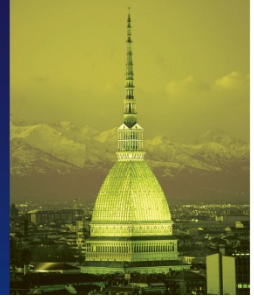
TURIN,
October
25th-27th
2018
Starhotels
Majestic

GIORNATE
CARDIOLOGICHE
TORINESI



UNIVERSITÁ DEGLI STUDI DI TORINO

AZIENDA OSPEDALIERO - UNIVERSITARIA
Città della Salute e della Scienza di Torino

University of Torino
Department of Medical Sciences
Division of Internal Medicine
Director: Prof. Franco Veglio

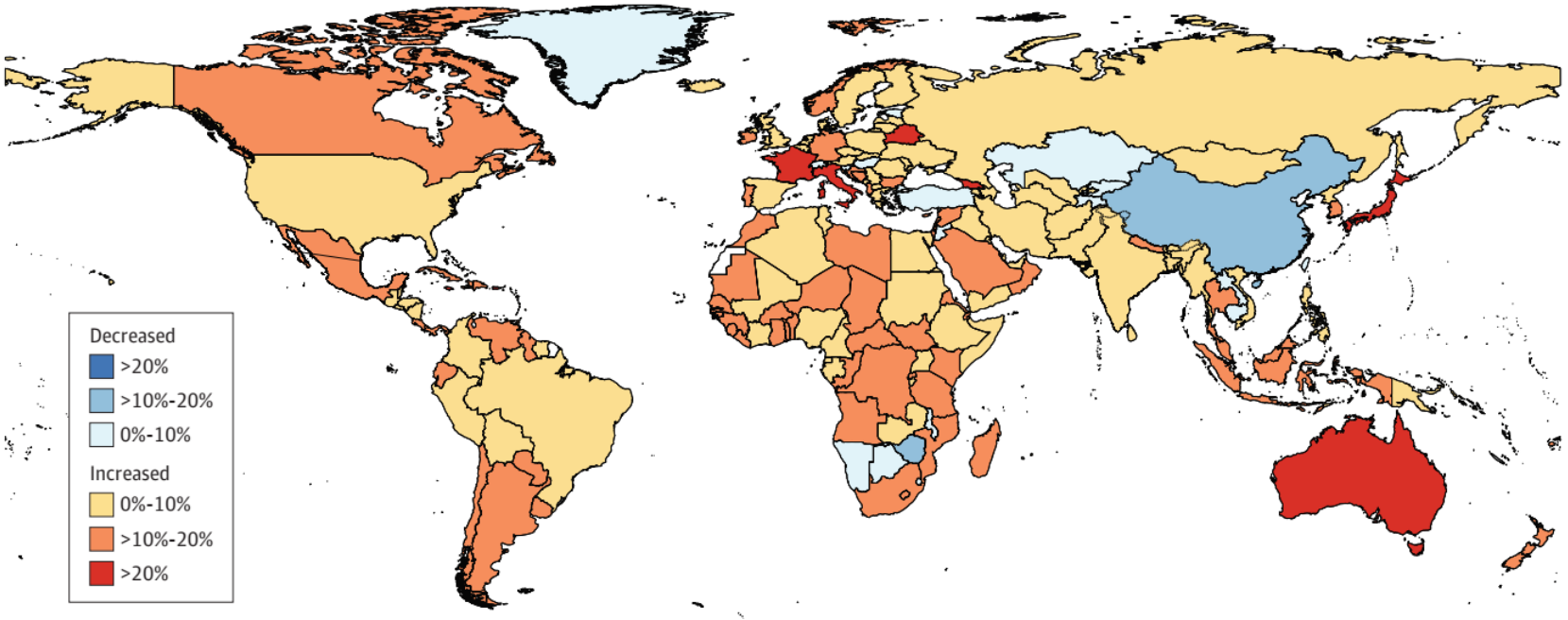
Janus-faced: Mieloma and amyloidosis Hypertension

Alberto Milan

Disclosures (last 2 years)

- **AMGEN**: grant for Advisory Board & Consultant
- **Boheringher**: grant partecipazione a Advisory Board
- **Janssen:** grant for Advisory Board & Consultant

Epidemiology

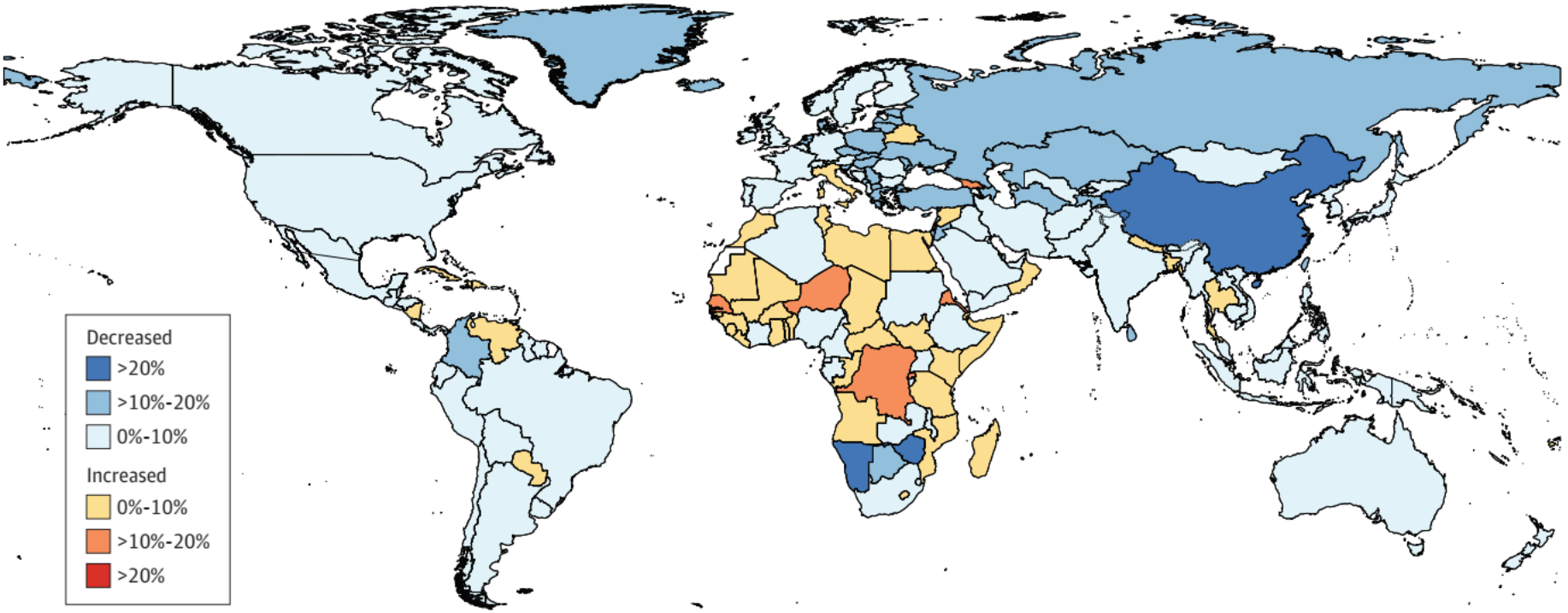


Increasing incidence of tumor

Global Burden of Disease Cancer Collaboration JAMA 2017


EXCLUSIVE
GOOD NEWS!

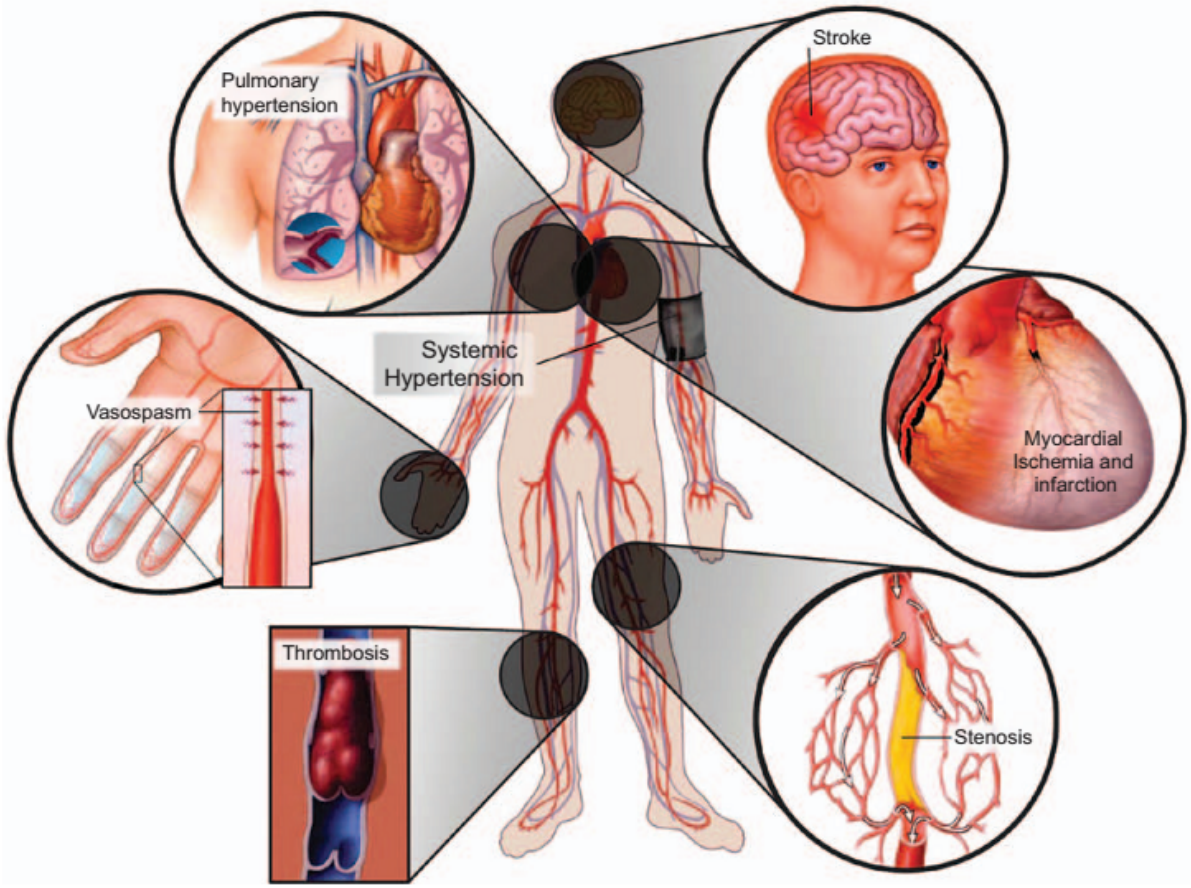
The good news



Tumor mortality reduction

Global Burden of Disease Cancer Collaboration JAMA 2017

Vascular Toxicities of Cancer Therapies



Herrmann J et al. Circulation 2016

Hypertension and anti-hypertensive drugs

Natural agents: Vinca Alkaloids

Vincristine
Vinblastine

Taxanes

Docetaxel
Paclitaxel

Anti Tyr K

Dasatinib
Imatinib
Lapatinib
Sorafenib
Sunitinib
Pazopanib

Ab anti VEGF

Bevacizumab

Steroids

Prednisone

Proteasome inhibitors

(Bortezomib)

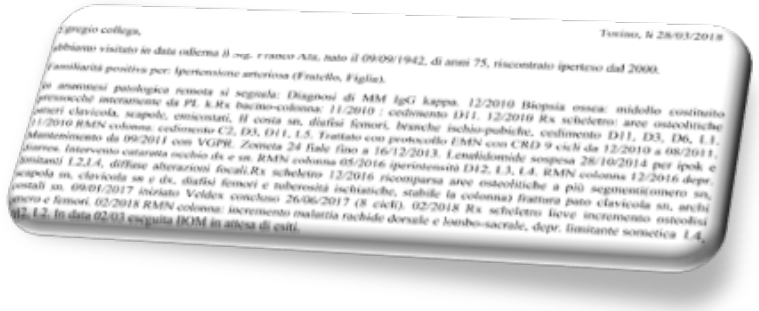
Carfilzomib

Modified from Milan A et al, Int J of Cancer 2014

Clinical Scenario Franco

- 75 years old male

Myeloma related organ damage	YES



Diagnosis
2010

Therapy

Ciclofosfamide
Desametasone
Lenalidomide

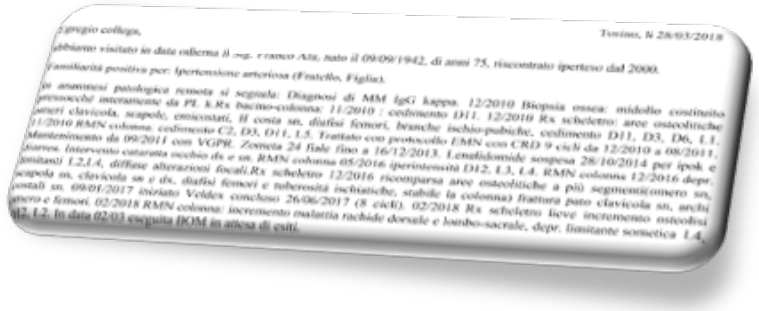
11c

(Diarrhea e hypoK)

Clinical Scenario Franco

- 75 years old male

Myeloma related organ damage	YES



Diagnosis
2010

Therapy → Continuation

Ciclofosfamide
Desametasone
Lenalidomide

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(Diarrhea e hypoK)

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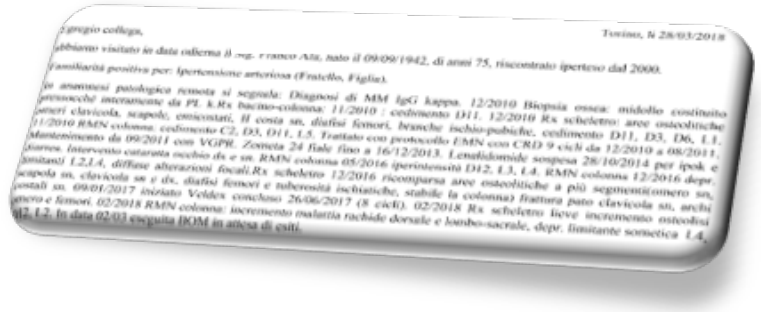


Diagnosis 2010 → VGPR → Relapse 2017 → 2018 Relapse

Therapy → Continuation → Therapy

Ciclofosfamide
Desametasone
Lenalidomide

11c

(Diarrhea e hypoK)

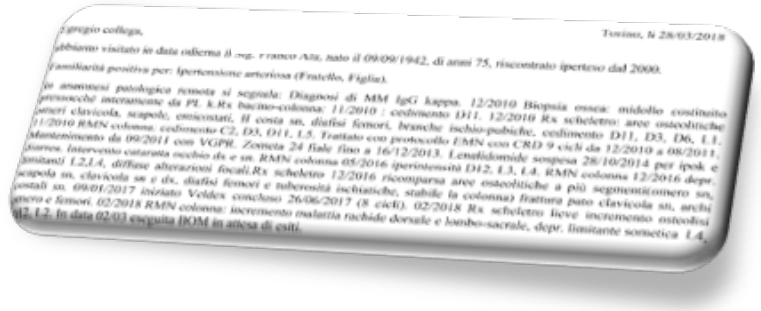
Bortezomib
Desametasone

8c

Clinical Scenario Franco

- 75 years old male

Myeloma related organ damage	YES



Hypertension
2010

Diagnosis
2010

VGPR

Relapse
2017

2018
Relapse

Lercanidipine

Terapia → Mantenim → Terapia

Ciclofosfamide
Desametasone
Lenalidomide

11c

Bortezomib
Desametasone

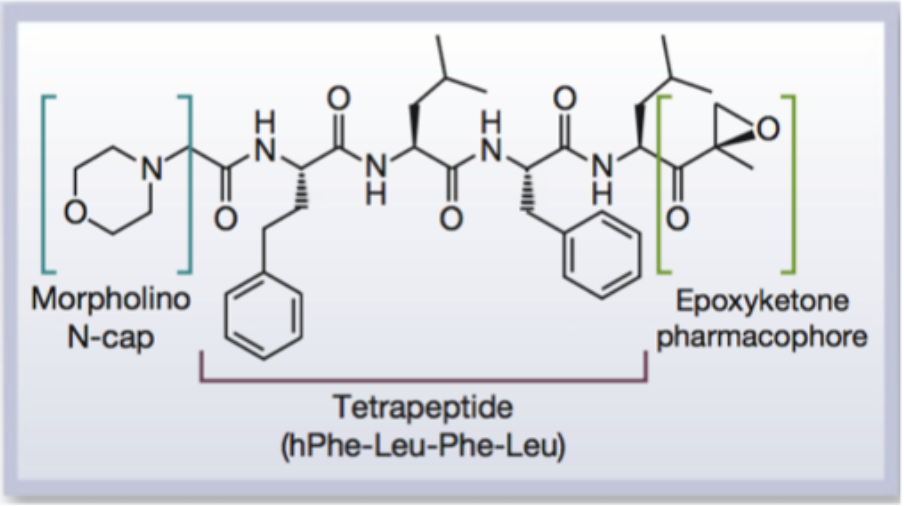
8c

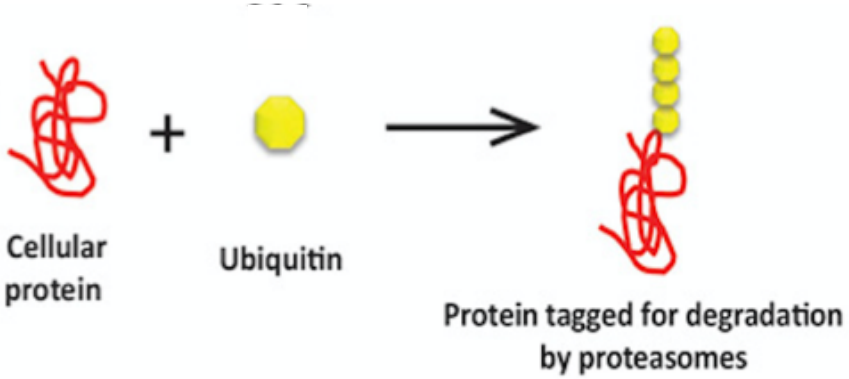
(Diarrea e ipoK)

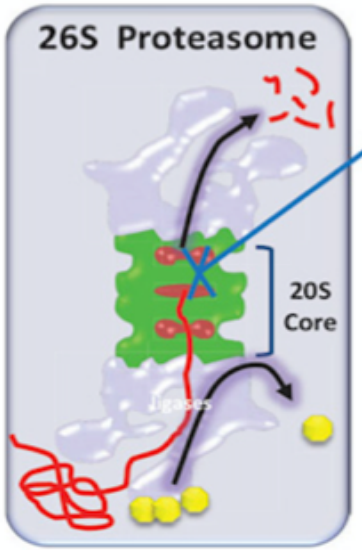
Clinical Scenario

- Carfilzomib therapy suggested

CARFILZOMIB







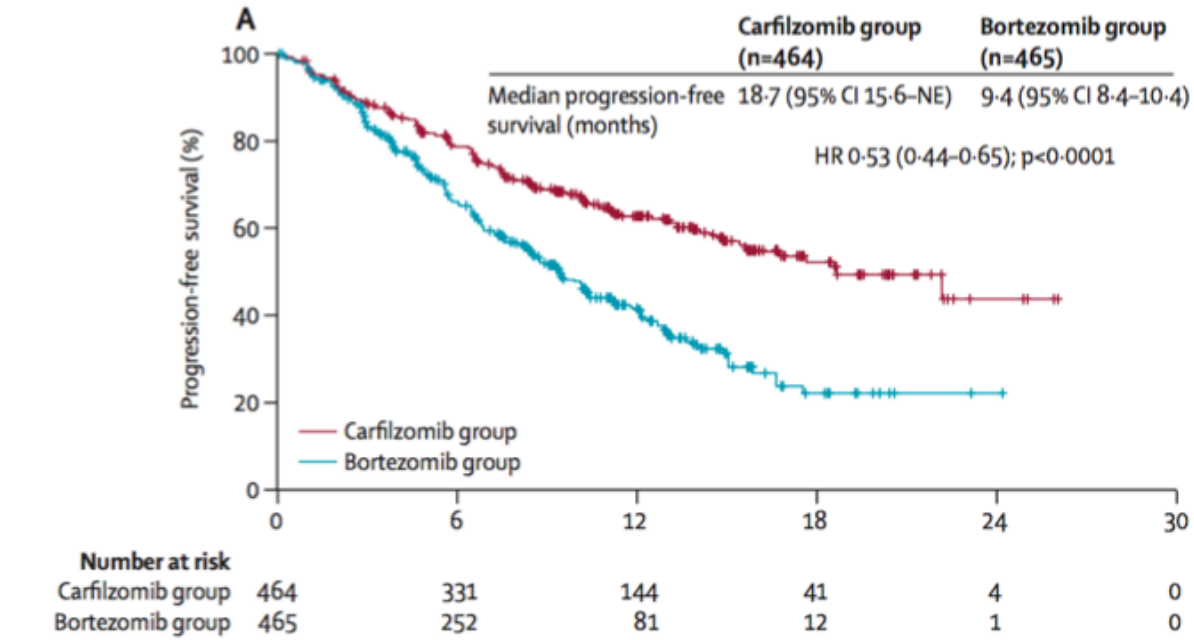
Carfilzomib inhibits the proteasome

Milan et al Curr Hyp review 2018

CARFILZOMIB

Carfilzomib and dexamethasone versus bortezomib and dexamethasone for patients with relapsed or refractory multiple myeloma (ENDEAVOR): a randomised, phase 3, open-label, multicentre study

Meletios A Dimopoulos, Philippe Moreau*, Antonio Palumbo, Douglas Joshua, Ludek Pour, Roman Hájek, Thierry Facon, Heinz Ludwig, Albert Oriol, Hartmut Goldschmidt, Laura Rosiñol, Jan Straub, Aleksandr Suvorov, Carla Araujo, Elena Rimashevskaya, Tomas Pika, Gianluca Gaidano, Katja Weisel, Vesselina Goranova-Marinova, Anthony Schwarer, Leonard Minuk, Tamás Masszi, Ievgenii Karamanesht, Massimo Offidani, Vania Hungria, Andrew Spencer, Robert Z Orlowski, Heidi H Gillenwater, Nehal Mohamed, Shibao Feng, Wee-Joo Chng, for the ENDEAVOR investigators*



Lancet Oncol 2015

Carfilzomib and cardiovascular adverse events

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		

Clinical Scenario Franco

Agenda

Can the patient stbegin Carfilzomib therapy?

What’s his cardiovascular risk?

Do we need further informations?

Can the patient begin Carfilzomib therapy?

Indication for carfilzomib treatment is a clinical indication.

=> Haematological indication

Can the patient begin Carfilzomib therapy?

Indication for carfilzomib treatment is a clinical indication.

=> Haematological indication

		ASPIRE KRd	ENDEAVOR Kd
NNH	CHF grade ≥3	102.8	30.8
	Hypertension	75	12.9

Chari et al 2081 Blood Adv

Can the patient begin Carfilzomib therapy?

Indication for carfilzomib treatment is a clinical indication.

=> Haematological indication

		ASPIRE KRd	ENDEAVOR Kd
NNH	CHF grade ≥3	102.8	30.8
	Hypertension	75	12.9
NNT	PFS	8.5	2.5

Chari et al 2081 Blood Adv

Agenda

Can the patient stbegin Carfilzomib therapy?

What’s his cardiovascular risk?

Do we need further informations?

European Heart Journal
doi:10.1093/eurheartj/ehw211

ESC CPG POSITION PAPER

2016 ESC Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines

Zamorano et al 2016

Fattori di rischio

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 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

Risk stratification

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)

Agenda

Can the patient stbegin Carfilzomib therapy?

What’s his cardiovascular risk?

Do we need further informations?

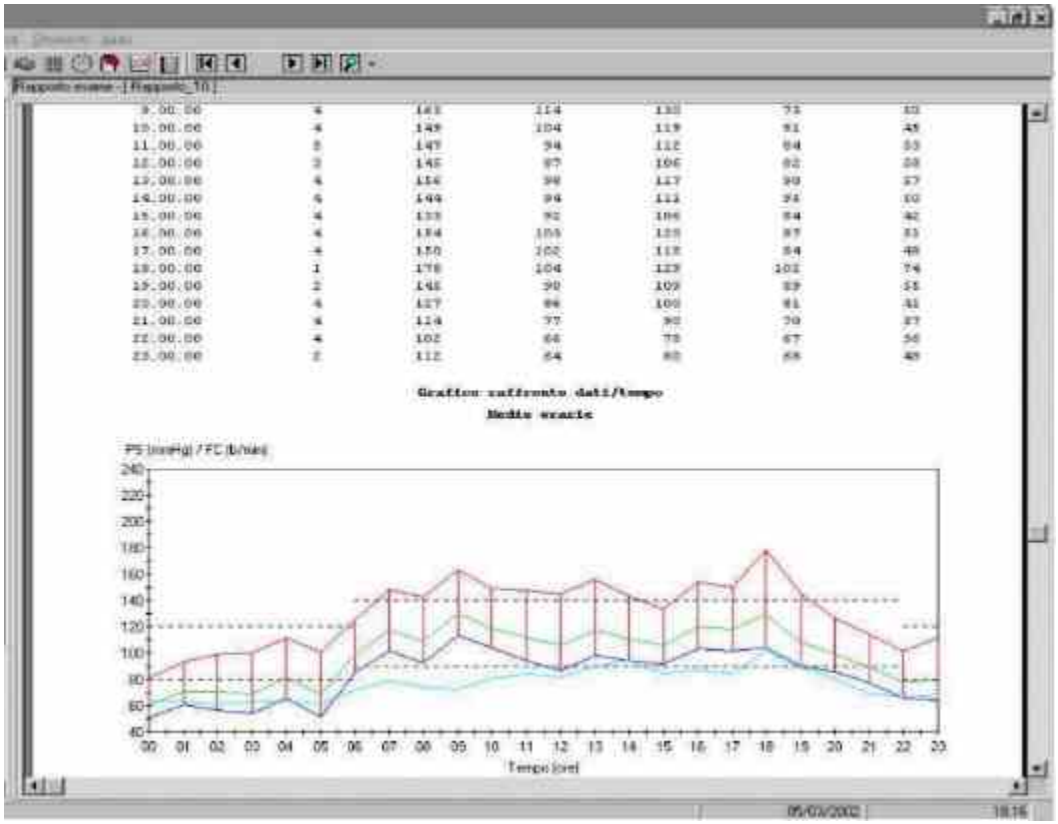
Which road map?

A. ‘Out of office’ BP assessment
   - Ambulatory blood pressure monitoring
   - HBPM (home blood pressure)

B. Hypertensive mediated organ damage (HMOD)

C. Hypertensive therapy

24h ambulatory blood pressure monitoring

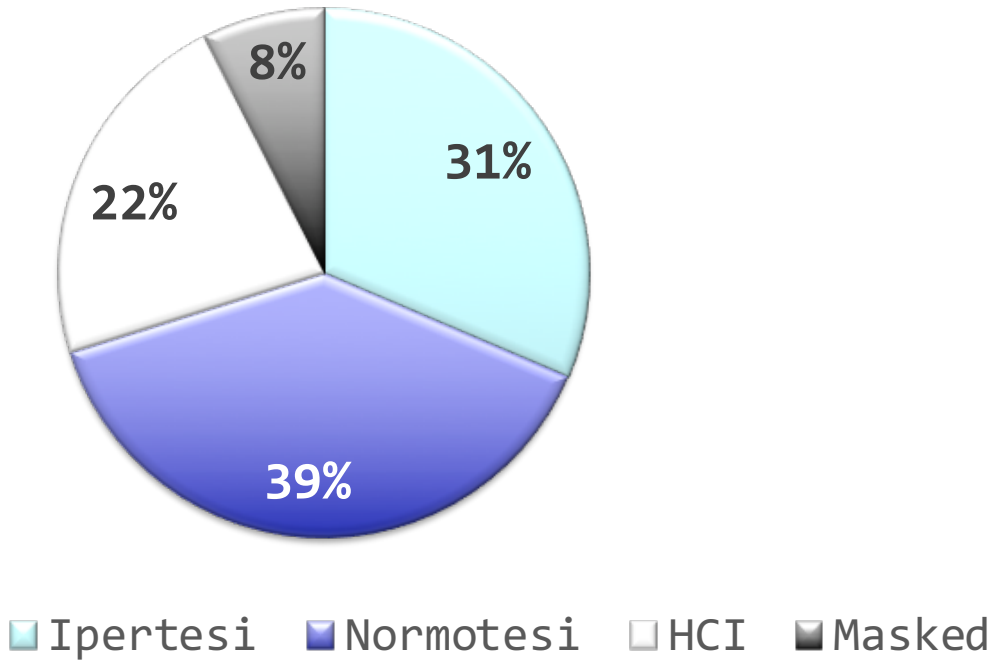


About 96 samples in 24h

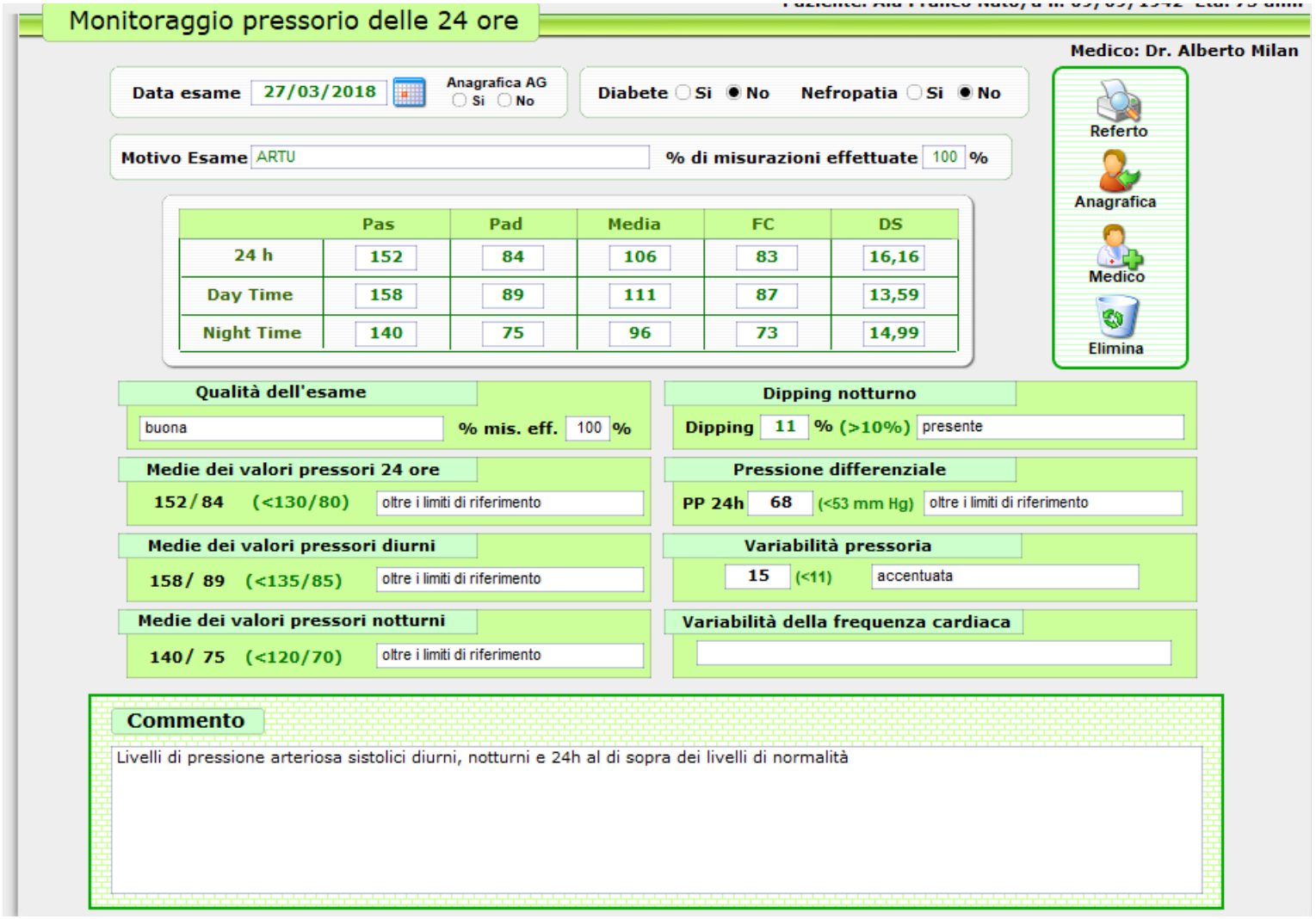
Blood pressur pattern

24h ambulatory blood pressure monitoring

n. 70 pt CARF



24h ambulatory blood pressure monitoring



Home blood pressure monitoring

Mean of 3 measurements

Date	SBP	DBP	hour

Which road map?

A. ‘Out of office’ BP assessment
   - Ambulatory blood pressure monitoring
   - HBPM (home blood pressure)

B. Hypertensive mediated organ damage (HMOD)

C. Hypertensive therapy

Which road map?

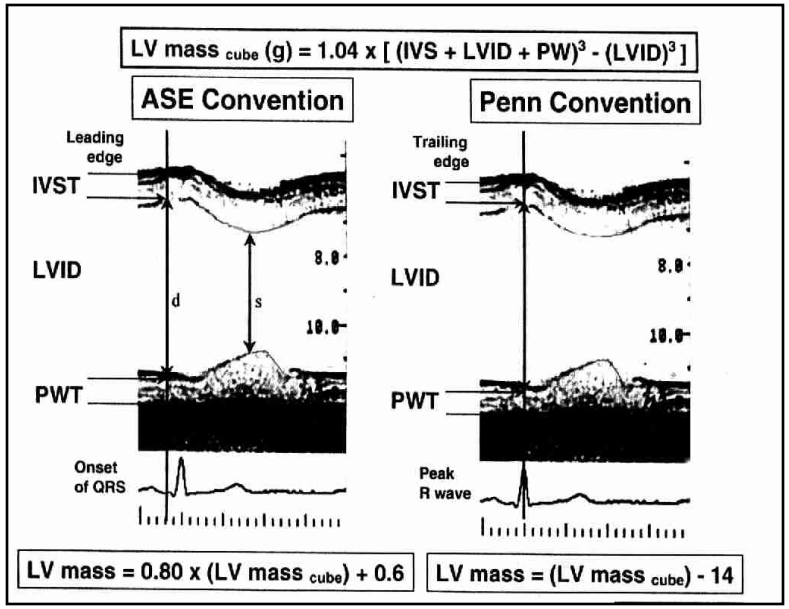
Table 6 Proposed diagnostic tools for the detection of cardiotoxicity

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

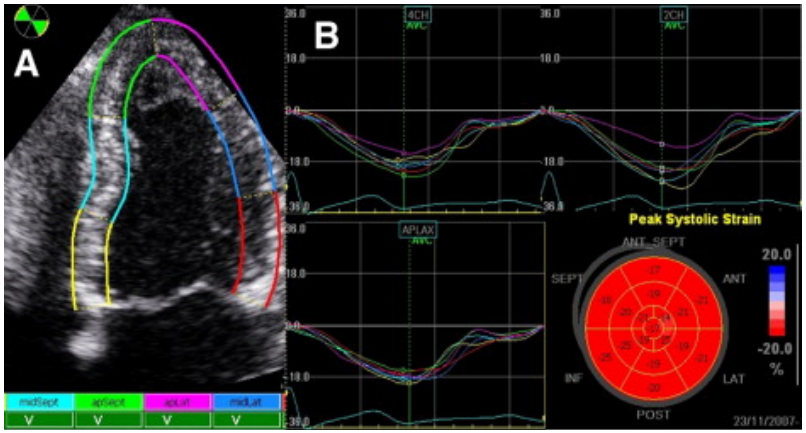
Echocardiography

Heart morphology



Left ventricular mass

Heart function

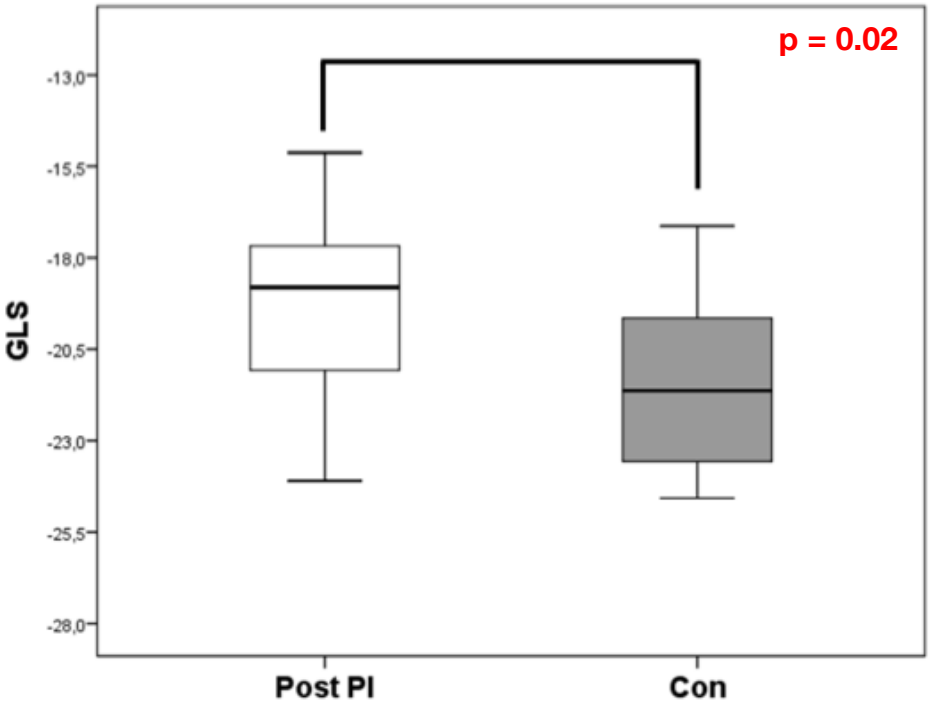


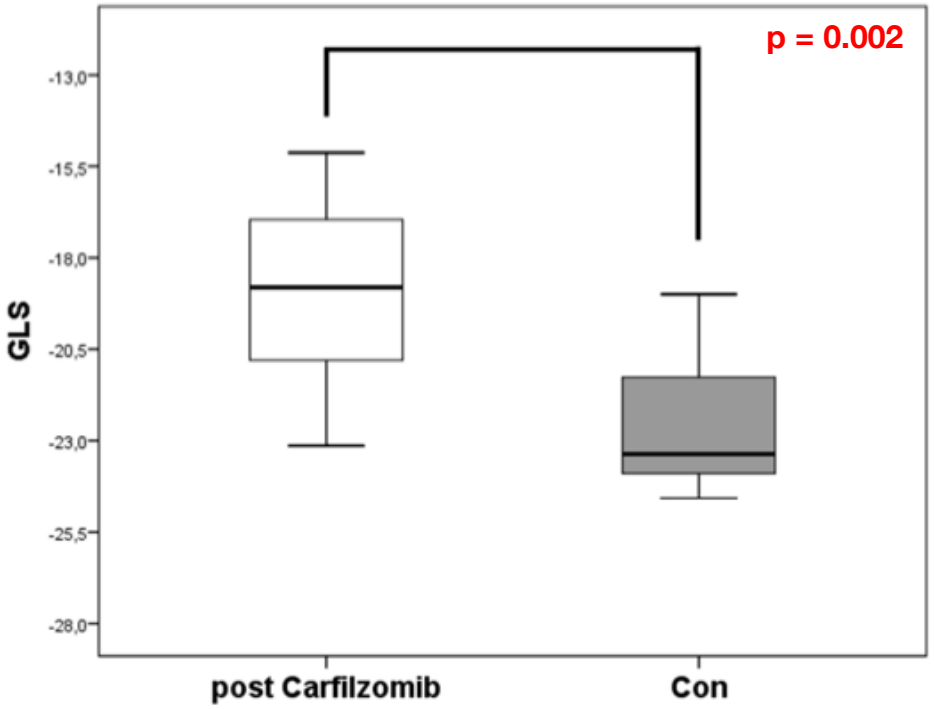
Systolic daistolic and
Global longitudinal strain

ArTu - Results

Hypertensive mediated organ damage (HMOD)

Global longitudinal strain



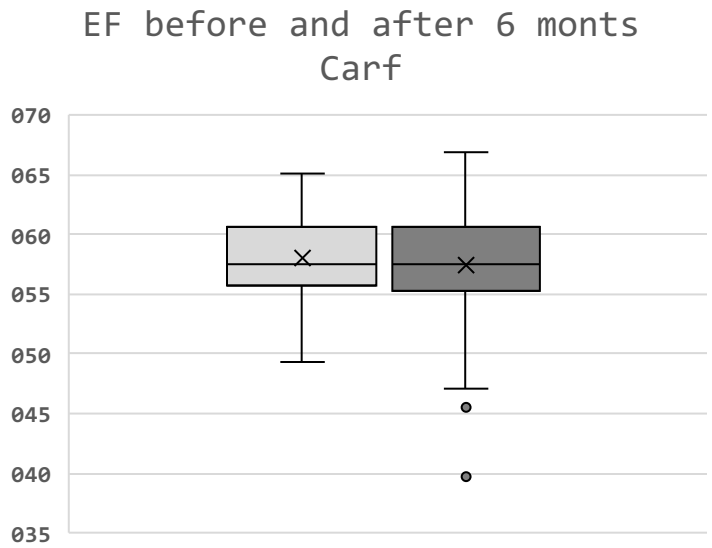


Iannaccone et al. High blood pressure & cardiovasc disease 2018

EF & GLS

Cardiovascular toxicity

n.40 pts post Carfilzomib therapy



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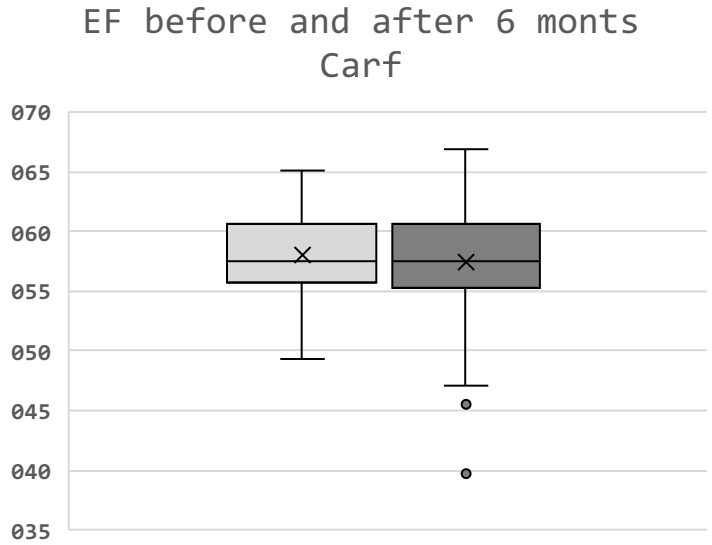
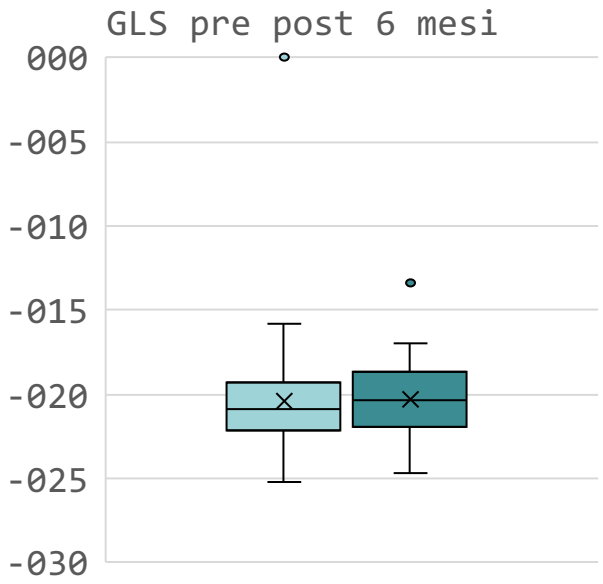
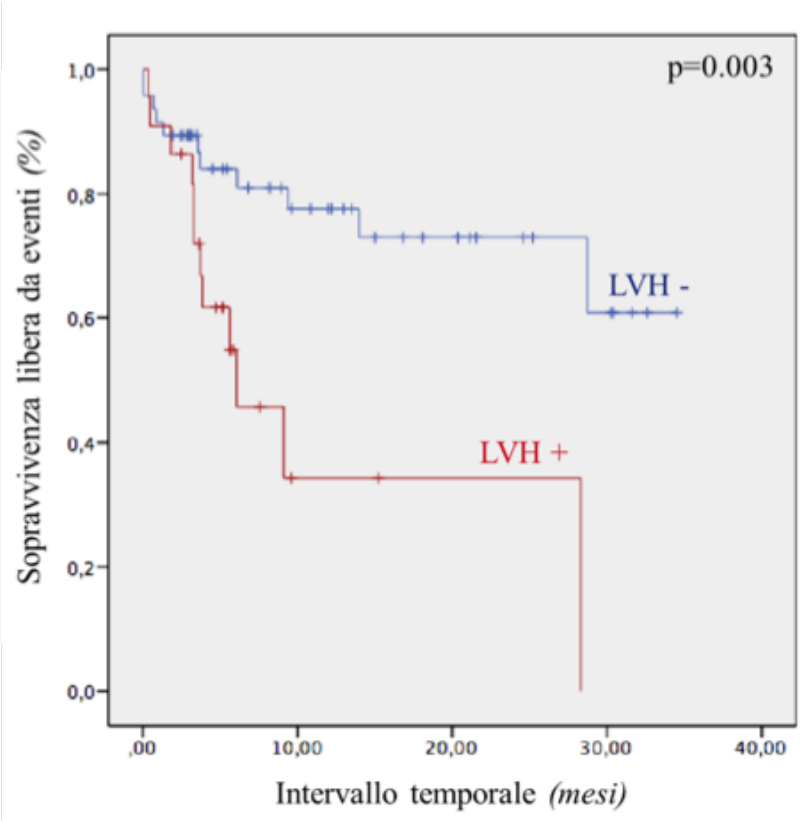
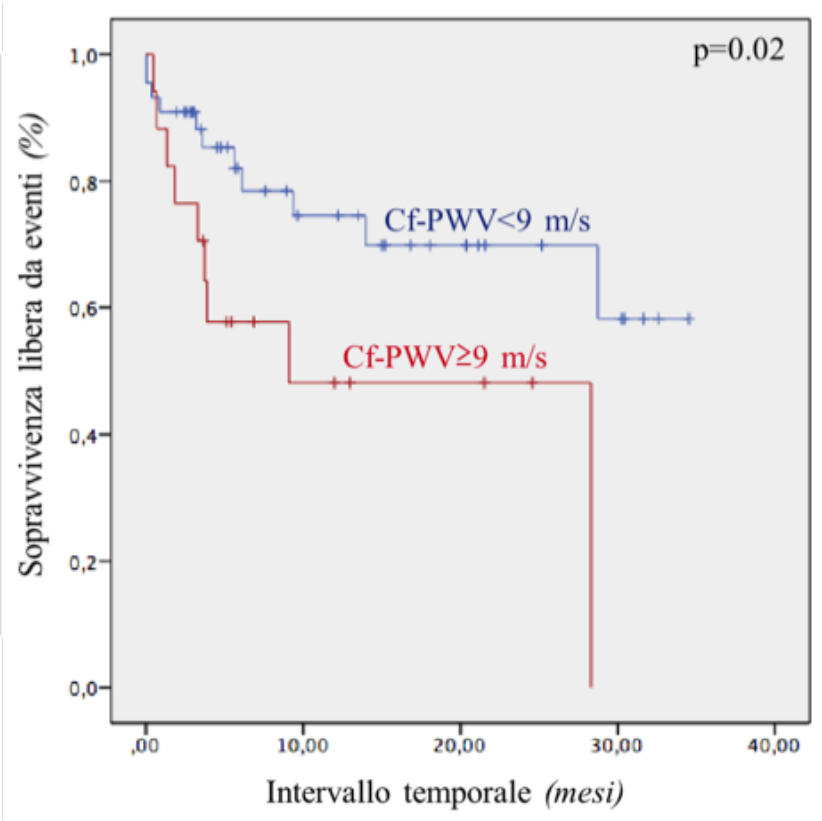




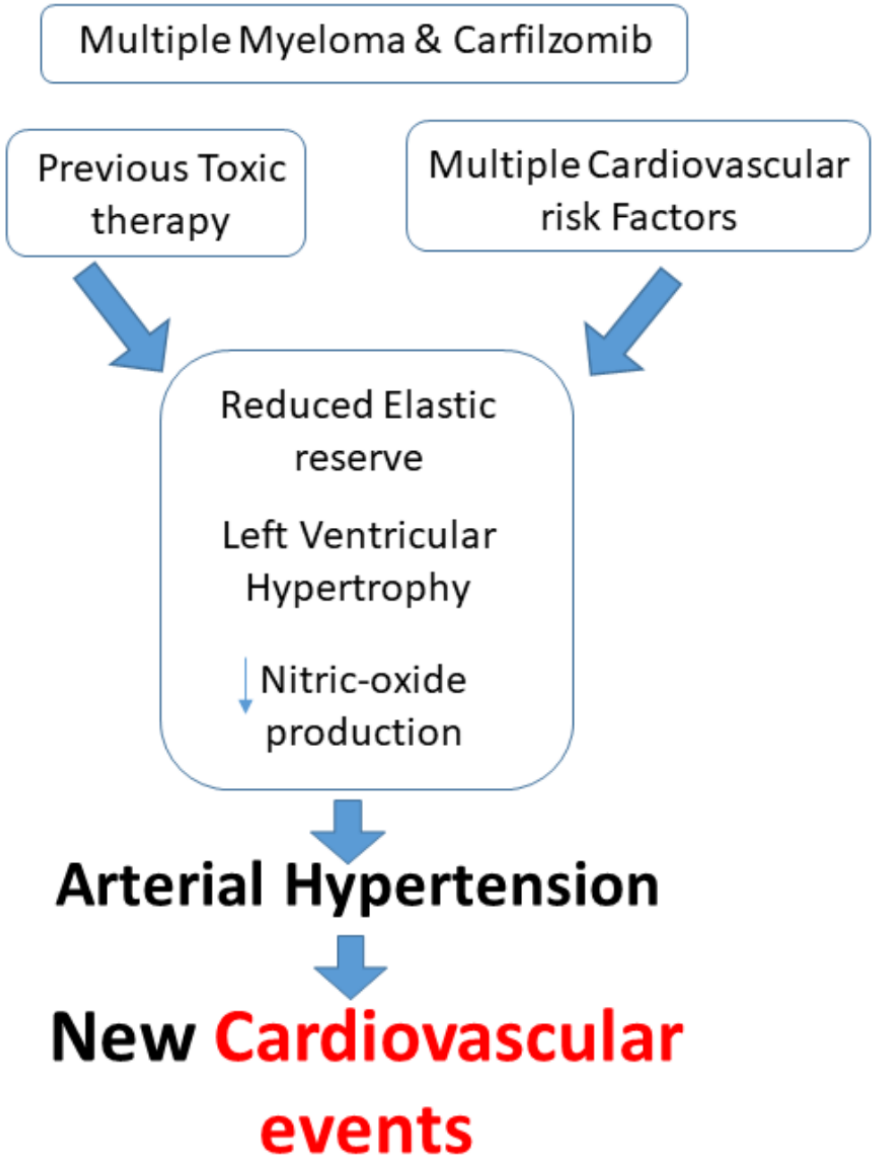
Left ventricular mass and Pulse wave velocity

Adverse cardiovascular events prediction





Bruno G, Bringhen S et al submitted 2018



Milan A et al. Curr Hypert Review 2018

Which road map?

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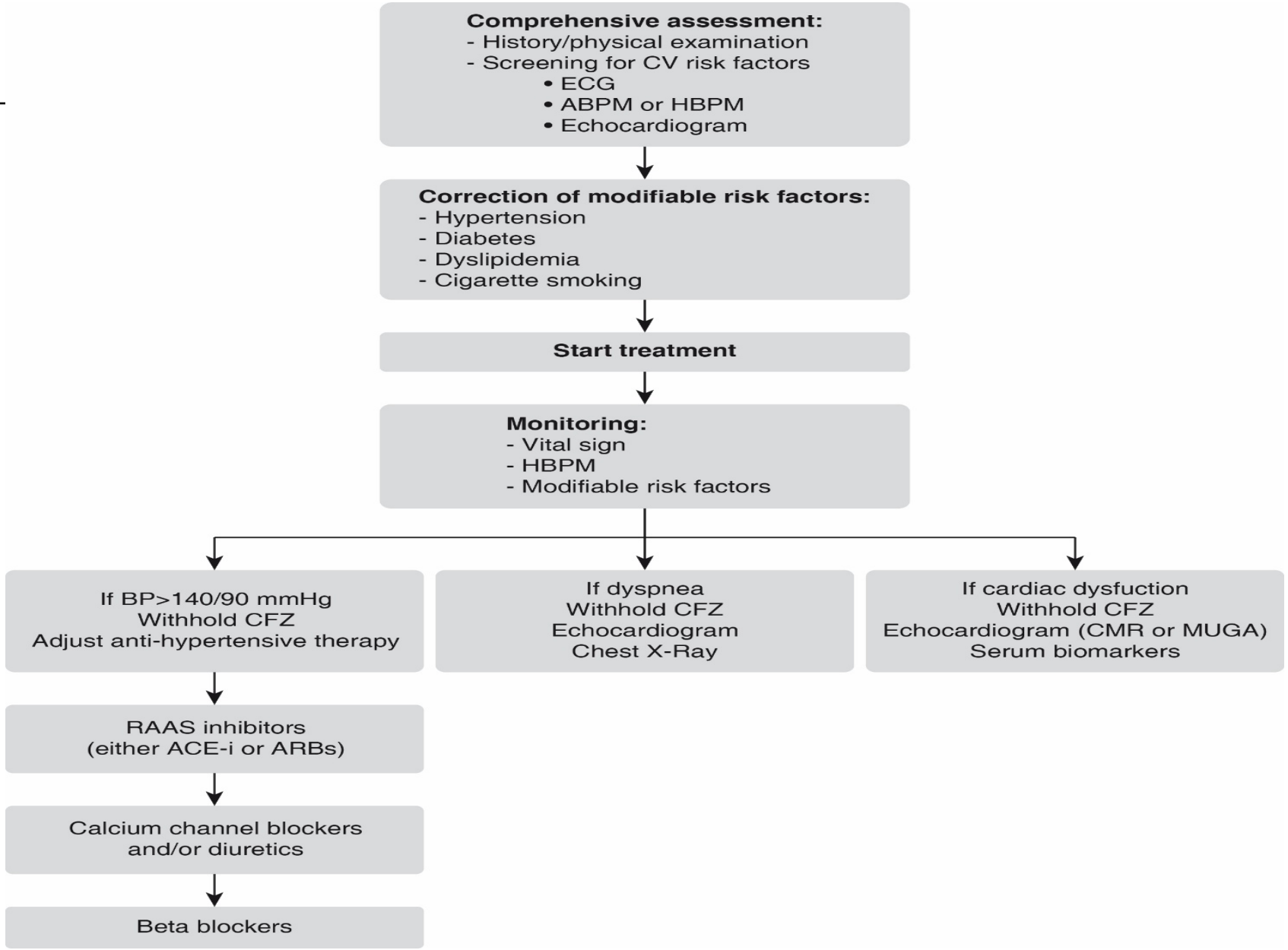
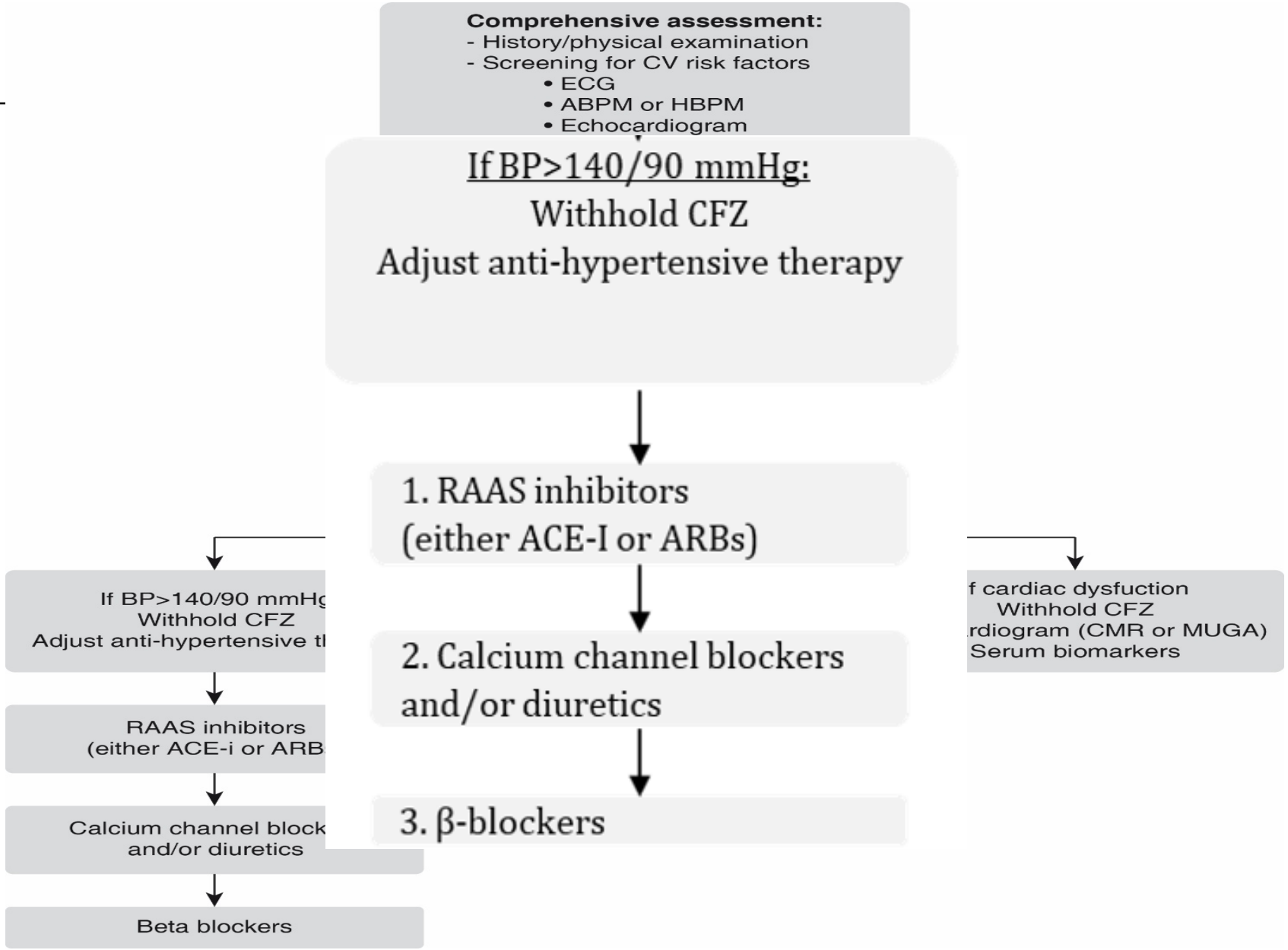


Bringhen s, Milan A et al *Submitted*



Bringhen s, Milan A et al *Submitted*

Clinical senario

28/3/2018

Lercanidipine 10 mg

Postpone Therapy

Lercanidipine 10 mg
Ramipril 10 mg

Clinical senario

28/3/2018

Lercanidipine 10 mg

Postpone Therapy

Lercanidipine 10 mg
Ramipril 10 mg

17/4/2018

Lercanidipine 10 mg	**Ramipril 10 mg**
Hydroclortiazide 25 mg	**Spironolactone 25 mg**

Clinical senario

28/3/2018 Lercanidipine 10 mg

Postpone Therapy

Lercanidipine 10 mg
Ramipril 10 mg

17/4/2018

Lercanidipine 10 mg
Hydroclortiazide 25 mg

Ramipril 10 mg
Spironolactone 25 mg

2/5/2018 Begin of the carfilzomib therapy

Clinical senario

28/3/2018 Lercanidipine 10 mg

↓ Postpone Therapy

Lercanidipine 10 mg
Ramipril 10 mg

↓

17/4/2018

Lercanidipine 10 mg
Hydroclortiazide 25 mg

Ramipril 10 mg
Spironolactone 25 mg

2/5/2018 Begin of the carfilzomib therapy

↓

8 maggio PAO 145/89

Lercanidipine 10 mg
Hydroclorthizide 25 mg
Nebivolol ½ cp

Ramipril 10 mg
Spironolattone 25 mg
Isosorb Mononitr 10 mgx3

What we already knew…

Arterial hypertension can be secondary to oncological therapy

Cardiac toxicity due to cancer therapy

Change of our perspective

HMOD as predictive factor for cardiovascular adverse events due to cancer therapy

alberto.milan@gmail.com