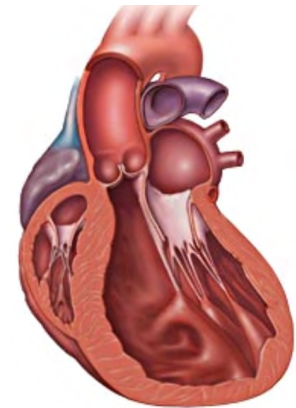# Management of the patient with heart failure

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Potential conflicts of interest

- Consultant, Novartis, maker of sacubitril-valsartan (Entresto)
- Consultant, Invitae

Overview

- Updated guidelines for treatment of HFrEF and HFpEF

- Myocarditis after Covid
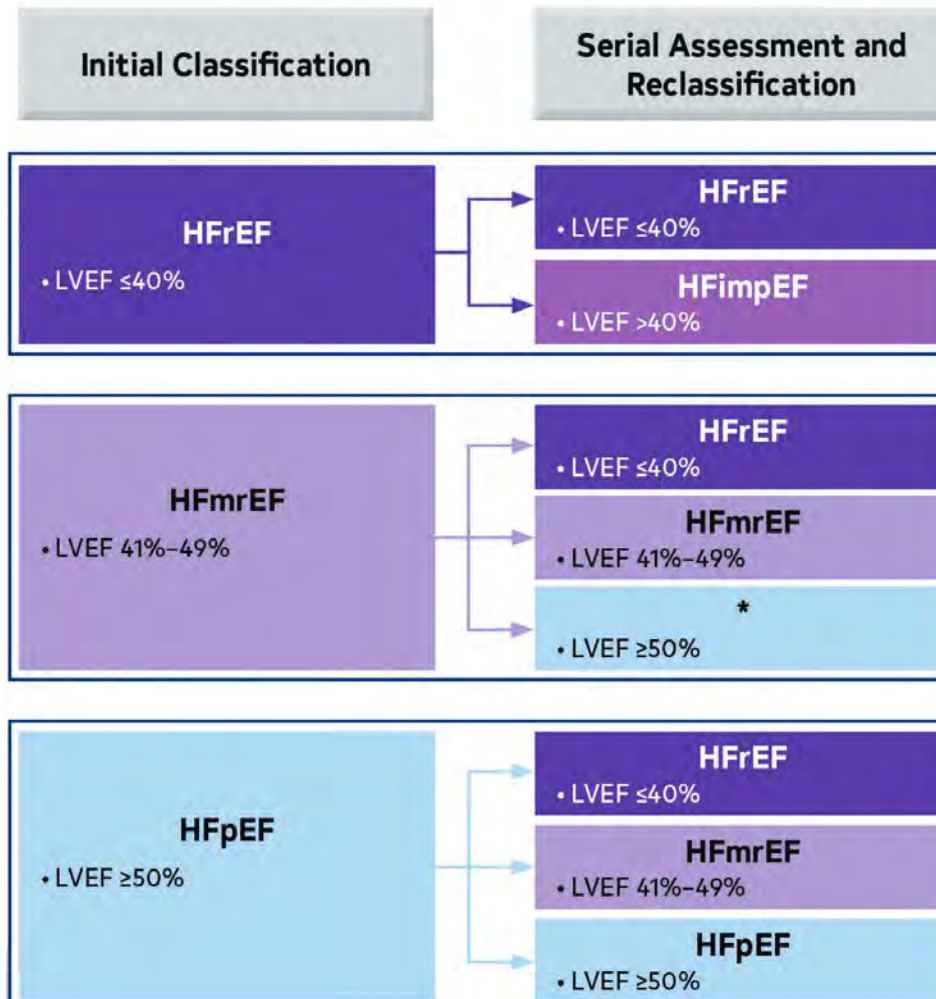
- Myocarditis after Covid vaccination

- Updated guidelines for treatment of HFrEF and HFpEF
- Myocarditis after Covid
- Myocarditis after Covid vaccination

references

- 2013 ACCF/AHA Guideline on Management of Heart Failure

- 2016 ACC/AHA/HFSA Focused Update on New Pharmacological Therapy for Heart Failure

- 2017 ACC/AHA/HFSA Focused Update on Heart Failure

- **2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure**

HF subtypes

- New universal definition 2021
    - HFpEF ≥ 50% (preserved)
    - HFmrEF 41-49% (mildly reduced)
    - HFrEF ≤ 40% (reduced)
    - HFimpEF (improved) baseline ≤ 40% w 10pt improvement to > 40%

Bozkurt JCF 2021, 2022 Guidelines Circuation

Initial Classification	Serial Assessment and Reclassification

HFrEF
• LVEF ≤40%
→ **HFrEF** • LVEF ≤40%
→ **HFimpEF** • LVEF >40%

HFmrEF
• LVEF 41%–49%
→ **HFrEF** • LVEF ≤40%
→ **HFmrEF** • LVEF 41%–49%
→ ***** • LVEF ≥50%

HFpEF
• LVEF ≥50%
→ **HFrEF** • LVEF ≤40%
→ **HFmrEF** • LVEF 41%–49%
→ **HFpEF** • LVEF ≥50%

HFpEF specific etiologies

- Transthyretin (TTR) cardiac amyloidosis
  - Wild-type (senile) or mutant/variant TTR
  - Diagnosed with TcPYP scan, CMR, biopsy
  - Treatable with TTR stabilizers, silencers

Maurer NEJM 2018

Goals of care in HFpEF

- Control hypertension

- Avoid/prevent atrial fibrillation

- Avoid uncontrolled rate in AF

- Identify cause of anemia and treat

- Manage congestion with loop diuretics

  - Careful to avoid volume overload in patients with CKD

New RCT data to support additional therapies in HFpEF: all are therapies used in HFrEF

Will review after discussing HFrEF therapies

HF with reduced EF

- multiple disease-modifying therapies
- guideline-directed medical therapy (GDMT)
- titrated to target dose or limiting side effect
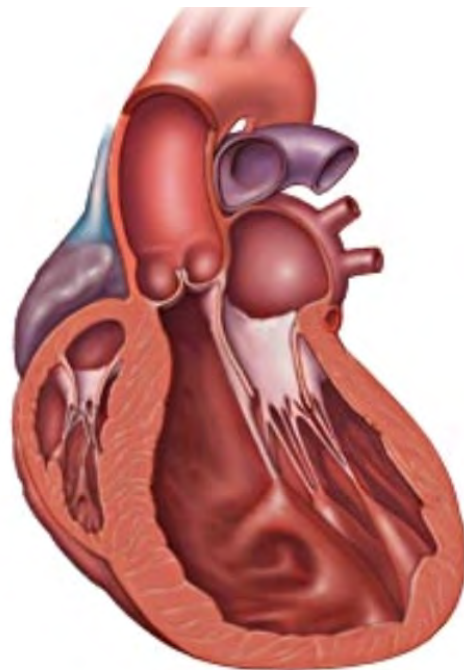
AHA stages

A at risk for HF (e.g. HTN, post-MI)

B asymptomatic (pre-HF)

C symptomatic (symptomatic HF)

D severe symptoms (severe HF)

NYHA symptom classes

- NYHA I: no limitation
- NYHA II: comfortable at rest but ordinary physical activity causes symptoms
- NYHA III: comfortable at rest but less than ordinary physical activity causes symptoms
- NYHA IV: symptoms at rest and with trivial activity: brushing teeth, dressing
- Crude classification with subjectivity and variable reproducibility but used in HF trials

loop diuretics to control congestion

- furosemide 20-80 mg QD up to 160 mg BID

- torsemide up to 80 mg BID (better absorption)

- bumetanide up to 4 mg BID (better absorption)

- 1 bumetanide = 20 torsemide = 40 furosemide

- when on max dose loop, metolazone at 1.25 or 2.5, generally not more than 1-2x/week
  - Frequent K, Cr checks and supplementation

sacubitril/valsartan

- Combines neprilysin inhibitor with ARB
- marketed as Entresto, "sac-val"
  - 24mg sacubitril – 26 mg valsartan "50"
  - 49mg sacubitril – 51 mg valsartan "100"
  - 97mg sacubitril – 103 mg valsartan "200"
- start lowest dose for
  - lisinopril <=10 mg/d, valsartan <= 80 BID
  - eGFR < 30 or moderate hepatic impairment
- otherwise medium dose
- double dose p. 2-4 wks, check K, Cr
- Avoid ARNI in pts with ACEi-angioedema

sGLT2 inhibitors

- Sodium-glucose co-transporter-2

  - reduces proximal tubular resorption resulting in glycosuria

- Empagliflozin surprisingly shown to lower CV events (mostly HF) in diabetics Empa-Reg (NEJM 2015)

- Dapagliflozin neutral on overall MACE in patients with T2D, but lowered HF hospitalization (NEJM 2018)

- Begged question of whether effect only in T2D & only prevention

DAPA-HF

- McMurray NEJM 2019
- 4,744 patients with HFrEF on GDMT w/ or w/o T2D
- 66yo
- 23% female
- 67% NYHA II & 32% NYHA 3
- 42% T2D

DAPA-HF results @ median 18.2 mos

- 26% reduction in worsened HF
  - ARR 4.9%, NNT = 21
- 17% reduction in mortality
  - ARR 2.3%, NNT = 43
- No excess AEs in dapagliflozin
  - Slightly lower rate of renal AE w/dapa
- Major hypoglycemia rare
- Now FDA approved in US

McMurray NEJM 2019

EMPEROR-Reduced

- Empagliflozin vs placebo in treated HFrEF (EF ≤ 40%)

- 25% reduction in CV death/HF hospitalizations at median 16 months f/u

- Blunted rate of decline in eGFR

- Increased rate of uncomplicated urogenital infection

- Now FDA approved

Packer NEJM 2020

Straw Open Heart 2021

At Risk for HF (Stage A)

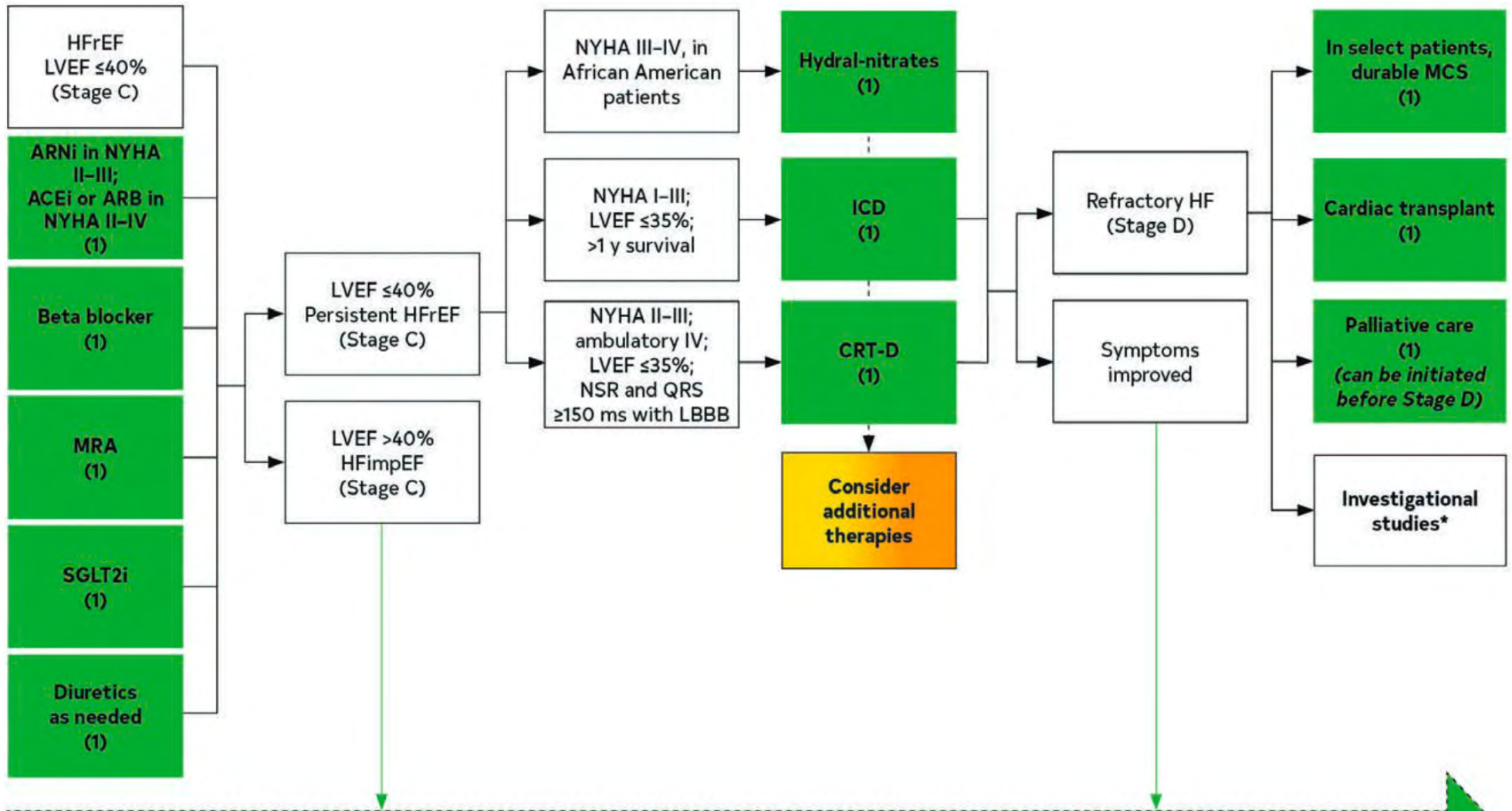| Patients with hypertension | → | **Optimal control of BP** (1) |
Patients with type 2 diabetes and CVD or high risk for CVD	→	**SGLT2i** (1)
Patients with CVD	→	**Optimal management of CVD** (1)
Patients with exposure to cardiotoxic agents	→	**Multidisciplinary evaluation for management** (1)
First-degree relatives of patients with genetic or inherited cardiomyopathies	→	**Genetic screening and counseling** (1)
Patients at risk for HF	→	**Natriuretic peptide biomarker screening** (2a)
Patients at risk for HF	→	**Validated multivariable risk scores** (2a)

Pre-HF (Stage B)

Patients with LVEF ≤40%	→	**ACEi** (1)
Patients with a recent MI and LVEF ≤40%	→	**ARB if ACEi intolerant** (1)
Patients with LVEF ≤40%	→	**Beta blocker** (1)
Patients with LVEF ≤30%; >1 y survival; >40 d post MI	→	**ICD** (1)
Patients with nonischemic cardiomyopathy	→	**Genetic counseling and testing** (2a)

Continue lifestyle modifications and management strategies implemented in Stage A, through Stage B

Step 1	**Step 2**	**Step 3**	**Step 4**	**Step 5**	**Step 6**
Establish diagnosis of HFrEF. Address congestion. Initiate GDMT	Titrate to target dosing as tolerated, labs, health status, and LVEF	Consider these patient scenarios	Implement additional GDMT and device therapy, as indicated	Reassess symptoms, labs, health status, and LVEF	Referral for HF specialty care for additional therapy

Step 1

HFrEF LVEF ≤40% (Stage C)

ARNi in NYHA II–III; ACEi or ARB in NYHA II–IV (1)

Beta blocker (1)

MRA (1)

SGLT2i (1)

Diuretics as needed (1)

Step 2

LVEF ≤40% Persistent HFrEF (Stage C)

LVEF >40% HFimpEF (Stage C)

Step 3

NYHA III–IV, in African American patients

NYHA I–III; LVEF ≤35%; >1 y survival

NYHA II–III; ambulatory IV; LVEF ≤35%; NSR and QRS ≥150 ms with LBBB

Step 4

Hydral-nitrates (1)

ICD (1)

CRT-D (1)

Consider additional therapies

Step 5

Refractory HF (Stage D)

Symptoms improved

Step 6

In select patients, durable MCS (1)

Cardiac transplant (1)

Palliative care (1) *(can be initiated before Stage D)*

Investigational studies*
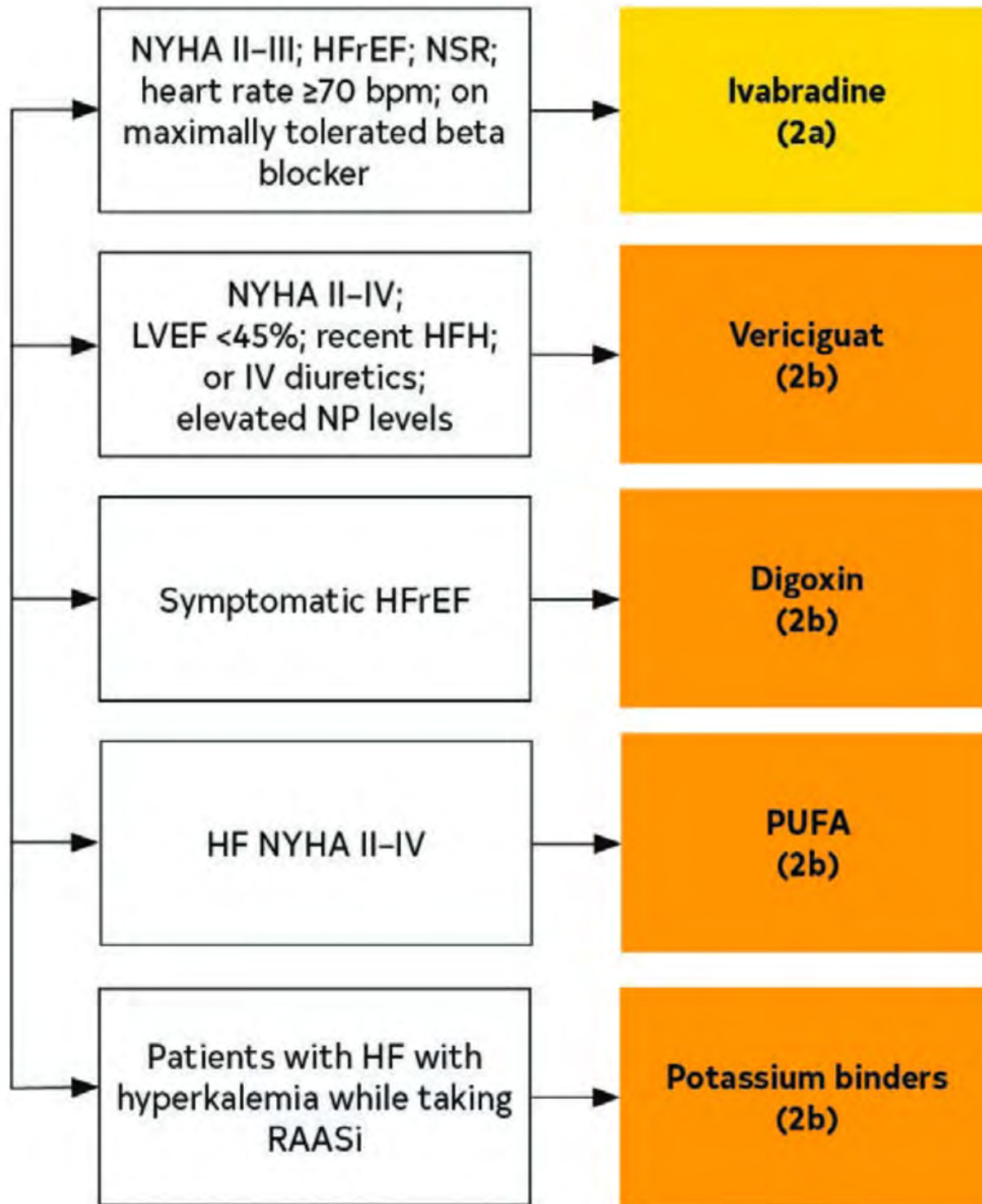
Continue GDMT with serial reassessment and optimize dosing, adherence and patient education, address goals of care

Condition	Treatment
NYHA II–III; HFrEF; NSR; heart rate ≥70 bpm; on maximally tolerated beta blocker	Ivabradine (2a)
NYHA II–IV; LVEF <45%; recent HFH; or IV diuretics; elevated NP levels	Vericiguat (2b)
Symptomatic HFrEF	Digoxin (2b)
HF NYHA II–IV	PUFA (2b)
Patients with HF with hyperkalemia while taking RAASi	Potassium binders (2b)

ivabradine

- $I_{f} =$ funny channel, pacemaker current
- funny channel blocker
- causes sinus rate slowing directly, with modest AV blocking effect
- (as opposed to beta blockers, antagonizing the adrenergic system)
- motivated by epidemiology suggesting increasing mortality with increasing heart rate

SHIFT trial

- chronic HFrEF (EF < 35%)

- sinus rhythm, heart rate > 70 bpm

- on neurohormonal blockade, max tolerated doses

- randomized to ivabradine vs placebo planned 2yr f/u

- primary outcome: CV death + HF admission

Swedberg Lancet 2010

SHIFT results

	Ivabradine group (n=3241)	Placebo group (n=3264)	HR (95% CI)	p value
Primary endpoint				
Cardiovascular death or hospital admission for worsening heart failure	793 (24%)	937 (29%)	0·82 (0·75–0·90)	<0·0001
Mortality endpoints				
All-cause mortality	503 (16%)	552 (17%)	0·90 (0·80–1·02)	0·092
Cardiovascular mortality	449 (14%)	491 (15%)	0·91 (0·80–1·03)	0·128
Death from heart failure	113 (3%)	151 (5%)	0·74 (0·58–0·94)	0·014
Other endpoints				
All-cause hospital admission	1231 (38%)	1356 (42%)	0·89 (0·82–0·96)	0·003
Hospital admission for worsening heart failure	514 (16%)	672 (21%)	0·74 (0·66–0·83)	<0·0001
Any cardiovascular hospital admission	977 (30%)	1122 (34%)	0·85 (0·78–0·92)	0·0002
Cardiovascular death, or hospital admission for worsening heart failure, or hospital admission for non-fatal myocardial infarction	825 (25%)	979 (30%)	0·82 (0·74–0·89)	<0·0001

Swedberg Lancet 2010

SHIFT adverse events

	Patients with an adverse event			Patients with an adverse event leading to drug withdrawal		
	Ivabradine group (n=3232)	Placebo group (n=3260)	p value	Ivabradine group (n=3232)	Placebo group (n=3260)	p value
All	2439 (75%)	2423 (74%)	0·303	467 (14%)	416 (13%)	0·051
Heart failure	804 (25%)	937 (29%)	0·0005	70 (2%)	82 (3%)	0·367
Symptomatic bradycardia	150 (5%)	32 (1%)	<0·0001	20 (1%)	5 (<1%)	0·002
Asymptomatic bradycardia	184 (6%)	48 (1%)	<0·0001	28 (1%)	5 (<1%)	<0·0001
Atrial fibrillation	306 (9%)	251 (8%)	0·012	135 (4%)	113 (3%)	0·137
Phosphenes*	89 (3%)	17 (1%)	<0·0001	7 (<1%)	3 (<1%)	0·224
Blurred vision	17 (1%)	7 (<1%)	0·042	1 (<1%)	1 (<1%)	1·000

Swedberg Lancet 2010

Vericiguat in HFrEF

- Victoria trial, Armstrong NEJM 2020
- Addition of soluble guanylate cyclase activator to GDMT
- CV death/HF hosp lower at 10.8 mos
    - 10% reduction, ARR 3%, NNT = 33
- More hypotension, slightly more syncope
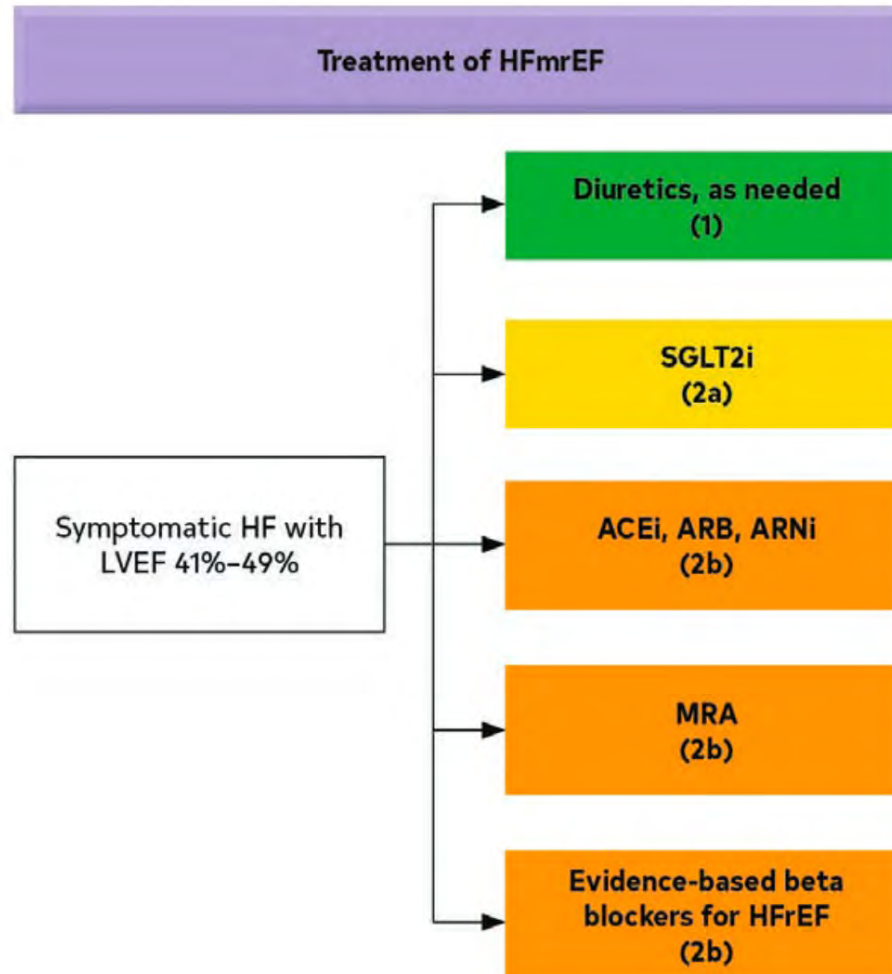- FDA approved Jan 2021

Table 15. Benefits of Evidence-Based Therapies for Patients With HFrEF[3–6,8,10–14,23,31–42]

Evidence-Based Therapy	Relative Risk Reduction in All-Cause Mortality in Pivotal RCTs, %	NNT to Prevent All-Cause Mortality Over Time*	NNT for All-Cause Mortality (Standardized to 12 mo)	NNT for All- Cause Mortality (Standardized to 36 mo)
ACEi or ARB	17	22 over 42 mo	77	26
ARNi†	16	36 over 27 mo	80	27
Beta blocker	34	28 over 12 mo	28	9
Mineralocorticoid receptor antagonist	30	9 over 24 mo	18	6
SGLT2i	17	43 over 18 mo	63	22
Hydralazine or nitrate‡	43	25 over 10 mo	21	7
CRT	36	12 over 24 mo	24	8
ICD	23	14 over 60 mo	70	23

7.3.7. Drugs of Unproven Value or That May Worsen HF

COR	LOE	Recommendations
3: No Benefit	**A**	1. In patients with HFrEF, dihydropyridine calcium channel-blocking drugs are not recommended treatment for HF.[1,2]
3: No Benefit	**B-R**	2. In patients with HFrEF, vitamins, nutritional supplements, and hormonal therapy are not recommended other than to correct specific deficiencies.[3-9]
3: Harm	**A**	3. In patients with HFrEF, nondihydropyridine calcium channel-blocking drugs are not recommended.[10-13]
3: Harm	**A**	4. In patients with HFrEF, class IC antiarrhythmic medications and dronedarone may increase the risk of mortality.[14-16]
3: Harm	**A**	5. In patients with HFrEF, thiazolidinediones increase the risk of worsening HF symptoms and hospitalizations.[17-21]
3: Harm	**B-R**	6. In patients with type 2 diabetes and high cardiovascular risk, the dipeptidyl peptidase-4 (DPP-4) inhibitors saxagliptin and alogliptin increase the risk of HF hospitalization and should be avoided in patients with HF.[22-24]
3: Harm	**B-NR**	7. In patients with HFrEF, NSAIDs worsen HF symptoms and should be avoided or withdrawn whenever possible.[25-28]

Recommendations for Drugs of Unproven Value or Drugs That May Worsen HF
Referenced studies that support the recommendations are summarized in the Online Data Supplements.

HFmrEF

Treatment of HFmrEF

Symptomatic HF with LVEF 41%–49%

- Diuretics, as needed (1)
- SGLT2i (2a)
- ACEi, ARB, ARNi (2b)
- MRA (2b)
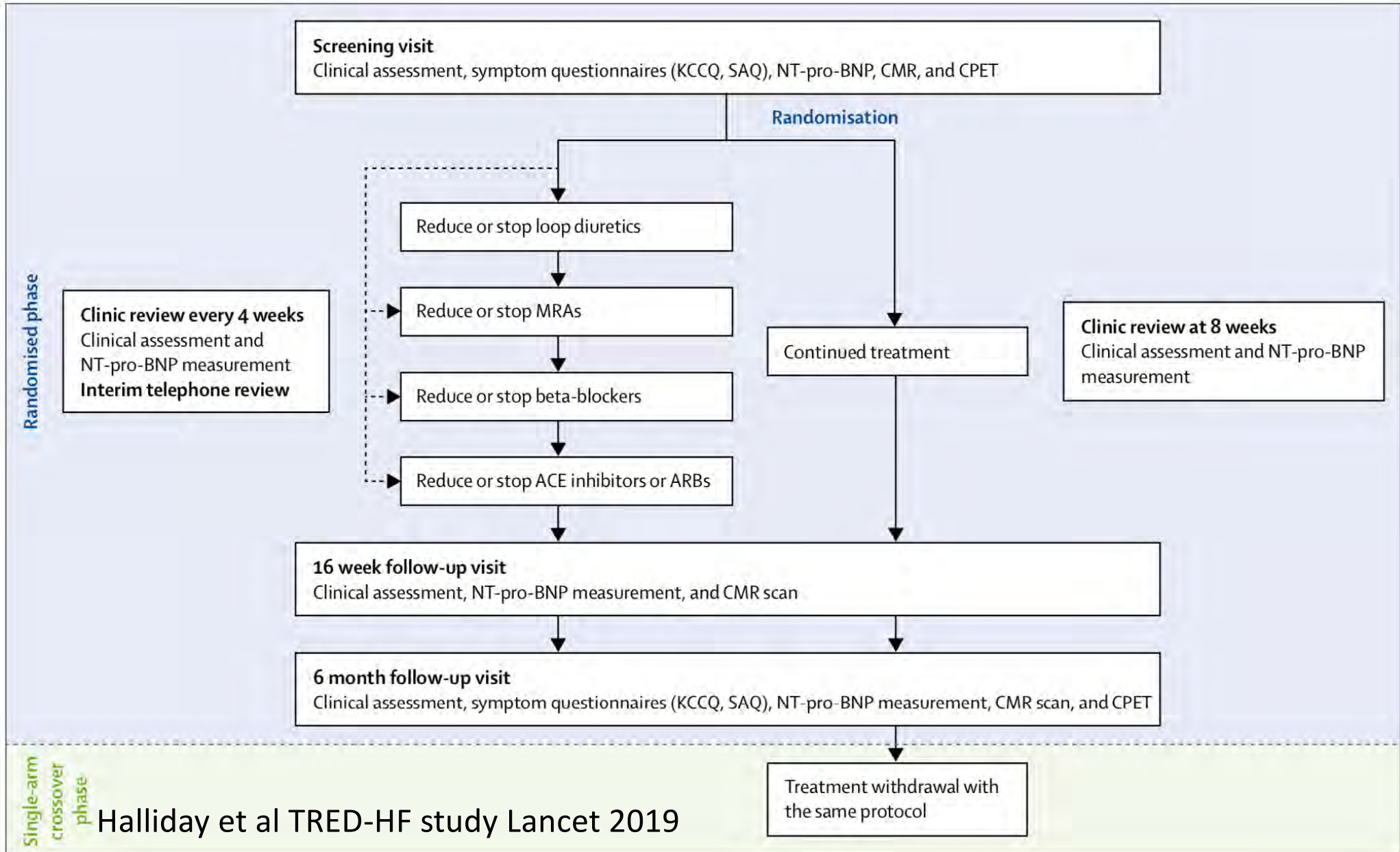- Evidence-based beta blockers for HFrEF (2b)

HF with recovered EF

- Open-label, randomized pilot
- 51 patients w/DCM with EF < 40% in whom
  - EF rose to >50% with ACEi/ARB/BB/MRA
  - NTproBNP < 250 ng/L
- Randomized to
  - 6 month structured withdrawal of HF meds
  - 6 months continued HF meds, followed by structured withdrawal

Halliday et al TRED-HF study Lancet 2019

HFrecEF: withdrawal protocol

Screening visit
Clinical assessment, symptom questionnaires (KCCQ, SAQ), NT-pro-BNP, CMR, and CPET

Randomisation

Randomised phase

Clinic review every 4 weeks
Clinical assessment and
NT-pro-BNP measurement
Interim telephone review

Reduce or stop loop diuretics

Reduce or stop MRAs

Reduce or stop beta-blockers

Reduce or stop ACE inhibitors or ARBs

Continued treatment

Clinic review at 8 weeks
Clinical assessment and NT-pro-BNP measurement

16 week follow-up visit
Clinical assessment, NT-pro-BNP measurement, and CMR scan

6 month follow-up visit
Clinical assessment, symptom questionnaires (KCCQ, SAQ), NT-pro-BNP measurement, CMR scan, and CPET

Single-arm crossover phase

Treatment withdrawal with the same protocol

Halliday et al TRED-HF study Lancet 2019

HFrecEF: DCM recurrence at 6 mos

- Composite primary outcome at 6 mos:
    - EF falls >10% pts to < 50%
    - LVEDV incr >10% to > ULN
    - NTproBNP doubling to > 400 ng/L
    - Symptomatic heart failure

Halliday et al TRED-HF study Lancet 2019

HFrecEF: baseline

- Median 4.9 yrs since DCM diagnosis

- 2.0 yrs since EF > 50%

- Most ACEi/ARB/BB

- 47% MRA

- 12% loop diuretic

- Non-ischemic: 35 idiopathic, 7 familial, 9 pregnancy/alcohol/doxorubicin/thyroid

Halliday et al TRED-HF study Lancet 2019

HFrecEF: results

- 11/25 (44%) in WD grp relapsed w/in 6 mos after withdrawal, 0/26 in continuation group

- 25/26 in continuation group crossed over to WD after 6 mos (1 had AF, 0 had HF)

- 9/25 (36%) relapsed after cross-over to WD

- Overall 20/50 (40%) of those withdrawn from GDMT relapsed within 6 months

- 13 relapses w/in 4 mos of start, all w/in 2 mos of last medication discontinuation

Halliday et al TRED-HF study Lancet 2019

HFrecEF: DON'T STOP THE MEDS

- Wean loop diuretics guided by weight, LE edema, dyspnea, potassium, possibly NTproBNP

- Continue maximum tolerated dose of BB and ACEi/ARB/ARNI

- Probably continue MRA indefinitely but monitor potassium, creatinine

- No data re SGLT2i

HFpEF
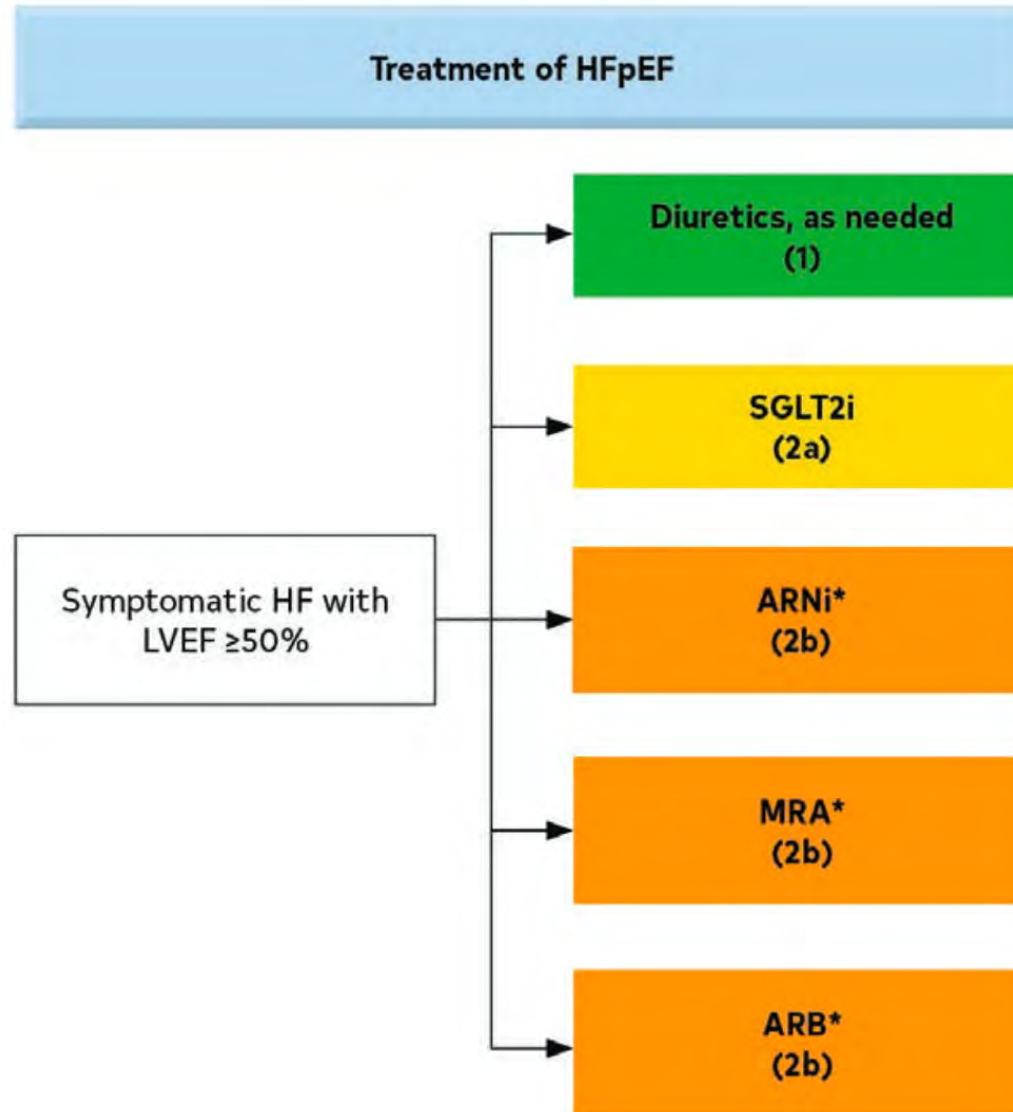
- Updated guidelines for treatment of HFrEF and HFpEF
- **Myocarditis after Covid**
- Myocarditis after Covid vaccination

Myocarditis & Acute Covid

- Rates of troponin elevation >99%ile in 5-25% of hospitalized patients with Covid

- Prognostically, increased risk of arrhythmia, mechanical ventilation, mortality

- Unclear mechanisms

- ACS, PE, supply-demand mismatch can underlie

- Some patients with isolated, significant troponin elevations appear to have myocarditis

- Mechanisms unclear

What do we know from pathology studies?

- Halushka & Vander Heide, Cardiovasc Pathology 2020

- Post-mortem autopsy

- Literature review

- 22 reports, 2-80 patients (med 10.5)

- 277 patients total (7 papers total 165)

Demographic and histopathologic findings

Study characteristics	Median/Count	Percent	Available data points
Autopsied hearts	277		
Reports	22		
Consecutive autopsies	165	73.0%	226
Demographics			
Male	172	62.1%	277
Age	75 (range 22-97)		254
BMI	26.9 (range 14.9-59)		139
Disease length[1]	10 days (range 1-51)		167
Heart disease	153	55.2%	277
Hypertension	152	54.9%	277
Diabetes[2]	89	32.1%	277
Obesity	44	15.9%	277
COPD/emphysema	70	25.3%	277
Renal disease	51	18.4%	277
Malignancy	44	15.9%	277
Sleep apnea	12	4.3%	277
Dementia	34	12.3%	277
Cardiovascular findings			
Heart weight	483 gm (range 250-1070)		73
Cardiac amyloidosis	11	4.0%	277
Myocarditis	20	7.2%	277
Pericarditis	19	6.9%	277
Nonmyocarditis inflammation	35	12.6%	277
Single cell ischemia	38	13.7%	277
Small vessel thrombi	30	10.8%	277
Macrothrombi	53	19.1%	277
Intravascular megakaryocytes	9	3.2%	277
Acute myocardial infarction	13	4.7%	277

Halushka, Vander Heide CV Path 2020
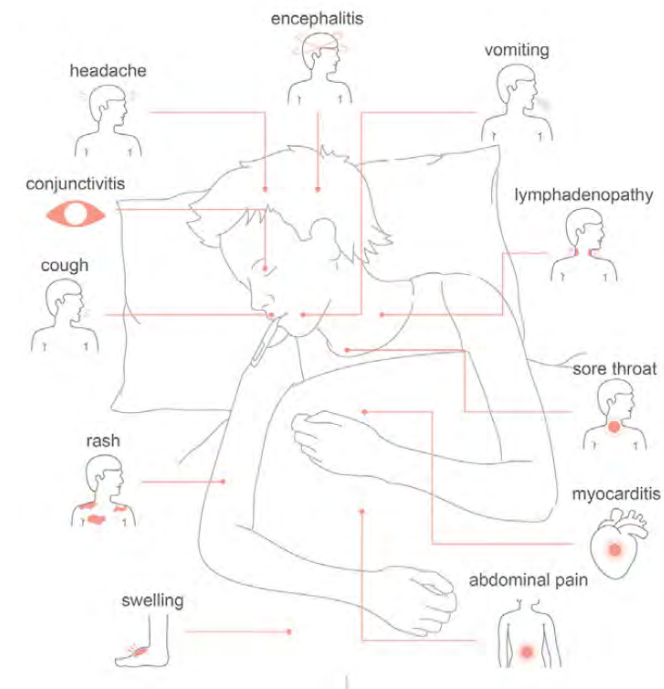
Halushka, Vander Heide CV Path 2020
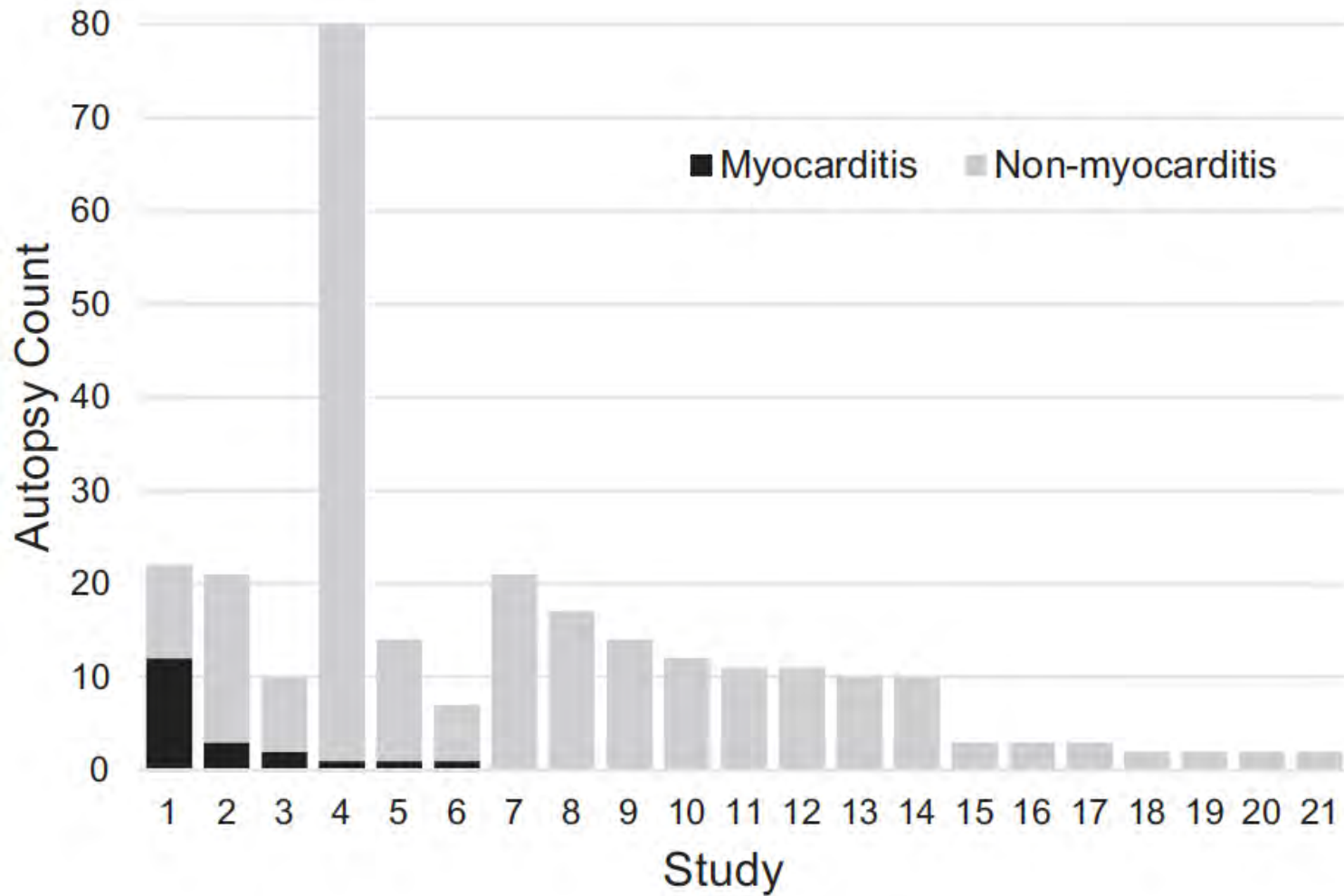
Detailed histopathology from hearts in Covid-19 is limited

- CD68+ infiltrates > CD4/CD8 in autopsies (mostly pulmonary deaths)

- SARS-CoV-2 by ISH in macrophages, some endothelial cells, small #s of myocytes

- Of 41 MGH deceased pts, 4 met criteria for myocarditis (Bearse et al)
  - 3 lymphocytic
  - 1 hypersensitivity

Fox CV Path '21; Bearse Modern Path '21

MIS-C / MIS-A

- Multisystem illness syndrome in children
- High fever, high CRP/cytokines, vasodilatory > cardiogenic shock
- Cardiac (80%), GI (90%) involvement typical
- Often occurs 2-6 weeks after presumed exposure
- Commonly Ab+, NP Ag-, NP PCR+/-
- 50+% require ICU
- Treatment IVIG, steroids + others
- Occurs in adults, rarely
  - Morris et al, MMWR '20, MIS-A case series
  - Belay et al, CID '21
- Treatment guidance MIS-C Henderson Arthritis & Rheumatology '21
- Pathophysiology unclear, hypothesized due to superantigen regions of spike and antigenemia due to altered gut permeability

MISC-C

encephalitis
headache
vomiting
conjunctivitis
lymphadenopathy
cough
sore throat
rash
myocarditis
swelling
abdominal pain

Levy JAMA '21, Patel JAMA '21, Feldstein JAMA '21, Holm Acta Paed '21, Yonker JCI '21

Vaccine protection against MIS-C

- 33 adolescents (12-18yo) detected through 41 PICUs or national reporting in France

- 91% (95%CI: 79-96%) VE against MIS-C at least 1 dose (mostly Pfizer)

- Among 31 adolescents
  - 0 fully vaccinated
  - 7 s/p 1st dose only, median 25d post-vax (implying infection c. vax date)
  - 26 unvaccinated

Olson MMWR '21

# Vaccine protection against MIS-C

- 102 hospitalized cases 12-18yo at 24 US pediatric hospitals 7/1-12/9/2021 (Delta epoch)

- Matched on site, age grp, hosp'n date to 181 controls (either Covid-like sxs but PCR neg or other hospitalized patient)

- 28d post-Pfizer #2 or unvaccinated (excluded only 1 dose)

- 5/102 (4.9%) cases vaxed vs 65/181 (36%) controls

- VE 91% (95%CI: 78-97%)

Zambrano MMWR '21

- Updated guidelines for treatment of HFrEF and HFpEF

- Myocarditis after Covid

- **Myocarditis after Covid vaccination**

CDC case definitions

CDC Working Case Definitions

Acute Myocarditis

Probable Case

- Presence of ≥ 1 new or worsening of the following clinical symptoms
  - chest pain/ pressure/ discomfort
  - dyspnea/shortness of breath
  - palpitations
  - syncope
- AND ≥ 1 new finding of
  - elevated troponin above upper limit of normal
  - abnormal ECG or rhythm monitoring findings consistent with myocarditis*
  - abnormal cardiac function or wall motion abnormalities on echocardiogram
  - cardiac MRI findings consistent with myocarditis [†]
- AND no other identifiable cause of the symptoms and findings

Confirmed Case

- Presence of ≥ 1 new or worsening of the following clinical symptoms
  - chest pain/ pressure/ discomfort
  - dyspnea/shortness of breath
  - palpitations
  - syncope
- AND
  - histopathologic confirmation of myocarditis [‡]
  - OR
  - elevated troponin above upper limit of normal AND cardiac MRI findings consistent with myocarditis [†]
- AND no other identifiable cause of the symptoms and findings

Acute Pericarditis

Probable Case

- Presence of ≥ 2 new or worsening of the following clinical symptoms
  - acute chest pain (typically described as pain made worse by lying down, deep inspiration, cough, and relieved by sitting up or leaning forward, although other types of chest pain may occur) [§]
  - pericarditis rub on exam
  - new ST-elevation or PR-depression on ECG
  - new or worsening pericardial effusion on echocardiogram or MRI
- Autopsy cases may be classified as pericarditis on basis of meeting histopathologic criteria of the pericardium

Bozkurt Circ '21 from CDC ACIP mtg 6.23.21

Paradigm Shift in Myocarditis Diagnosis

Law Circ 2022
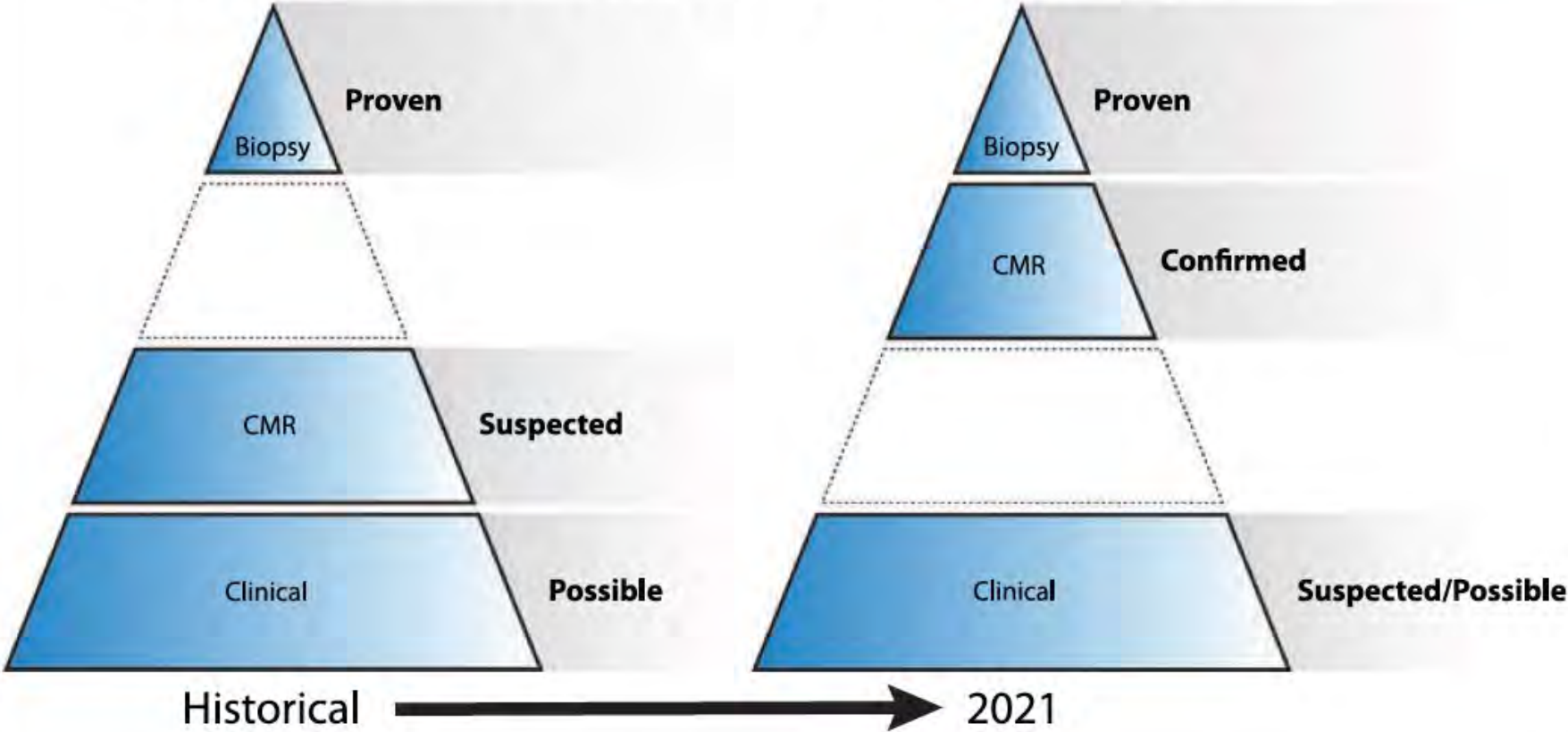
2022 VAERS update

- 1626 myocarditis all ages (only 8 >40yo)
- Med age 21, 82% male

Table 1. Characteristics of Reports to VAERS After mRNA-Based COVID-19 Vaccination That Met the CDC's Case Definition for Myocarditis Between December 14, 2020, and August 31, 2021

	Vaccination with BNT162b2			Vaccination with mRNA-1273			Overall
	First dose	Second dose	Dose unknown	First dose	Second dose	Dose unknown	
No. of myocarditis reports to VAERS	147	928	61	126	337	27	1626
No. of vaccination doses administered	114 246 837	95 532 396		78 158 611	66 163 001		354 100 845
Age, median (IQR), y	19 (16-37)	18 (16-25)	22 (16-35)	31 (23-47)	26 (21-36)	29 (22-39)	21 (16-31)
Time to symptom onset, median (IQR), d	3 (1-8)	2 (2-3)	3 (2-4)	3 (2-9)	2 (1-3)	2 (1-5)	2 (1-3)
Reported sex, No. (%)	(n = 147)	(n = 928)	(n = 61)	(n = 125)	(n = 337)	(n = 27)	(n = 1625)
Male	111 (76)	795 (86)	53 (87)	89 (71)	265 (79)	21 (78)	1334 (82)
Female	36 (24)	133 (14)	8 (13)	36 (29)	72 (21)	6 (22)	291 (18)
Reported race and ethnicity, No. (%)[a]	(n = 123)	(n = 772)	(n = 40)	(n = 100)	(n = 277)	(n = 18)	(n = 1330)
American Indian or Alaska Native	1 (1)	4 (1)	0	1 (1)	0	0	6 (<1)
Asian	10 (8)	58 (8)	1 (3)	5 (5)	10 (4)	0	84 (6)
Black	11 (9)	31 (4)	3 (8)	5 (5)	14 (5)	4 (22)	68 (5)
Hispanic	28 (23)	127 (16)	9 (23)	23 (23)	36 (13)	5 (28)	228 (17)
Multiple races	1 (1)	10 (1)	0	0	5 (2)	1 (6)	17 (1)
Native Hawaiian or Pacific Islander	0	5 (1)	1 (3)	1 (1)	0	0	7 (1)
White	72 (59)	531 (69)	26 (65)	65 (65)	212 (77)	8 (44)	914 (69)
Other[b]	0	6 (1)	0	0	0	0	6 (<1)

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7-day counts per million

Table 2. Reports to VAERS After mRNA-Based COVID-19 Vaccination That Met the CDC's Case Definition for Myocarditis Within a 7-Day Risk Interval per Million Doses of Vaccine Administered

| | Reported cases of myocarditis within a 7-d risk interval per million doses of vaccine administered (95% CI)[a] | | | | Expected cases of myocarditis in a 7-d risk interval per million doses (95% CI)[c] |
| | Vaccination with BNT162b2 | | Vaccination with mRNA-1273[b] | | |
	First dose	Second dose	First dose	Second dose	
Males					
Age group, y					
12-15	7.06 (4.88-10.23)	70.73 (61.68-81.11)			0.53 (0.40-0.70)
16-17	7.26 (4.45-11.86)	105.86 (91.65-122.27)			1.34 (1.05-1.72)
18-24	3.82 (2.40-6.06)	52.43 (45.56-60.33)	10.73 (7.50-15.34)	56.31 (47.08-67.34)	1.76 (1.58,1.98)
25-29	1.74 (0.78-3.87)	17.28 (13.02-22.93)	4.88 (2.70-8.80)	24.18 (17.93-32.61)	1.45 (1.21-1.74)
30-39	0.54 (0.20-1.44)	7.10 (5.26-9.57)	3.00 (1.81-4.97)	7.93 (5.61-11.21)	0.63 (0.54.0.73)
40-49	0.55 (0.21-1.48)	3.50 (2.28-5.36)	0.59 (0.19-1.82)	4.27 (2.69-6.78)	0.78 (0.67-0.90)
50-64	0.42 (0.17-1.01)	0.68 (0.33-1.43)	0.62 (0.28-1.39)	0.85 (0.41-1.79)	0.77 (0.68-0.86)
≥65	0.19 (0.05-0.76)	0.32 (0.10-1.00)	0.18 (0.05-0.72)	0.51 (0.21-1.23)	
Females					
Age group, y					
12-15	0.49 (0.12-1.98)	6.35 (4.05-9.96)			0.17 (0.11-0.29)
16-17	0.84 (0.21-3.37)	10.98 (7.16-16.84)			0.42 (0.27-0.66)
18-24	0.18 (0.03-1.31)	4.12 (2.60-6.54)	0.96 (0.31-2.96)	6.87 (4.27-11.05)	0.38 (0.30-0.49)
25-29	0.26 (0.04-1.84)	2.23 (1.07-4.69)	0.41 (0.06-2.94)	8.22 (5.03-13.41)	0.48 (0.35-0.65)
30-39	0.72 (0.32-1.60)	1.02 (0.49-2.14)	0.74 (0.28-1.98)	0.68 (0.22-2.10)	0.47 (0.39-0.57)
40-49	0.24 (0.06-0.97)	1.73 (0.98-3.05)	0.18 (0.02-1.25)	1.89 (0.98-3.63)	0.89 (0.77-1.04)
50-64	0.37 (0.15-0.88)	0.51 (0.23-1.14)	0.65 (0.31-1.36)	0.43 (0.16-1.15)	1.00 (0.89-1.13)
≥65	0.08 (0.01-0.54)	0.35 (0.13-0.92)		0.26 (0.08-0.81)	

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Symptoms & outcomes

Table 3. Symptoms, Treatment, and Outcomes in 826 Patients Younger Than 30 Years of Age With Myocarditis

	Cases of myocarditis, No./total (%)
Presenting symptoms	
Chest pain, pressure, or discomfort	727/817 (89.0)
Dyspnea or shortness of breath	242/817 (29.6)
Palpitations	65/817 (8.0)
Abnormal findings	
Elevated troponin level[a]	792/809 (97.9)
Electrocardiogram	569/794 (71.7)
Echocardiogram	123/721 (17.1)
Decreased LVEF (<50%) on echocardiogram	84/721 (11.7)
Cardiac magnetic resonance imaging[b]	223/312 (71.5)
Hospitalized	784/813 (96.4)
Treatment	
Nonsteroidal anti-inflammatory drugs	589/676 (87.1)
Glucocorticoids	81/676 (12.0)
Anticoagulant therapy	54/676 (8.0)
Antiarrhythmic therapy	18/676 (2.7)
Low- or high-flow nasal cannula oxygen support	12/676 (1.8)
Diuretics	11/676 (1.6)
Intensive therapy	
Intravenous immunoglobulin	78/676 (11.5)
Vasoactive medications	12/676 (1.8)
Intubation or mechanical ventilation	2/676 (0.3)
Heart transplant	0
Extracorporeal membrane oxygenation or ventricular assist device	0
Outcome among those who were hospitalized	
Discharged from the hospital	747/762 (98.0)
Still hospitalized at time of review	15/762 (2.0)
Died	0
Resolution of presenting symptoms by hospital discharge	577/661 (87.3)

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North American VAM series (n = 139)

- 26 pediatric AMCs in US & Canada
- Confirmed or probable myocarditis in 12-21yo w/in 30d of vaccine
- Retrospective, no standardized diagnostics/care
- 139 individuals, 140 episodes

Truong Circulation '21

Demographics

Table 2. Demographic Variables and History of COVID-19 Infection

	N=139
Age (years)	15.8 (range 12.1-20.3; IQR 14.5-17.0)
12 to <16 years old	73 (52.5%)
16 to ≤20 years old	66 (47.5%)
Sex (male)	126 (90.6%)
Race	
White	92 (66.2%)
Black	6 (4.3%)
Asian	9 (6.5%)
Native American/Alaskan native	2 (1.4%)
Other	13 (9.4%)
Unknown/Refused to answer	17 (12.2%)
Ethnicity	
Hispanic	29 (20.9%)
Unknown/Refused to answer	14 (10.1%)
Known prior COVID-19 infection	
Yes (by history)	10 (7.2%)
Months from known COVID-19 infection	5 (range <1-10)
Yes (by COVID-19 nucleocapsid antibody) (N=82)	10 (7.2%)
No history and/or negative nucleocapsid antibody	94 (67.6%)
Unknown history and no nucleocapsid antibody tested	30 (21.6%)

Truong Circulation '21

Table 3. COVID-19 Vaccine and Clinical Data

|	N=139
Brand of COVID-19 vaccine	
Pfizer-BioNTech	131 (94.2%)
Moderna	5 (3.6%)
Johnson and Johnson	1 (0.7%)
Unknown	2 (1.4%)
Dose of Vaccine with Symptoms (N=140)	
1st dose	12 (8.6%)
2nd dose	128 (91.4%)
Days from vaccine administration to symptom onset	2 (range 0-22; IQR 1-3)
Symptoms	
Chest pain	138 (99.3%)
Fever (temperature ≥100.4F or tactile)	43 (30.9%)
Shortness of breath	38 (27.3%)
Headache	22 (15.8%)
Myalgias	19 (13.7%)
Vomiting	17 (12.2%)
Fatigue	11 (7.9%)
Palpitations	7 (5.0%)
Rash	5 (3.6%)
Diarrhea	3 (2.2%)
Conjunctivitis	1 (0.7%)
Intensive care unit stay	26 (18.7%)
Inotropes used	2 (1.4%)
Hospital length of stay (days)	2 (range 0-10; IQR 2-3)
Mortality	0

Truong Circulation '21

Laboratory values

Table 4. Laboratory, ECG, and Imaging Data	
Peak lab values	
Troponin (N=139)	
Troponin I (ng/mL) (N=111) (Reference normal <0.04 ng/mL)	8.12 (IQR 3.50-15.90)
Troponin T (ng/mL) (N=28) (Reference normal ≤0.014 ng/mL)	0.61 (IQR 0.25-1.30)
BNP (pg/mL) (N=101) (Reference normal <100 pg/mL)	55.0 (IQR 18.9-147.0)
NT-Pro-BNP (pg/mL) (N=8) (Reference normal <125 pg/mL)	159 (IQR 91.5-810.3)
C-Reactive protein (mg/dL) (N=116) (Reference normal <0.3 mg/dL)	3.3 (IQR 1.1-6.2)

Truong Circulation '21

ECG/imaging

Testing/Imaging	
ECG (N=138)	
Abnormal	97 (69.8%)
Normal	41 (29.5%)
Abnormal ECG findings or arrhythmias (N=97)	
ST or T wave changes/elevation	95 (97.9%)
Non-sustained VT (ECG, telemetry, or ambulatory monitoring)	7 (5.0%)
Low voltage QRS	5 (3.6%)
PVCs (ECG, telemetry, or ambulatory monitoring)	3 (2.2%)
Atrial tachycardia (ECG, telemetry, or ambulatory monitoring)	1 (0.7%)
Premature atrial contractions	1 (0.7%)
First-degree atrioventricular block	1 (0.7%)
Complete heart block	1 (0.7%)
Echocardiogram (N=139)	
Left ventricular ejection fraction	
Normal/≥55%	113 (81.3%)
Mild dysfunction (45-54%)	22 (15.8%)
Moderate dysfunction (35-44%)	2 (1.4%)
Severe dysfunction (<35%)	2 (1.4%)
Pericardial effusion ≥small in size	1 (0.7%)
Cardiac MRI (N=97)	
Days from symptom onset to cardiac MRI	5 (range 1-88; IQR 3-17)
Left ventricular ejection fraction	60.0% (55.0-62.7%)
Right ventricular ejection fraction	57.3% (52.9-62.0%)
Abnormal findings	75 (77.3%)
Late gadolinium enhancement	74 (98.7%)
Myocardial edema	54 (72.0%)
Lake Louise criteria (Yes)	49 (50.5%)
CDC case definition of myocarditis (N=140)	
Confirmed	49 (35.0%)
Probable	91 (65.0%)

Truong Circulation '21

Therapies administered per local preference

Truong Circulation '21
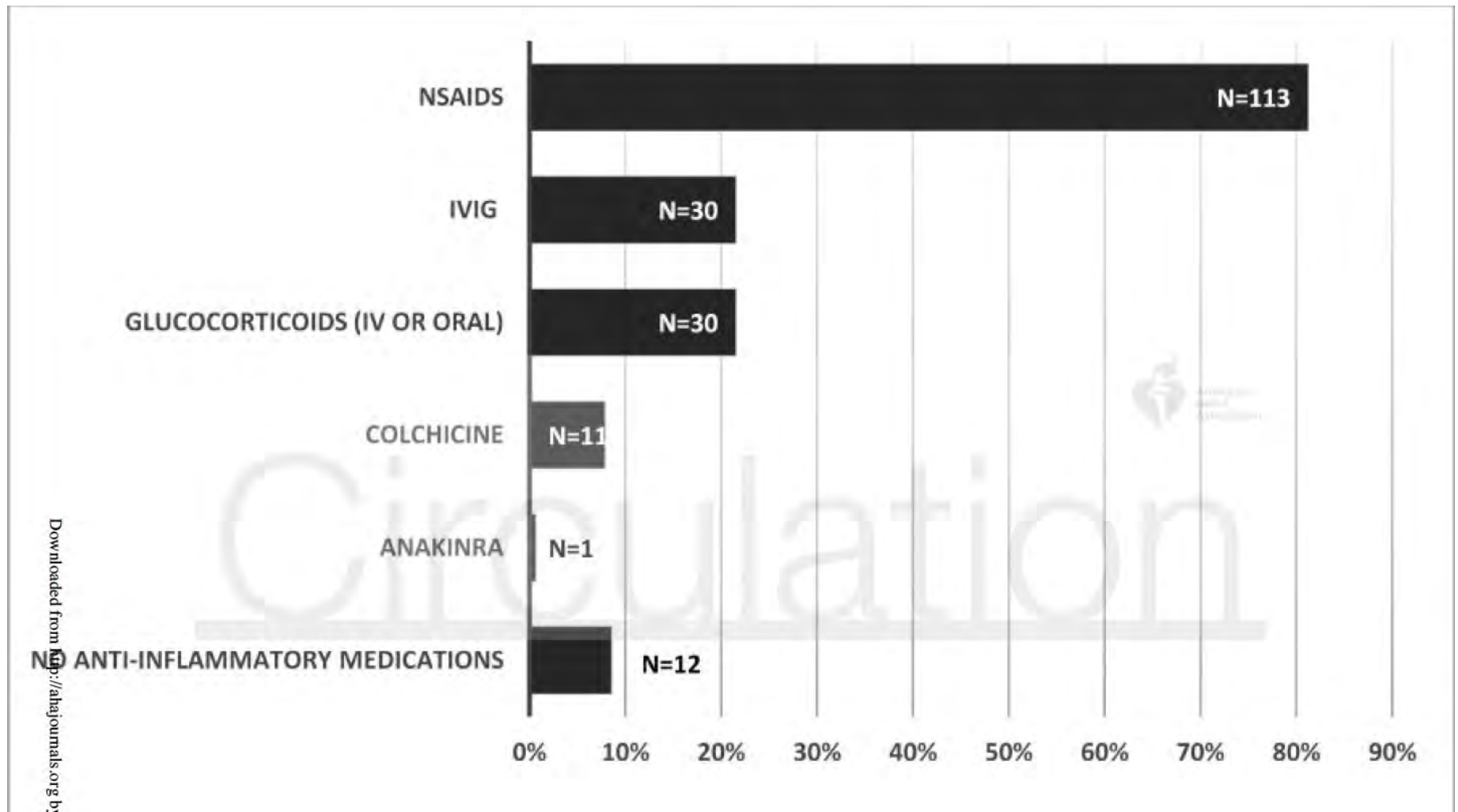
Patone et al, England

- 21m AstraZeneca, 17m Pfizer, 1m Moderna, 3m SARS-CoV-2 PCR positive

- England 12/1/20-8/24/21

- Immunization, hospitalization and PCR test databases combined

- Self-controlled case series method uses case-only analysis of pre-/post-exposure periods (reducing confounding)

Patone Nat Med '21

Myocarditis risk in England

Incidence rate ratio	1-7d post	1-28d post
Pfizer 1	1.5	1.3
Moderna 1	8.4	3.0
Pfizer 2	1.8	1.3
Moderna 2	23	9.8
PCR SARS-CoV-2 +	21	9.8

Patone Nat Med '21

IRR for myocarditis

Patone Nat Med '21
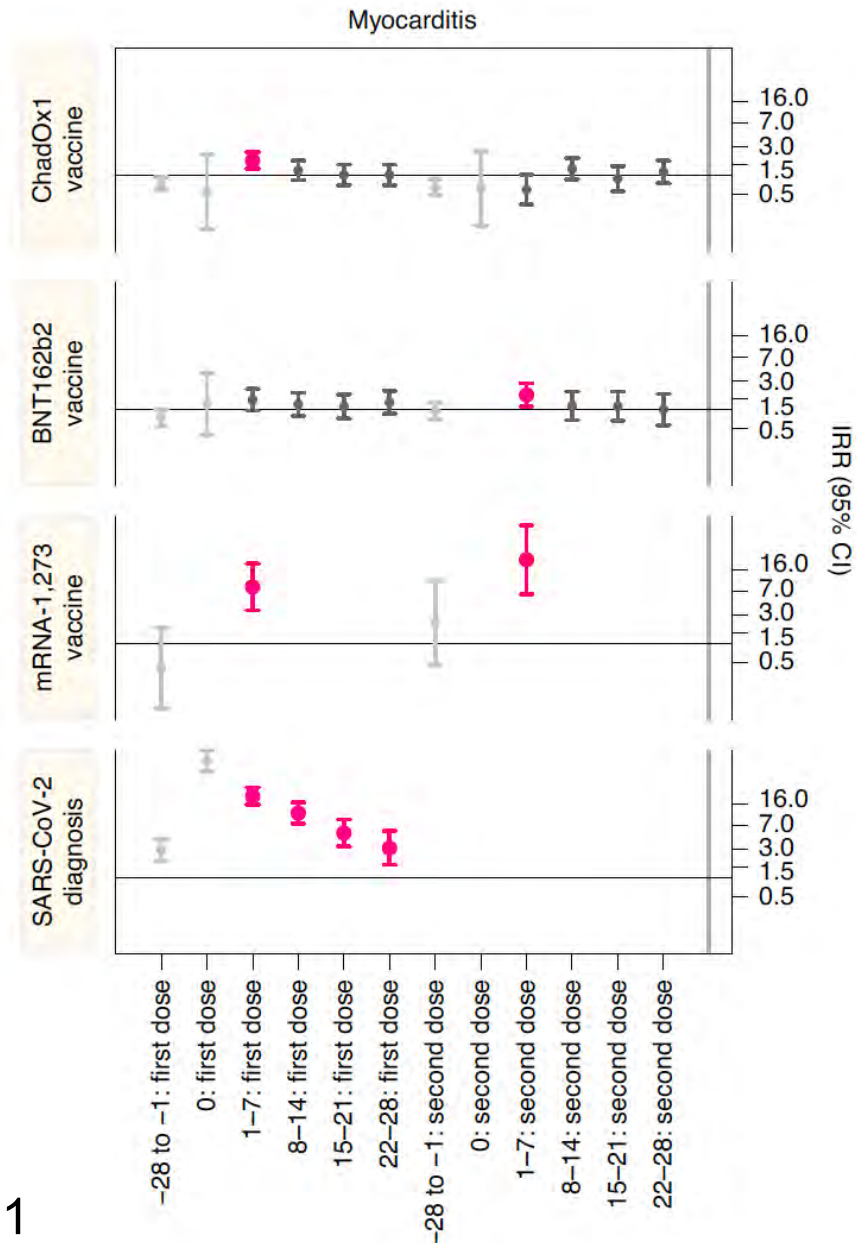
Excess events 1-28d per million

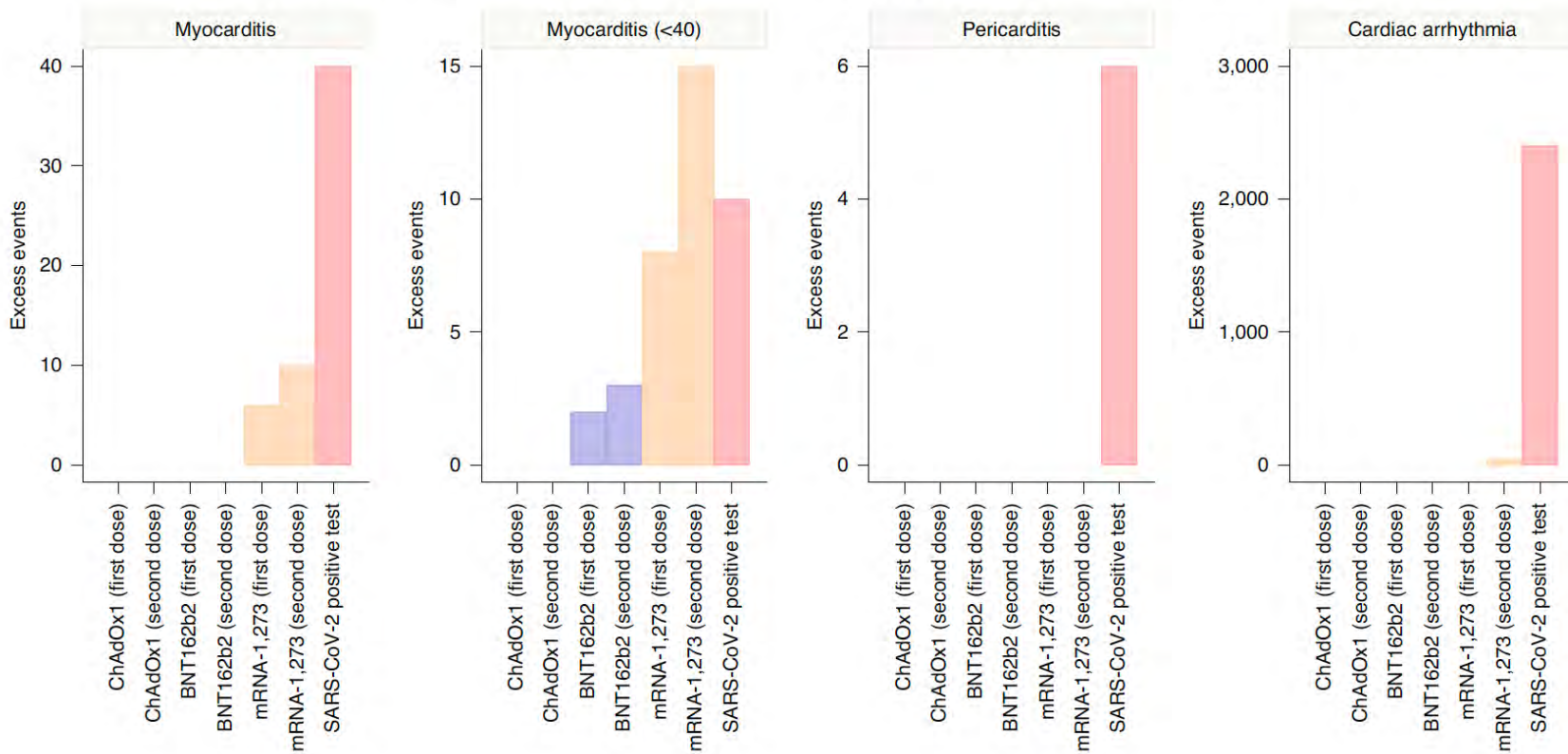Number of excess events in the 1–28 days postvaccination/SARS-CoV-2 positive test per 1 million vaccinated/infected

Fig. 2 | Number of excess events due to exposure per 1 million exposed, as reported in Supplementary Table 10. When IRR did not show a significant increase of incidence over the 1–28 days postvaccination or a SARS-CoV-2 positive test, absolute measures are not given.

Patone Nat Med '21

If one ignores the benefits in preventing Covid-19 illness generally, incl Post-Acute Sequelae of Covid (PASC) or reducing transmission to the vulnerable, vaccination w/mRNA x2 doses reduces myocarditis risk, at times of high SARS-CoV-2 community transmission

Thanks