Cardiovascular Complications of Hematologic Malignancy Treatment

David Lewandowski MD

15th Annual Controversies in Hematologic Malignancies Symposium

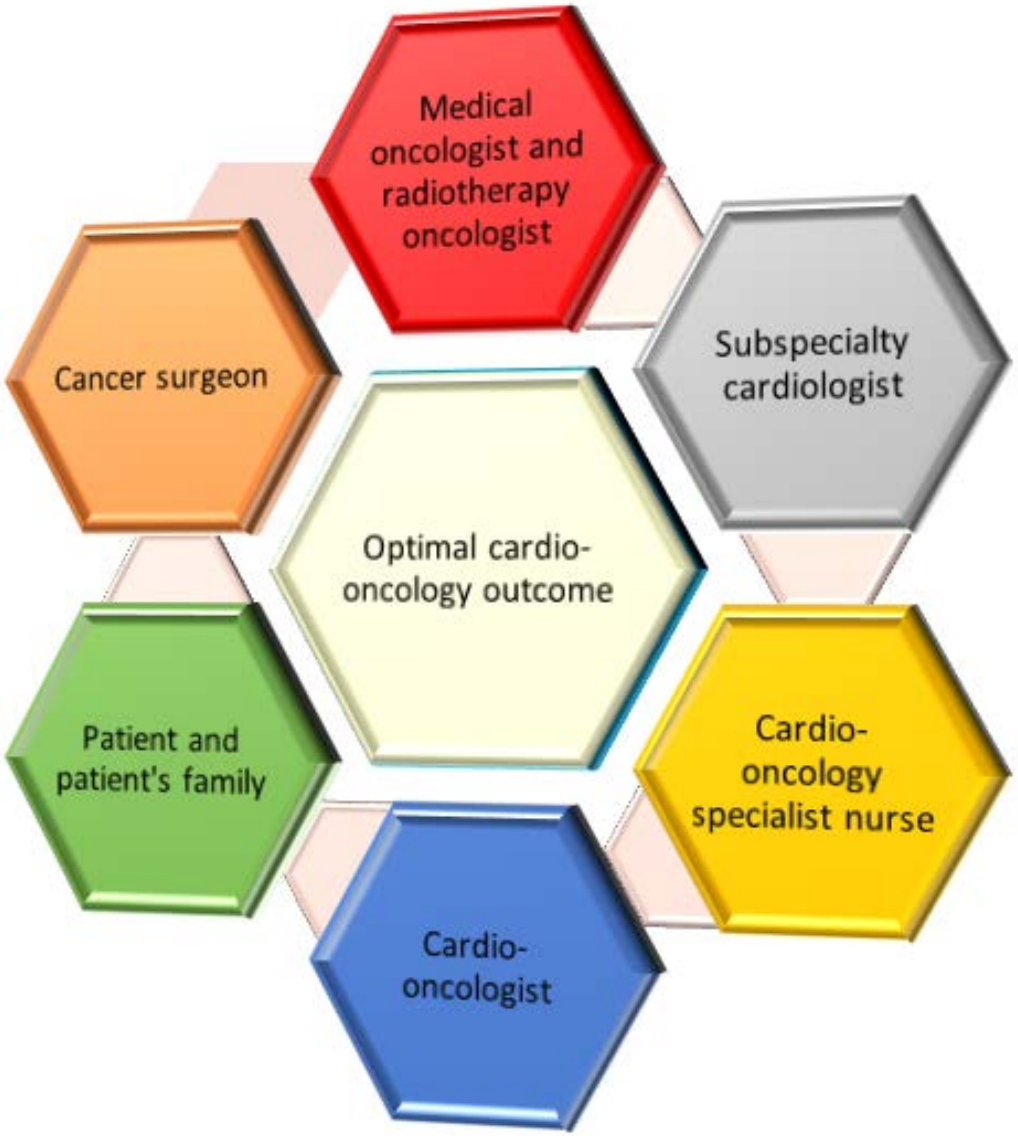
March 7, 2026

Objectives

- Be able to recognize and collaboratively manage the potential cardiovascular complications of:
  - Proteosome inhibitors
  - BTK inhibitors, BCR-ABL TKI's
  - CAR-T
  - Stem cell transplantation
  - AL amyloidosis
- What we do not have time for: discussing cardiovascular complications of hematologic malignancies themselves (pericardial effusions, tumor invasion, etc)

Goals of Cardio-Oncology

- Risk stratify patients undergoing cancer therapy to anticipate and prevent complications.
- Manage existing CV disease in the context of cancer therapy
- Mitigate the adverse effect of cancer therapy on the CV system while also minimizing interruptions to cancer therapy
- Manage long term complications and establish long term surveillance for cancer survivorship
- Provide collaborative management and support to other providers in primary care and cancer center.
- Engage in groundbreaking research to advance knowledge in a nascent field
- Educate healthcare providers and patients on contemporary practices in the care of this unique patient population

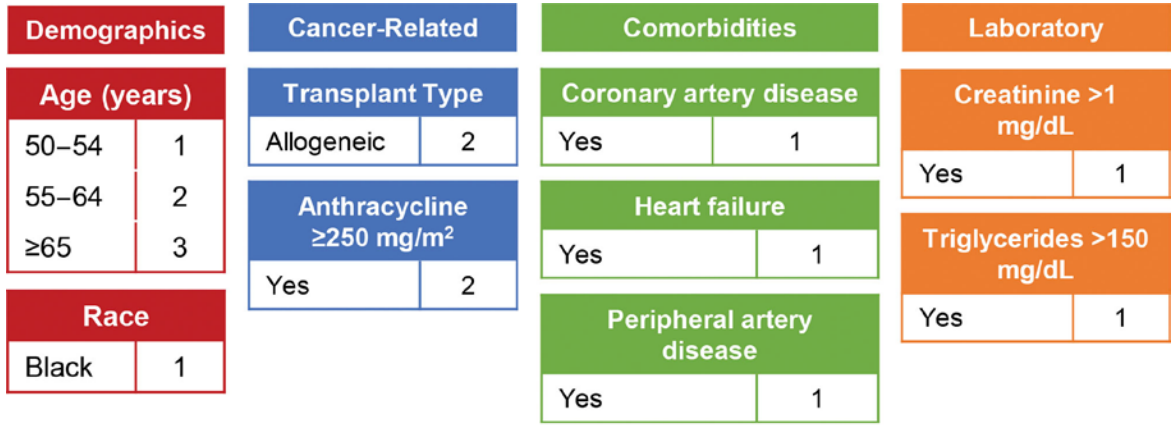


How to Build a Cardio-Oncology Service

Oct 24, 2017 | Arjun K Ghosh, MBBS, MSc, PhD, FACC

Stem cell transplant: risk stratification

- During and early after transplant patients are at elevated risk for atrial arrhythmia and heart failure.
- Patients are at increased long term risk of HTN, DM2, dyslipidemia, CHF, vascular disease, CAD, stroke
- Factors that increase risk include patient specific factors (age, pre-existing CVD), cancer specific factors, and treatment factors (conditioning regimen, GVHD)



Demographics	
Age (years)	
50–54	1
55–64	2
≥65	3
Race	
Black	1

Cancer-Related	
Transplant Type	
Allogeneic	2
Anthracycline ≥250 mg/m²	
Yes	2

Comorbidities	
Coronary artery disease	
Yes	1
Heart failure	
Yes	1
Peripheral artery disease	
Yes	1

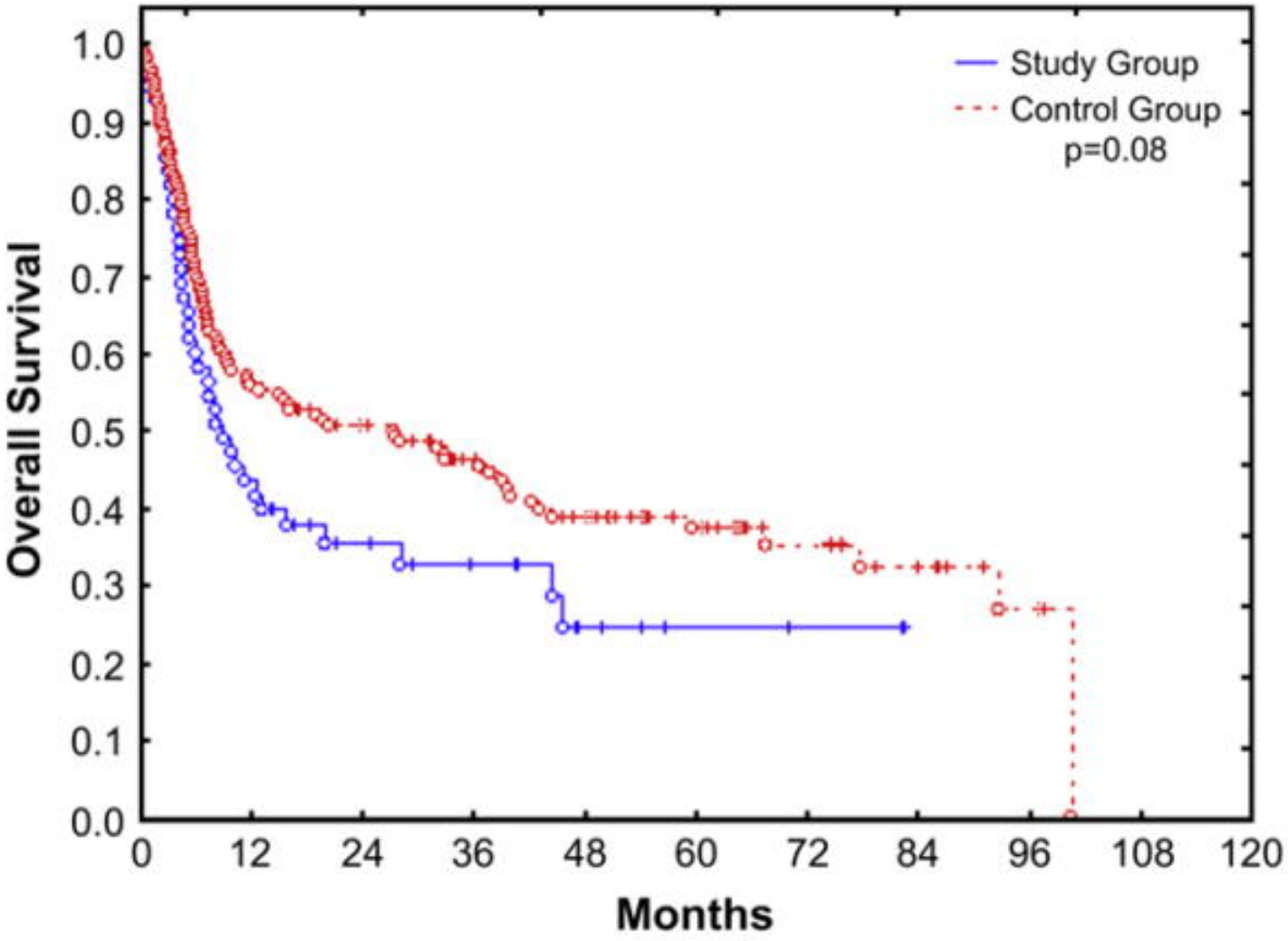
Laboratory	
Creatinine >1 mg/dL	
Yes	1
Triglycerides >150 mg/dL	
Yes	1

Total Score	Score	Risk Group	1-Year Incidence of CV Event	5-Year Incidence of CV Event
0–16 points	0–1 points	Low-risk	1.7%	4.0%
	2–4 points	Intermediate-risk	4.0%	10.3%
	≥5 points	High-risk	11.3%	22.4%

Hayek et al. Circulation

How much does ejection fraction matter?

- Ejection fraction often a major factor for transplant candidacy.
- Multiple studies have correlated AC dose and lower ejection fraction with worse CV outcomes.
- Newer retrospective data suggests similar outcomes with allo SCT with EF >45% and <45%
- Recommend cardiology (cardio-onc) consultation for patients with cardiomyopathy for further risk stratification.
- Options for mitigating risk includes intensive cardiac optimization, auto instead of allo transplant, or attenuation of conditioning regimens.



Qazilbash et al. Biol Blood Marrow Transplant.

Evaluating cardiomyopathy: beyond EF

- Evaluating for history/physical exam signs of CHF decompensation, cardiac biomarkers, exercise testing, advanced cardiac imaging can provide more nuanced risk stratification.
- Studies suggest VO2 max testing via cardio-pulmonary exercise testing may be a way to both risk stratify and track cardiorespiratory fitness.
- Goal-directed medical therapy for HF and possibly cardiac rehabilitation play a role in optimization for transplant.

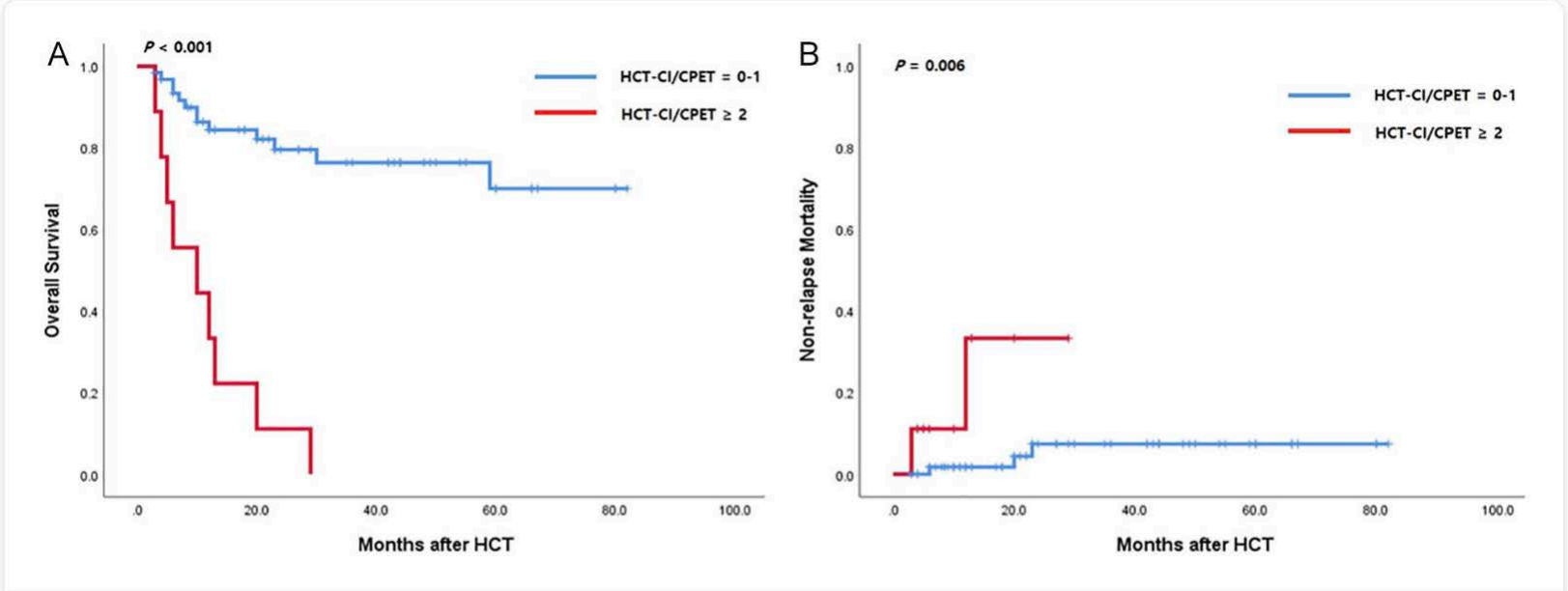


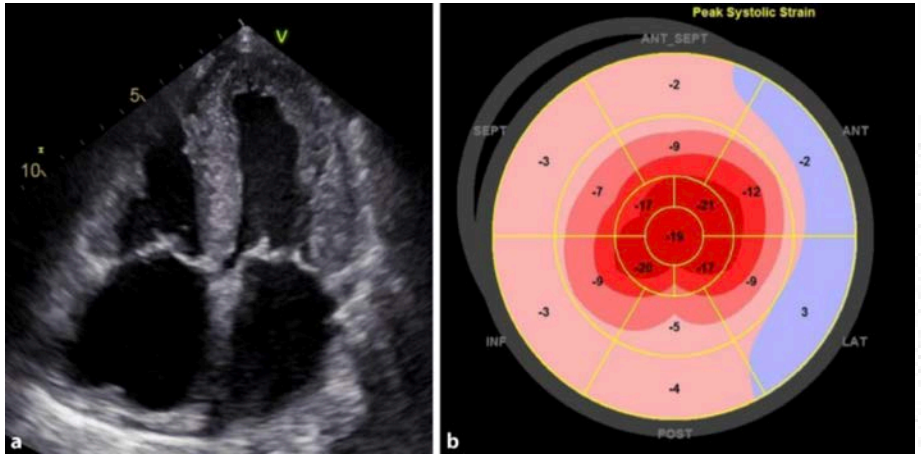
Figure 3. Overall survival (A) and non-relapse mortality (B) according to HCT-CI/CPET (N = 72).

Sang Hoon Yeon et al. Integrative cancer therapies

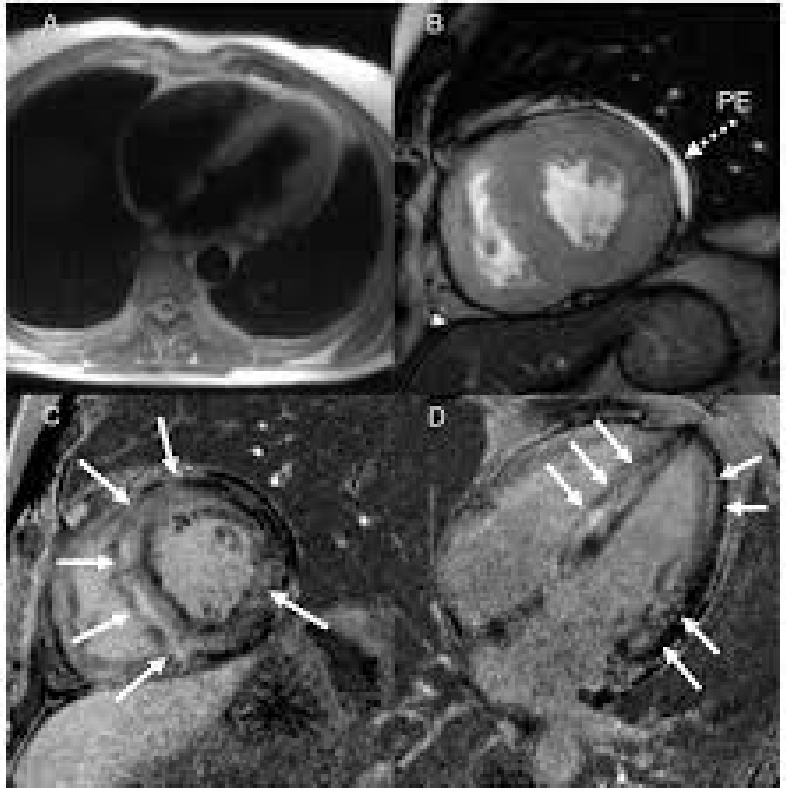
AL amyloidosis

- AL amyloidosis can lead to rapidly progressive restrictive cardiomyopathy which in advanced cases can lead to cardiogenic shock.
- High index of suspicion is required.
- Familiarity with light chain and serum/urine electrophoresis with immunofixation is critical
- Partner with cardiology to understand strengths/limitations of cardiovascular imaging (echocardiogram, cardiac MRI, nuclear scintigraphy), and when/what to biopsy.
- Management of CV pathology can be complicated by renal failure/nephrotic syndrome, autonomic neuropathy, pre-load dependent state.
- Prognosis significantly improved with new(er) treatment options

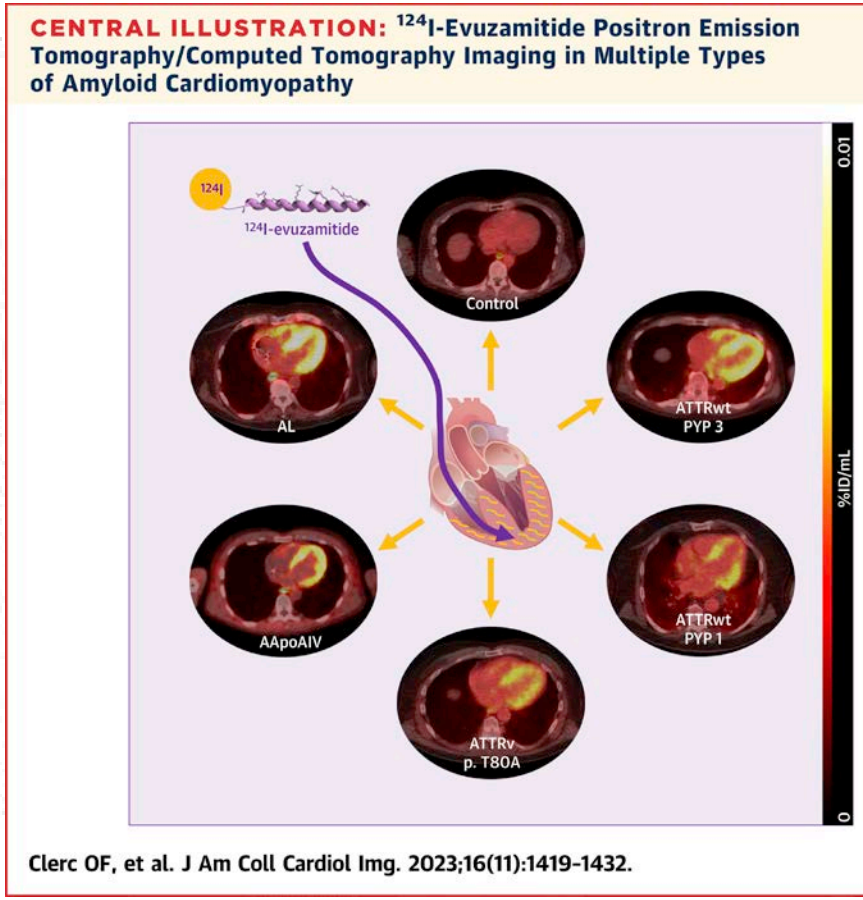
Diagnosis of AL-CA



Echocardiography

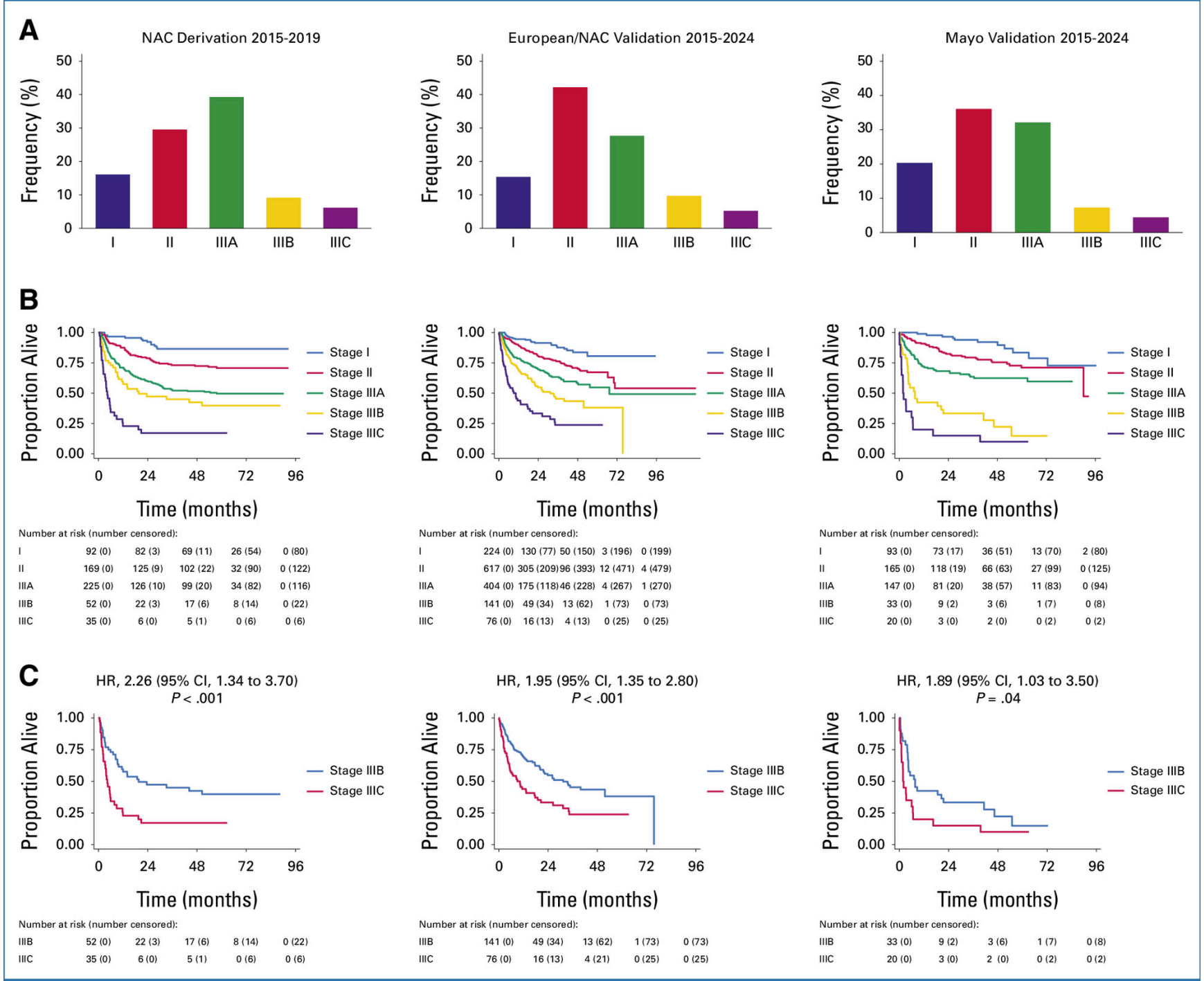


Cardiac MRI



Novel PET radiotracers

Newer risk stratification model incorporates NT-BNP, troponin, and LV GLS. De-emphasizes dLFC.



Khwaja et al. JCO

RESEARCH SUMMARY

Daratumumab-Based Treatment for Immunoglobulin Light-Chain Amyloidosis

Kastritis E et al. DOI: 10.1056/NEJMoa2028631

CLINICAL PROBLEM

Immunoglobulin light-chain (AL) amyloidosis results in organ damage, most frequently affecting the heart and kidneys. Rates of hematologic complete response to standard therapy are suboptimal, and early mortality is high. Daratumumab is a human monoclonal antibody targeting CD38, a glycoprotein expressed on plasma cells.

CLINICAL TRIAL

Design: A phase 3, open-label, randomized, controlled trial was conducted to compare the efficacy of standard therapy (bortezomib, cyclophosphamide, and dexamethasone) with that of standard therapy plus daratumumab.

Intervention: 388 patients were assigned to receive six cycles of bortezomib, cyclophosphamide, and dexamethasone either alone (control group) or with subcutaneous daratumumab followed by single-agent daratumumab every 4 weeks for up to 24 cycles (daratumumab group).

RESULTS

Efficacy: The percentage of patients with a hematologic complete response was significantly higher in the daratumumab group than in the control group, and survival free from major organ deterioration or hematologic progression favored the daratumumab group.

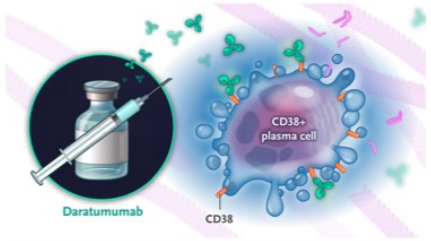
Safety: Lymphopenia, pneumonia, cardiac failure, and diarrhea were more common in the daratumumab group. Deaths in both groups were primarily due to AL amyloidosis–related cardiomyopathy.

LIMITATIONS AND REMAINING QUESTIONS

Further study is required to understand the following:

- Whether maintenance therapy as received by patients in the daratumumab group affects outcomes
- Whether a longer follow-up would show that daratumumab added to standard therapy improves overall survival

Links: Full article | NEJM Quick Take



Hematologic Complete Response

Most Common Adverse Events of Grade 3 or 4

	Daratumumab Group (N=193)	Control Group (N=188)
Lymphopenia	13.0%	10.1%
Pneumonia	7.8%	4.3%
Cardiac Failure	6.2%	4.8%
Diarrhea	5.7%	3.7%

CONCLUSIONS

The addition of daratumumab to standard therapy with bortezomib, cyclophosphamide, and dexamethasone was associated with a significantly higher frequency of hematologic complete response than standard therapy alone.

NEWS RELEASE

Prothena Announces Phase 3 AFFIRM-AL Clinical Trial for Birtamimab in Patients with AL Amyloidosis Did Not Meet Primary Endpoint

Case example

- 55 yr old male presents with hypotension and respiratory failure and is admitted to the ICU.
- Infectious testing is performed and patient is positive for Influenza A.
- After extubation patient reports feeling weak and dizzy but denies chest pain.
- Transthoracic echo is performed and is very poor quality, but normal left and right ventricular ejection fraction are confirmed.
- High sensitivity troponin elevated to 722—> 600

February hospitalization

Me

Based on evaluation of transthoracic echo, mixed venous O2 saturation, and physical exam, patient's shock state is most likely predominantly distributive in nature, with no apparent evidence of cardiogenic shock. Recommend continuing to wean milrinone. With low CVP's could consider additional fluid resuscitation.

Troponin elevation most likely demand ischemia from shock. No clear evidence of myocarditis at this time.

ICU attending

Middle aged man presenting with rather acute onset of fever, chills, mallaise and found to be influenza A positive, followed by rapid circulatory collapse and intubation for Type IV respiratory failure.

On exam
Intubated and sedated
Flat neck veins, RRR, no obvious gallop or heave
Lungs are clear, good compliance on vent
Belly soft
Extremities are cold, mottled though interestingly cap refill is not too bad
No edema, no rashes, no stigmata of liver disease or embolic phenomena

Arterial line with narrow pulse pressure, CVP ~ 10 on NE at 0.8 and Vas at 0.03

POCUS with very tough windows; dubious IVC that is ~2.5 CM
CT PE showing minimal bibasilar atelectasis vs infiltrate and tiny pleural effusions

We have performed an extensive evaluation of cause of shock; phenotypically he appears to be in some combination of possibly distributive and cardiogenic shock. At first we figured this was 'cold sepsis' but he has failed to respond to IVF bolus nor to 'widen' his pulse pressure.
We have not identified e/o Obstructive nor hypovolemic shock. No obvious pulmonary source. Nothing obvious intra-abdominal though no CT abdomen is obtained. No skin or soft tissue breakdown, nothing suggest mitochondrial poisoning. We swabbed for strep throat (hoping we could treat for GAS TSS) but this is negative. No e/o thyrotoxicosis nor rhabdo

I still think this man could have early stages of myocarditis. As this could very well be viral triggered, then he will have conccurrent distributive physiology. If he has any degree of that then he will have mitochondrial poisoning making tests like ScV02 completely unreliable as a test of whether this is cardiogenic in nature. Unfortunately treatment remains supportive

1. Broaden Abx to pip/tazo + Linezolid (empiric toxin covereage
2. Add milrinone and up-titrate
3. Deep sedation, low threshold to paralyze
4. Increase MV on vent
5. Await Blood and other cultures, IVIG in GAS is recovered
6. We will request cardiology input +/- MCS?
7. Discussed with family at bedside. Prognosis is very guarded at this time

March Hospitalization

[redacted] a 55 Y old male patient with past medical history that includes asthma, dyslipidemia, obstructive sleep apnea and uses CPAP, nephrolithiasis, recent history of complicated influenza A infection (complicated by cytokine storm and related shock, acute kidney injury, and respiratory failure requiring vent support) who was admitted on 3/16/2024 for worsening of renal function, hyperkalemia, and hypotension. He was diagnosed to have adrenal insufficiency. Clinical condition improved with the initiation of hydrocortisone and florinef. Renal function has improved and is back to where it was a week prior to admission. Patient and fiance extensively counseled on home management of adrenal insuffiencey. Per recommendation of endocrinologist, pt discharged with hydrocortisone 30 mg BID for 3 days. After that 20 mg in the morning when pt wakes up and 10 mg 8 hrs after the morning dose. Pt advised to double dose for three days if he feels fatigued or ill. In addition, advised to go to the ER if could not take his hydrocortisone for any reason, e.g-GI upset like vomiting. Pt is expected to see endocrinologist in 4 weeks and nephrologist in 1-2 weeks.

March echo report

Interpretation Summary
Focused transthoracic study performed.
Left ventricle is normal in size.
There is normal left ventricular systolic function.
The quantitative LVEF based on modified Simpson's method is 65%.
There is mild concentric left ventricular hypertrophy based on linear measurement of left ventricular wall thickness.
Right ventricle is normal in size.
There is normal right ventricular systolic function.
The left atrium is moderately enlarged in size based on measured volume
indexed to body surface area.
There is no aortic valve vegetation identified.
There is no mitral valve vegetation identified.
There is mild mitral regurgitation.
There is no tricuspid valve vegetation identified.
There is trace tricuspid regurgitation.
There is no evidence of endocarditis identified.
Compared to prior Froedtert Health echocardiogram that was performed on
2/20/24, no significant change

March lab testing

IMMUNOFIXATION ELECTROPHO...	
Free Kappa	57.4 ▲
Free Lambda	167.5 ▲
Kappa/Lambda Ratio	0.34 ▼
Protein, Urine Calculation U/...	

N-TERMINAL PRO B-TYPE NATRI...	13,626 ▲
B-TYPE NATRIURETIC PEPTIDE	
CHEM	
SODIUM	131 ▼
Sodium, Whole Blood	
POTASSIUM	4.8
Potassium, Whole Blood	
CHLORIDE	100
Chloride, Whole Blood, POC	
CO2, Total	21 ▼
CO2 Total, Whole Blood, POC	
BLOOD UREA NITROGEN	45 ▲
Blood Urea Nitrogen, Whole Blood...	
CREATININE	5.29 ▲
WHOLE BLOOD CREATININE	
CALCIUM	8.5 ▼
ANION GAP	10
Anion Gap, Whole Blood	
GLUCOSE	94
Glucose, POC	
eGFR (CKD-EPI 2021)	12 ▼

April hospitalization

Final Diagnosis

A-C. Native kidney biopsy:

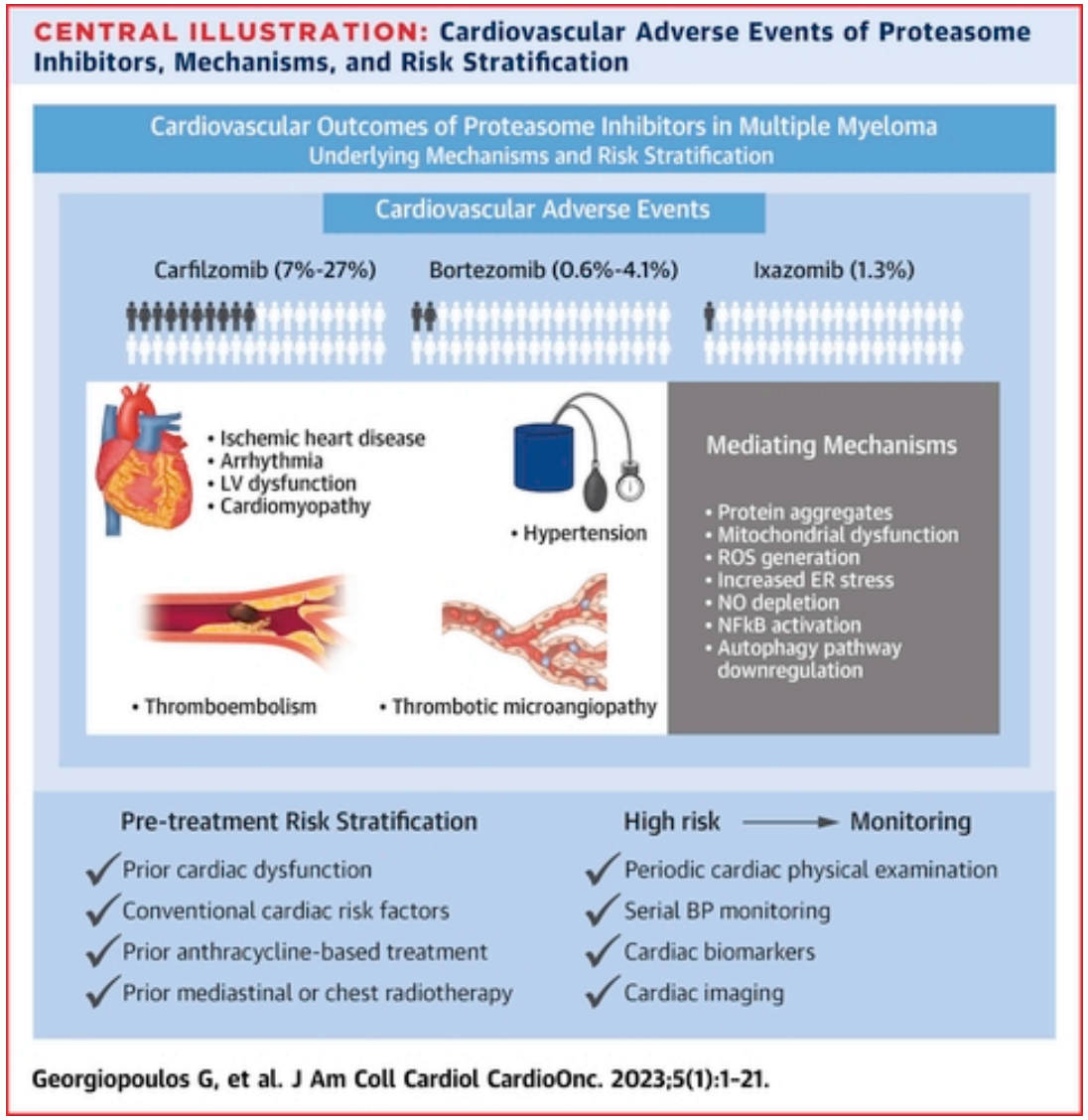
- Amyloidosis, AL-type (lambda-restricted).
- Focal global glomerular sclerosis (29%).
- Moderate to severe interstitial fibrosis and tubular atrophy (40-50%).

Case resolution

- Patient started on Dara-CyBorD chemotherapy and quickly achieved hematologic remission.
- Dyspnea has improved, and he is back to work. His hypotension has been well managed on low dose midodrine. His NT-BNP decreased to 5200 and his creatinine has stabilized around 2.5.

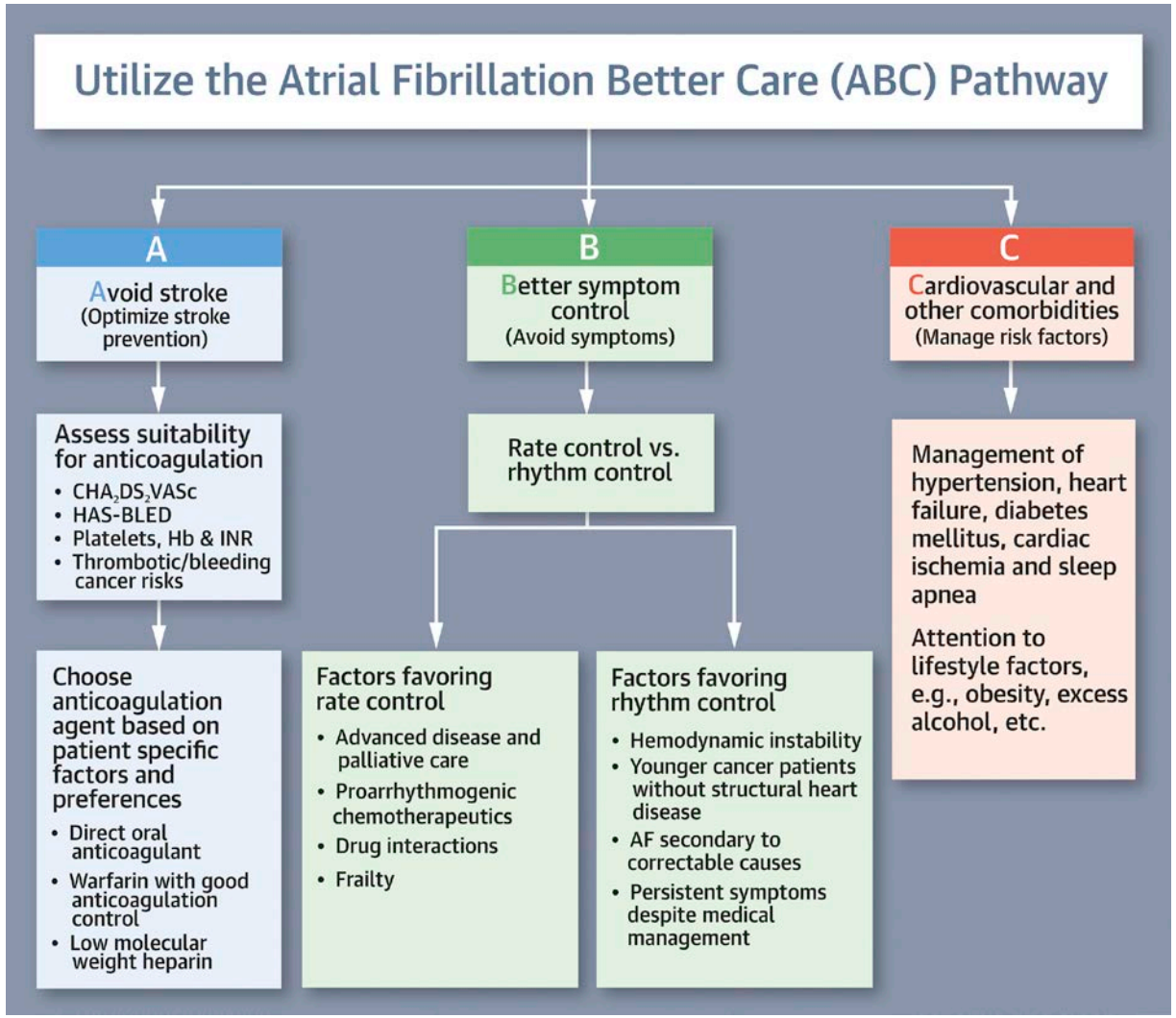
Proteosome inhibitors

- Drug class includes carfilzomib, bortezomib, ixazomib used often for treatment of multiple myeloma.
- PI's, in particular carfilzomib, have been associated with hypertension, arrhythmia, and heart failure in up to 10% of patients.
- Heart failure has been noted with carfilzomib in up to 5% of patients and fulminant cases have been reported.



BTK inhibitors

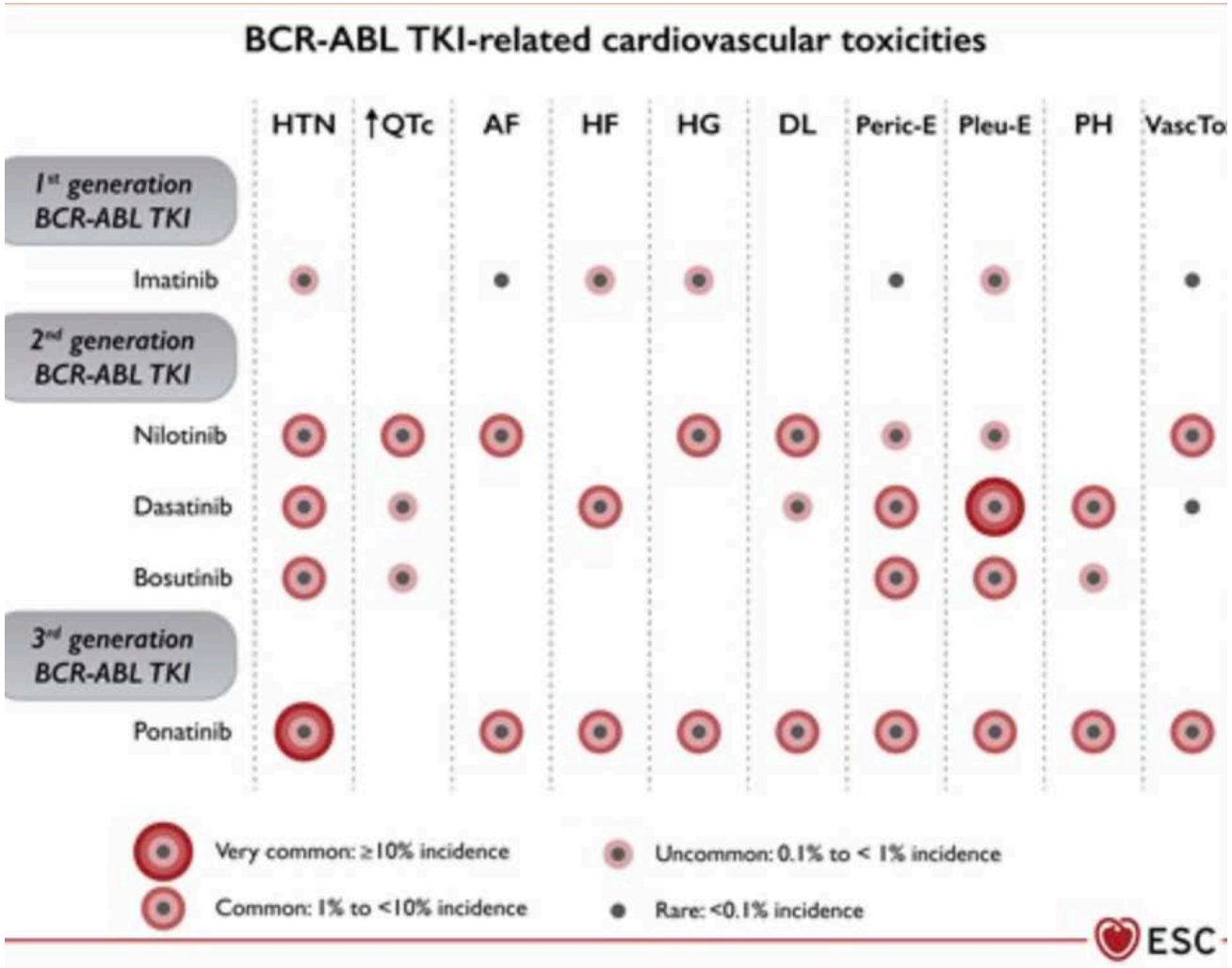
- All BTKi's are recognized to cause arrhythmia (atrial>>>ventricular), but first generation Ibrutinib is higher risk
- Questions to answer: Rate vs Rhythm control, continuation of BTKi, use of anticoagulation, how to monitor?
- BTKi's also increase bleeding risk, which can complicate the use of anticoagulation for stroke prevention in patients who develop atrial fibrillation.
- Rarely would BTKi need to be discontinued
- Very helpful if hematologist can provide prediction for future treatments.



Essa et al. JACC CardioOnc

BCR-ABL TKI's

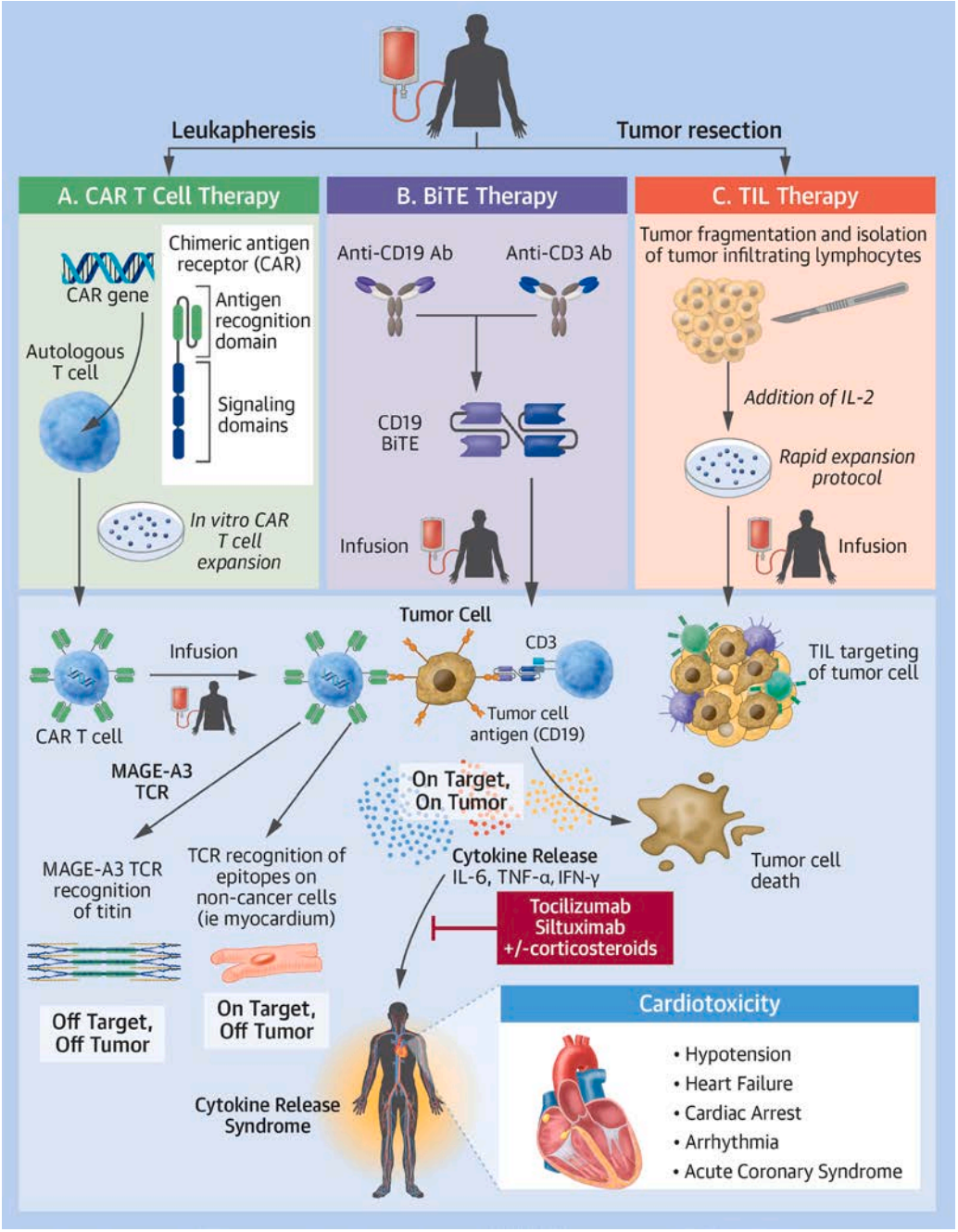
- Wide variety of potential CV toxicities.
- 2nd gen Dasatinib with higher risk for heart failure, pericardial/pleural effusions, and pulmonary HTN.
- Pontainib with higher concern for vascular toxicity though endothelial cell dysfunction/apoptosis.
- Aggressive risk factor management and monitoring needed for ponatinib



Lyon et al. EHJ

CAR-T therapy

- CAR-T is associated with cardiomyopathy, heart failure, arrhythmia, cardiac arrest, hypotension, and acute coronary syndrome.
- MACE has been reported in up to 10-20% of patients receiving CAR-T
- Treatment of CRS includes IL-6 inhibitor tociliuzumab +/- steroids



Ganatra et al. JACC CardioOnc

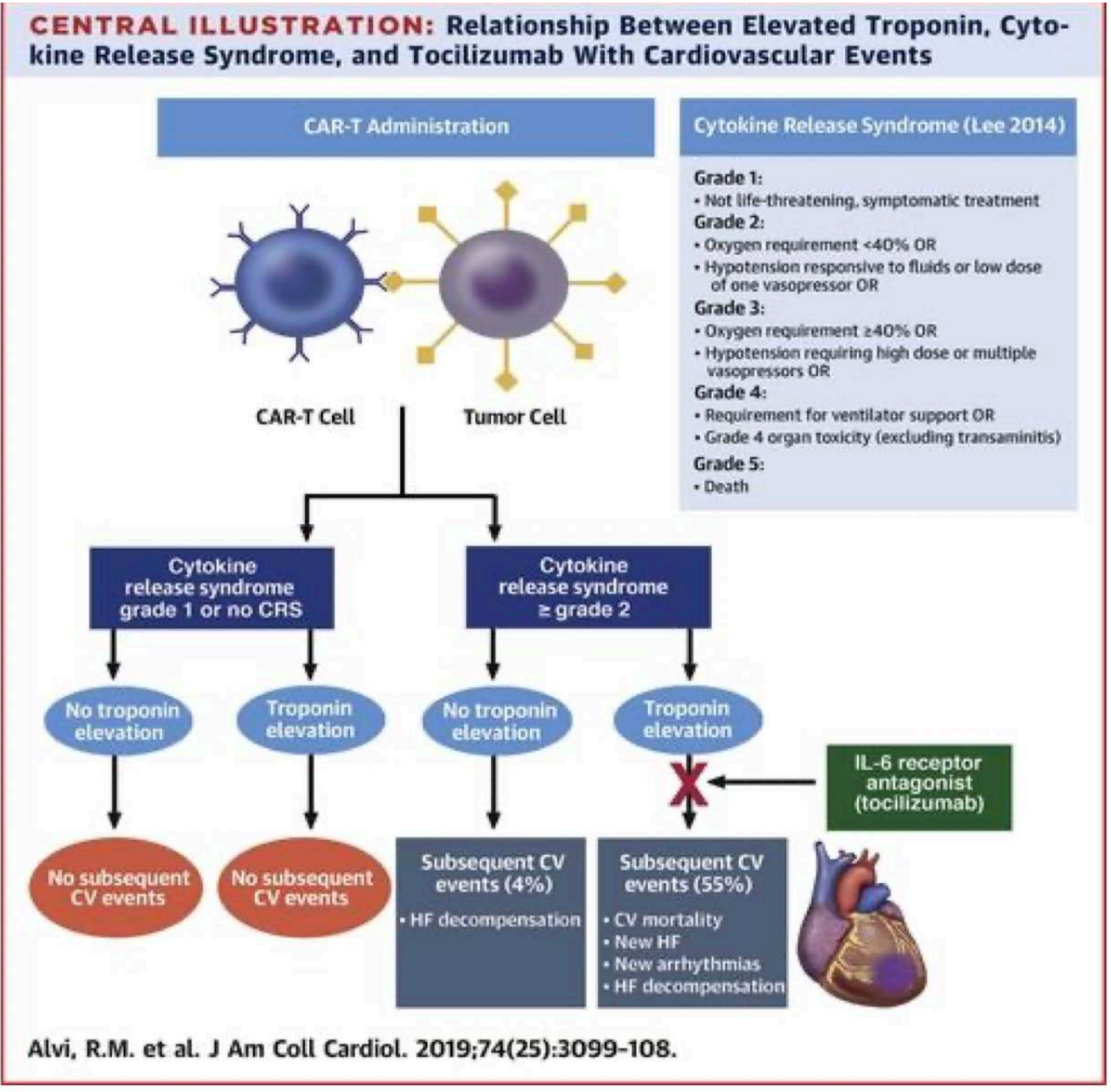


TABLE 4 Association With MACE Determined Using Multivariable Cox Proportional Cause-Specific Hazards Regression Analyses

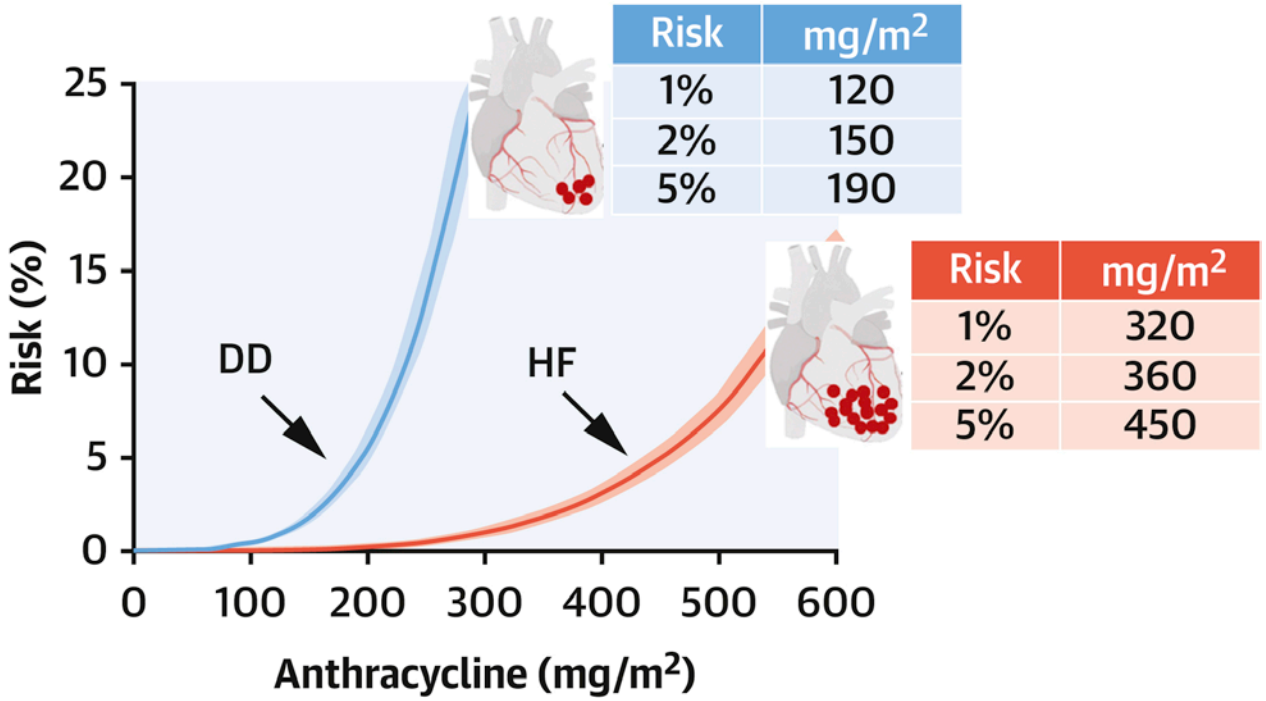
	Hazard Ratio (95% CI)	p Value
Statin	1.83 (0.88-3.81)	0.105
Creatinine	15.54 (3.67-65.86)	<0.001
CRS grade 1	0.49 (0.06-3.74)	0.489
CRS grade 2	0.95 (0.33-2.71)	0.917
CRS grade 3	8.42 (3.48-20.40)	<0.001
CRS grade 4	29.86 (9.80-90.94)	<0.001

Adapted from Lefebvre et al. JACC: CardioOnc. 2020;2:193-203.

There is suspicion that direct cardio-toxicity from CAR-T therapy is rare, and most severe CV events correlate with increasing severity of CRS. This supports CV risk stratification prior to CAR-T similar to how one would approach surgery, or HSCT.

Anthracyclines

- Mechanism of cardiomyopathy not completely elucidated. Thought to be due to inhibition of topoisomerase 2-B causing activation of cell death pathway and inhibition of biogenesis.
- Toxicity typically manifests most frequently within the first year. Can occur as early as after the first dose, or can manifest years later
- Historically thought to be irreversible, but newer data suggests that early intervention can lead to improvements in LV function.
- Risk of cardio-toxicity is dose dependent. Beyond 250 mg/m2 the risk becomes more rises rapidly. History of cardiovascular pathologies also increase risk



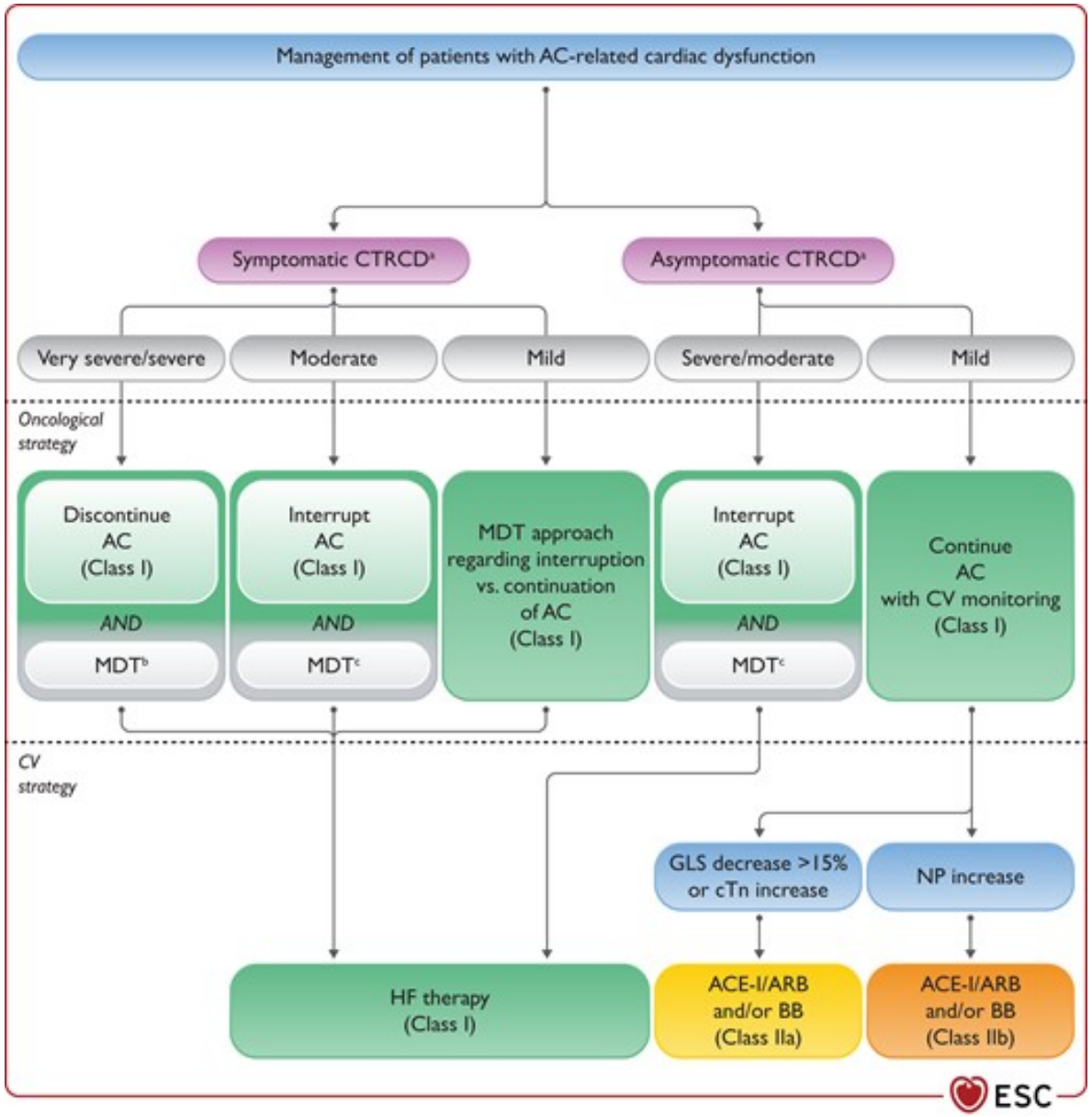
Risk	mg/m²
1%	120
2%	150
5%	190

Risk	mg/m²
1%	320
2%	360
5%	450

Minotti et al. JACC CardioOnc

Anthracycline management principles

- Concept of “permissive cardiotoxicity”
- Asymptomatic decline in echo strain usually means intensify monitoring or protection, rather than stop treatment.
- Strategies to reduce toxicity include utilizing alternative regimens, ?slower infusion? (1 hour preferred over push. No data for longer infusions), cardio protective therapy, liposomal formulation, use of dexrazoxane.
- Data on cardio-protective medications are limited, but include beta blockers, ACEI/ARB/ARNI, statins?, MRA’s?, SGLT-2?
- For higher risk patients we obtain q3 month echoes while on therapy and then 6 months after therapy. Long term surveillance every 2-5 years.



Lyon et al. EHJ

Summary

- Multiple life-saving treatments for hematologic malignancy carry significant potential cardiovascular risk
- Awareness of amyloidosis is increasing, but cardiologists remain confused about how to interpret light chain/SPEP/UPEP testing.
- Partnering with cardiology/cardio-onc can help collaboratively manage pre-treatment risk stratification and management of CV risk from anthracyclines, PI’s, BCR-ABL and bruton TKIs, CAR-T, and stem cell transplants.