Which elderly patient can be considered for inotropic therapy.

Dr. Phyllis Billia MD PhD FRCPC

University Health Network

Medical Director - Mechanical Circulatory Support Program

HF update May 7-8th, 2021

Conflict of Interest Disclosures

- **Grants/research support (physician-initiated studies)**:
    - Abbott Laboratories
    - Mallinkrodt

- **None relevant to this presentation**

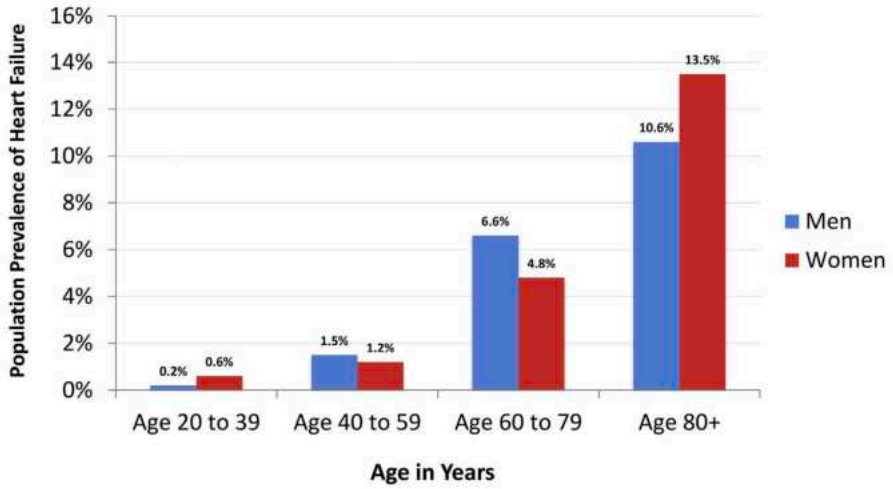
Learning objectives

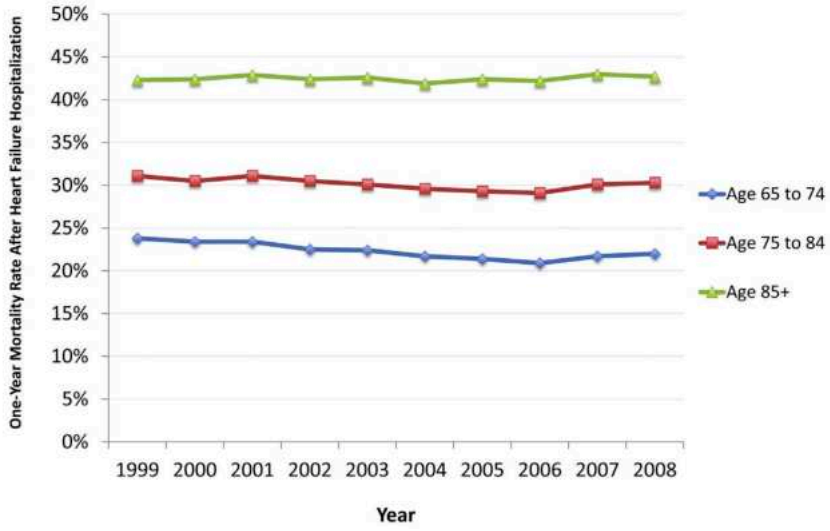
1. Discuss the role of inotropes in advanced heart failure and cardiogenic shock

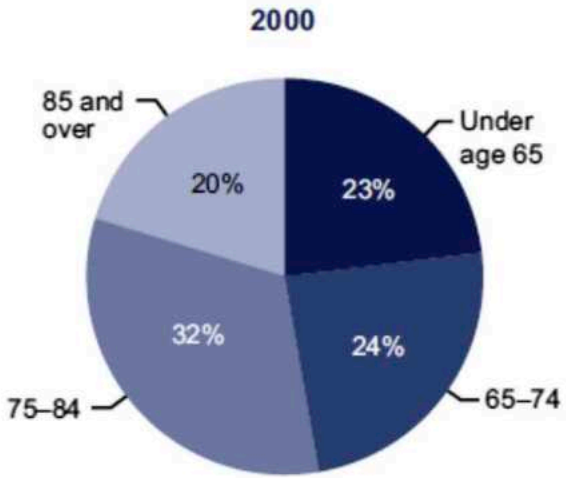
2. Identify outcomes of elderly patients with cardiogenic shock

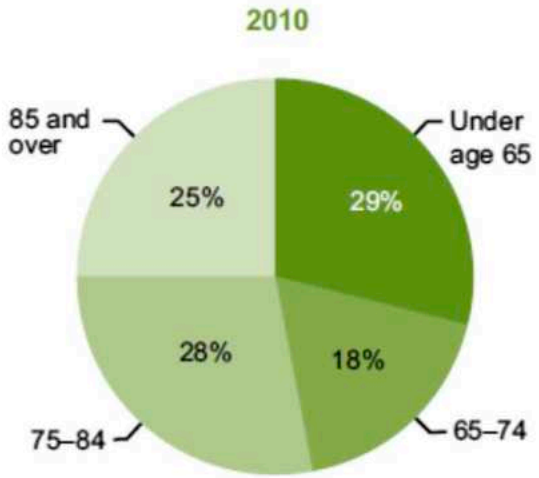
3. Provide a rationale for palliative inotrope therapy

Changing landscape of HF and age









Dharmarajan et al HF Clinics 2017
Dooley et al HF Clinics 2017

Cardiogenic shock

- Acute cardiac hemodynamic instability with ineffective CO with clinical/biochemical manifestations of inadequate tissue perfusion
- Typically – persistent hypotension (unresponsive to fluid resuscitation) + end-organ hypoperfusion requiring drugs or MCS
  - SBP <90 mmHg
  - urine output <30 ml/hr
  - cool extremities
  - CI < 2.2 L/min/m2
  - PCWP >15 mmHg
  - Lactate > 2
  - metabolic acidosis
  - elevated Creatinine
- Mortality persistent >50%

Van Diepen et al 2017 Circulation
Shock trial, NEJM 1999
IABP-shock, NEJM 2012
ECHF guidelines EHJ 2016

Not all shock is the same

Table 2. Hemodynamic Profiles of Cardiogenic Shock Subtypes

Hemodynamic Variables	Preshock Normotensive Hypoperfusion[25,26]	Preshock Hypotensive Normoperfusion[26]	LV Dominant Shock[1]	RV Dominant Shock[23,24]	BiV Shock[24]
Systolic arterial pressure, mm Hg	>90	<90	<90	<90	<90
CVP, mm Hg	Variable	Variable	<14	>14	>14
PCWP, mm Hg	Variable	Variable	>18	<18	Variable
CVP/PCWP	Depends on degree of LV and RV involvement	Depends on degree of LV and RV involvement	<0.86	>0.86	>0.86
PAPi (PAS – PAD)/RA[24,28–30]	Depends on degree of RV involvement	Depends on degree of RV involvement	>1.5	<1.5*	<1.5
Cardiac index, L/min/m^2	<2.2	≥2.2	<2.2	<2.2	<2.2
SVR, dynes-s/cm^{-5}	>1600	800–1600	800–1600	800–1600	800–1600
CPO, W[27]	Variable	Variable	<0.6	<0.6	<0.6

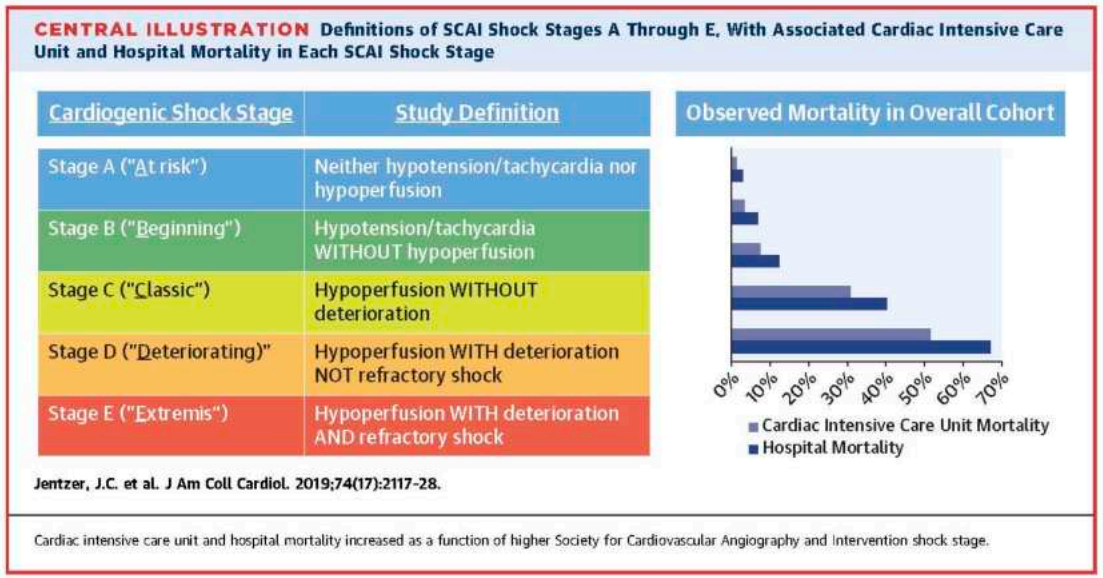
BiV indicates biventricular; CPO, cardiac power output; CVP, central venous pressure; LV, left ventricular; PAD, pulmonary artery diastolic pressure; PAS, pulmonary artery systolic pressure; PAPi, pulmonary artery pulsatility index; PCWP, pulmonary capillary wedge pressure; RA, right atrial pressure; and SVR, systemic vascular resistance.

*Right ventricular (RV) dominant shock primarily attributable to RV dysfunction.

Saxena et al 2020 Circulation

Not all shock is the same

		Volume Status: Wet	Volume Status: Dry
Peripheral Circulation	Cold	Classic Cardiogenic Shock (↓CI; ↑SVRI; ↑PCWP)	Euvolemic Cardiogenic Shock (↓CI; ↑SVRI; ↔PCWP)
	Warm	Vasodilatory Cardiogenic Shock or Mixed Shock (↓CI; ↓/↔SVRI; ↑PCWP)	Vasodilatory Shock (Not Cardiogenic Shock) (↑CI; ↓SVRI; ↓PCWP)



Jentzer et al 2019 JACC
Van Diepen et al 2017 Circulation

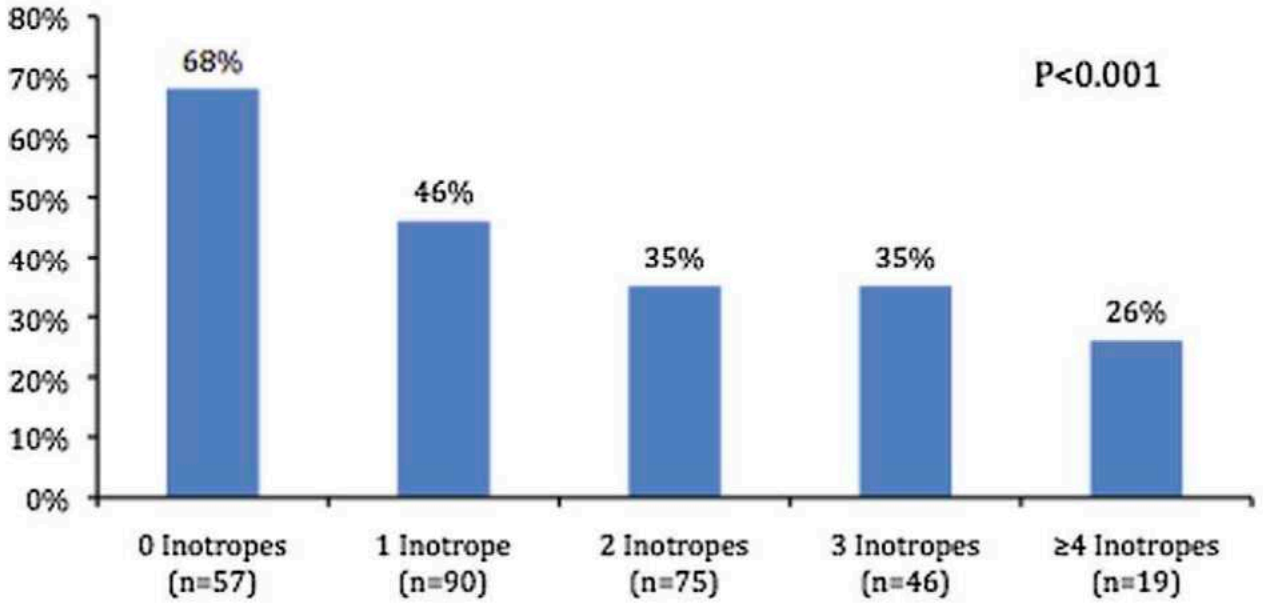
Table 4. Mechanism of Action and Hemodynamic Effects of Common Vasoactive Medications in CS

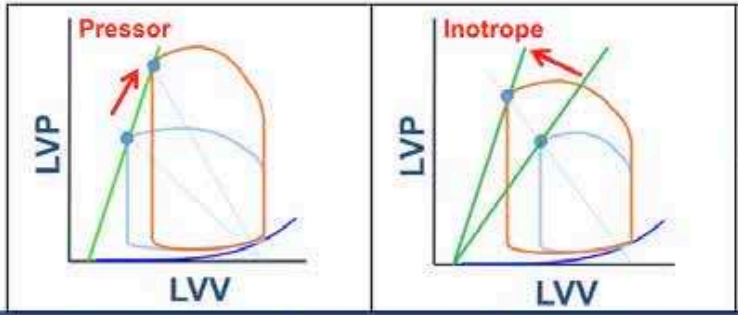
Medication	Usual Infusion Dose	Receptor Binding				Hemodynamic Effects
		α_1	β_1	β_2	Dopamine	
Vasopressor/inotropes						
Dopamine	0.5–2 μg·kg^{-1}·min^{-1}	–	+	–	+++	↑CO
	5–10 μg·kg^{-1}·min^{-1}	+	+++	+	++	↑↑CO, ↑SVR
	10–20 μg·kg^{-1}·min^{-1}	+++	++	–	++	↑↑SVR, ↑CO
Norepinephrine	0.05–0.4 μg·kg^{-1}·min^{-1}	++++	++	+	–	↑↑SVR, ↑CO
Epinephrine	0.01–0.5 μg·kg^{-1}·min^{-1}	++++	++++	+++	–	↑↑CO, ↑↑SVR
Phenylephrine	0.1–10 μg·kg^{-1}·min^{-1}	+++	–	–	–	↑↑SVR
Vasopressin	0.02–0.04 U/min	Stimulates V_1 receptors in vascular smooth muscle				↑↑SVR, ↔PVR
Inodilators						
Dobutamine	2.5–20 μg·kg^{-1}·min^{-1}	+	++++	++	–	↑↑CO, ↓SVR, ↓PVR
Isoproterenol	2.0–20 μg/min	–	++++	+++	–	↑↑CO, ↓SVR, ↓PVR
Milrinone	0.125–0.75 μg·kg^{-1}·min^{-1}	PD-3 inhibitor				↑CO, ↓SVR, ↓PVR
Enoximone	2–10 μg·kg^{-1}·min^{-1}	PD-3 inhibitor				↑CO, ↓SVR, ↓PVR
Levosimendan	0.05–0.2 μg·kg^{-1}·min^{-1}	Myofilament Ca^{2+} sensitizer, PD-3 inhibitor				↑CO, ↓SVR, ↓PVR

CO indicates cardiac output; CS, cardiogenic shock; PD-3, phosphodiesterase-3; PVR, pulmonary vascular resistance; and SVR, systemic vascular resistance.

Van Deipen et al 2017 Circulation

Survival vs inotropic support





	Vasopressor	Inotrope
Mechanism	Peripheral vasoconstriction	Increased myocyte calcium cycling
LV Contractility	↔ or ↑	↑
TPR	↑	↔ or ↑ or ↓
LV Flow	↓	↑
Total CO	↓	↑
CVP	↔ or ↑	↔
PCWP	↔ or ↑	↔ or ↓
MAP	↑	↑
Total CPO	↔ or ↑	↑
PVA	↑	↑
MVO2	↑	↑
Sheath size	NA	NA

Basir et al 2017 Am J Card
Saxena et al 2020 Circulation

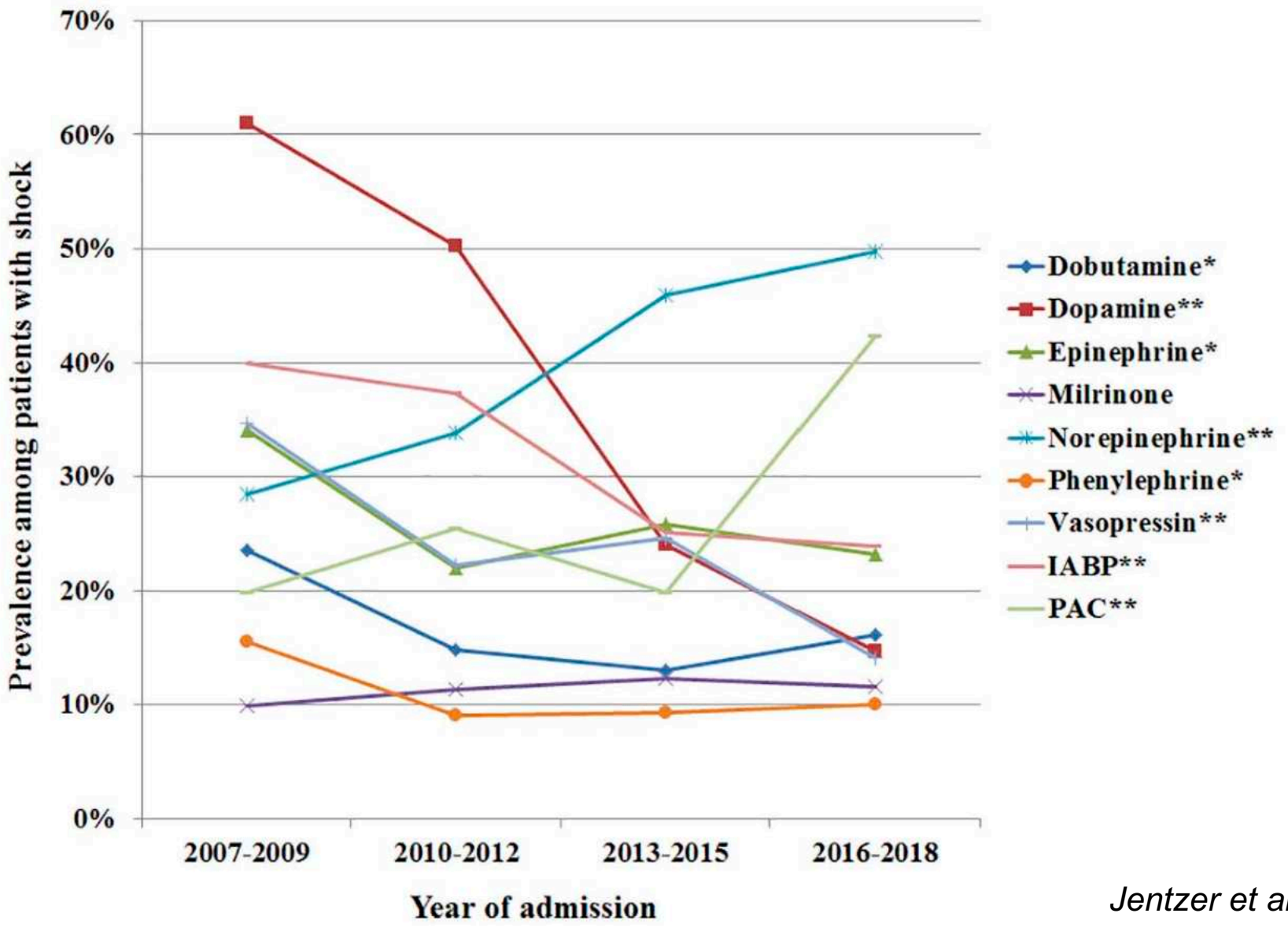
RCTs of Inotropes

Table 1
Randomized controlled trials of positive inotropes in patients with heart failure and reduced ejection fraction

Study	Year	Study Drug	Mean Age (y)	Number of Subjects	Results
PROMISE	1991	Oral milrinone	64	1088	Higher risk of all-cause mortality ($P = .038$)[a] and CV mortality ($P = .016$) with milrinone compared with placebo
PICO	1996	Oral low-dose pimobendan	65	317	Improved exercise tolerance for 2.5 mg/d ($P = .03$) and 5 mg/d ($P = .05$) compared with placebo[a]
DIG Trial	1997	Oral digoxin	63	6800	No significant difference in all-cause mortality ($P = .80$)[a]; decrease in number of all-cause hospitalizations per subject with digoxin compared with placebo ($P = .01$)
DICE	1999	Intermittent low-dose dobutamine	65	38	No significant difference in HF hospitalizations[a] or mortality
OPTIME-CHF	2002	Short-term intravenous milrinone	65	951	No significant difference in days hospitalized at 60-d follow up ($P = .71$)[a]; higher risk of sustained hypotension ($P<.001$) and new atrial arrhythmias ($P = .004$) with milrinone compared with placebo
EPOCH	2002	Oral low-dose pimobendan	64	298	Lower risk of adverse cardiac events with pimobendan compared with placebo ($P = .035$) and no significant difference in combined death and hospitalization for cardiac causes ($P = .202$)[a]
SURVIVE	2007	Short-term intravenous levosimendan vs dobutamine	67	1327	No difference in risk of all-cause mortality at 180 d follow-up ($P = .40$)[a]
ESSENTIAL	2009	Oral enoximone	62	1854	No difference in composite of time to all-cause mortality or hospitalization ($P = .71$)[a]
REVIVE	2013	Short-term intravenous levosimendan	63	700	Improved rapid symptomatic relief and lower likelihood of clinical worsening ($P = .015$)[a] for levosimendan compared with placebo

Dooley et al HF clinic 2017

Inotrope use in a CCU – changes over time



Jentzer et al Am Heart J 2021

Inotropes and age – finding the data

- One of the most common etiologies for Cardiogenic shock is acute myocardial infarction (AMI)
- Several studies have explored the beneficial role of different interventions in the setting of AMI complicated by cardiogenic shock
  - SHOCK trial – MCS + revascularization were shown to decrease mortality
  - GUSTO-I - Early revascularization with PCI/CABG shown to decrease mortality
- RCT often have had difficulty assessing therapies in the elderly because the inclusion criteria of many trials precludes participation of the elderly

Sonborn et al JACC 2000
Berger et al Circulation 1999
Hochman et al NEJM 1999

Assessing baseline characteristics in the elderly with cardiogenic shock

- Tedesco et al 2003 (retrospective)
  - Olmsted county, Minnesota – 1263 consecutive patients with AMI (1988 – 2000)
  - 73/1263 (6%) had cardiogenic shock
  - Patients ≥ 65 yo
    - More co-morbidities
    - More likely to have NSTEMI
    - More likely to get CABG over PCI
    - Trend towards less to use PAC, inotropes or IABP
    - No increase in complications

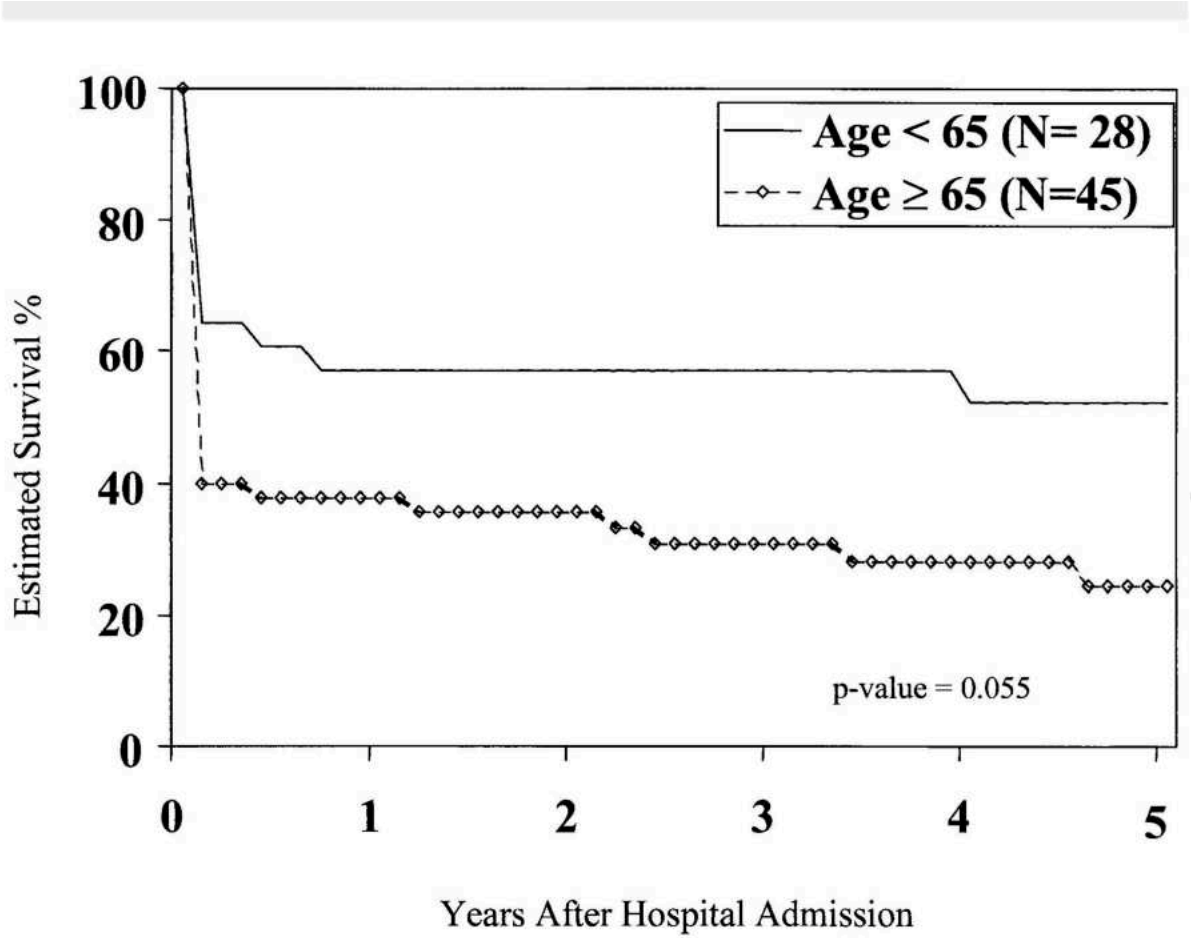
Table II. Demographics and clinical profile of patients with cardiogenic shock as a function of age

	Age ≥65 y	Age <65 y	P
Number of patients	45	28	
Female (%)	20 (44)	8 (29)	.18
Family history of CAD (%)	10 (22)	6 (21)	.94
Diabetes (%)	11 (24)	5 (18)	.51
Hypercholesterolemia (%)	21 (47)	12 (43)	.75
Hypertension (%)	22 (49)	6 (21)	.02
Current smoker (%)	6 (13)	13 (46)	.002
Former smoker (%)	11 (24)	8 (29)	.50
Stroke (%)	8 (18)	3 (11)	.51
Prior MI (%)	15 (33)	5 (18)	.15
Prior CABG (%)	5 (11)	2 (7)	.70
Prior PTCA (%)	3 (7)	4 (14)	.42
Systolic BP, mm Hg	119 (100, 141)	105 (80, 150)	.41
Diastolic BP, mm Hg	82 (60, 96)	70 (48, 92)	.19
Heart rate, beats/min	90 (79, 114)	94 (82, 120)	.62
ST elevation (%)	22 (49)	22 (79)	.01
Q waves (%)	7 (16)	9 (32)	.10
Peak CK, Iμ/L	1192 (428, 2405)	2705 (727, 4699)	.02
Peak MB, ng/mL	37 (16, 172)	163 (67, 378)	.02

Tedesco et al AHJ 2003

Olmstead County

- Patients ≥ 65 y.o. with cardiogenic shock
  - Increased short/long-term mortality
  - In-hospital mortality 58% in elderly as compared to 36% in younger cohort
- Study limitation: non-randomized
- Physician bias in the treatment of the elderly?

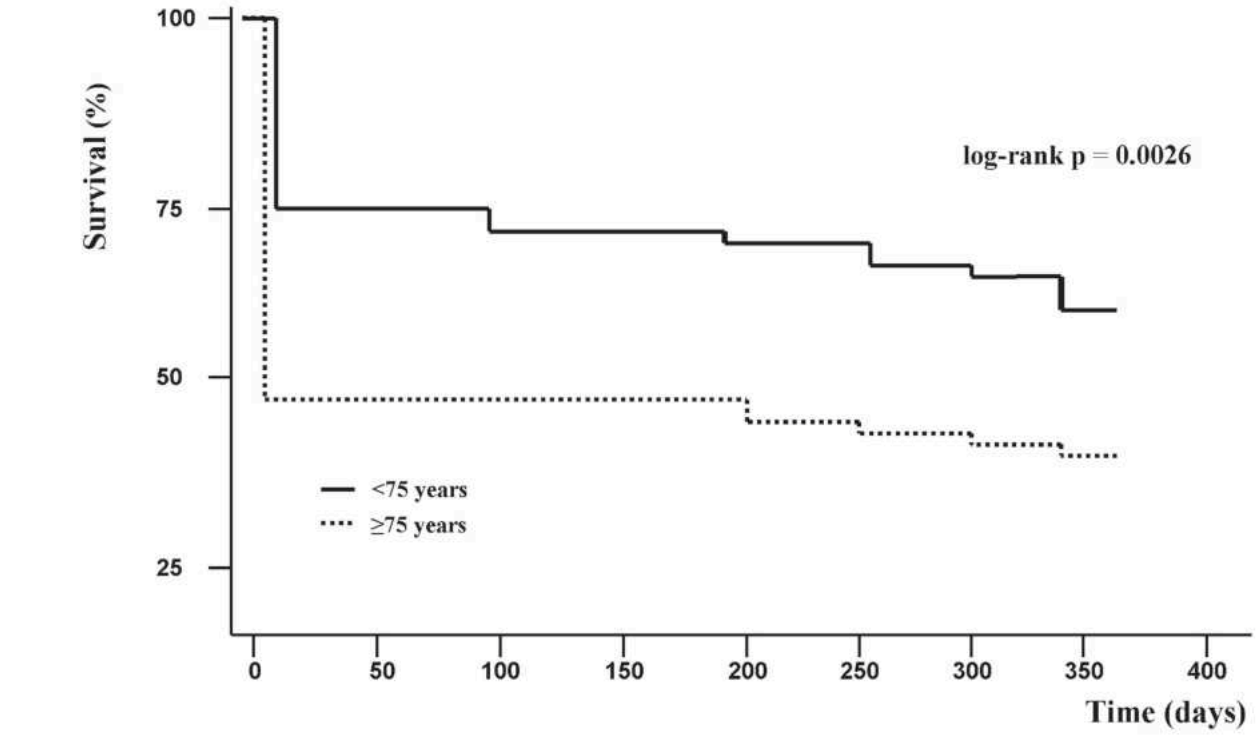


Kaplan-Meier analysis of long-term survival in patients with AMI and CGS as a function of age.

Tedesco et al AHJ 2003

Outcomes in patients aged ≥75 yo and shock

- SHOCK trial – patients aged ≥ 75 years did not derive mortality benefit from early revascularization
- BUT trend to:
  - Higher proportion of females
  - Lower rate of CHF in the early revascularization group
  - Those that received early revascularization had a lower mean LVEF (27.5+/-12.7 versus 35.+/- 11.6, P=0.05
- Genoa/Italy - retrospective analysis of AMI patients 2003 – 2008
  - 167 patients developed cardiogenic shock post AMI

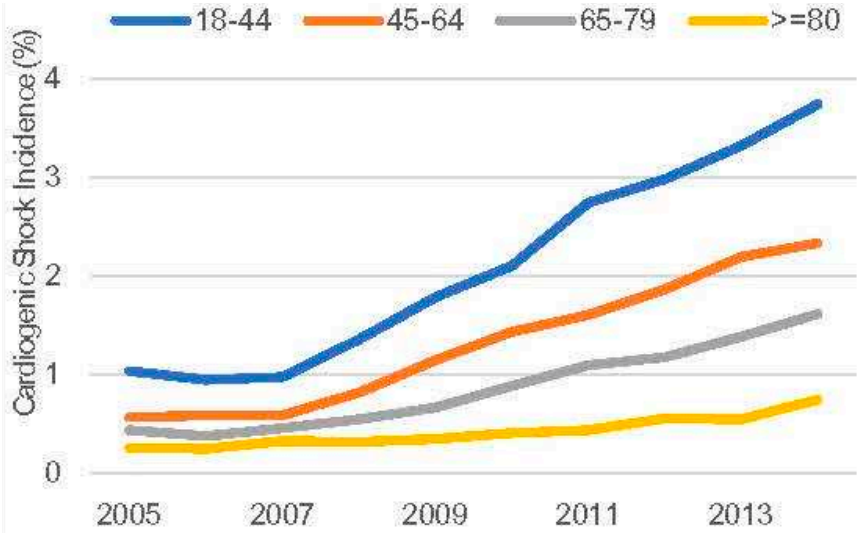


Kaplan-Meier estimates of 12 months-cumulative mortality in patients < 75 years versus ≥ 75 years

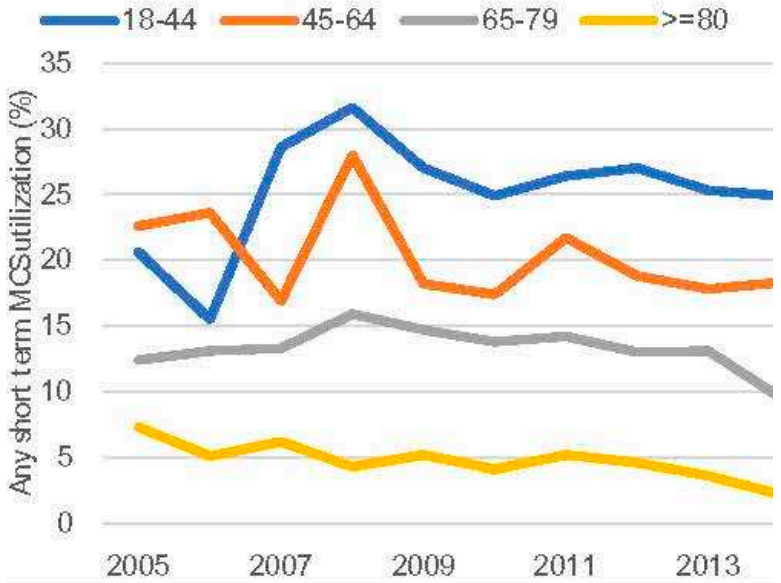
Fig. 1. Kaplan-Meier estimates of 12-month cumulative survival in all patients and in patients ≥75 years versus <75 years.

Tomassini et al Cath Cardiov Interventions 2011
Dzavik et al AHJ 2005

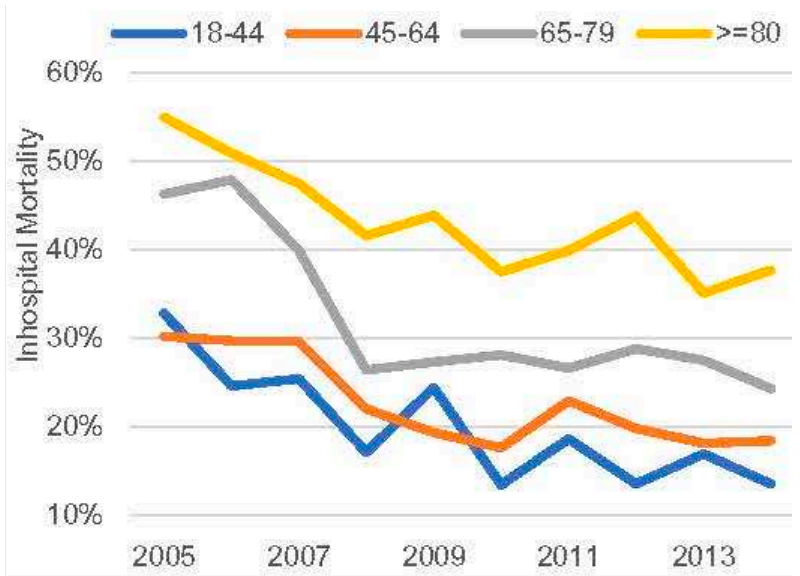
Incidence and outcomes for cardiogenic shock during HF hospitalizations



Mean patient age 66.8 years
2/3 were male
63% were white race
Risk factors include: IHD, HTN, CKD
AF, DM



Overall MCS use 15%
Mostly IABP
Overall decrease in IABP
Increase use in ECMO and temp
VAD



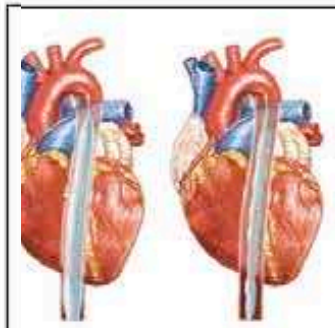
Overall in-hospital mortality 27%
Higher in females,
Highest in >80 years of age

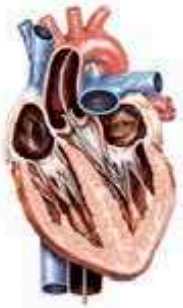
Yandrapalli et al Am Heart J 2019

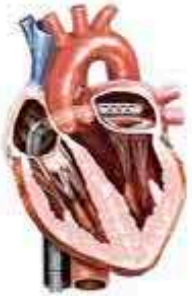
Exit strategy

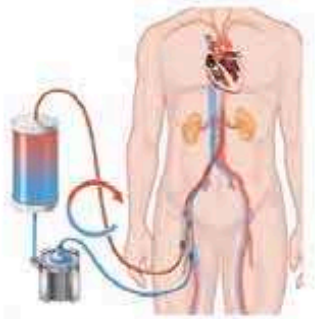
- Etiology of Cardiogenic shock – reversible?
- Inotrope dependence?
- Need for short/long-term mechanical circulatory support
- Need to define the exit strategy
  - Recovery
  - Bridge to decision
  - Bridge to transplant
  - Palliation

Alternatives of drugs









	IABP	IMPELLA	TANDEMHEART	VA-ECMO
Mechanism	Aortic counter-pulsation	Left ventricle (LV) to aorta transvalvular circulatory support (LVADs)	Left atrium (LA) to arterial circulatory support	Right atrium (RA) to peripheral artery circulatory support with gas exchange unit
LV Contractility	↔	↔	↔	↔
TPR	↔	↔	↔	↔
LV Flow	↑	↓	↓	↓
Total CO	↑	↑↑	↑↑	↑↑↑
CVP	↔ or ↓	↔ or ↓	↔ or ↓	↓
PCWP	↔ or ↓	↓	↓	↔ or ↑
MAP	↑	↑↑	↑↑	↑↑
Total CPO	↑	↑↑	↑↑	↑↑
PVA	↔ or ↓	↓↓	↔ or ↓	↑↑
MVO2	↓	↓↓	↔ or ↓	↑↑
Sheath size	7-8 French arterial	14 French arterial	15-17 French arterial 21 French Venous	15 – 17 French arterial 21-23 French venous

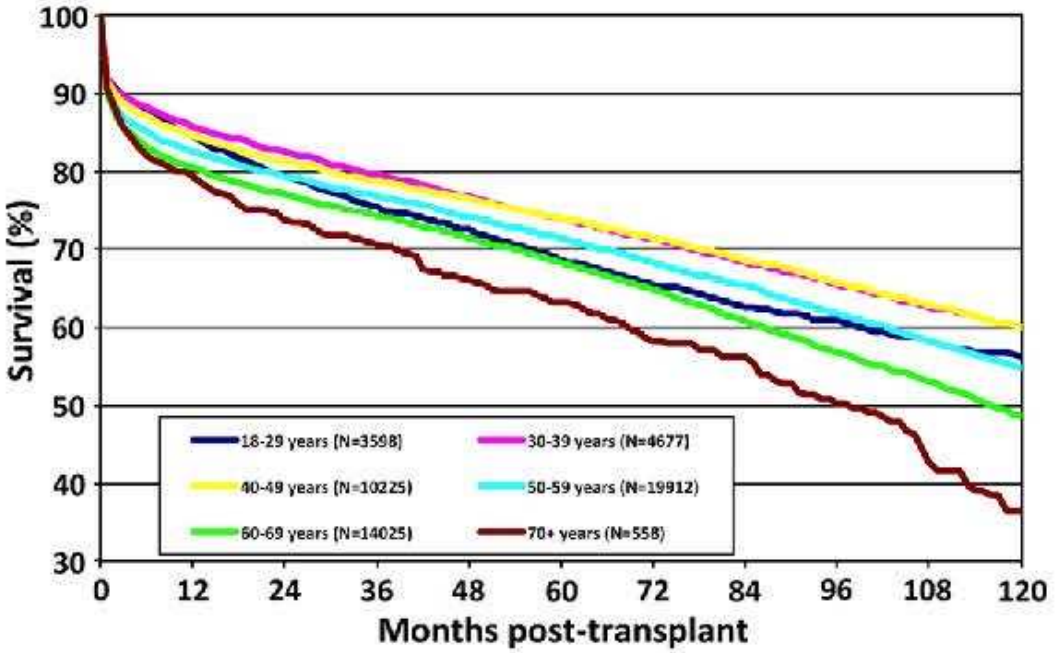
Saxena et al 2020 Circulation

Exit strategy

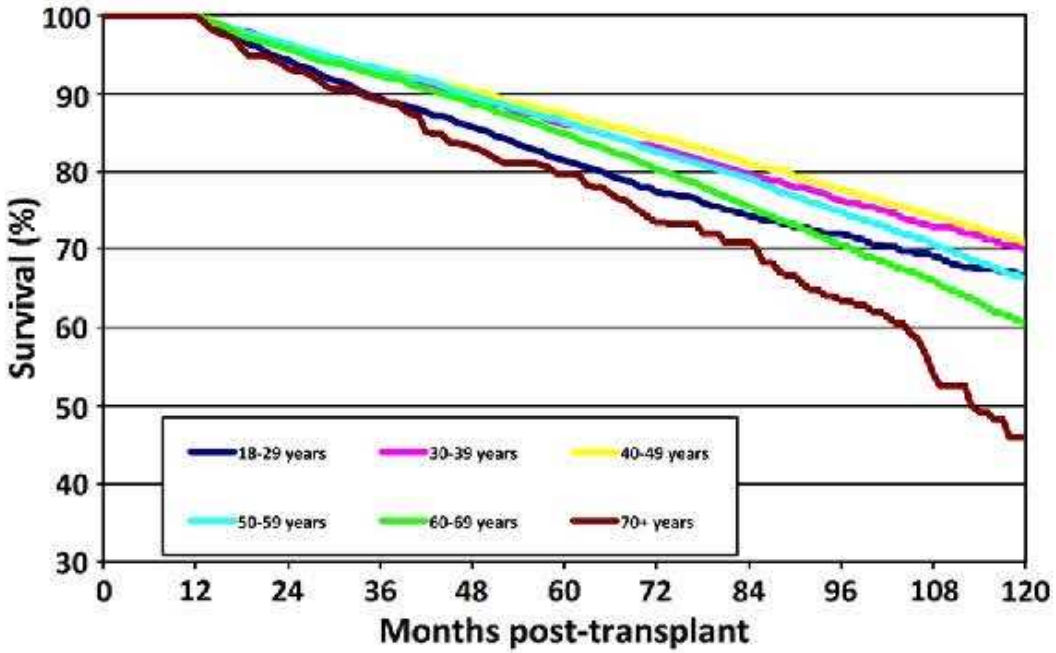
- Etiology of Cardiogenic shock – reversible?
- Inotrope dependence?
- Need for short/long-term mechanical circulatory support
- Need to define the exit strategy
  - Recovery
  - Bridge to decision
  - Bridge to transplant
  - Palliation

Post-transplant survival stratified by age

52,995 recipients – ISHLT registry 1995-2011



Post-transplant survival stratified by age

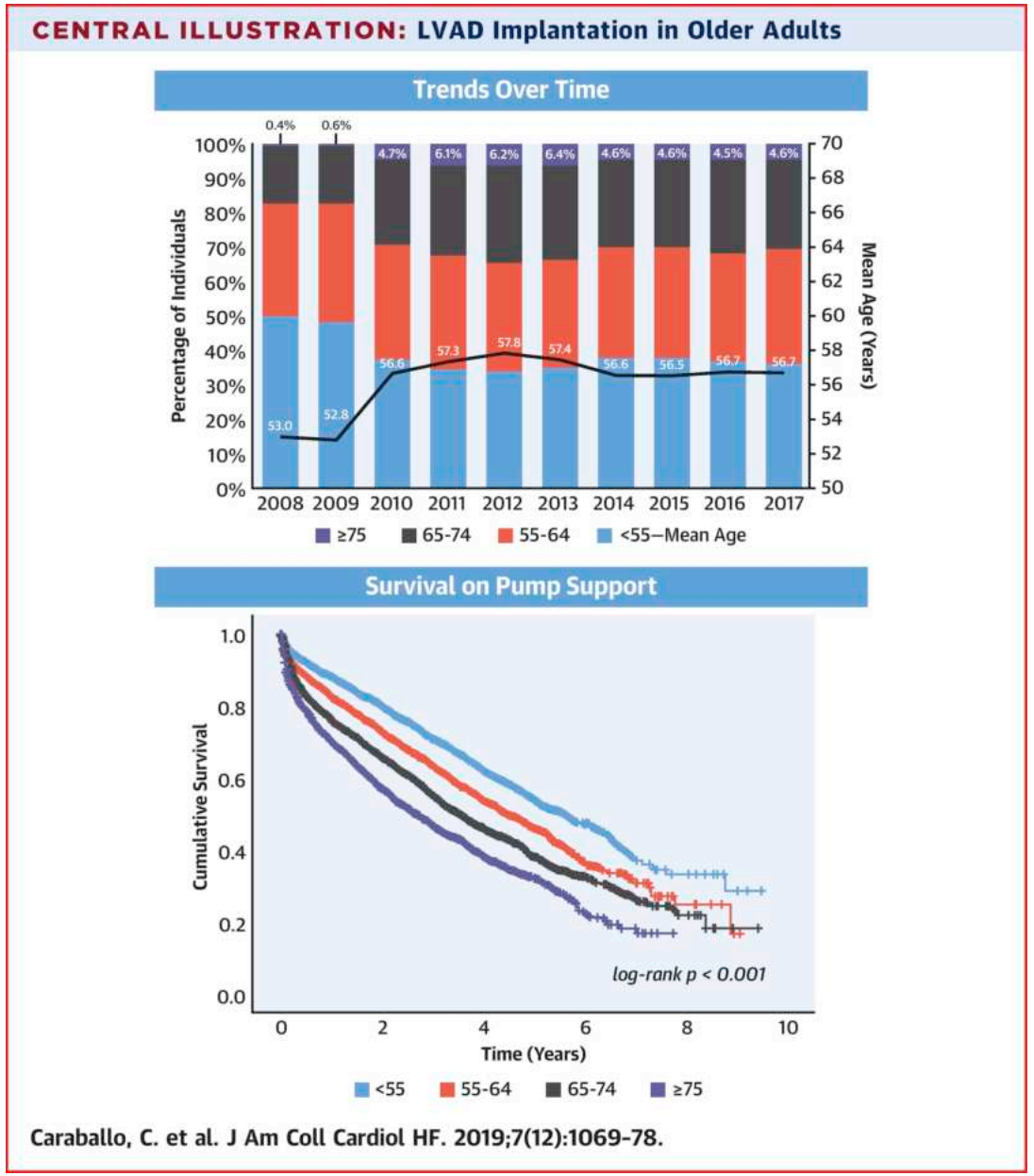


Conditional post-transplant survival stratified by age

Wever-Pinzon et al, JHLT 2017

Post-LVAD survival stratified by age

- In LVAD patients ≥ 75 yo from INTERMACS (2008 – 2017); >20,000 patients
- Patients were stratified by 4 age groups: <55 years of age, 55 to 64 years of age, and >75 years of age.
- Adults ≥75 years of age had increased mortality post-LVAD implantation.
- Elderly patients with LVADs had a higher incidence of gastrointestinal bleeding but lower rates of device thrombosis.
- 84.5% of patients <55 yo discharged home
- 46.8% of adults ≥75 yo discharged



Caraballo et al JAC HF 2019

Palliation and HF

- Predicting mortality in patients with ADHF – difficult
- There are many independent predictors of mortality in HF (LVEF, NYHA class, Na, intolerance to medications, BNP)
- Not candidates for advanced heart failure therapies to change prognosis
- Consideration for continuous chronic inotropic infusions (Class IIb, AHA/ACC recommendation)
  - Offer increased quality of life
  - Lead to reduced symptom burden
  - Does not improve survival
- Challenges
  - Drug selection
  - Route of administration
  - Transition between care setting
  - During of therapy
  - Acceptance of end of life/palliative approach

Malotte et al Palliative Care Rounds 2018
Patel et al Am J. Hospice & Pall Med 2019
Groninger et al J Pain Sympt Management 2020

Summary

- Mortality in patients with HF increases significantly with age
- Most common mode of death in HFrEF is pump failure – cardiogenic shock
- Inotropes are the first line treatment to maintain organ perfusion and may be the final line of treatment
- Long-term inotrope treatment associated with mortality
  - Need an ‘exit strategy’
- Elderly patients have decrease survival post-transplant and post-LVAD
- Support with inotropes can be considered in the elderly patient for quality of life and improvement in symptom burden for palliation