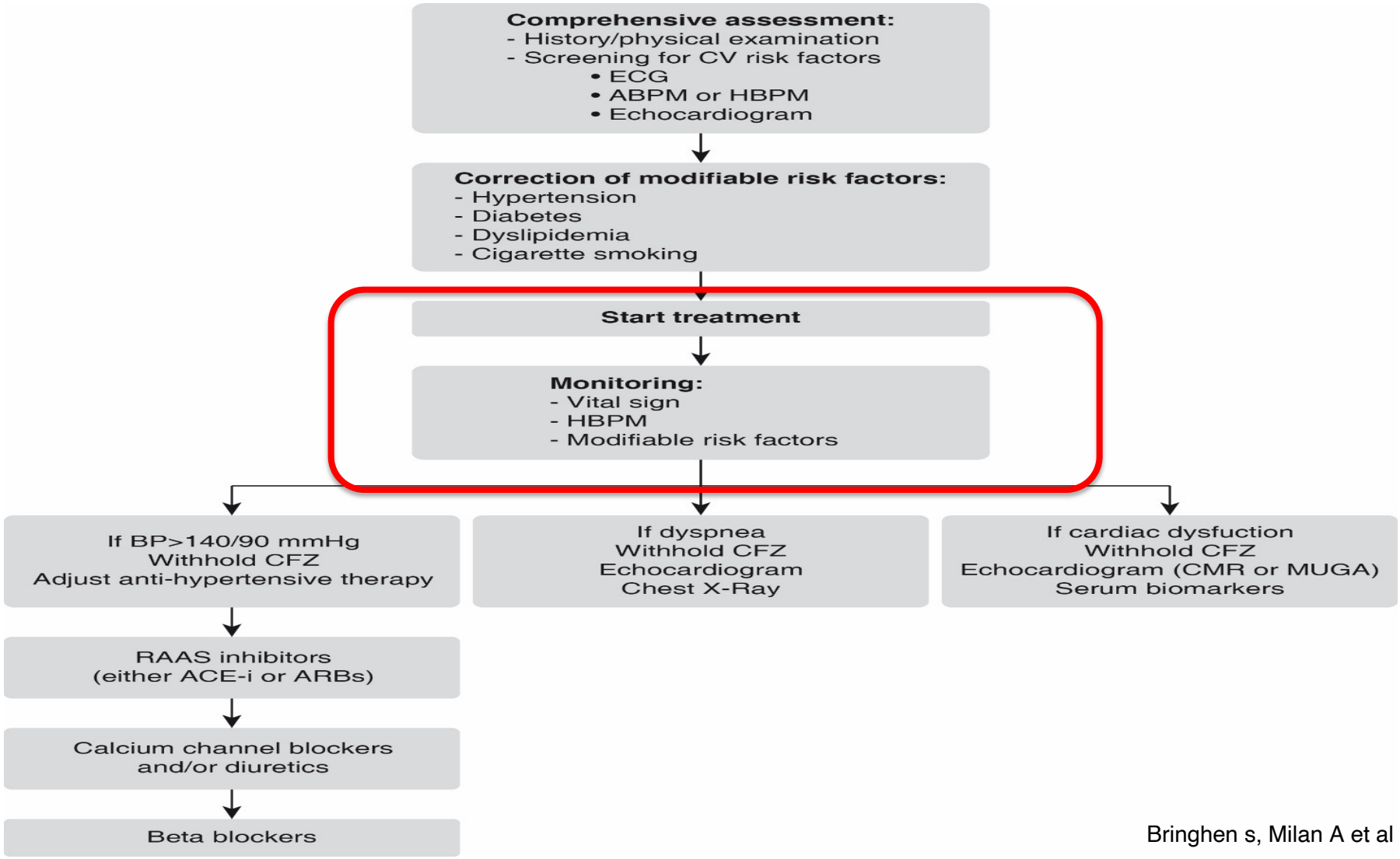
Detection of cardiotoxicity

Table 6 Proposed diagnostic tools for the detection of cardiotoxicity

Technique	Currently available diagnostic criteria	Advantages	Major limitations
Echocardiography: **- 3D-based LVEF** **- 2D Simpson's LVEF** **- GLS**	• LVEF: >10 percentage points decrease to a value below the LLN suggests cardiotoxicity. • GLS: >15% relative percentage reduction from baseline may suggest risk of cardiotoxicity.	• Wide availability. • Lack of radiation. • Assessment of haemodynamics and other cardiac structures.	• Inter-observer variability. • Image quality. • GLS: inter-vendor variability, technical requirements.
Nuclear cardiac imaging (MUGA)	• >10 percentage points decrease in LVEF with a value <50% identifies patients with cardiotoxicity.	• Reproducibility.	• Cumulative radiation exposure. • Limited structural and functional information on other cardiac structures.
Cardiac magnetic resonance	• Typically used if other techniques are non-diagnostic or to confirm the presence of LV dysfunction if LVEF is borderlines.	• Accuracy, reproducibility. • Detection of diffuse myocardial fibrosis using T1/T2 mapping and ECVF evaluation.	• Limited availability. • Patient's adaptation (claustrophobia, breath hold, long acquisition times).
Cardiac biomarkers: **- Troponin I** **- High-sensitivity Troponin I** **- BNP** **- NT-proBNP**	• A rise identifies patients receiving anthracyclines who may benefit from ACE-Is. • Routine role of BNP and NT-proBNP in surveillance of high-risk patient needs futher investigation.	• Accuracy, reproducibility. • Wide availability. • High-sensitivity.	• Insufficient evidence to establish the significance of subtle rises. • Variations with different assays. • Role for routine surveillance not clearly established.

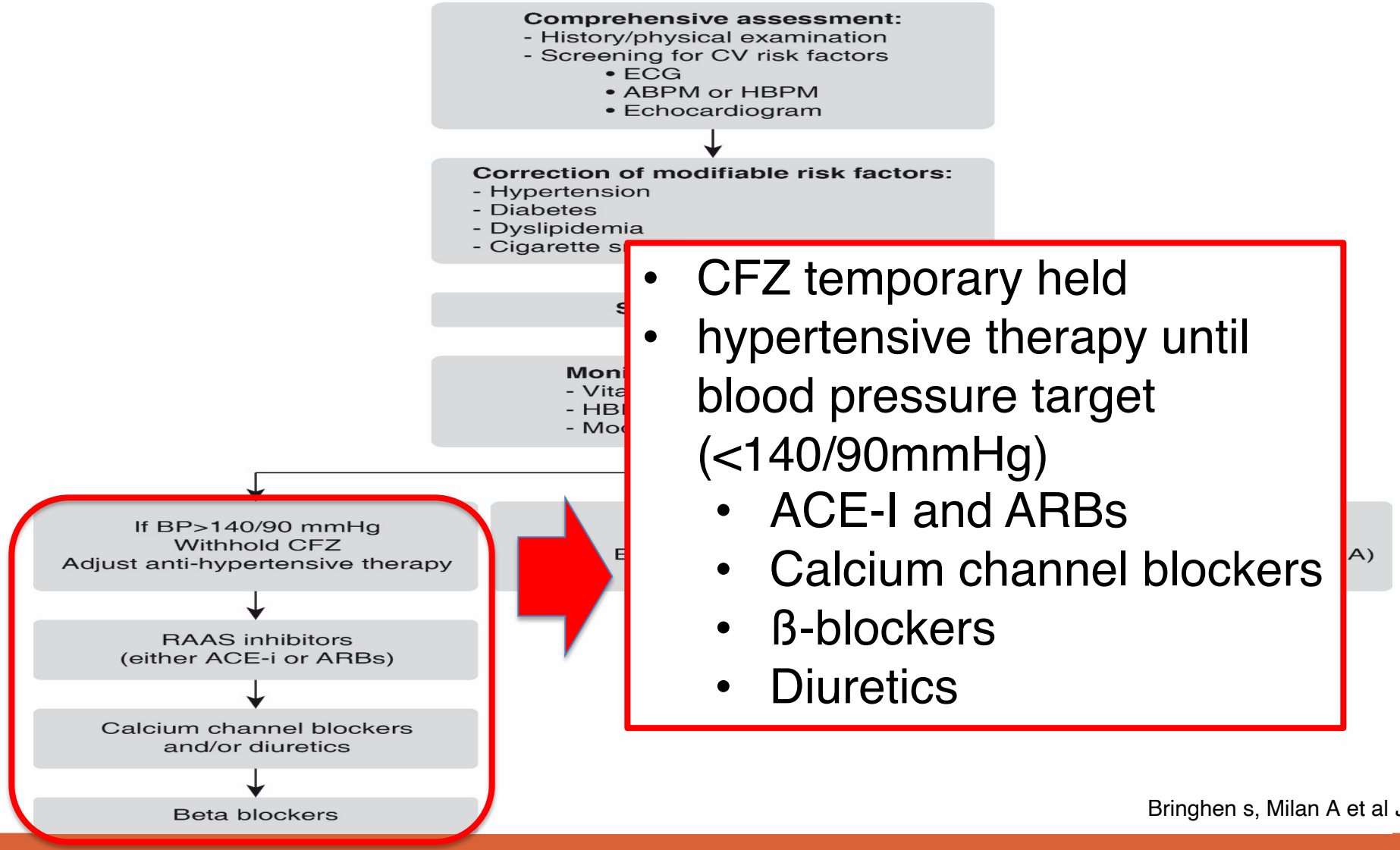
Zamorano ESC Position paper 2016

EHA - EMN – SIIA *Consensus*



Bringhen s, Milan A et al *J of Internal Medicine 2019*

EHA - EMN – SIIA *Consensus*

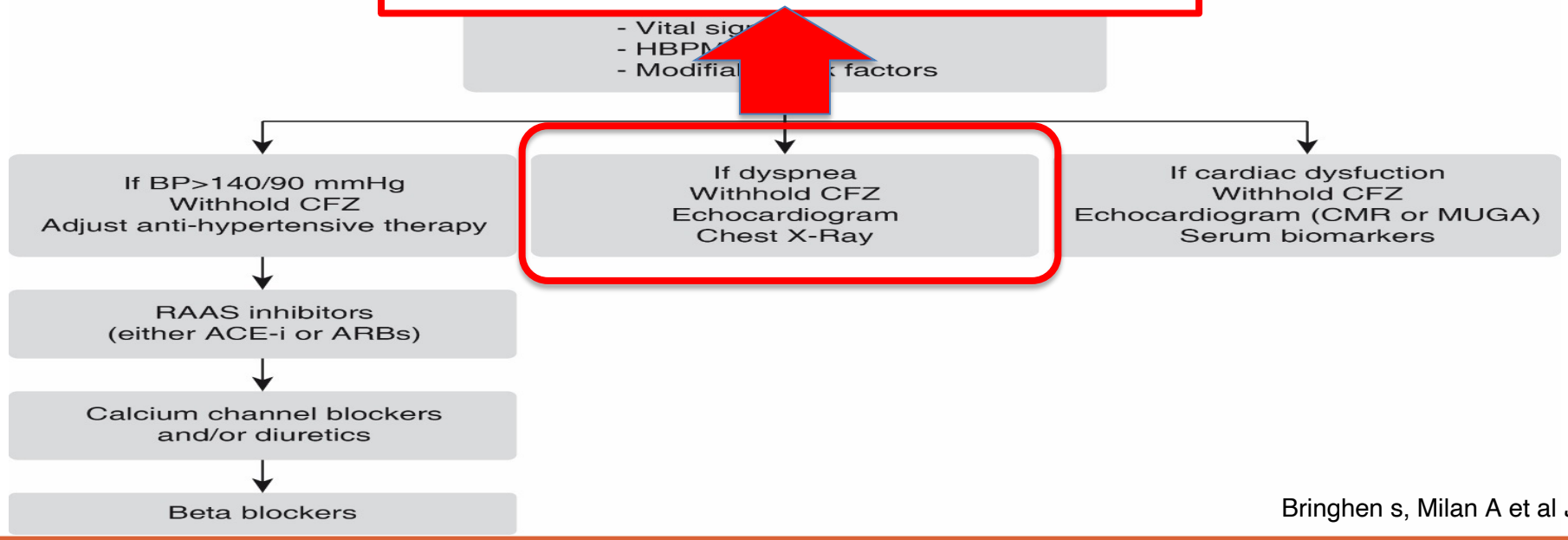


- CFZ temporary held
- hypertensive therapy until blood pressure target (<140/90mmHg)
  - ACE-I and ARBs
  - Calcium channel blockers
  - ß-blockers
  - Diuretics

Bringhen s, Milan A et al *J of Internal Medicine 2019*

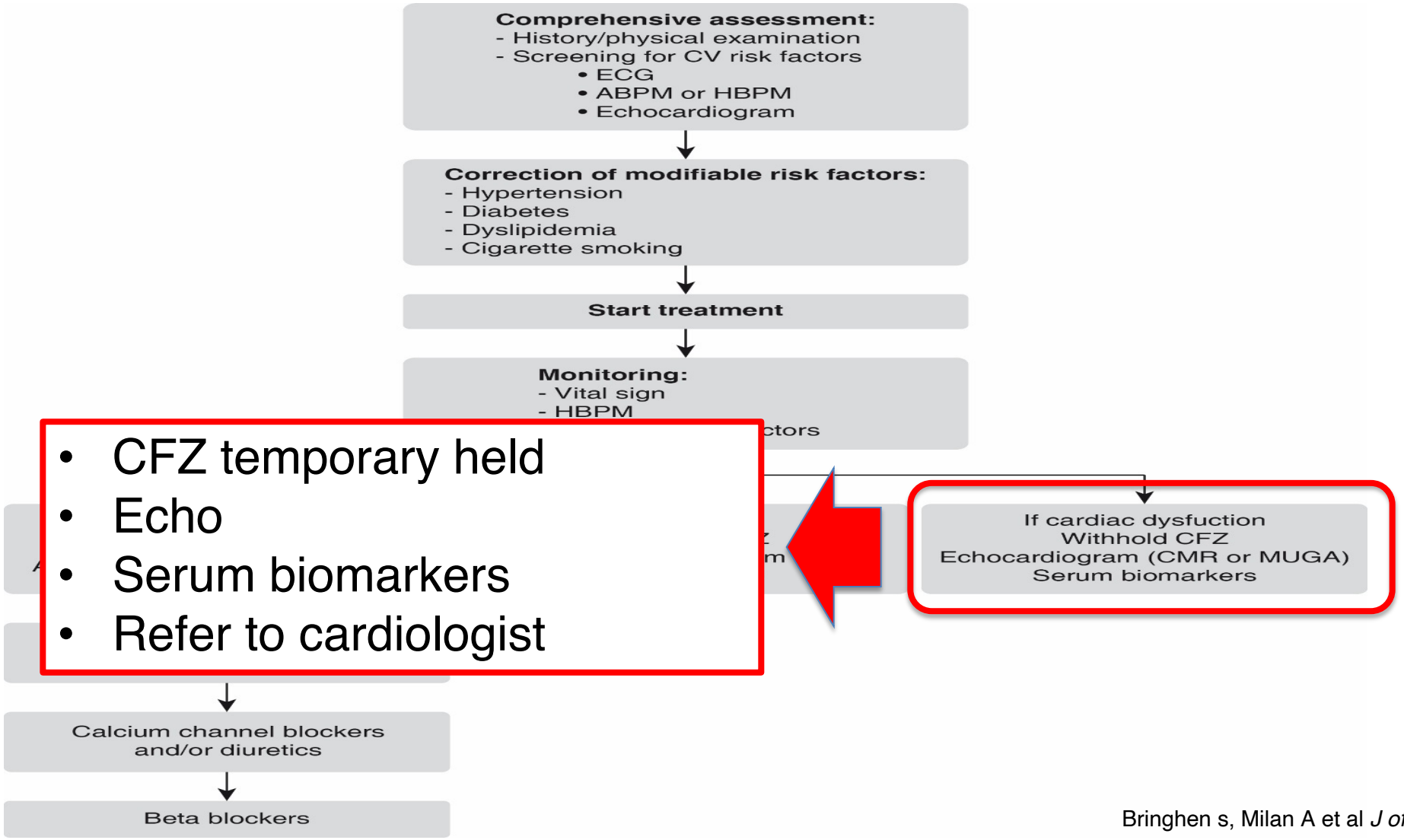
EHA - EMN – SIIA *Consensus*

- CFZ temporary held
- Echo
- Chest X-Ray
- Most patients with dyspnea do not typically show an EF impairment or other evidences of myocardial dysfunction.
- CFZ could be restarted as soon as symptoms improve.



Bringhen s, Milan A et al *J of Internal Medicine 2019*

EHA - EMN – SIIA *Consensus*



Bringhen s, Milan A et al *J of Internal Medicine 2019*

What to do after cardiovascular AEs

IN CASE OF CARDIOVASCULAR AEs DURING CARFILZOMIB TREATMENT:

- Cardiac disfunction during treatment → after cardiac function has recovered to grade 1 or baseline, no specific recommendations regarding further continuation or discontinuation of CFZ therapy.
- This decision should be taken by the hematologist in close collaboration with the cardiologist, evaluating both the clinical circumstances and the risks and benefits.
- Grade 3/4 cardiovascular AEs RELATED to CFZ → dose reductions or definitive discontinuation may be needed.
- Grade 3/4 cardiovascular AEs are NOT related to CFZ → CFZ treatment could be restarted at the dose used before the event or at a reduced dose.

Courtesy of Dr. Sara Bringhen

Cardiovascular toxicity

Cardiac side effects:

- Congestive heart failure (CHF)
- Acute coronary syndrome (ACS)
- Arrhythmias
- Cardiomyopathy

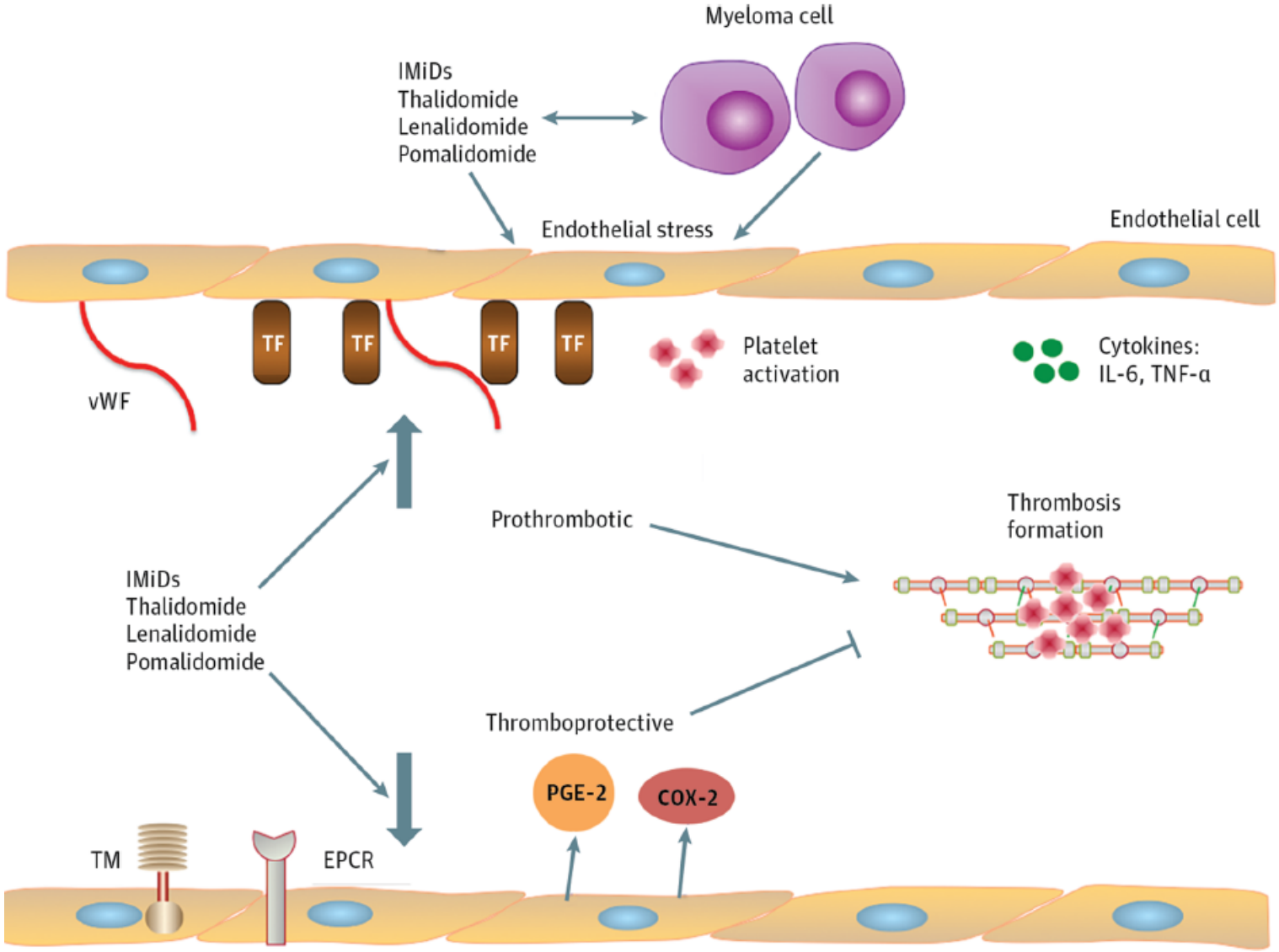
Proteasome Inhibitors

Vascular side effects:

- Hypertension
- Venous thromboembolic events
- Arterial thromboembolic events

IMIDs

Cardiovascular toxicity with IMiDs



Patel VG and Cornell RD, Curr Oncol Rep (2019) 21: 29

Thromboembolic risk

Regimen	Grade 3-4 VTE (%)
Rd vs placebo RRMM[1,2]	**15** vs 4 **11** vs 5
MPT vs MP at diagnosis[3]	**17** vs 2 ↓ **3**
Rd vs MPT at diagnosis[4]	**6-8** vs 5
Poma-dex vs dex in RRMM[5]	**1** vs 0

Prophylaxis NOT mandatory

Prophylaxis mandatory

1. Weber DM, et al. N Engl J Med. 2007 22;357(21):2133-42. 2. Dimopoulos M, et al. N Engl J Med. 2007 22;357(21):2123-32.
3. Palumbo A, et al. Lancet 2006;367(9513):825–831 4. Benboubker L, et al. N Engl J Med. 2014 4;371(10):906-17. 5, Miguel JS, et al. Lancet Oncol.

Thromboprophylaxis with IMIDs

IMWG recommendation

Individual Risk Factors	Actions
▪ Obesity ▪ Previous VTE ▪ Central venous catheter, pacemaker ▪ Associated diseases – Cardiac – Chronic renal disease – Diabetes – Acute infection – Immobilization – Blood clotting disorders ▪ Surgery, anesthesia, or trauma ▪ Medications • ESAs	▪ LMWH (enoxaparin 40 mg/day or equivalent) ▪ Warfarin (target INR: 2-3) In general: ▪ Low risk (1 risk factor): patient should receive ASA 81-325 mg/day ▪ High risk: patient should receive therapeutic prophylactic anticoagulation with LMWH, warfarin ***MYELOMA IS A RISK FACTOR***
Myeloma-Related Risk Factors	
▪ Diagnosis ▪ Hyperviscosity ▪ Myeloma therapy – High-dose dexamethasone – Doxorubicin – Multiagent chemotherapy	▪ LMWH (enoxaparin 40 mg/day or equivalent) ▪ Warfarin (target INR: 2-3)

Palumbo A, et al. Leukemia. 2008 Feb;22(2):414-23

What to do in case of VTE

IMWG recommendation

Diagnosis:

- DVT: compression ultrasonography
- PE: computed tomography pulmonary angiography

Therapy:

- LMWH at therapeutic dose
- Oral anticoagulant

Briefly discontinue IMIDs

Resume the treatment when full anticoagulation has been established

Palumbo A, et al. Leukemia. 2008 Feb;22(2):414-23

Conclusion

- PIs (mainly Carfilzomib) are associated with increased risks of CVAEs (Mainly hypertension, dyspnea, followed by cardiac failure and ischemic heart disease)
- The benefit of Carfilzomib treatment in both PFS and OS outweighs CV risks
- Risk stratification and correction of modifiable risk factors is mandatory for a proper management
- In presence of CV risk factors → consider to reduce Carfilzomib dose
- In high-risk patients or age ≥ 75 yrs → carefully consider the risk/benefit ratio. In very high-risk patients consider other MM treatments
- IMIDs (mostly in combination with steroids or chemotherapy) have an increased risk of VTE → Routine thromboprophylaxis according to the type of therapy and the individual risk of patients is mandatory.

THANK YOU

Seràgnoli Institute of Hematology

Myeloma Research Unit
Michele Cavo

Clinical Research Unit
Elena Zamagni
Paola Tacchetti
Lucia Pantani
Katia Mancuso
Chiara Sartor
Miriam Iezza
Michele Puppi
Marco Talarico
Flavia Bigi
Ilaria Sacchetti
Enrica Manzato
Roberta Restuccia
Simone Masci

Data Management
Giorgia Lazzarini
Francesca Trombetta
Alessandra Scatà
Simona Barbato
Margherita Musella
Nicola Paprusso
Nicola Francesco Parisi
Federica di Camillo

Lab of Cytogenetics
Nicoletta Testoni
Giulia Marzocchi

Lab of Molecular Biology
Carolina Terragna
Marina Martello
Enrica Borsi
Silvia Armuzzi
Ilaria Vigliotta
Barbara Taurisano
Ignazia Pistis

Statistical Analysis
Vincenza Solli
Andrea Poletti
Gaia Mazzocchetti