Miocardite da checkpoint inhibitors

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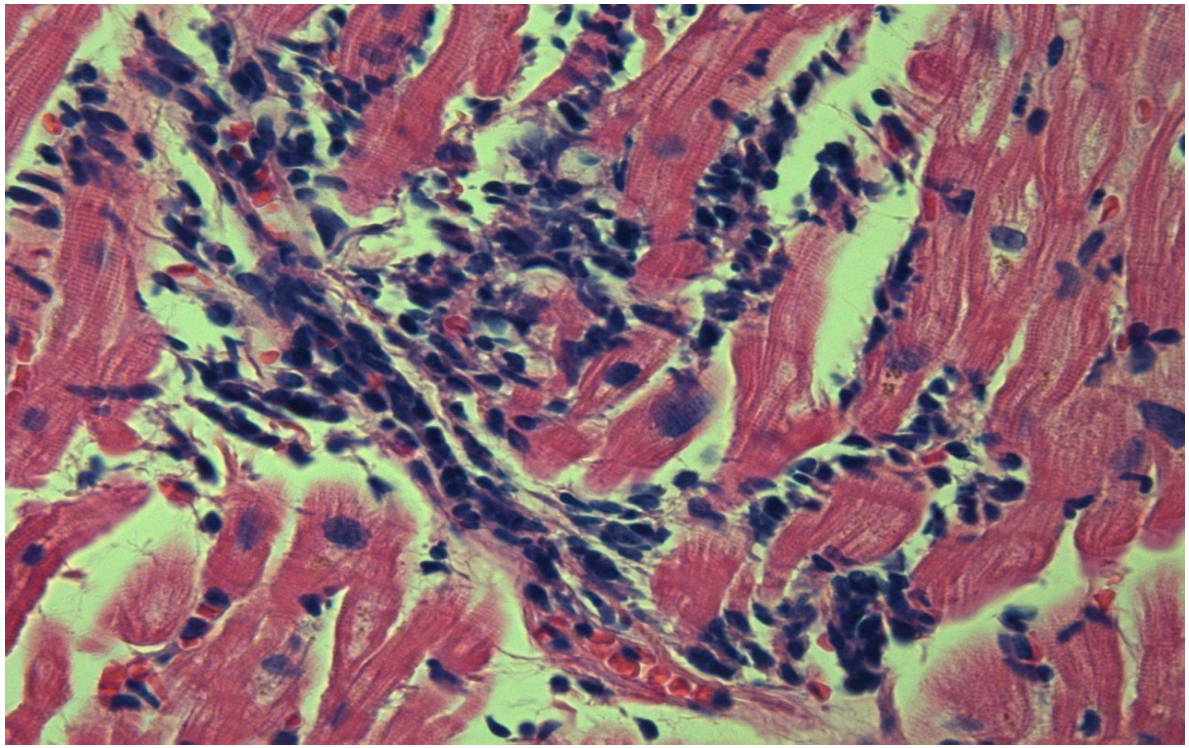
Circulation. 1996 Mar 1;93(5):841-2.

Report of the 1995 World Health Organization/International Society and Federation of Cardiology Task Force on the Definition and Classification of cardiomyopathies.

Richardson P, McKenna W, Bristow M, Maisch B, Mautner B, O'Connell J, Olsen E, Thiene G, Goodwin J, Gyarfas I, Martin I, Nordet P.

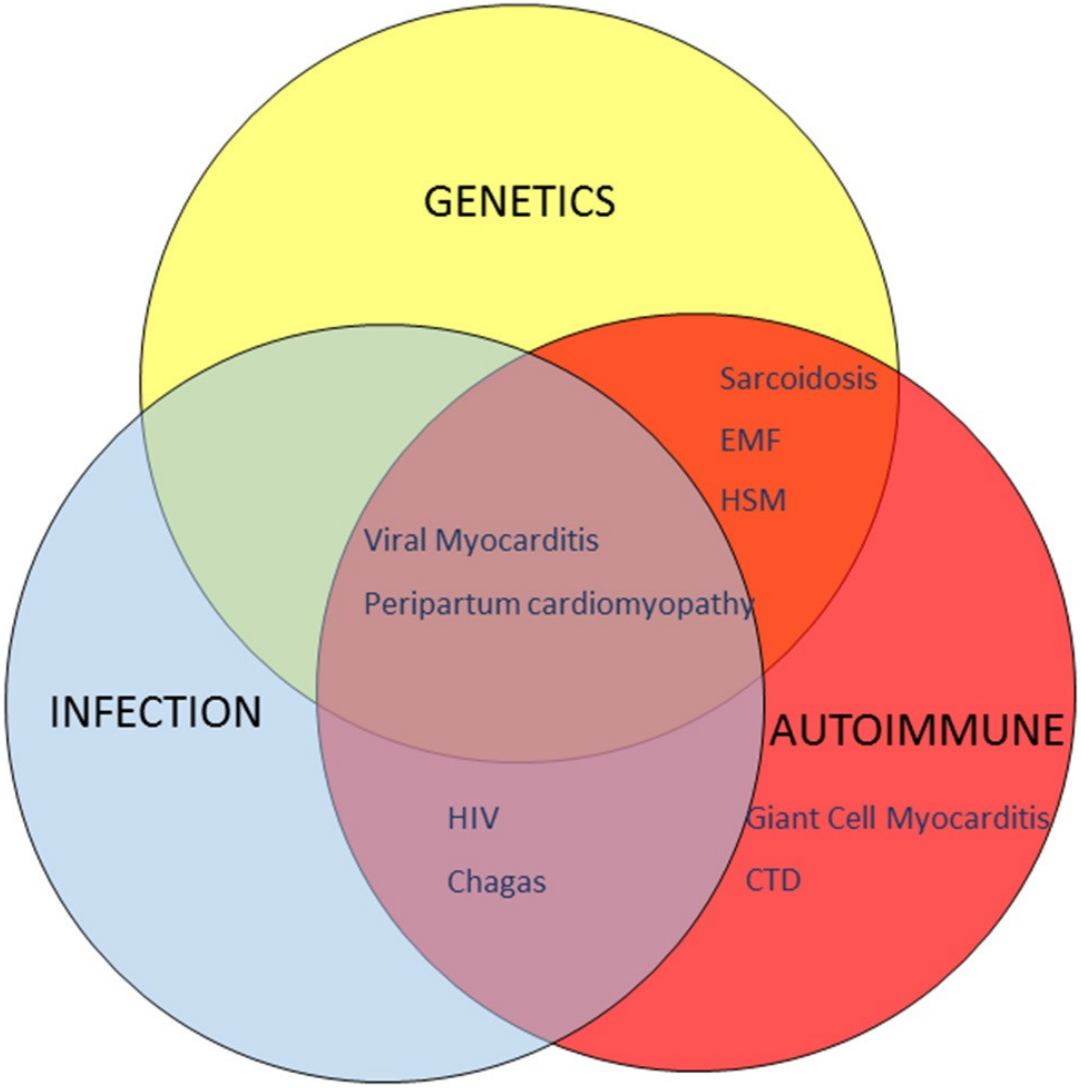


La MIOCARDITE è una malattia infiammatoria del miocardio, con coinvolgimento di miociti, interstizio ed endotelio vascolare. La diagnosi si basa su criteri istopatologici ed immunoistochimici

Inflammatory Cardiomyopathic Syndromes

Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

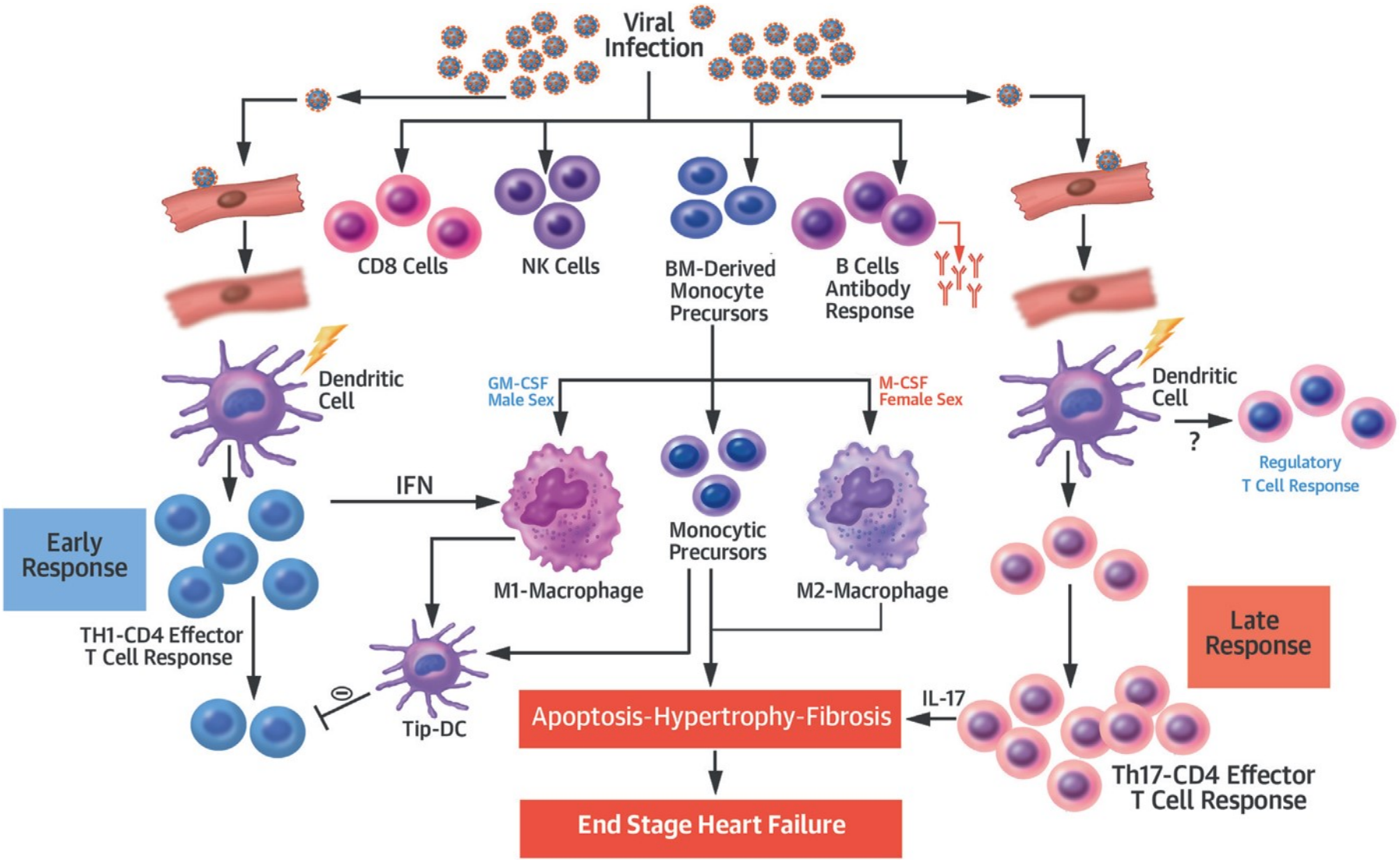
Diagram showing current evidence for overlapping theories of common causes of inflammatory cardiomyopathy



Trachtenberg, Circ Res. 2017;121:803-818

The Quest for New Approaches in Myocarditis and Inflammatory Cardiomyopathy

JACC
Journal of the American College of Cardiology



Heymans et al. J Am Coll Cardiol 2016;68:2348–64

Miocardite: manifestazioni cliniche ed evoluzione

Assenza di sintomi

Dolore toracico

Aritmie ipocinetiche/ ipercinetiche

Scompenso cardiaco

Forma fulminante

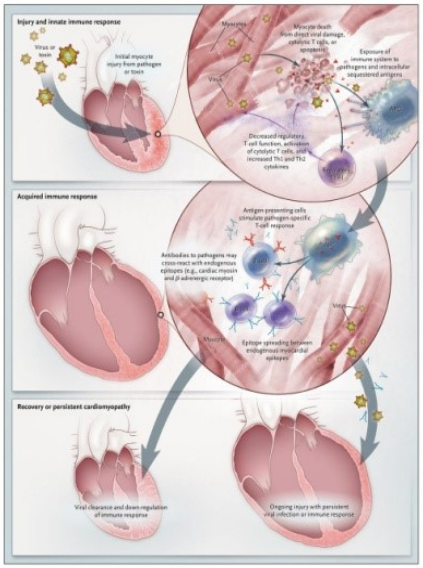
Guarigione completa o incompleta

CMPD

Morte improvvisa

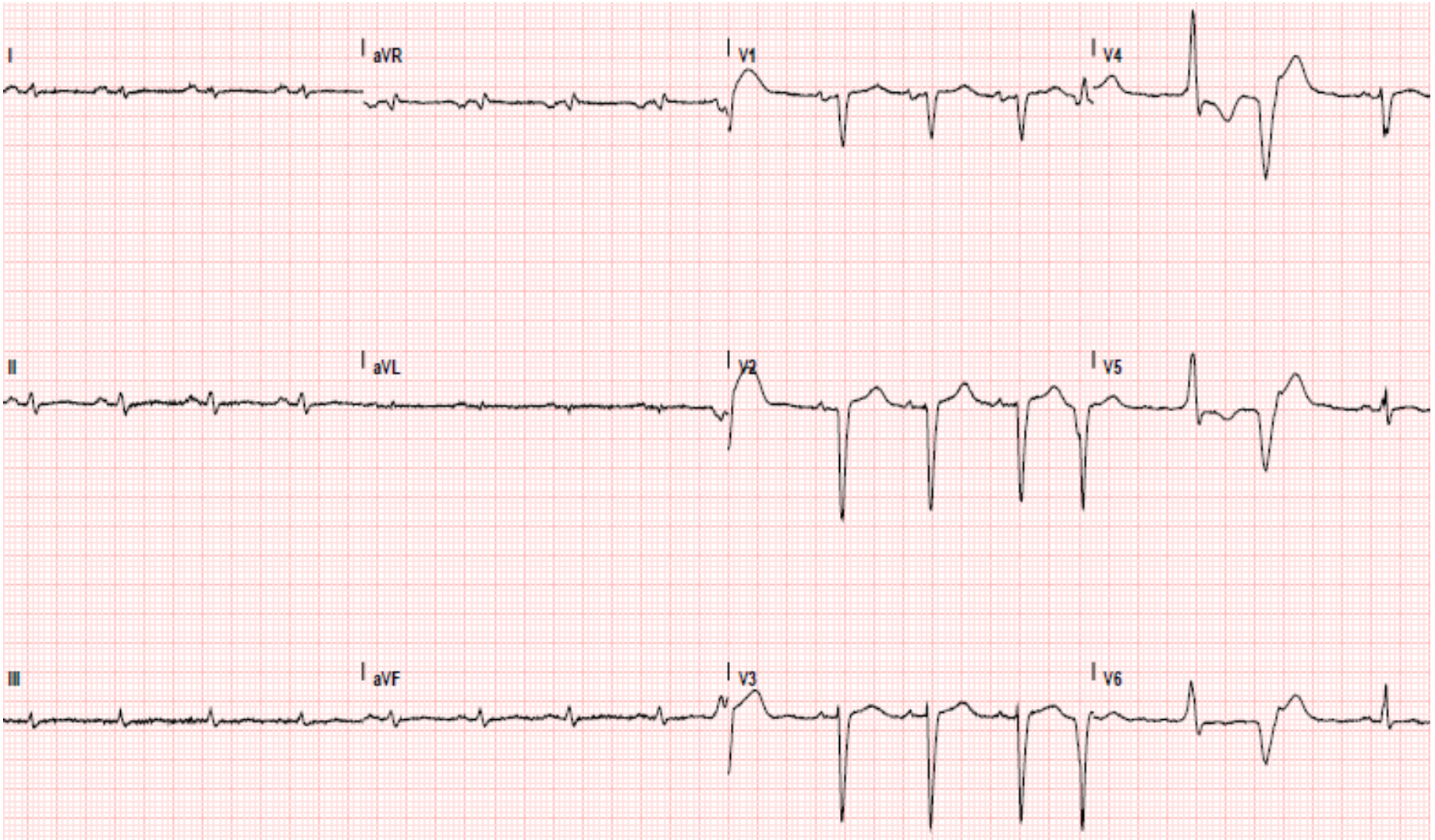
Morte in shock e MOF

-·-·-·- evoluzione possibile



Sinagra et al. Trattato di Cardiologia; Excerpta Medica 2000;2013-33

Ospedali Riuniti di Trieste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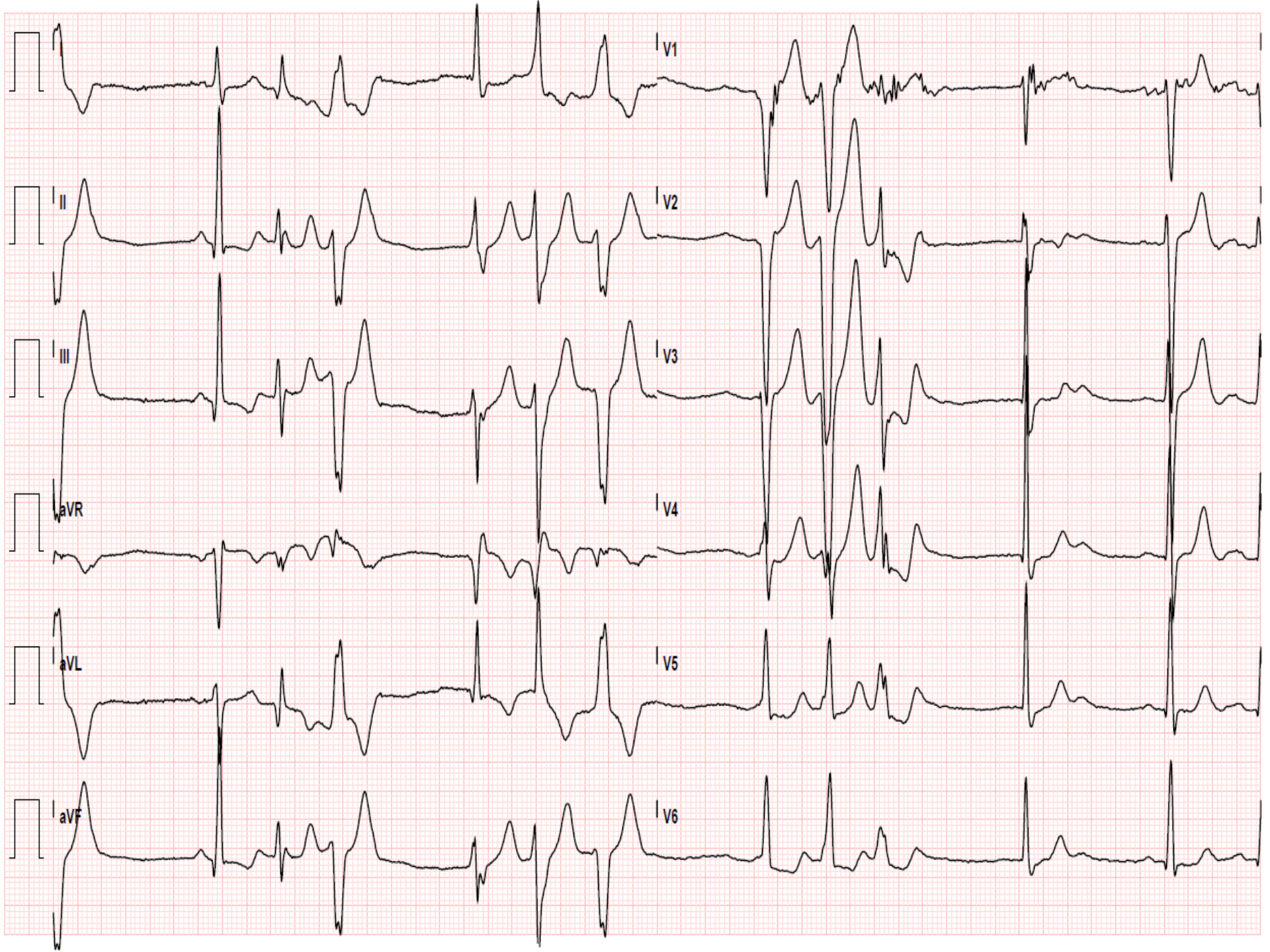
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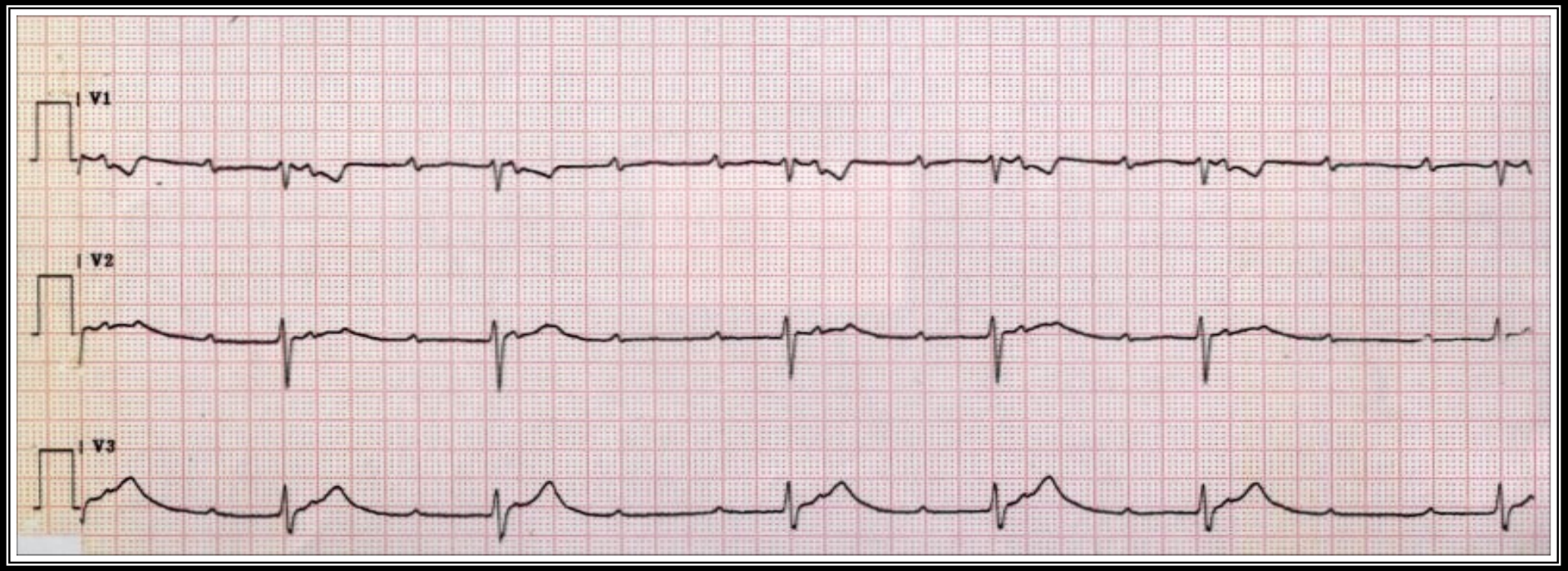
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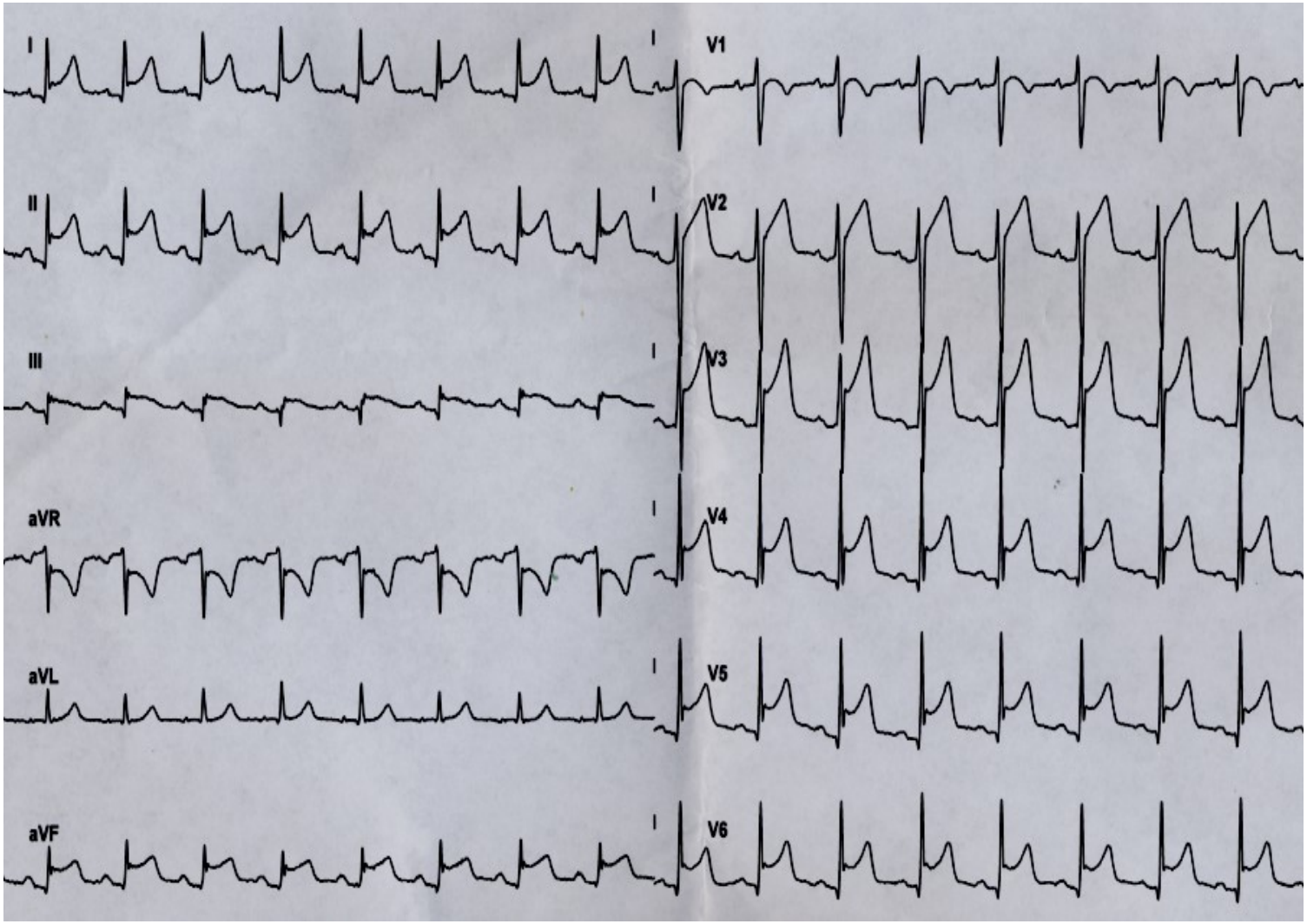
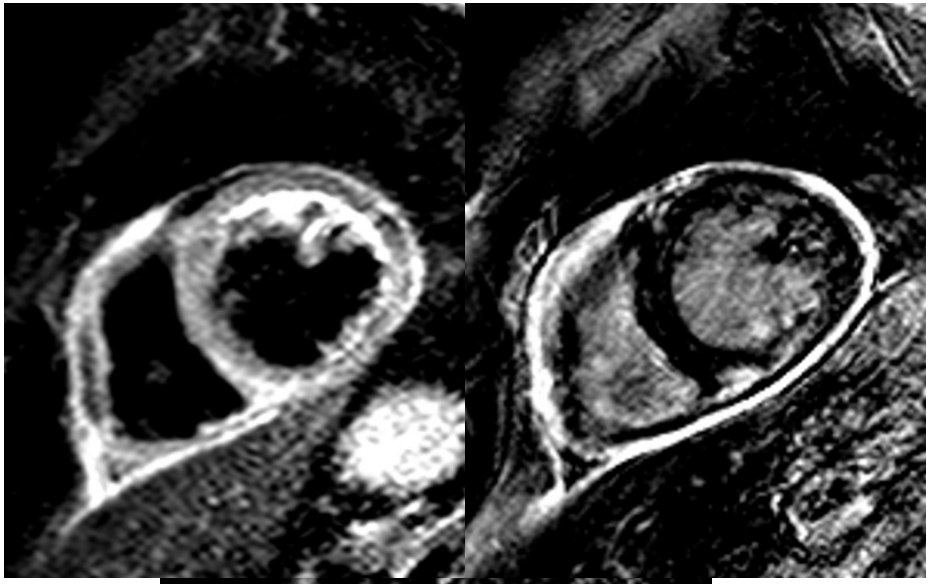


Ospedali Riuniti di Trieste



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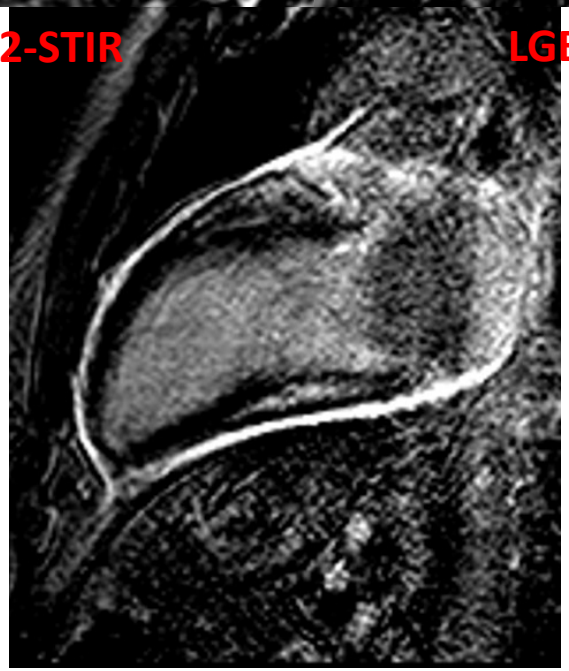
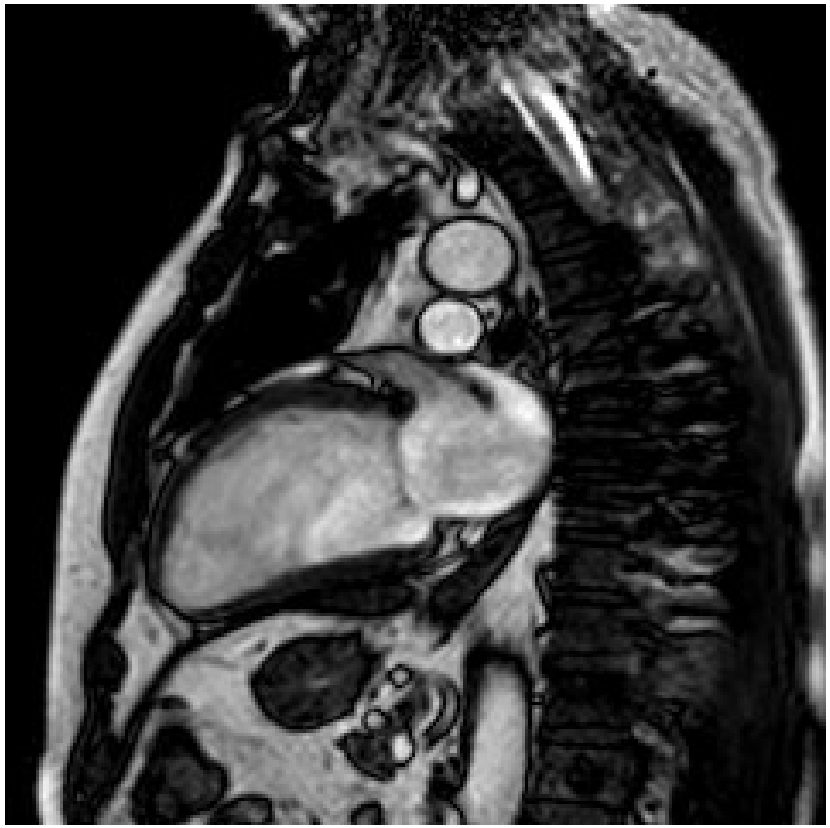




GENNAIO 2018

European Heart Journal (2016) **37**, 2768–2801
doi:10.1093/eurheartj/ehw211

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

The Task Force for cancer treatments and cardiovascular toxicity of the European Society of Cardiology (ESC)

Table 1 Incidence of left ventricular dysfunction associated with chemotherapy drugs[10–21]

Chemotherapy agents	Incidence (%)
Anthracyclines (dose dependent)	
Doxorubicin (Adriamycin) 400 mg/m² 550 mg/m² 700 mg/m²	 3–5 7–26 18–48
Idarubicin (>90 mg/m²)	5–18
Epirubicin (>900 mg/m²)	0.9–11.4
Mitoxanthone >120 mg/m²	2.6
Liposomal anthracyclines (>900 mg/m²)	2
Alkylating agents	
Cyclophosphamide	7–28
Ifosfamide <10 g/m² 12.5–16 g/m²	 0.5 17
Antimetabolites	
Clofarabine	27
Antimicrotubule agents	
Docetaxel	2.3–13
Paclitaxel	<1
Monoclonal antibodies	
Trastuzumab	1.7–20.1[18a]
Bevacizumab	1.6–4[14b]
Pertuzumab	0.7–1.2
Small molecule tyrosine kinase inhibitors	
Sunitinib	2.7–19
Pazopanib	7–11
Sorafenib	4–8
Dasatinib	2–4
Imatinib mesylate	0.2–2.7
Lapatinib	0.2–1.5
Nilotinib	1
Proteasome inhibitors	
Carfilzomib	11–25
Bortezomib	2–5
Miscellanous	
Everolimus	<1
Temsirolimus	<1

[a]When used in combination with anthracyclines and cyclophosphamide.
[b]In patients receiving concurrent anthracyclines.

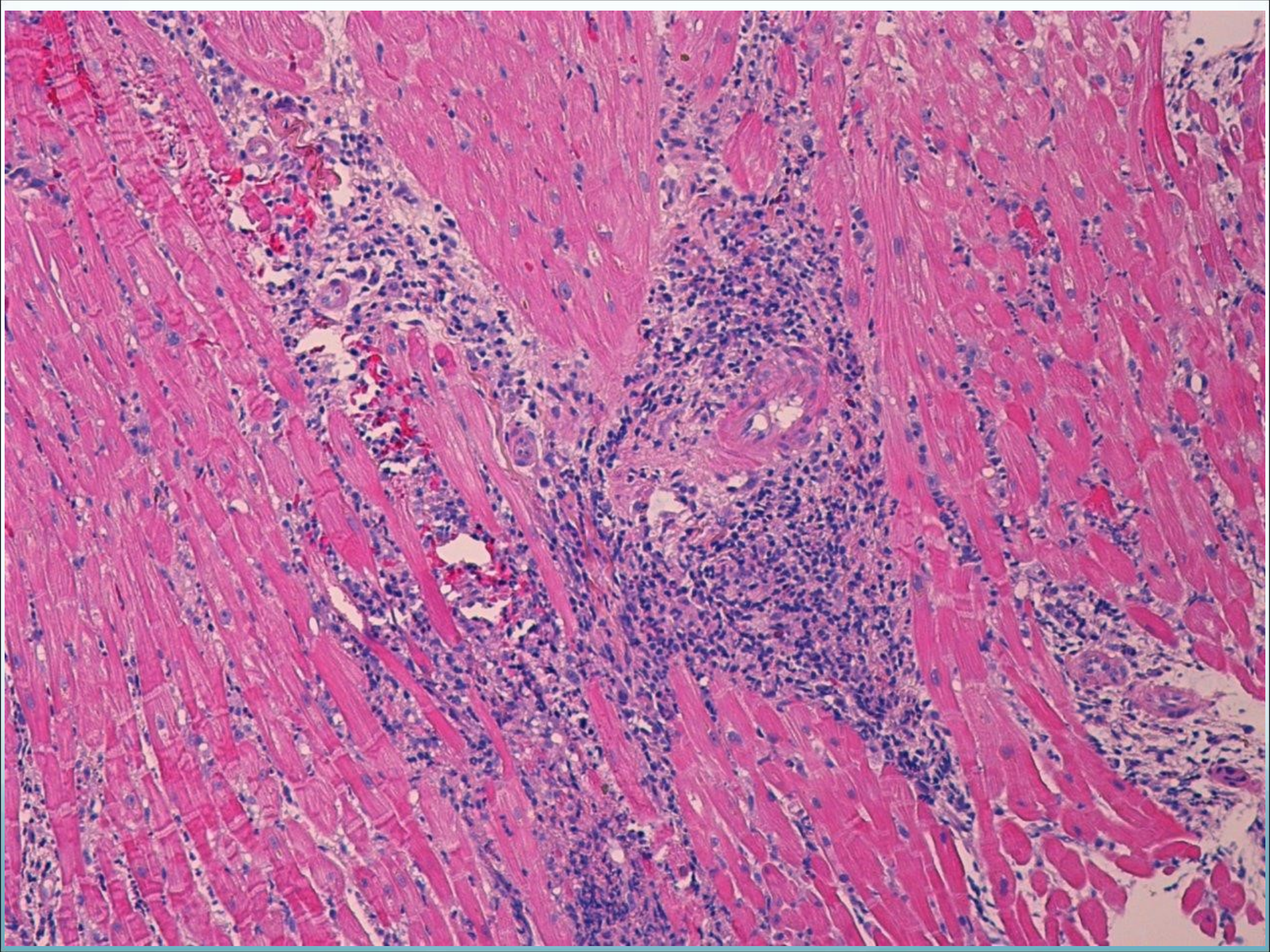
Fulminant Myocarditis with Combination Immune Checkpoint Blockade

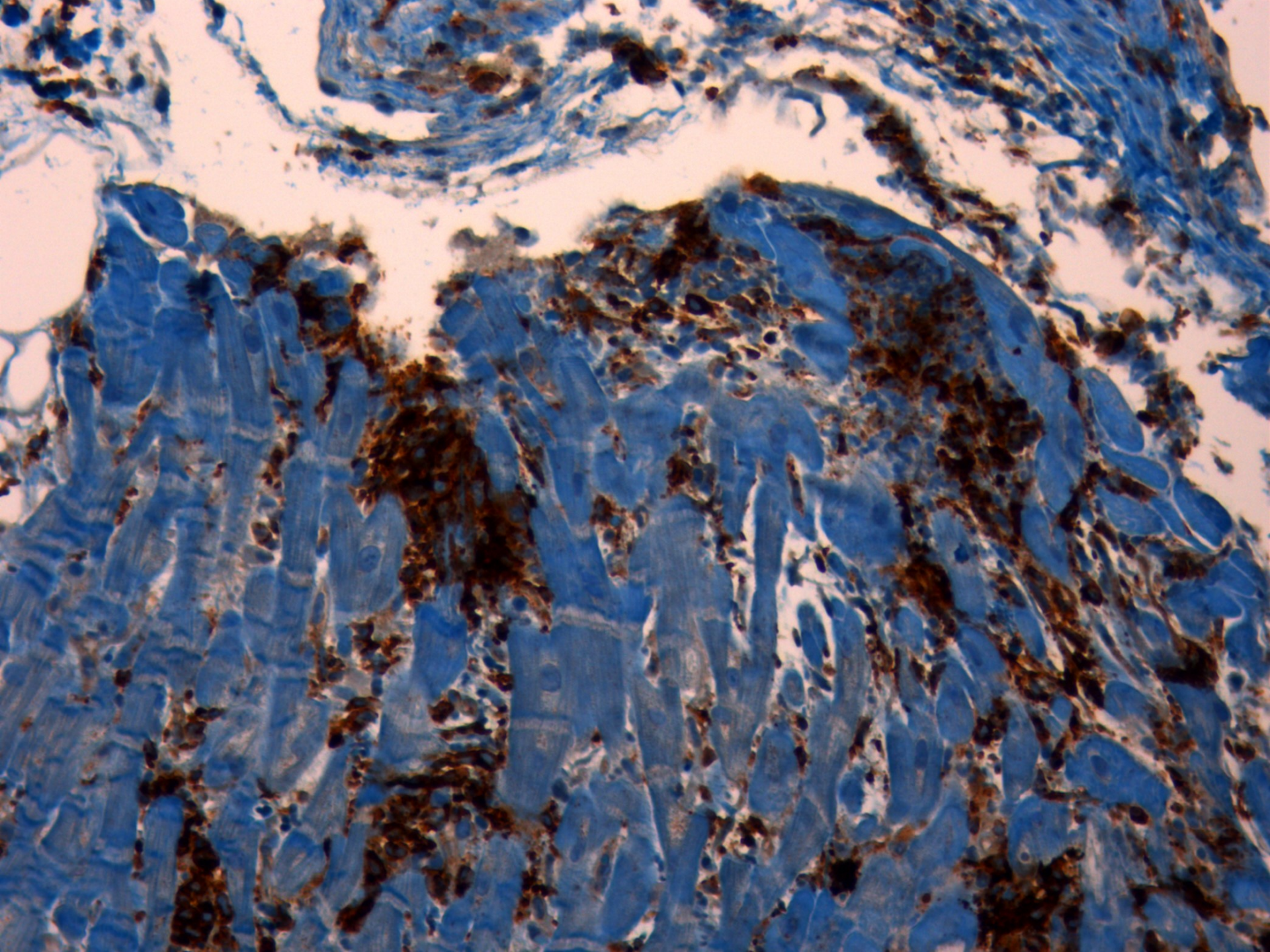
Immune checkpoint inhibitors have improved clinical outcomes associated with cancers, but high-grade, immune-related adverse events can occur. In two patients with melanoma fatal myocarditis developed after treatment with ipilimumab and nivolumab

Table 1. Incidence of Myocarditis and Myositis in Patients Receiving Nivolumab or Ipilimumab plus Nivolumab.

Characteristic	Nivolumab (N = 17,620)	Nivolumab plus Ipilimumab (N = 2974)
	no. (%)	
Myocarditis		
Any*	10 (0.06)	8 (0.27)
Fatal events	1 (<0.01)	5 (0.17)
Myositis		
Any	27 (0.15)	7 (0.24)
Fatal events	2 (0.01)	1 (0.03)

Johnson et al. N Engl J Med 2016;375:1749-55





The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

Immune-Related Adverse Events Associated with Immune Checkpoint Blockade

Michael A. Postow, M.D., Robert Sidlow, M.D., and Matthew D. Hellmann, M.D.

Table 1. Immune Checkpoint–Blocking Antibodies Approved by the Food and Drug Administration.*

Drug	Target	Indication
Ipilimumab	CTLA-4	Melanoma
Nivolumab	PD-1	Melanoma, non–small-cell lung cancer, renal-cell carcinoma, hepatocellular carcinoma, classic Hodgkin's lymphoma, squamous-cell carcinoma of the head and neck, urothelial carcinoma, colorectal cancer with high microsatellite instability or mismatch-repair deficiency
Pembrolizumab	PD-1	Melanoma, non–small-cell lung cancer, classic Hodgkin's lymphoma, squamous-cell carcinoma of the head and neck, urothelial carcinoma, gastric cancer, solid tumors with high microsatellite instability or mismatch-repair deficiency
Atezolizumab	PD-L1	Non–small-cell lung cancer, urothelial carcinoma
Avelumab	PD-L1	Merkel-cell carcinoma, urothelial carcinoma
Durvalumab	PD-L1	Urothelial carcinoma

anti–programmed death-1/ligand-1 (PD-1/PD-L1) and anti–cytotoxic T lymphocyte antigen-4 (CTLA-4)

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Immune-Related Adverse Events Associated with Immune Checkpoint Blockade

The NEW ENGLAND JOURNAL of MEDICINE

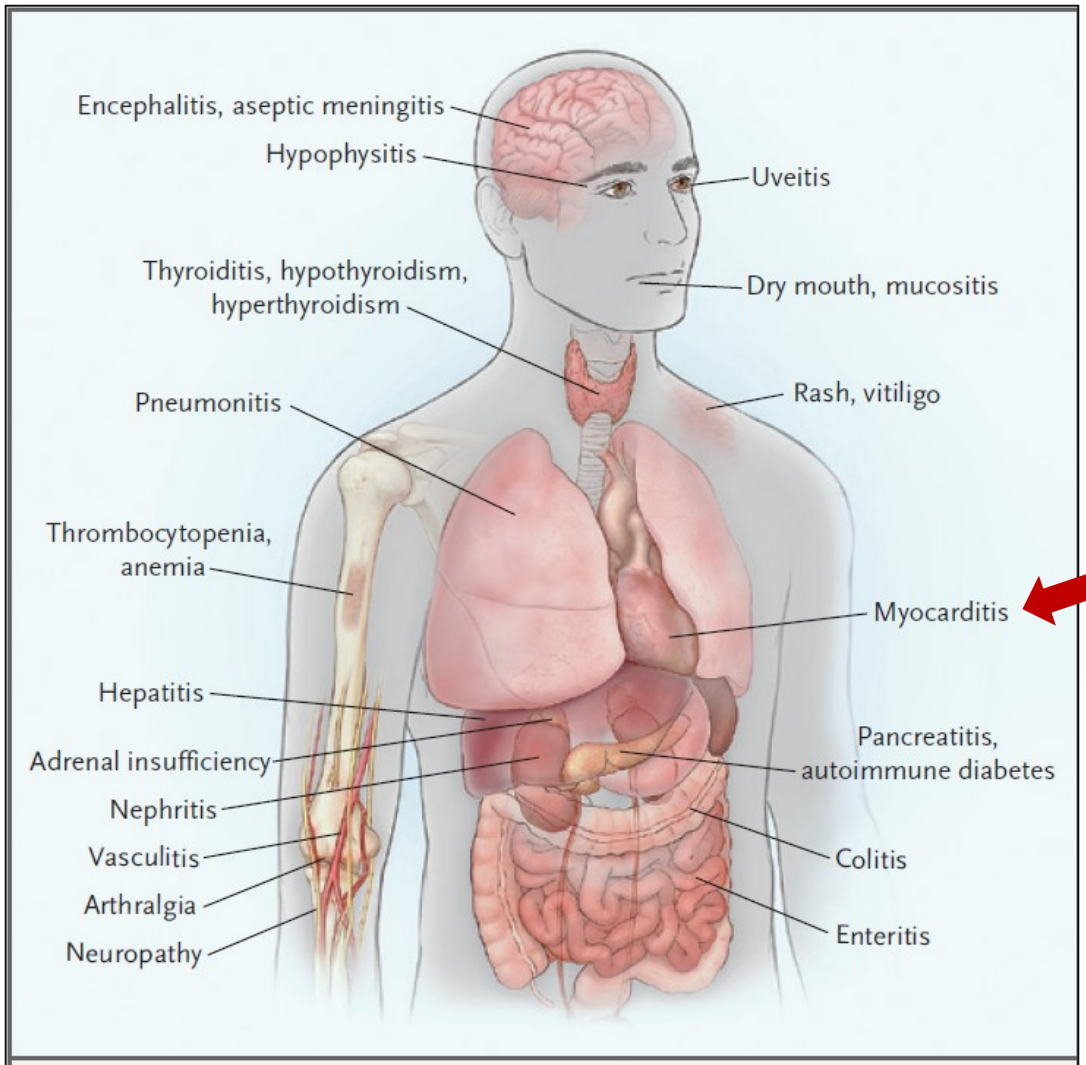

Figure 1. Organs Affected by Immune Checkpoint Blockade.

Immune-Related Adverse Events Associated with Immune Checkpoint Blockade

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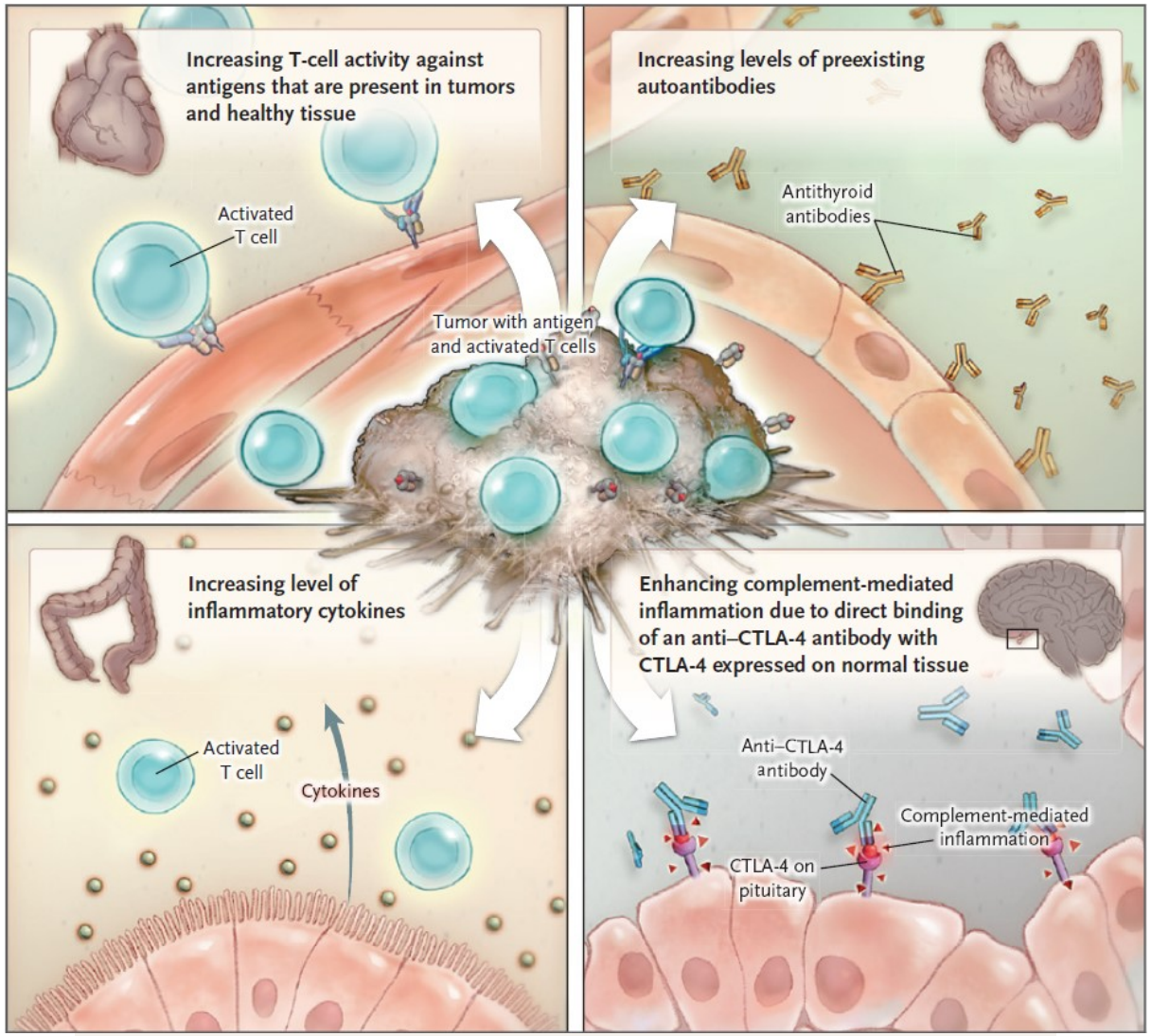

Possible Mechanisms Underlying Immune-Related Adverse Events.

Among 38 patients who were retreated, 50% had no further immune-related adverse events, 24% had a recurrence of the initial event, and 26% had a new event. Thus, clinicians should recognize that restarting immune checkpoint blockade after the resolution of immune-related adverse events may trigger recurrent or new immune-related adverse events. Although recurrent adverse events are usually less severe than the initial events (probably because of heightened surveillance), a decision to restart treatment with immune checkpoint blockade is likely to depend on the severity of the prior event, the availability of alternative treatment options, and the overall status of the cancer. An absolute contraindication to restarting treatment with immune checkpoint blockade is life-threatening toxicity, particularly cardiac, pulmonary, or neurologic toxicity.

JAMA Oncology | Original Investigation

Fatal Toxic Effects Associated With Immune Checkpoint Inhibitors

A Systematic Review and Meta-analysis

Daniel Y. Wang, MD; Joe-Elie Salem, MD; Justine V. Cohen, MD; Sunandana Chandra, MD; Christian Menzer, MD; Fei Ye, PhD; Shilin Zhao, PhD; Satya Das, MD; Kathryn E. Beckermann, MD, PhD; Lisa Ha, MSN; W. Kimryn Rathmell, MD, PhD; Kristin K. Ancell, MD; Justin M. Balko, PharmD; Caitlin Bowman, PharmD; Elizabeth J. Davis, MD; David D. Chism, MD; Leora Horn, MD; Georgina V. Long, MBBS, PhD; Matteo S. Carlino, MBBS; Benedicte Lebrun-Vignes, MD; Zeynep Eroglu, MD; Jessica C. Hassel, MD; Alexander M. Menzies, MBBS, PhD; Jeffrey A. Sosman, MD; Ryan J. Sullivan, MD; Javid J. Moslehi, MD; Douglas B. Johnson, MD

JAMA Oncology

Table 1. Spectrum of Fatal Immune-Related Adverse Events in Vigilyze

Variable	No. (%) Ipilimumab (n = 193)	Anti-PD-1/PD-L1 (n = 333)	Combination (n = 87)	*P* Value
Types of cancer[a]				<.001
Melanoma	136 (96)	50 (18)	49 (66)	
Lung cancer	0	152 (54)	17 (23)	
Other	5 (4)	78 (28)	8 (11)	
Type of fatal irAE				
Colitis	135 (70)	58 (17)	32 (37)	<.001
Pneumonitis	15 (8)	115 (35)	12 (14)	<.001
Hepatitis	31 (16)	74 (22)	19 (22)	.23
Hypophysitis	10 (5)	3 (1)	2 (2)	.01
Cardiac	3 (2)	27 (8)	22 (25)	<.001
Myositis	1 (0.5)	22 (7)	11 (13)	<.001
Nephritis	1 (0.5)	7 (2)	3 (4)	.19
Adrenal	8 (4)	6 (2)	3 (4)	.26
Neurologic	11 (6)	50 (15)	7 (8)	.003
Hematologic	3 (2)	14 (4)	2 (2)	.22
Other (skin, thyroid, diabetes, other gastrointestinal)	13 (7)	24 (8)	7 (8)	.93
Other clinical features				
Median time to irAE, days	40	40	14	.01
>1 concurrent irAE, %	27 (14)	51 (15)	24 (28)	.01
Reporting year				
2014 or before	98 (51)	3 (1)	2 (2)	<.001
2015	45 (23)	20 (6)	9 (10)	<.001
2016	21 (11)	88 (28)	17 (20)	.001
2017	26 (13)	192 (58)	44 (51)	<.001
2018 (up to January 15)	3 (2)	30 (9)	15 (17)	<.001

Retrospectively queried WHO pharmacovigilance database (Vigilyze)
>16 000 000 ADR
meta-analysis of published trials
anti–programmed death-1/ligand-1 (PD-1/PD-L1) and
anti–cytotoxic T lymphocyte antigen-4 (CTLA-4)

Cardiovascular toxicities associated with immune checkpoint inhibitors: an observational, retrospective, pharmacovigilance study

THE LANCET Oncology

Joe-Elie Salem, Ali Manouchehri, Melissa Moey, Bénédicte Lebrun-Vignes, Lisa Bastarache, Antoine Pariente, Aurélien Gobert, Jean-Philippe Spano, Justin M Balko, Marc P Bonaca, Dan M Roden, Douglas B Johnson, Javid J Moslehi

	ICSRs reported for ICIs (n=31 321)
Myocarditis	122 (0·39%)
Pericardial diseases	95 (0·30%)
Cardiac supraventricular arrhythmias	222 (0·71%)
Vasculitis	82 (0·26%)
Temporal arteritis	18 (0·06%)
Polymyalgia rheumatica	16 (0·05%)
Heart failure	225 (0·72%)
Cerebral haemorrhage	250 (0·80%)
Endocardial disorders	8 (0·03%)
Haemorrhage (clinical events)	1023 (3·27%)
Cerebral arterial ischaemia	195 (0·62%)
Cardiac conductive disorders	37 (0·12%)
Myocardial infarction	167 (0·53%)
Biological haemostatic disorders favouring haemorrhage	135 (0·43%)
Arterial systemic ischaemia	203 (0·65%)
Cardiac death or shock	136 (0·43%)
Hypertension and related end-organ damages	198 (0·63%)
Vascular neoplasm	4 (0·01%)
Torsade de pointes or long-QT syndrome	22 (0·07%)
Cardiac ventricular arrhythmias	22 (0·07%)
Pulmonary hypertension and related cardiac involvement	17 (0·05%)
Cardiac valve disorders	2 (0·01%)
Dyslipidaemia	20 (0·06%)

	ICSRs reported with ICIs (n=31 321)		
	Anti-PD-1 or anti-PD-L1 monotherapy (n=20 643)	Anti-CTLA-4 monotherapy (n=8266)	Combination ICIs (n=2412)
Myocarditis	84 (0·41%)	6 (0·07%)	32 (1·33%)
Pericardial diseases	74 (0·36%)	13 (0·16%)	8 (0·33%)
Vasculitis	56 (0·27%)	18 (0·22%)	8 (0·33%)
Temporal arteritis	7 (0·03%)	10 (0·12%)	1 (0·04%)
Polymyalgia rheumatica	14 (0·07%)	1 (0·01%)	1 (0·04%)

Lancet Oncol 2018

Myocarditis with Immune Checkpoint Blockade

Cardiovascular Adverse Events Reported in Phase 3 Trials of Immune Checkpoint Inhibitors

Study and Year	Tumor Type	Drug	Exposed Patients	Reported Cases of Cardiovascular Toxicity
			no.	*no. (%)*
All studies			5347	10 (0.19)
Hodi et al., 2010	Melanoma	Ipilimumab	511	0
Robert et al., 2011	Melanoma	Ipilimumab	247	0
Weber et al., 2015	Melanoma	Nivolumab	268	0
Robert et al., 2015	Melanoma	Nivolumab	206	1 case of hypotension (0.49)
Robert et al., 2015	Melanoma	Pembrolizumab or ipilimumab	811	1 cardiac arrest associated with metabolic imbalances from ipilimumab-induced diarrhea; 4 cases of hypertension (0.62)
Larkin et al., 2015	Melanoma	Nivolumab, ipilimumab, or nivolumab plus ipilimumab	937	0
Eggermont et al., 2015 and 2016	Melanoma (adjuvant)	Ipilimumab	471	1 case of myocarditis (0.21)
Borghaei et al., 2015	Non-squamous non–small-cell lung cancer	Nivolumab	287	1 case of cardiac tamponade; 1 case of pericardial effusion (0.70)
Brahmer et al., 2015	Squamous non–small-cell lung cancer	Nivolumab	131	0
Reck et al., 2016	Non–small-cell lung cancer	Pembrolizumab	154	0
Herbst et al., 2016	Non–small-cell lung cancer	Pembrolizumab	682	1 case of myocardial infarction (0.15)
Motzer et al., 2015	Renal-cell carcinoma	Nivolumab	406	0
Ferris et al., 2016	Head and neck squamous-cell carcinoma	Nivolumab	236	0

Edhery et al. NEJM.2017:376;3

Myocarditis in Patients Treated With Immune Checkpoint Inhibitors

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Syed S. Mahmood, MD, MPH,[a,b] Michael G. Fradley, MD,[c] Justine V. Cohen, DO,[d] Anju Nohria, MD,[e] Kerry L. Reynolds, MD,[d] Lucie M. Heinzerling, MD, MPH,[f] Ryan J. Sullivan, MD,[d] Rongras Damrongwatanasuk, MD,[c] Carol L. Chen, MD,[g] Dipti Gupta, MD, MPH,[g] Michael C. Kirchberger, MD,[f] Magid Awadalla, MD,[b] Malek Z.O. Hassan, MD,[b] Javid J. Moslehi, MD,[h] Sachin P. Shah, MD,[i] Sarju Ganatra, MD,[i] Paaladinesh Thavendiranathan, MD,[j] Donald P. Lawrence, MD,[d] John D. Groarke, MB BCh, MPH,[e] Tomas G. Neilan, MD, MPH[b,k]

Mahmood, S.S. et al. J Am Coll Cardiol. 2018;71(16):1755-64.

TABLE 1 Description of Cases and Controls

	Myocarditis (n = 35)	Controls (n = 105)	Odds Ratio	95% Confidence Interval	p Value
Age at start of ICI, yrs	65 ± 13	65 ± 13	–	–	0.85
Female	10 (29.0)	33 (31.0)	0.87	0.38-2.02	0.83
CV risk factors					
Current or prior smoking	15 (43.0)	65 (62.0)	0.51	0.23-1.13	0.075
Hypertension	25 (71.0)	65 (62.0)	1.54	0.67-3.53	0.31
Diabetes mellitus	12 (34.0)	14 (13.0)	3.36	1.37-8.20	0.01
No CV risk factors	1 (2.9)	4 (3.8)	0.74	0.08-6.90	–
Coronary artery disease	7 (20.0)	17 (16.0)	1.29	0.49-3.44	0.61
Prior myocardial infarction	3 (8.6)	6 (5.7)	1.55	0.37-6.54	0.69
Prior coronary stenting	2 (5.7)	2 (1.9)	3.13	0.42-23.26	–
Coronary artery bypass graft	3 (8.6)	7 (6.7)	1.31	0.32-5.38	1.00
Stroke	2 (5.7)	11 (10.5)	0.52	0.11-2.46	0.52
Heart failure	1 (2.9)	9 (8.6)	0.31	0.04-2.57	0.45
Chronic obstructive pulmonary disease	4 (11.0)	14 (13.0)	0.84	0.26-2.74	1.00
Obstructive sleep apnea	5 (14.0)	4 (3.8)	4.2	1.06-16.67	0.04
Chronic kidney disease*	2 (5.9)	19 (18.0)	0.28	0.06-1.28	0.10
Body mass index, kg/m^2	29.0 ± 8.4	26.0 ± 6.0	–	–	0.02
Primary cancer type					
Head and neck	2 (5.7)	10 (9.5)	0.58	0.12-2.76	0.73
Breast	1 (2.9)	0 (0.0)	–	–	–
Hodgkin's lymphoma	1 (2.9)	2 (1.9)	1.52	0.13-17.24	–
Melanoma	16 (46.0)	50 (48.0)	0.19	0.02-1.51	1.00
Non-small cell lung cancer	4 (11.0)	26 (25.0)	0.39	0.13-1.22	0.15
Small cell lung cancer	0 (0.0)	4 (3.8)	–	–	0.57
Pancreatic	1 (2.9)	0 (0.0)	–	–	–
Renal cell carcinoma	2 (5.7)	1 (1.0)	6.29	0.55-71.43	–
Glioblastoma	1 (2.9)	0 (0.0)	–	–	–
Other	7 (20.0)	12 (11.0)	1.94	0.70-5.41	0.25

Massachusetts General Hospital ICI between November 2013 and July 2017

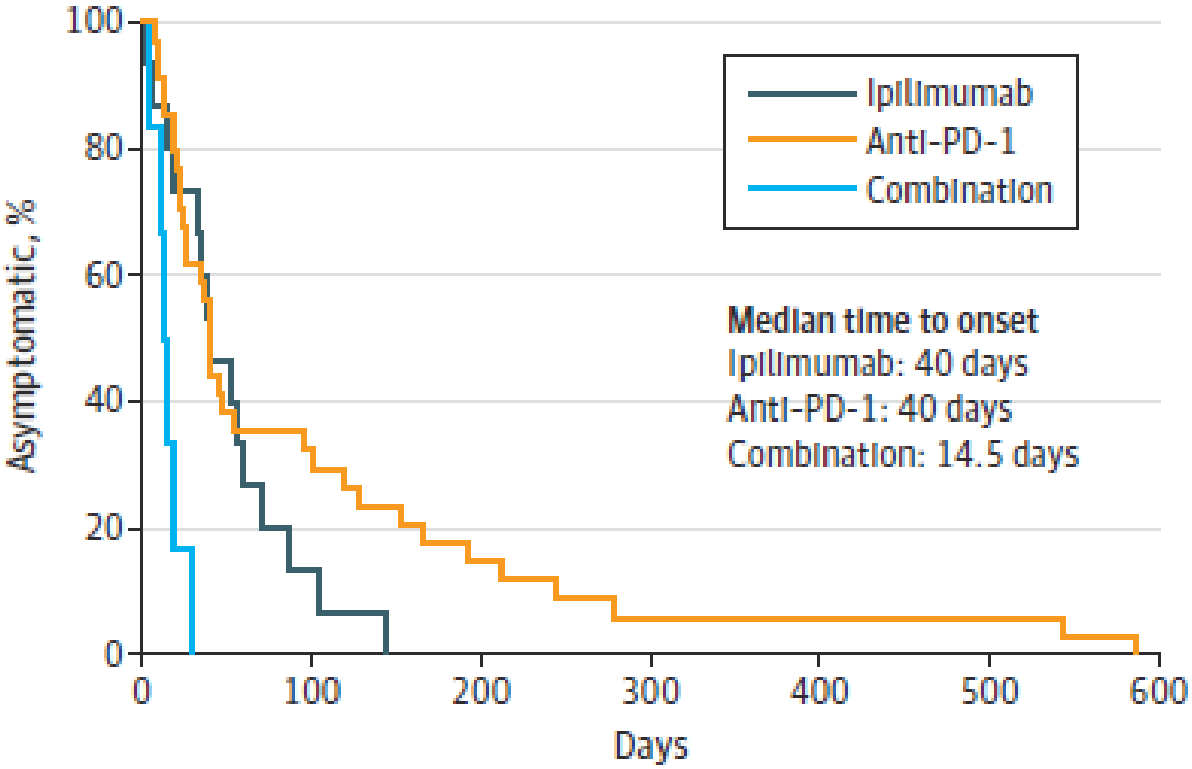
1.14% developed myocarditis and **0.52% developed a MACE**.

Fatal Toxic Effects Associated With Immune Checkpoint Inhibitors

A Systematic Review and Meta-analysis

JAMA Oncology

Figure 2. Time to Symptom Onset of Fatal Toxic Effects by ICI Regimen



No. at risk

Ipilimumab	15	2	0	0	0	0	0
Anti-PD-1	34	11	5	2	2	2	0
Combination	6	0	0	0	0	0	0

Myocarditis in Patients Treated With Immune Checkpoint Inhibitors

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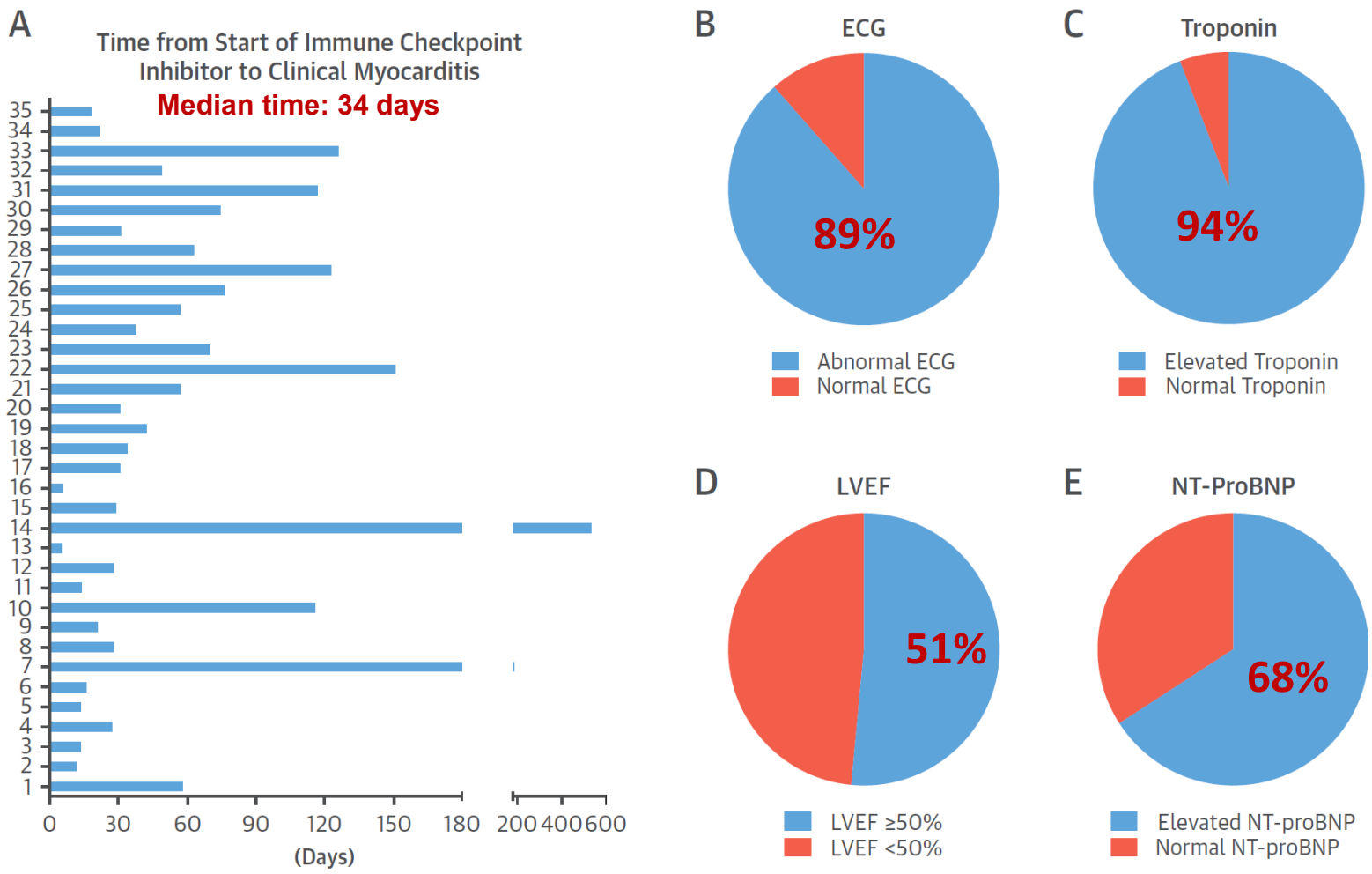
FIGURE 1 Clinical Presentation of Patients With ICI-Associated Myocarditis



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Fatal Toxic Effects Associated With Immune Checkpoint Inhibitors

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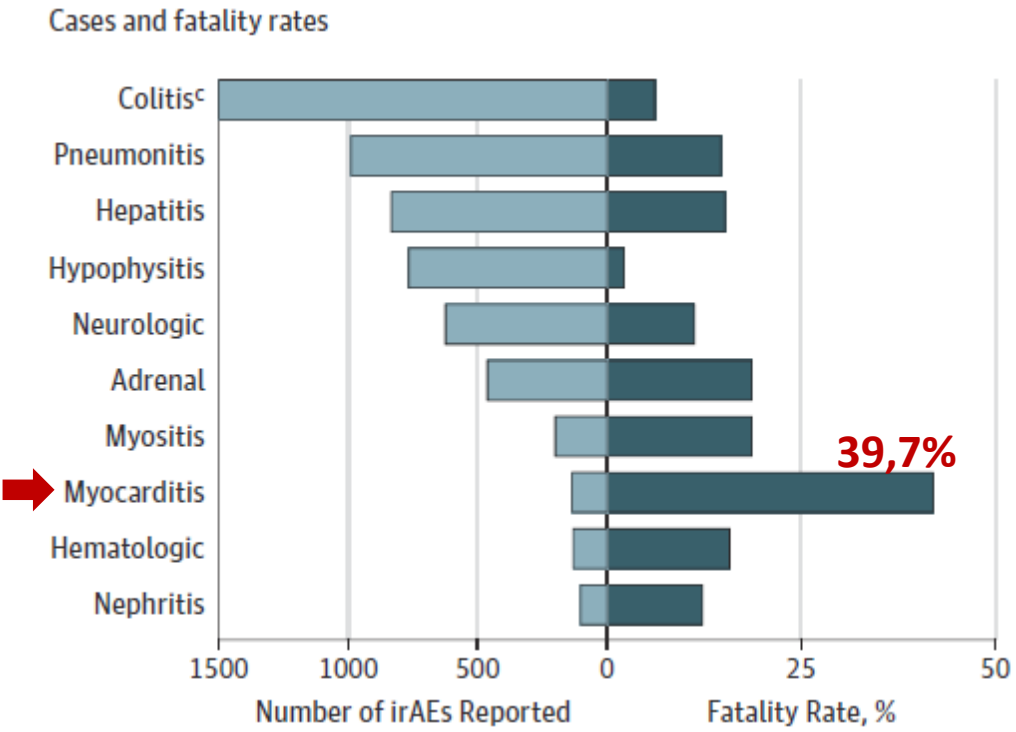

To determine the risk of fatality associated with particular toxic effects, we assessed fatality rates for different classes of toxic effects (Figure 1C). Myocarditis appeared to present the highest risk of death, with 52 (39.7%) deaths among 131 cases. Pneumonitis, hepatitis, myositis, nephritis, neurologic, and hematologic toxic effects all had fatalities in 10% to 17% of reported cases. Hypophysitis, adrenal insufficiency, and colitis had the lowest reported fatality rates (2%, 3.7%, and 5%, respectively).

Myocarditis in Patients Treated With Immune Checkpoint Inhibitors

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Mahmood, S.S. et al. J Am Coll Cardiol. 2018;71(16):1755-64.

		No MACE (n=19)	MACE (n=16)	P-value
Cardiovascular Complications* – n (%)				
	Cardiovascular death	0 (0)	6 (38)	**0.003**
	Ventricular fibrillation	0 (0)	5 (31)	**0.008**
	Cardiac arrest (non-ventricular fibrillation)	0 (0)	4 (25)	**0.021**
	Cardiogenic shock	0 (0)	8 (50)	**<0.001**
	Complete heart block	0 (0)	8 (50)	**<0.001**
	Atrial fibrillation or flutter	5 (26)	4 (25)	0.93
	Supraventricular tachycardia	1 (5.3)	2 (12.5)	0.45
	Mobitz 1 Heart block	0 (0)	3 (19)	0.05
	Mobitz 2 Heart block	0 (0)	3 (19)	0.05
	Heart failure	8 (42)	8 (50)	0.64

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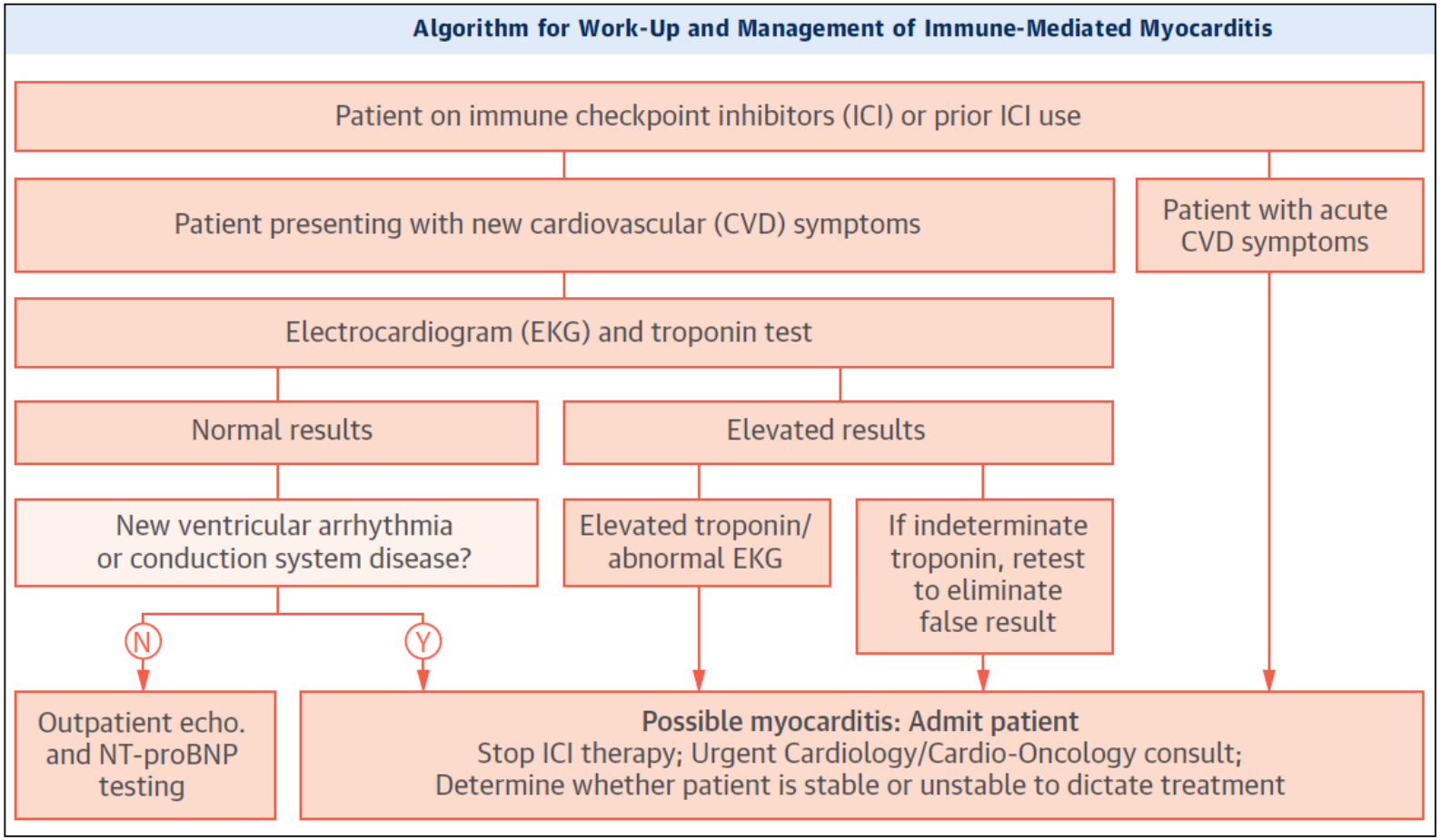

The implication of this finding is that **clinicians should not rely on ejection fraction as a discriminator of severity in ICI-associated myocarditis**.
By contrast, they did find that the degree of troponin elevation was useful in determining adverse cardiac outcomes. Specifically, they found that **troponin T >1.5 ng/dl had a 95% specificity for the development of MACE**.

Overall, **just >1% developed myocarditis after ICI therapy** and **approximately 0.5% had a MACE**.

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Management of immune checkpoint blockade dysimmune toxicities: a collaborative position paper

ANNALS OF ONCOLOGY

Table 4. Typical management of irAEs

Severity—CTCAE grade	Ambulatory versus inpatient care	Corticosteroids	Other immunosuppressive drugs	Immunotherapy
1	Ambulatory	Not recommended	Not recommended	Continue
2	Ambulatory	Topical steroids or Systemic steroids oral 0.5–1 mg/kg/day	Not recommended	Suspend temporarily[a]
3	Hospitalization	Systemic steroids Oral or i.v. 1–2 mg/kg/day for 3 days then reduce to 1 mg/kg/day	To be considered for patients with unresolved symptoms after 3–5 days of steroid course Organ Specialist referral advised	Suspend and discuss resumption based on risk/benefit ratio with patient
4	Hospitalization consider intensive care unit	Systemic steroids i.v. methylprednisolone 1–2 mg/kg/day for 3 days then reduce to 1 mg/kg/day	To be considered for patients with unresolved symptoms after 3–5 days of steroid course Organ specialist referral advised	Discontinue permanently

Some dysimmune toxicities may follow a specific management: this has to be discussed with the organ specialist.
[a]Outside skin or endocrine disorders where immunotherapy can be maintained.

Annals of Oncology 27: 559–574, 2016

European Heart Journal
doi:10.1093/eurheartj/ehw128

2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)

EMB should be considered in patients with rapidly progressive HF despite standard therapy when there is a probability of a specific diagnosis which can be confirmed only in myocardial samples and specific therapy is available and effective.	IIa	C	93

Cooper et al. Eur Heart J 2007;28:3076-3093

Take home messages

- The incidence of immune checkpoint inhibitor (ICI)-associated myocarditis is ranging from **0.06% to 1.33%**. The prevalence of myocarditis has been reported to be **higher with combination immune therapies**.

- The risk factors for ICI-associated myocarditis are not well understood but may include **underlying autoimmune disease** and **diabetes mellitus**.

- ICI-associated myocarditis occurs early with a median time of **34 days** and with **most of the cases occurring within 3 months** of starting ICI therapy.

- Nearly all myocarditis cases had a **troponin elevation (94%)** and **an abnormal ECG (89%)**. The **LVEF was normal in 51% of cases**. A **CMR is the gold standard noninvasive test** for the diagnosis of myocarditis.

- One-half of ICI-associated myocarditis cases **(46%)** experienced a MACE. As compared with non-MACE myocarditis cases, those who experienced a MACE had a **higher admission, peak, and discharge/final troponin T value.**

- Optimal management of myocarditis associated with ICI's is still unclear but temporarily or permanently **cessation of ICI therapy** and **immunosuppression with high-dose steroids** are the cornerstones of ICI-associated myocarditis treatment.

- ICI-associated myocarditis is a new syndrome and a key component will be **multidisciplinary collaborations**, which should include oncologists, general physicians, cardiologists, cardio-oncologists, and immunologists