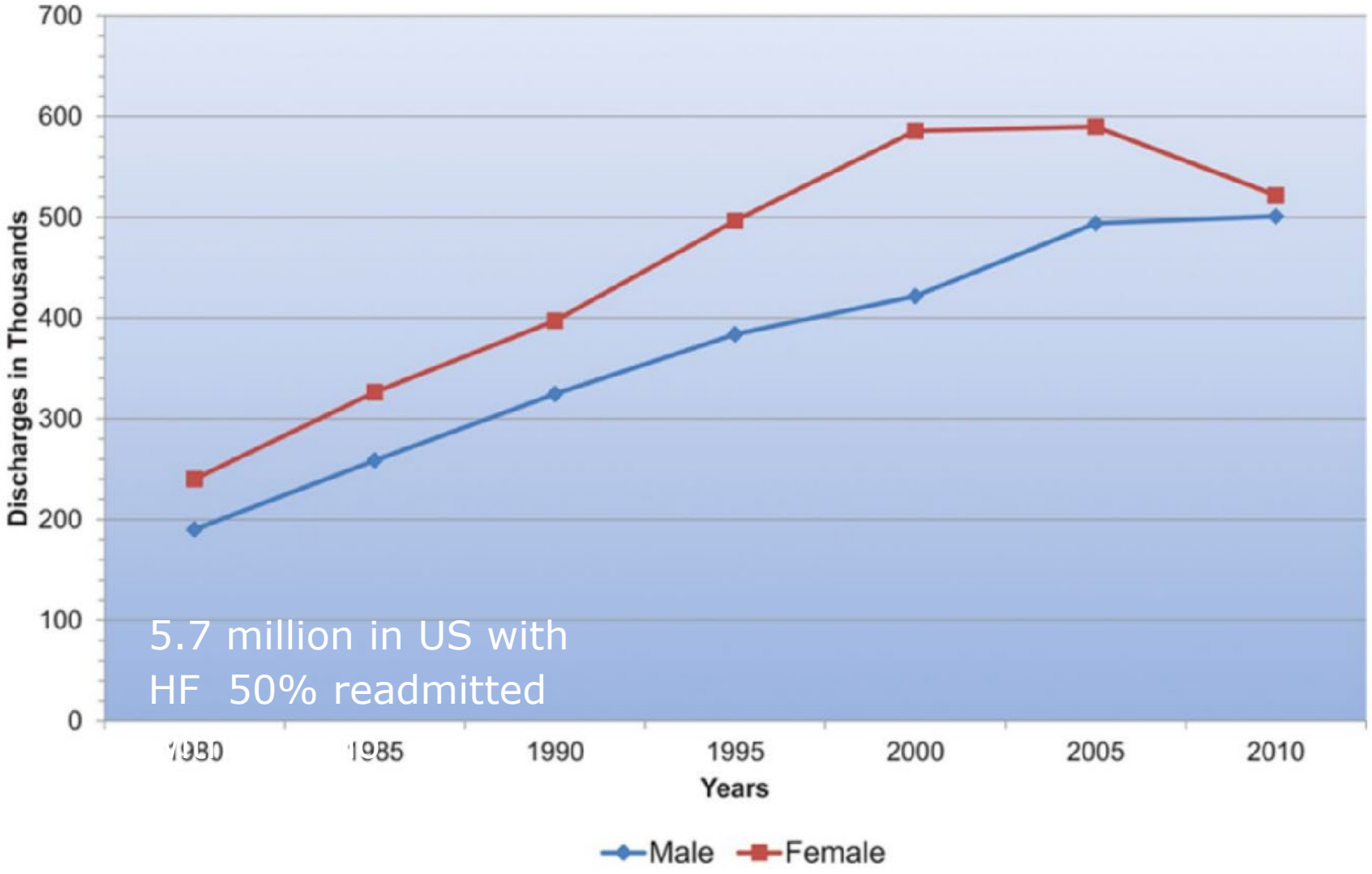
Heart Failure Update

Sequoia Heart Failure Symposium 2018

Mary S. Larson, MD

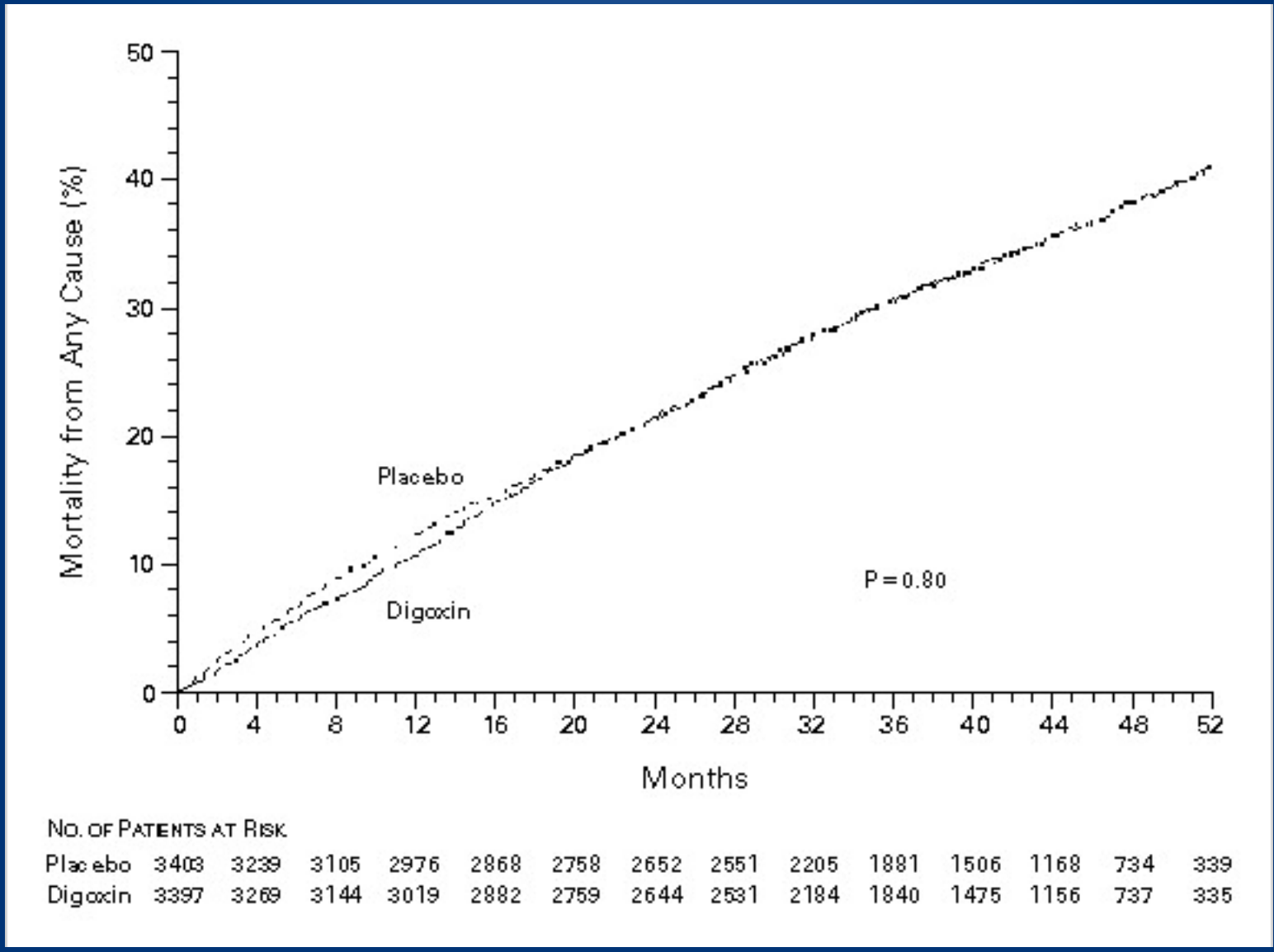
Hospital discharges for heart failure by sex (United States: 1980–2010).



American Heart Association.

Mozaffarian D et al. Circulation. 2015;131:e29-e322

DIG, 1997



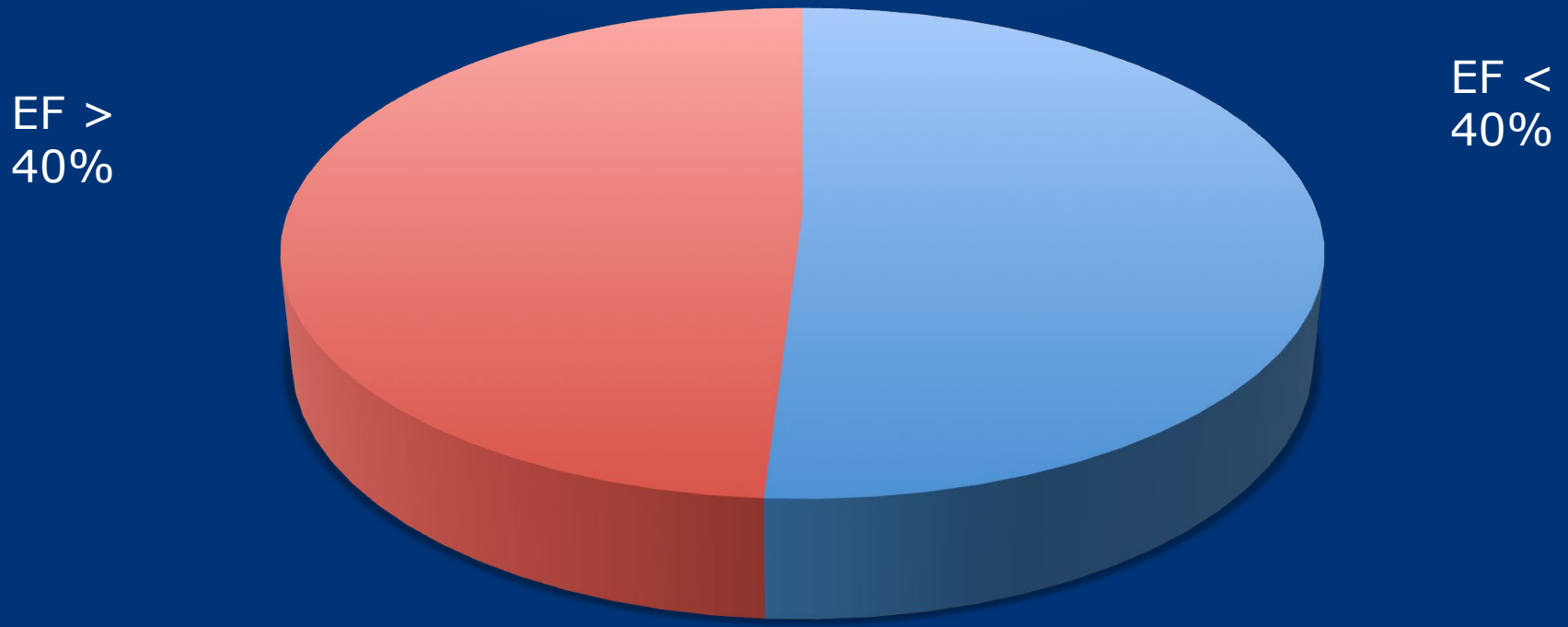
No. of Patients at Risk

Placebo	3403	3239	3105	2976	2868	2758	2652	2551	2205	1881	1506	1168	734	339
Digoxin	3397	3269	3144	3019	2882	2759	2644	2531	2184	1840	1475	1156	737	335

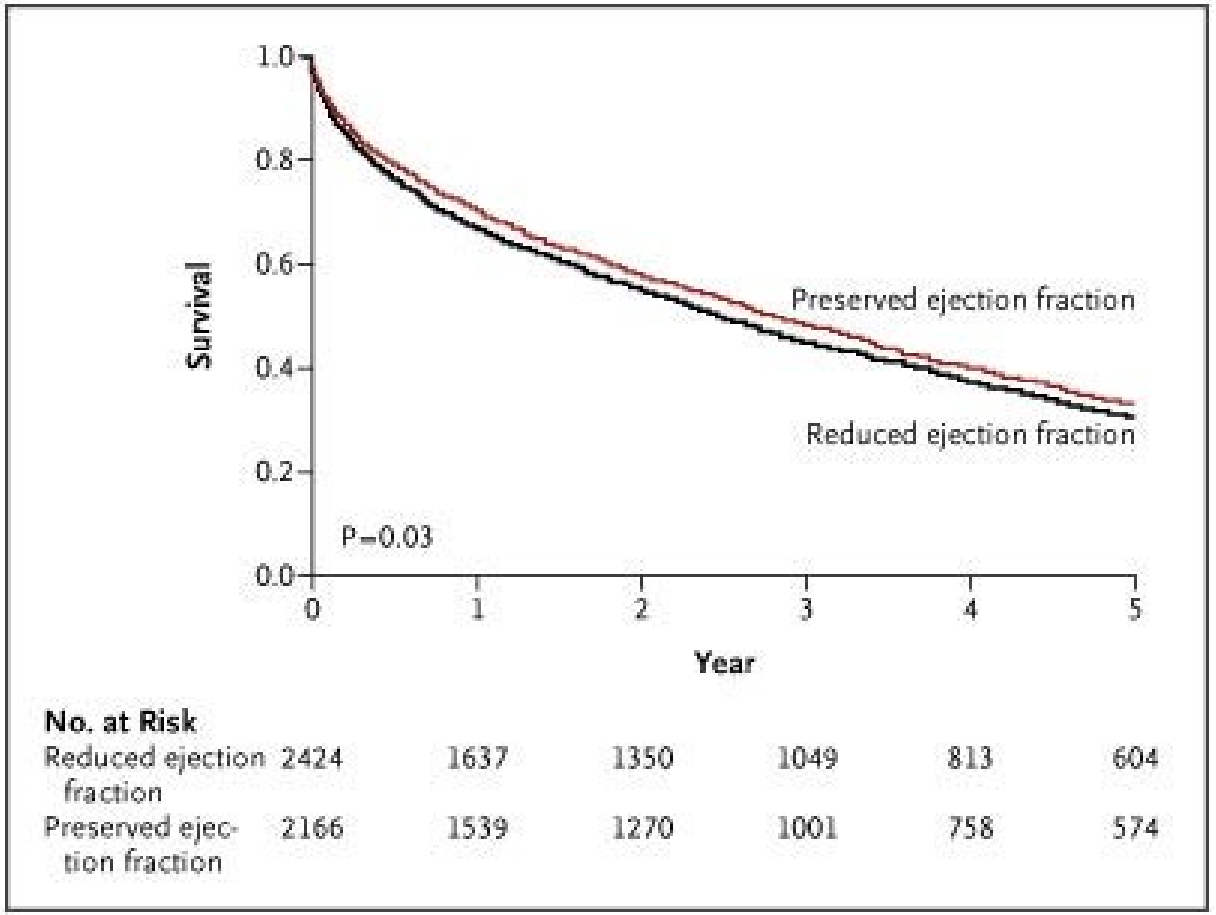
Heart Failure

- Complex clinical syndrome resulting from any structural or functional impairment of ventricular filling or ejection, due to disease of pericardium, myocardium, endocardium, valves, rhythm, or great vessels

Diseases of the LeQ Ventricle



Kaplan-Meier Survival Curves for Patients with Heart Failure and Preserved or Reduced Ejection Fraction.



No. at Risk

Reduced ejection fraction	2424	1637	1350	1049	813	604
Preserved ejection fraction	2166	1539	1270	1001	758	574

Owan TE et al. N Engl J Med 2006;355:251--259.

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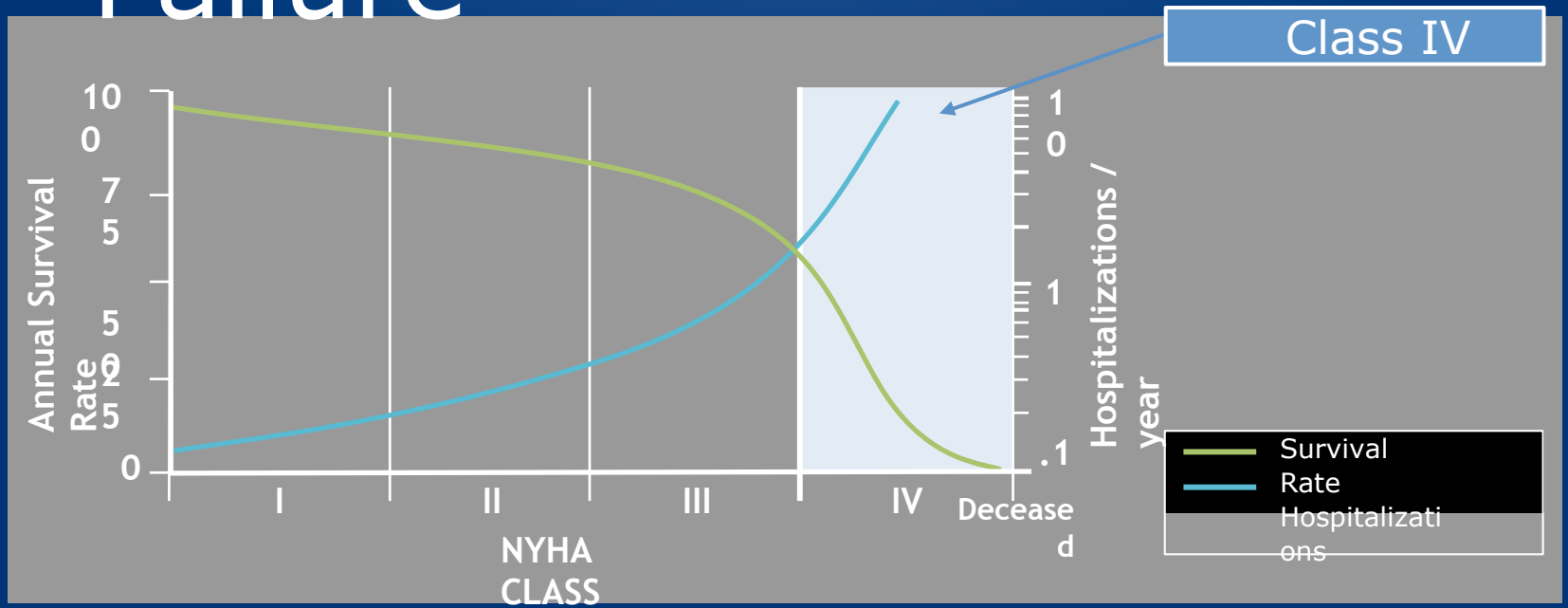
ACC/AHA Heart Failure Stages

- Stage A
  - At risk, no disease
- Stage B
  - Structural disease, no Sx/signs
- Stage C
  - Structural disease, current or past Sx/signs
- Stage D
  - Refractory

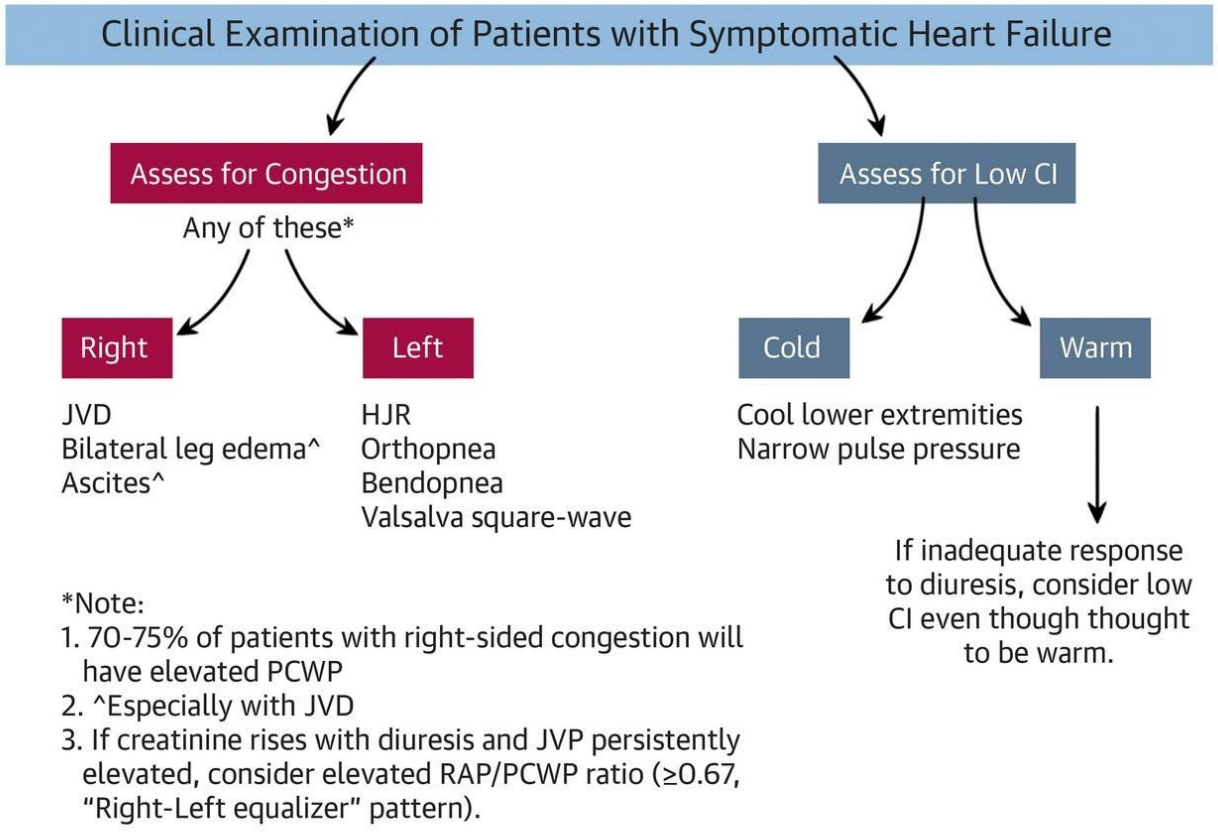
- New York Heart Association (NYHA) Functional Class
  - Based on symptoms
  - Fluctuates
    - I
    - II
    - III
    - IV

Natural History of Heart Failure



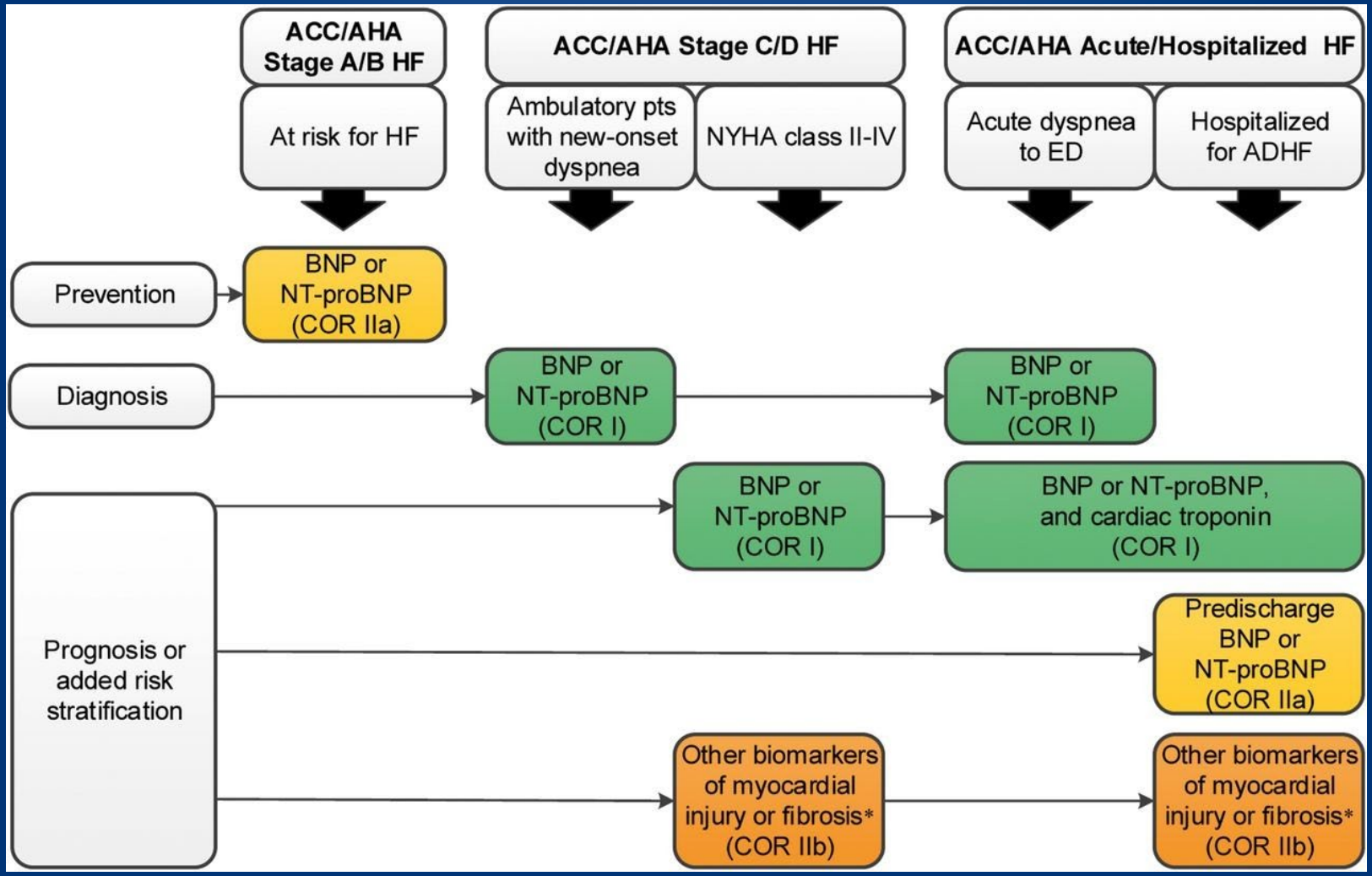
Dickstein K, *Eur Heart J*. 2008; 29: 2388--2442

CENTRAL ILLUSTRATION: Clinical Assessment of Hemodynamics in Patients With Heart Failure

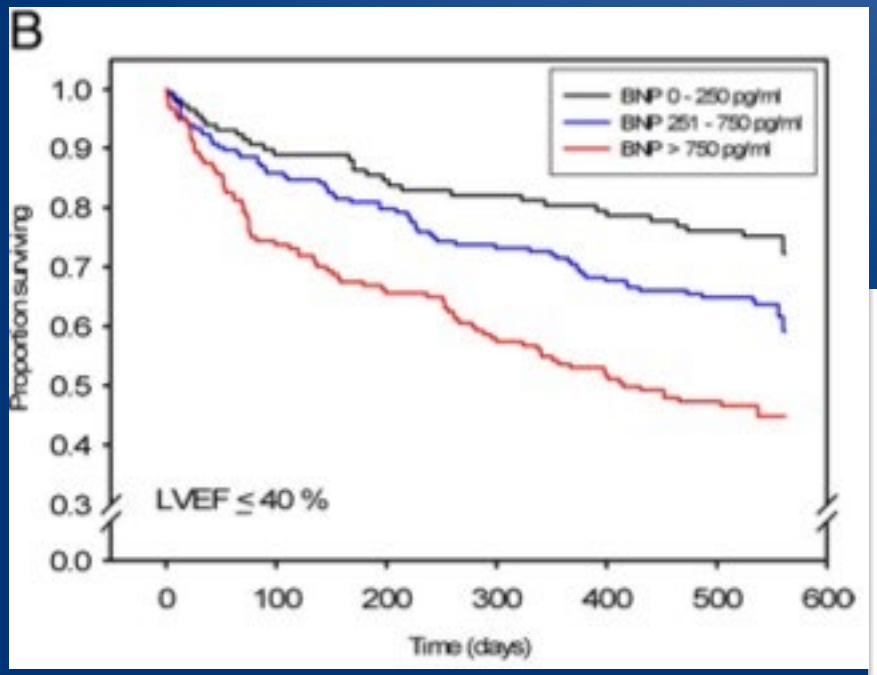


Thibodeau, J.T. et al. J Am Coll Cardiol HF. 2018;6(7):543-51.

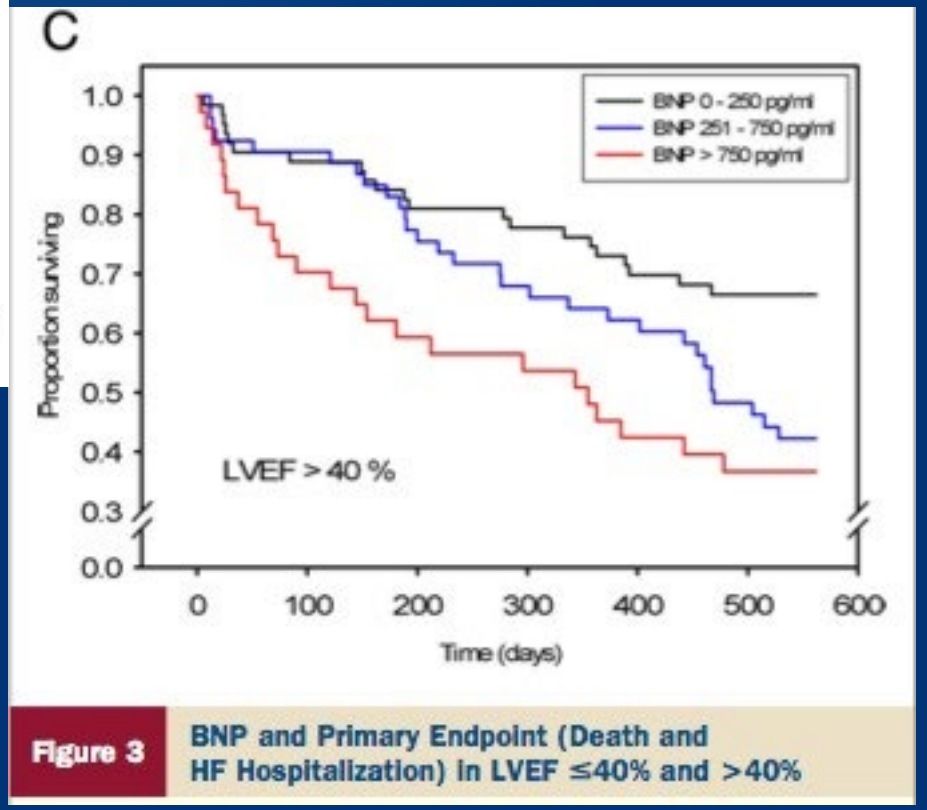
Jennifer T. Thibodeau, and Mark H. Drazner
JCHF 2018;6:543-551



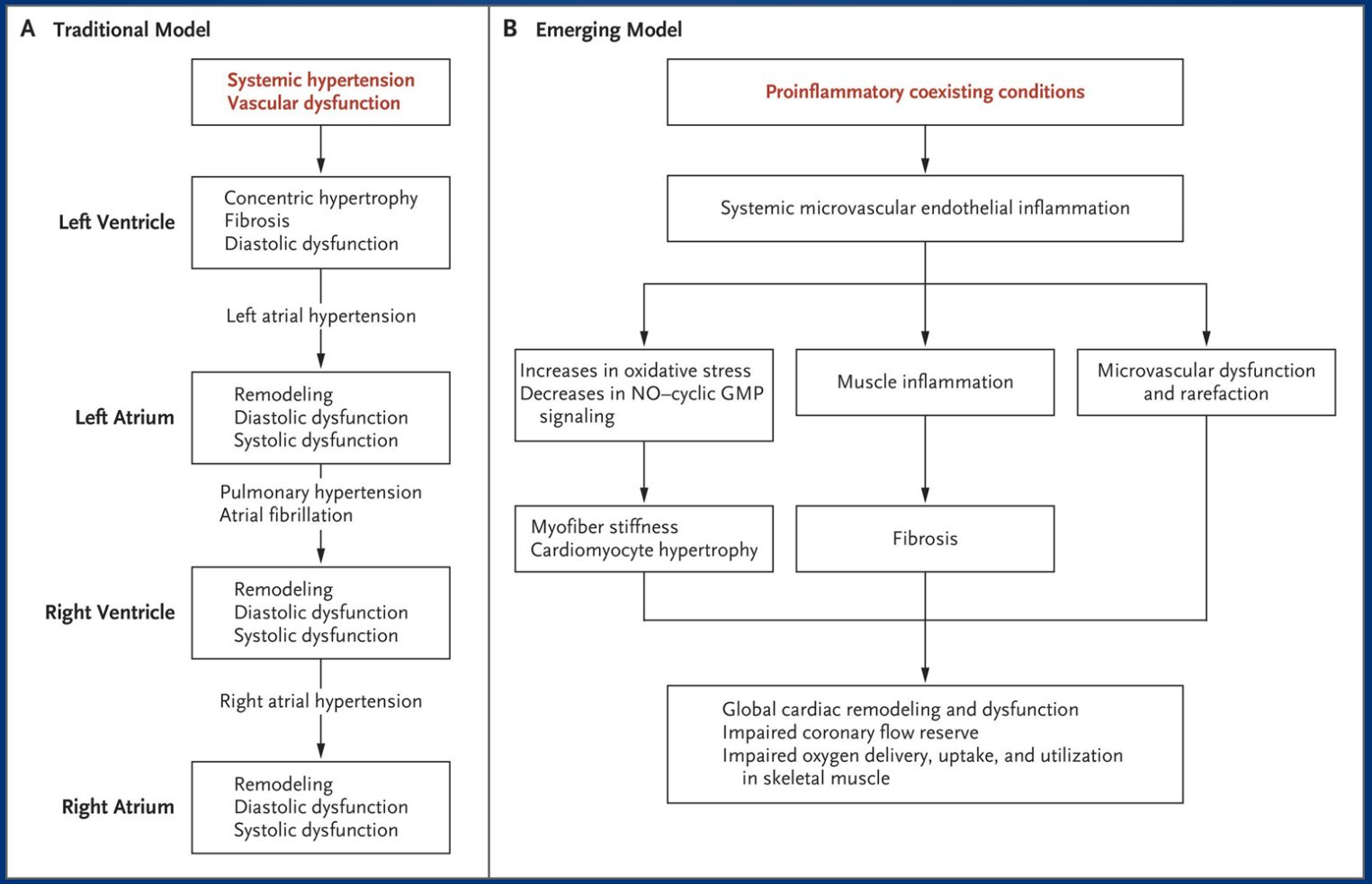
Clyde W. Yancy et al. JACC 2017;70:776-803



Data from RCT; measured BNP at end of hospitalization for HF: pt considered at optimally treated



Heart Failure preserved Ejection Fraction



Redfield MM. N Engl J Med 2016;375:1868-1877

HFpEF RCTs

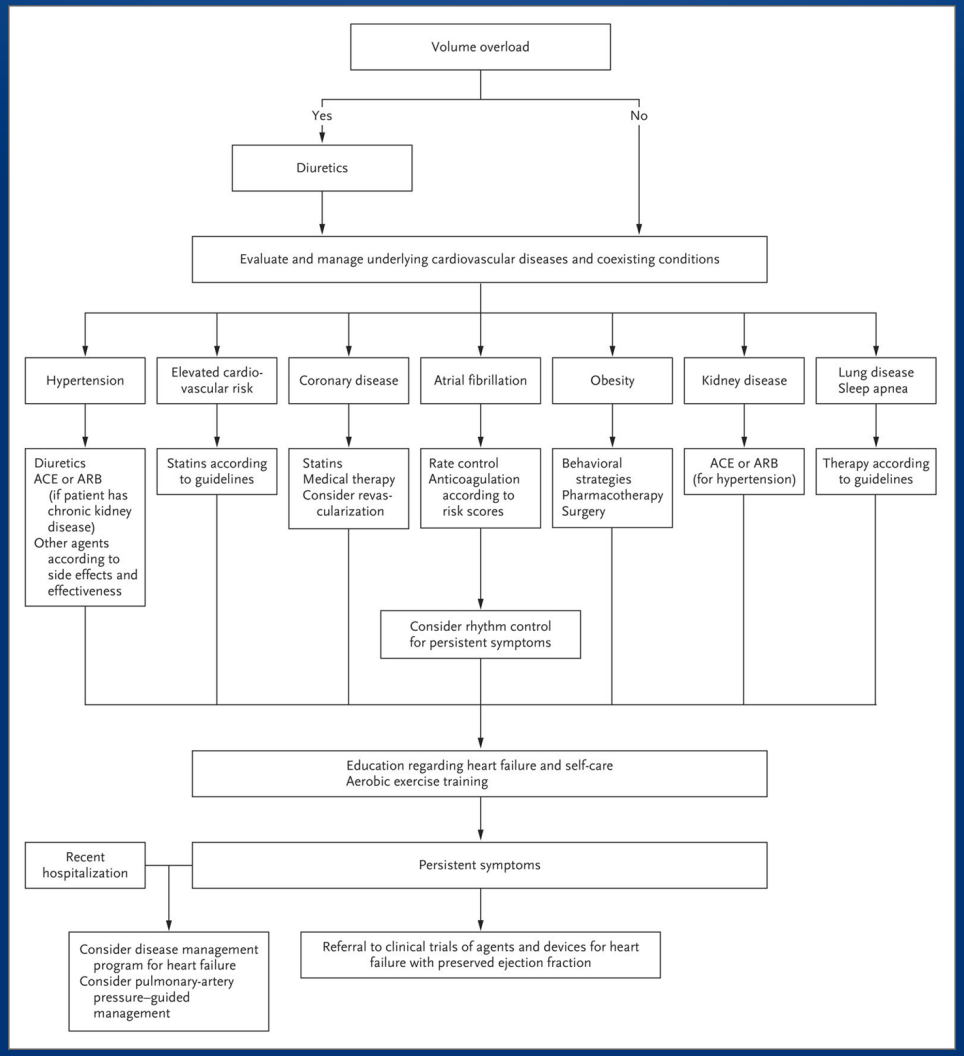
TABLE 1 Summary of Major Published HFpEF Randomized Clinical Trials (Phase 2-3)

Drug/Intervention (Ref. #)	Phase	Study Size	Primary Endpoint	Result
Candesartan (31)	3	3,023	Composite of cardiovascular mortality or HF hospitalization	Neutral
Irbesartan (30)	3	4,128	Composite of all-cause mortality or cardiovascular hospitalization	Neutral
Perindopril (29)	3	850	Composite of all-cause mortality and HF hospitalization	Neutral
Nebivolol (60)	3	752	Composite of all-cause mortality or cardiovascular hospitalization	Neutral
Carvedilol (61)	2	245	Composite of cardiovascular mortality or HF hospitalization	Neutral
Digoxin (62)	3	988	Composite of HF mortality or HF hospitalization	Neutral
Spironolactone (63)	2	422	E/e' on echocardiography; peak oxygen consumption	Positive; neutral
Spironolactone (64)	3	3,445	Composite of death from cardiovascular cause, aborted cardiac arrest, or HF hospitalization	Neutral
Eplerenone (65)	2	44	6-min-walk distance	Neutral
Sildenafil (66)	2	216	Peak oxygen consumption	Neutral
Ivabradine (67)	2	61	Exercise capacity/peak oxygen consumption	Positive
Ivabradine (68)	2	44	Peak oxygen consumption	Negative
Ivabradine (69)	2	179	E/e' on echocardiography; 6-min-walk distance; NT-proBNP	Neutral; neutral; neutral
Exercise training (70)	N/A	64	Peak oxygen consumption	Positive
Sacubitril/valsartan (71)	2	301	NT-proBNP	Positive
Vericiguat (72)	2	477	NT-proBNP; left atrial volume	Neutral; neutral
Isosorbide mononitrate (57)	2	110	Daily activity level	Negative

HF = heart failure; HFpEF = heart failure with preserved ejection fraction; NT-proBNP = N-terminal pro-B-type natriuretic peptide.

JACC

Treatment considerations in HFpEF



Redfield MM. N Engl J Med 2016;375:1868-1877

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Diuretics

- Cornerstone of treatment of congestion
  - HFpEF
  - HFrEF
- Inpatient treatment
- Outpatient treatment and maintenance
- No mortality benefit per se

90% of HF hospitalizations due to symptoms of pulmonary congestion[1,2]

AT DISCHARGE

Post--hoc analysis of 463 acute decompensated HF patients from DOSE---HF and CARRESS--HF

40% moderate to severe congestion[3]

60% absent or mild congestion[3]

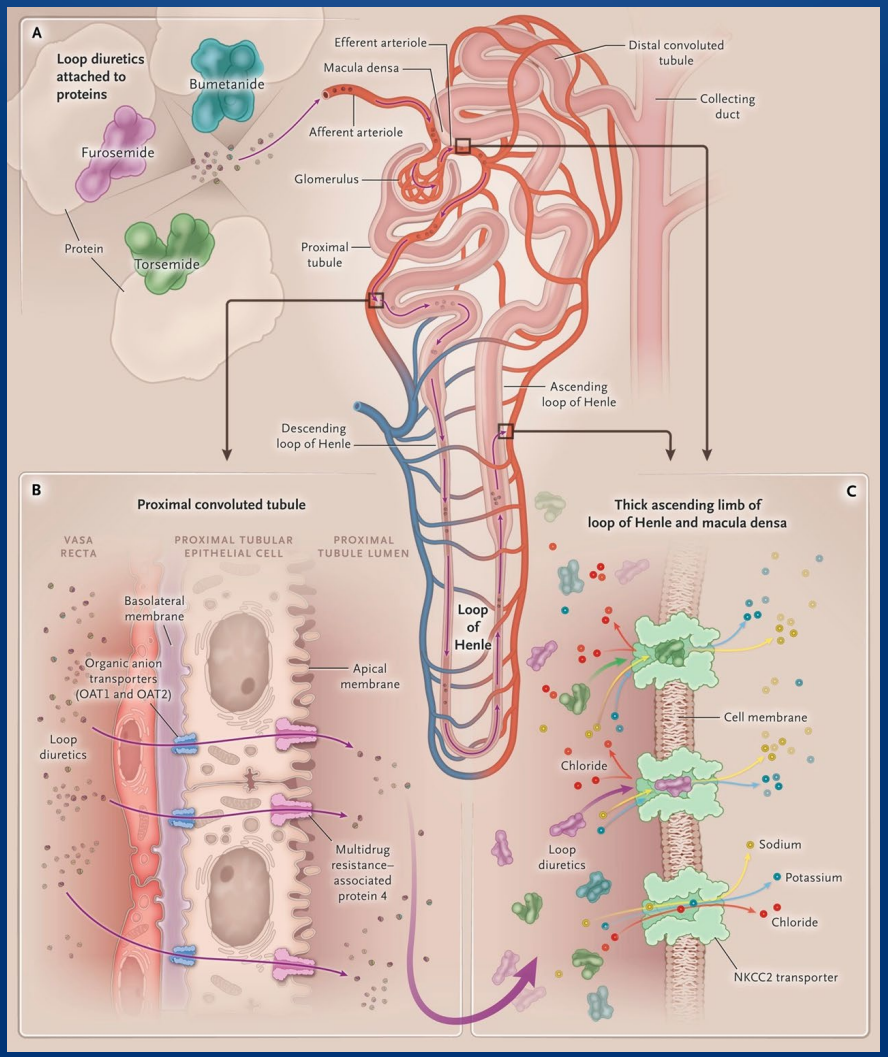
AT 60--DAY FOLLOW--UP

41% of previously decongested patients had severe or partial re--congestion[3]

Today's tools are INADEQUATE

1. Adams KF, et al. *Am Heart J*, 2005.
2. Krum H and Abraham WT. *Lancet*, 2009.
3. Lala A, et al. *J Cardiac Fail*, 2013.

Mechanisms of Loop Diuretic Action and Resistance.



Ellison DH, Felker GM. N Engl J Med 2017;377:1964-1975

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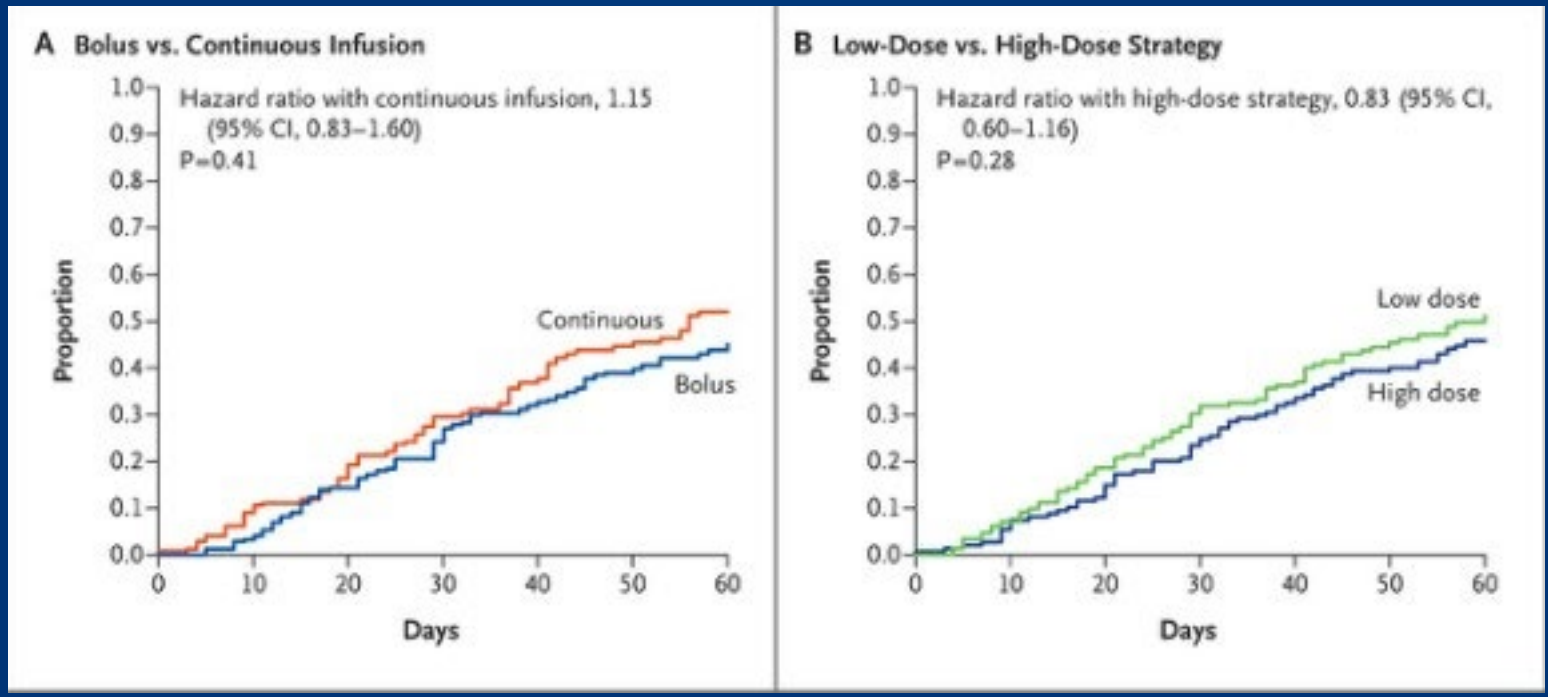
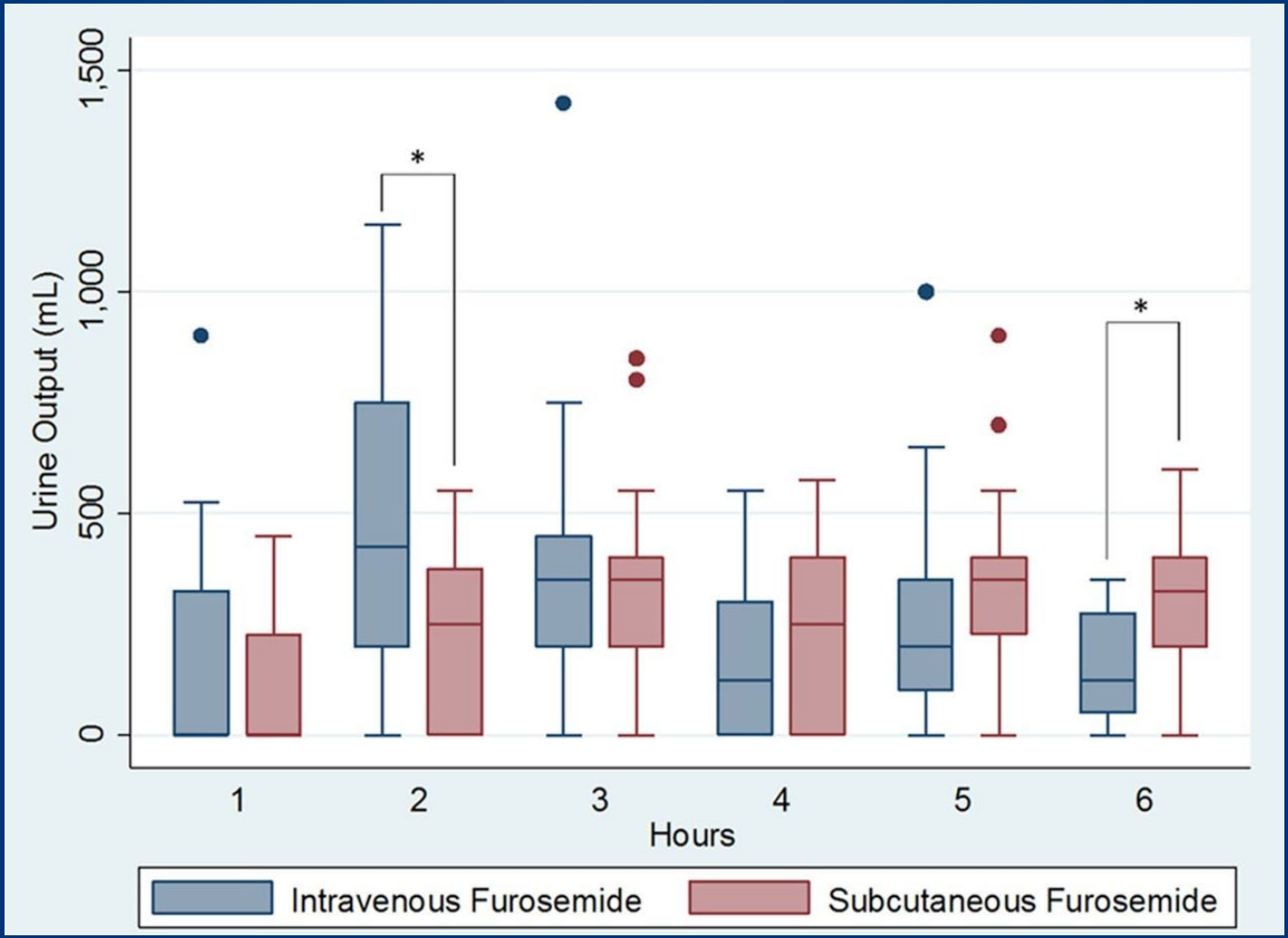
Diuretic therapy for heart failure



DOSE, 2011

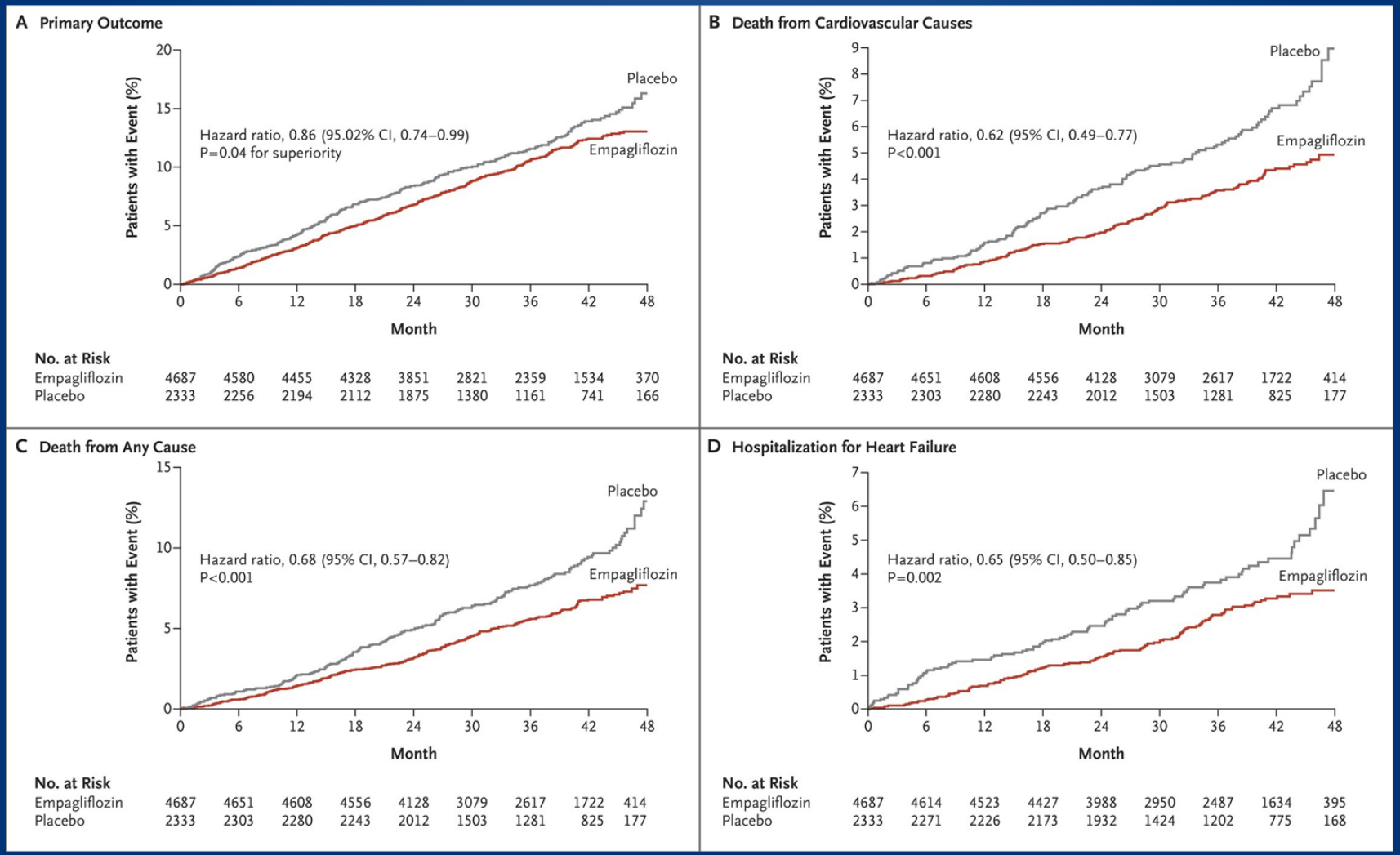


Nisha A. Gilotra et al. JCHF 2018;6:65-70

Decongestion

- No benefit
  - Tolvaptan
  - Renal dose DA
  - Nesiritide
  - High dose spironolactone
  - ultrafiltration
- Consider if loop diuretic resistent
  - Thiazide (po metolazone, IV chlorothiazide)
  - Carbonic anhydrase inhibitor if metabolic alkalosis

Cardiovascular Outcomes and Death from Any Cause.



Zinman B et al. N Engl J Med 2015;373:2117-2128

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Clinical Examinations are not Reliable for Assessing Rising Pressure – Poor Sensitivity and Specificity

VARIABLE	ESTIMATE OF	SENSITIVITY (%)	SPECIFICITY (%)	PPV (%)	NPV (%)
JVP	RAP	48	78	60	69
EDEMA		10	94	55	60
PULSE PRESS N = 366	Cardiac Index	27	69	52	44
S3	PCWP	36	81	69	54
DYSPNEA		50	73	67	57
RALES		13	90	60	48

Clinical examination has **LIMITED RELIABILITY** in assessing filling pressures.

Table adapted from Capomolla S, et al. *Eur J Heart Failure*, 2005.

27382--SJM--MEM--0814--0012(1)a(10) | Item approved for global use.

Weight Change is Not a Reliable Indicator of Rising Pressure or Impendi Decom nsati

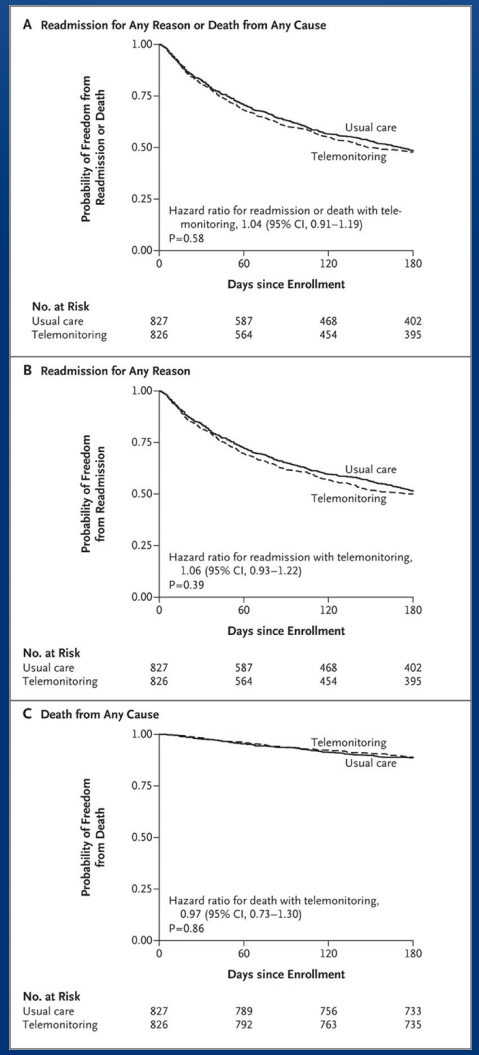
WEIGHT GAIN	SENSITIVITY	SPECIFICITY
2 kg weight gain over 48--72 hrs[2]	9%	97%
2% weight gain over 48--72 hrs[2]	17%	94%
3 lbs in 1 day or 5 lbs in 3 days[3]	22.5%	--

NO CORRELATION - Daily weights *do not* correlate with filling pressures

1.Data based on Zile MR, et al. *Circulation*, 2008. Presented at FDA Advisory Panel, October 9, 2013.
2.Lewin J, et al. *Eur J HF*, 2005.
3. Abraham WT, et al. *Cong Heart Failure*, 2011.

Kaplan–Meier Time-to-Event Estimates for the Primary End Point — Readmission for Any Reason or Death from Any Cause — and Each Component Separately, According to

RCT of 1600 pts who had been hospitalized, still with mild--mod HF, 30% HFpEF, 70% HFrEF: usual care vs. daily telemonitoring, including daily weights and Sx



Chaudhry 2010

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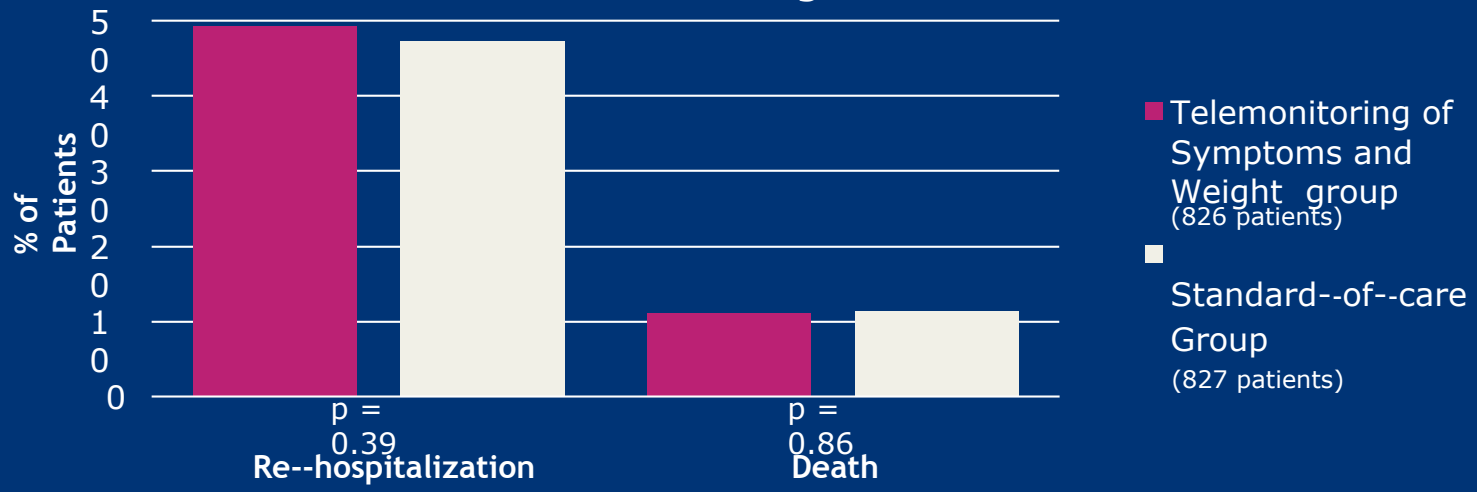
TELE--HF Trial

TELE--MONITORING OF WEIGHT AND SYMPTOMS DO NOT REDUCE READMISSION OR DEATH

- RANDOMIZED STUDY OF 1653 PATIENTS
- PRIMARY ENDPOINT
  - Readmission for any reason or death from any cause within 180 days aQer enrollment
- CONTROL GROUP
  - Standard--of--care (i.e., no tele--monitoring)
- TREATMENT GROUP
  - Tele--monitoring of symptoms and weight



Tele--monitoring resulted in no difference in number of deaths, or readmissions in the hospital.

Chaudhry SI, et al. *N Engl J Med*, 2010.

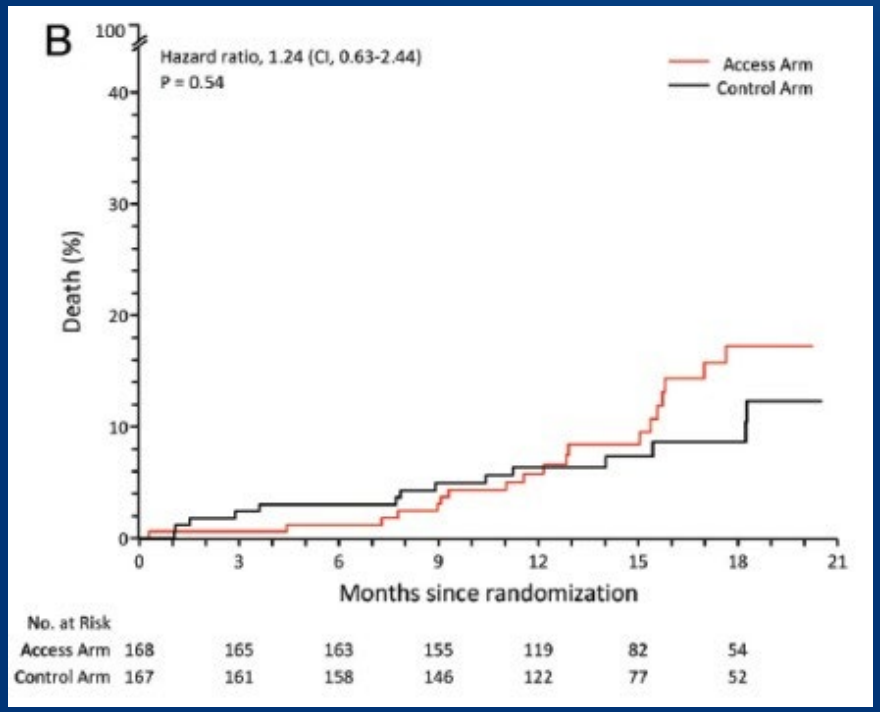
Non--hemodynamic--based Remote Monitoring

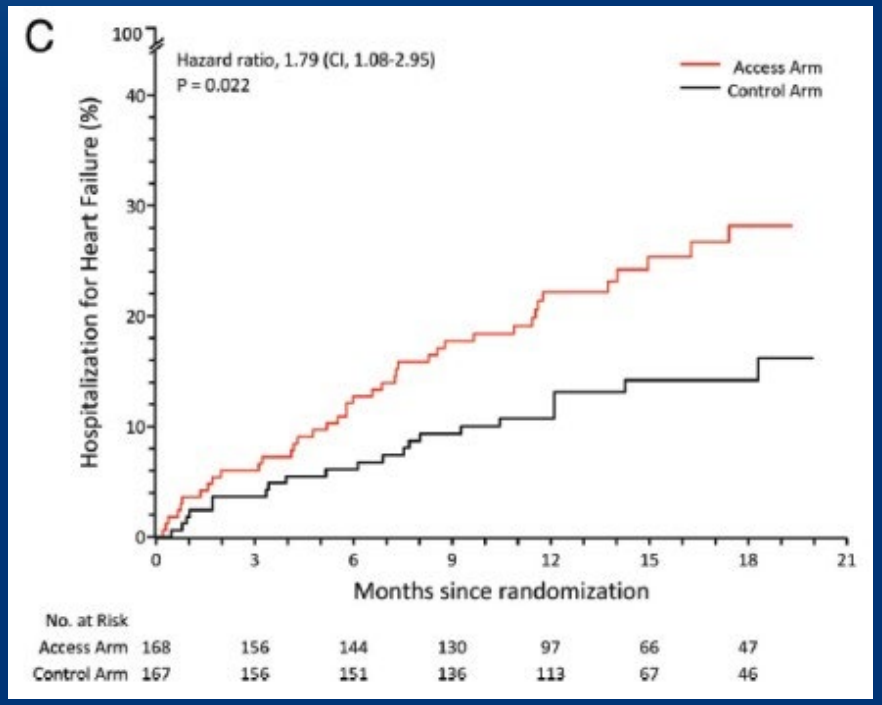
TRIAL	N	PARAMETER MONITORED	IMPACT ON HF HOSPITALIZATION	JOURNAL
TELE--HF[1]	1,653	Signs/symptoms, daily weights	None	*The New England Journal of Medicine, 2010*
TIM--HF[2]	710	Signs/symptoms, daily weights	None	*Circulation, 2011*
HMS[3]	426	Signs/symptoms, daily weights, BP, nurse telephone support	None	*Journal of the American College of Cardiology, 2005*
BEAT--HF[4]	1,437	Signs/symptoms, daily weights, nurse communications	None	*American Heart Association, 2016*
INH[5]	715	Signs/symptoms, telemonitoring, nurse coordinated DM	None	*Circulation Heart Failure, 2012*
DOT--HF[6]	335	Intrathoracic impedance with patient alert	Increased	*Circulation, 2011*
Optilink[7]	1,002	Intrathoracic impedance	None	*European Journal of Heart Failure, 2011*
REM--HF[8]	1,650	Remote monitoring via ICD, CRT--D or CRT--P	None	*European Society of Cardiology, 2017*
MORE CARE[9]	865	Remote monitoring of advanced diagnostics via CRT-	None	*European Journal of Heart Failure, 2016*
Total	8,793	**MULTIPLE TRIALS, > 8,500 PATIENTS:** No reduction in HF hospitalization		

1. Chaudhry SI, et al. *N Engl J Med*, 2010.
2. Koehler F, et al. *Circulation*, 2011.
3. Cleland JG, et al. *J Am Coll Cardiol*, 2005.
4. Ong MK, et al. *JAMA Intern Med*, 2016.
5. Angermann DE, et al. *Circ Heart Fail*, 2012.
6. van Veldhuisen DJ, et al. *Circulation*, 2011.
7. Brachmann J, et al. *Eur J Heart Fail*, 2011.
9. Boriani G, et al. *Eur J Heart Fail*, 2016.
8. Cowie MR, *ESC*. 2016.

DOT--HF Trial

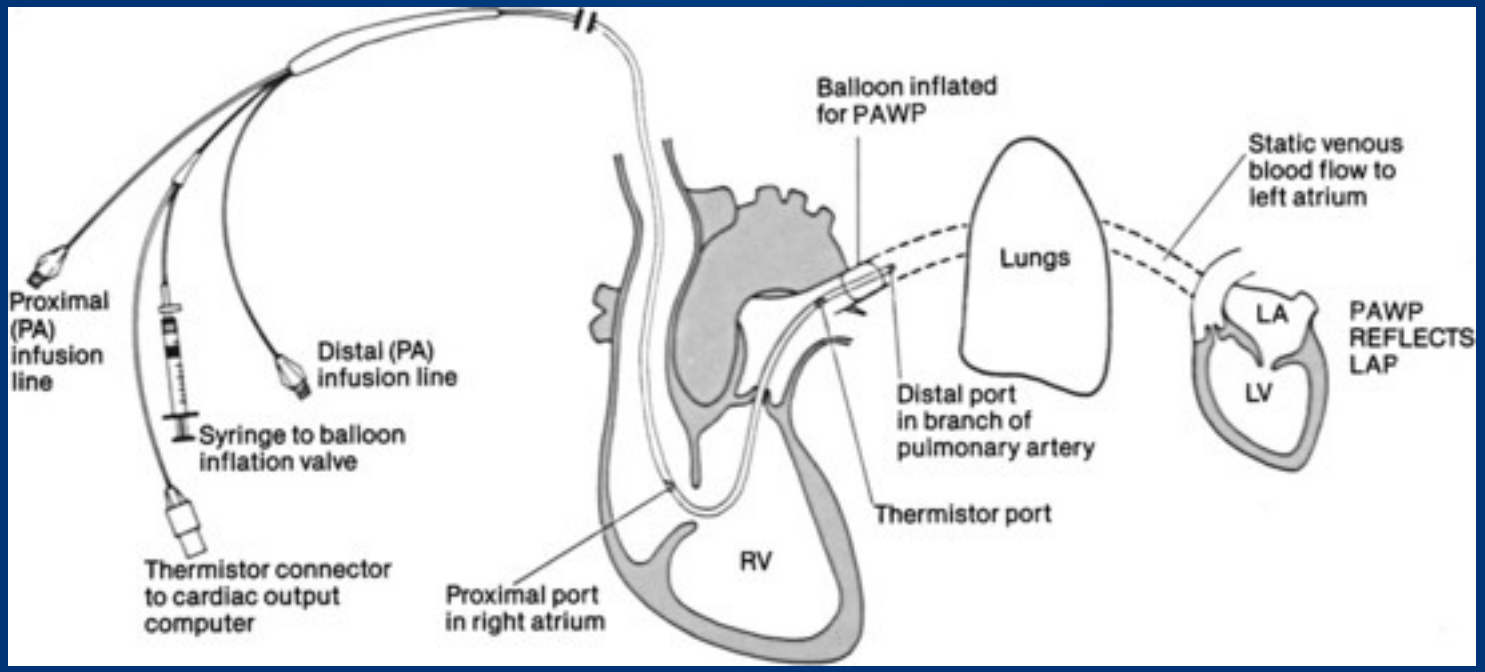
MONITORING IMPEDANCE WITH AUDIBLE ALERT ACTUALLY INCREASED HF HOSPITALIZATIONS





Monitoring intrathoracic impedance (Optivol‡ algorithm, Medtronic) with an audible alert did not improve mortality and actually increased hospitalizations.

van Veldhuisen DJ, et al. *Circulation*, 2011.

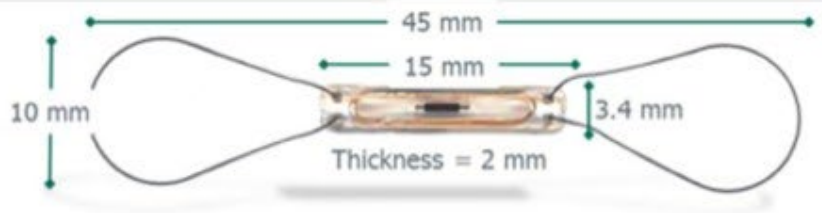

Balloon inflated for PAWP
Static venous blood flow to left atrium
Lungs
LA
LV
PAWP REFLECTS LAP
Proximal (PA) infusion line
Distal (PA) infusion line
Syringe to balloon inflation valve
Distal port in branch of pulmonary artery
Thermistor port
Thermistor connector to cardiac output computer
RV
Proximal port in right atrium

PA catheter

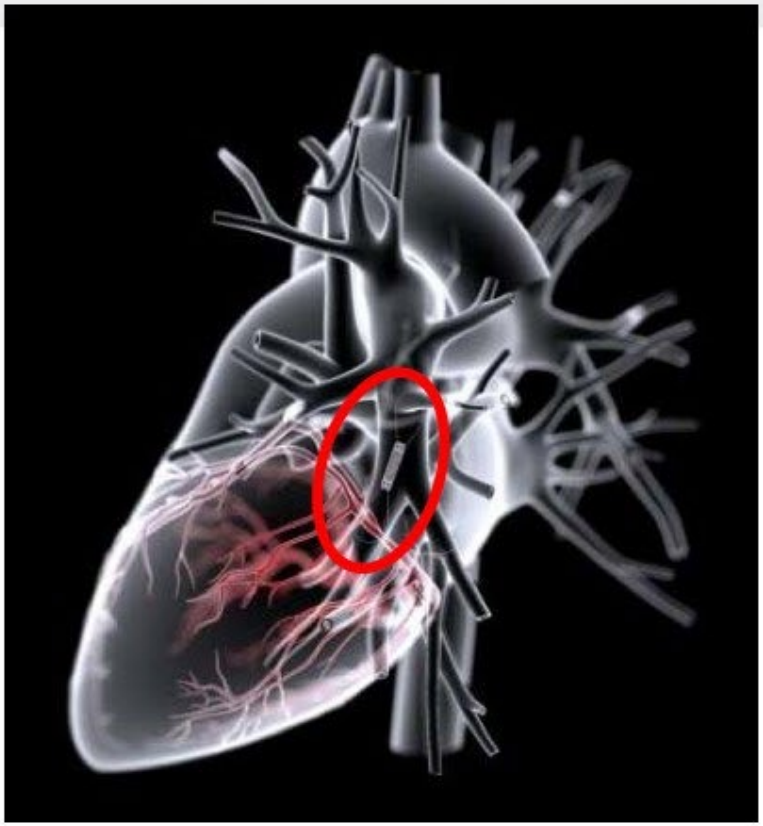
- Not routine to manage congestion
- Use in an inpatient if
  - Refractory Sx despite perceived adequate diuretics
  - Worsening renal function
  - Repeat hospitalizations for congestion
- Implantable sensors for outpatients
  - More changes to GDMT and diuretics
  - 37% relative reduction in HF hospitalization

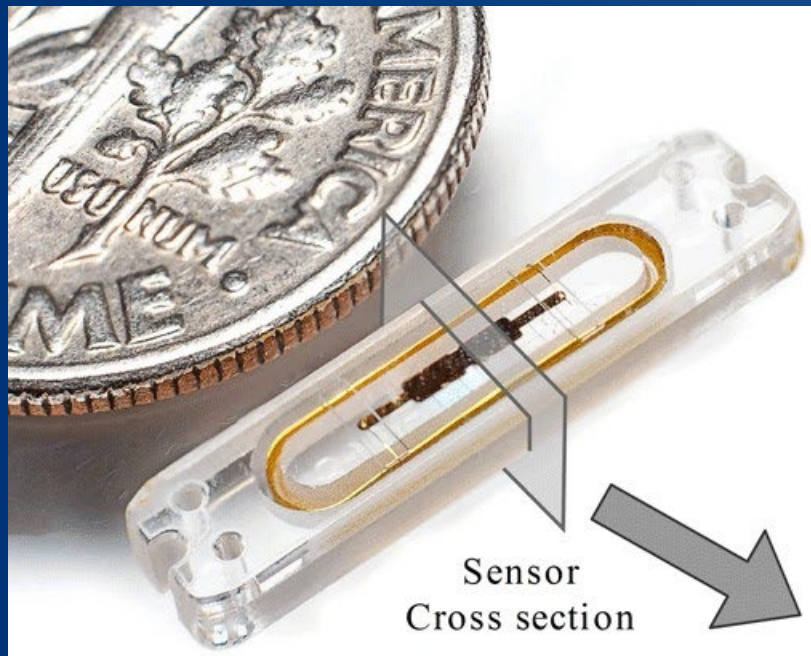
CARDIOMEMS™ HF SYSTEM

The pulmonary artery pressure sensor is implanted via a right heart catheterization procedure via femoral vein approach.

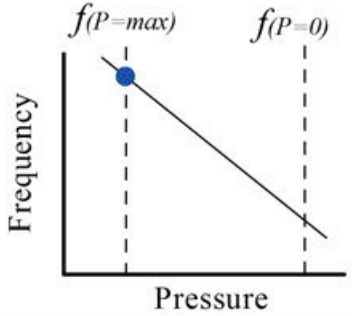


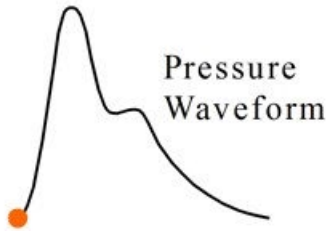
Target location for pulmonary artery pressure sensor

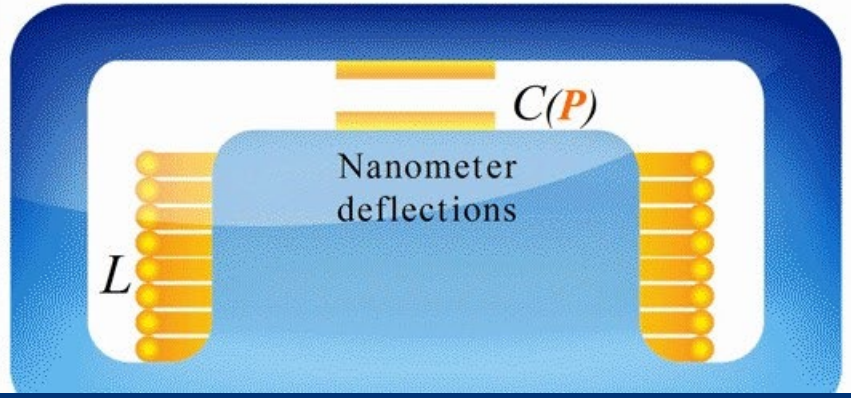




$$f = \frac{1}{2\pi\sqrt{L\ C(P)}}$$



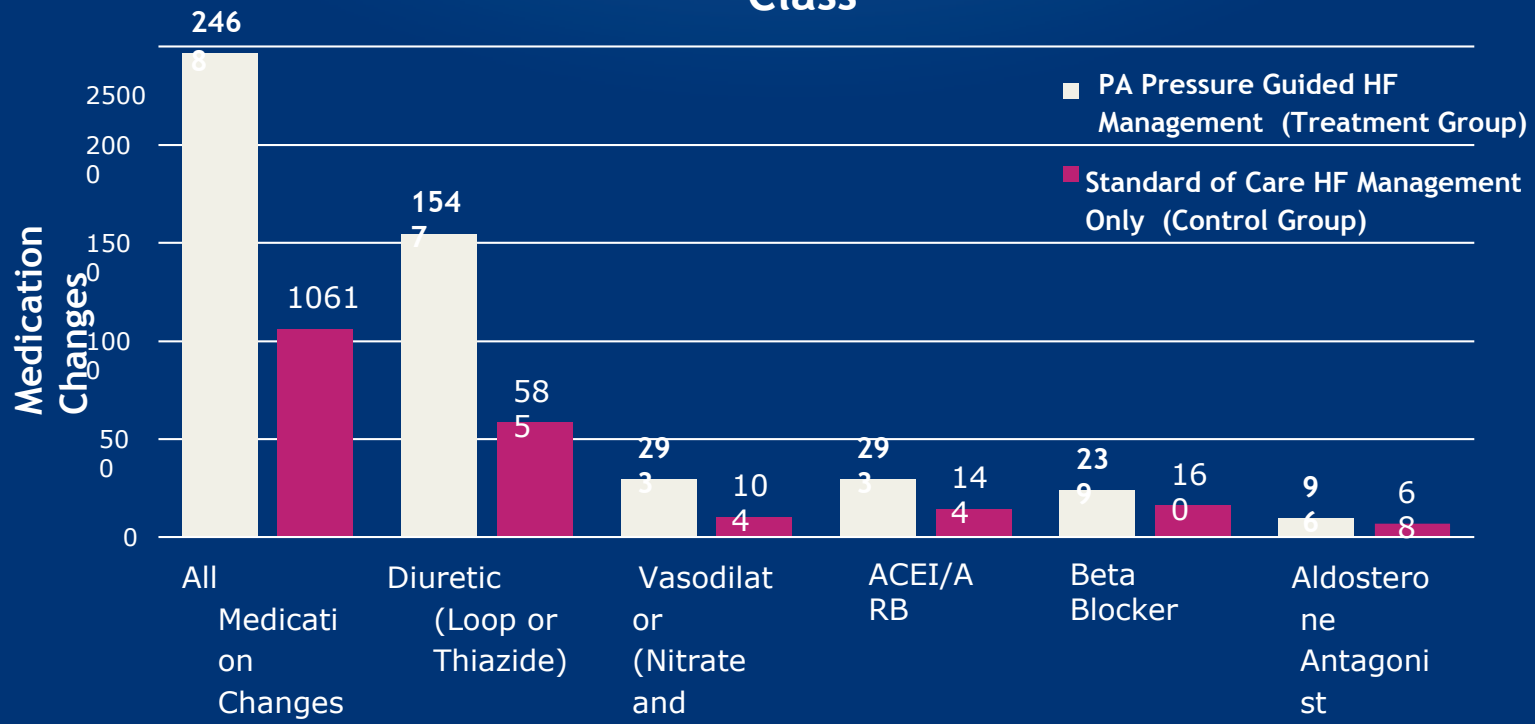




Subgroup Analysis:

PA--GUIDED MEDICAL MANAGEMENT

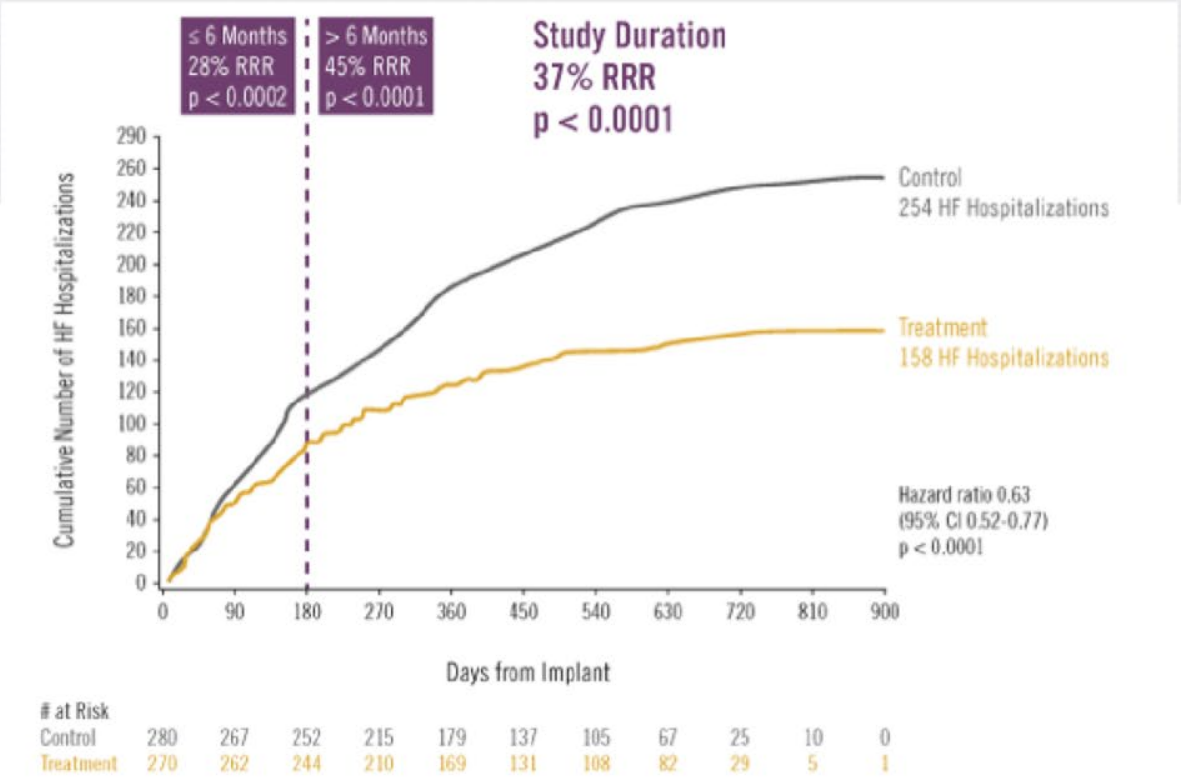
Frequency of Medication Changes by Drug Class



Medication changes based on PA pressure information were **MORE EFFECTIVE IN REDUCING HF HOSPITALIZATIONS** than using signs and symptoms alone.

Costanzo, et al. *J Am Coll Cardiol Heart Failure*, 2016.

CHAMPION CLINICAL TRIAL: PA PRESSURE-GUIDED THERAPY REDUCES HF HOSPITALIZATIONS



Patients managed with PA pressure data had **significantly fewer HF hospitalizations** as compared to the control group.

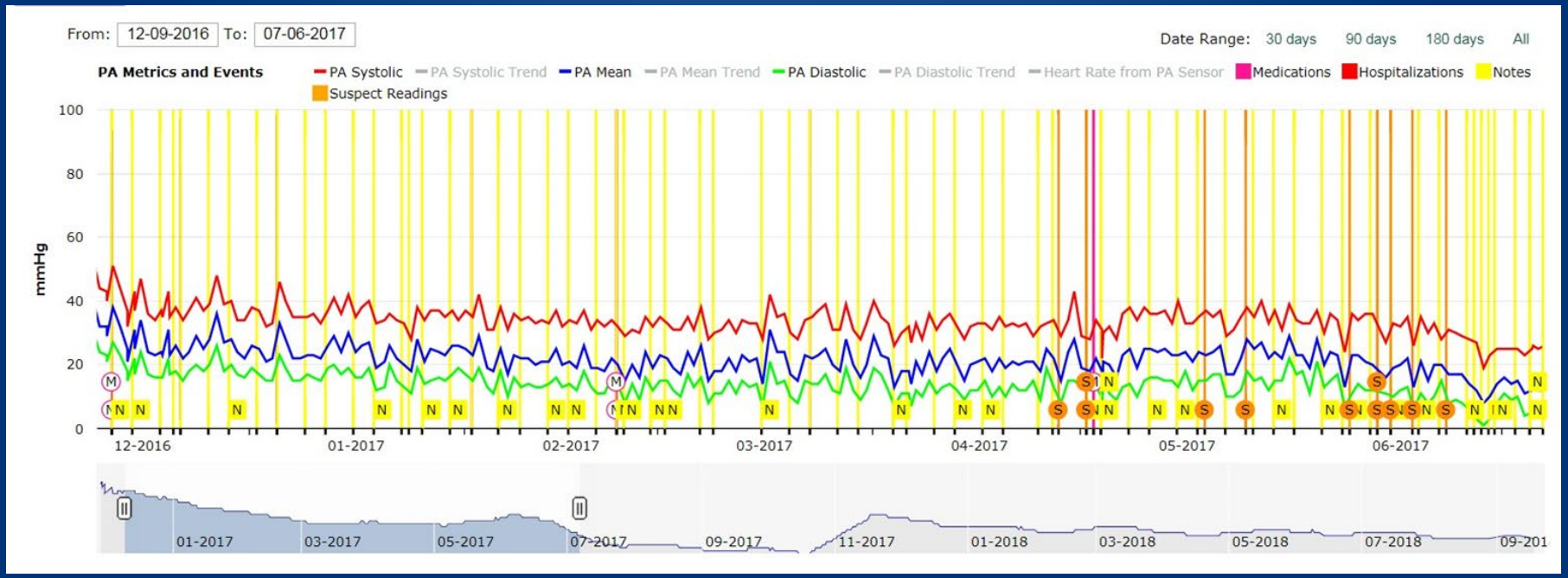
Abraham WT, et al. Lancet, 2011.

NNT to Prevent One HF Hospitalization

• PART 1: RANDOMIZED ACCESS

INTERVENTION	TRIAL	MEAN DURATION OF RANDOMIZED FOLLOW--UP	ANNUALIZED REDUCTION IN HF Hospitalization RATES	NNT/YEAR TO PREVENT 1 HF HOSPITALIZATION
Beta--blocker[1]	COPERNICUS	10 months	33%	7
Aldosterone antagonist[2]	RALES	24 months	36%	7
CRT[3]	CARE--HF	29 months	52%	7
Beta--blocker[4]	MERIT--HF	12 months	29%	15
ACE inhibitor[5]	SOLVD	41 months	30%	15
Aldosterone antagonist[6]	EMPHASIS--HF	21 months	38%	16
Digoxin[7]	DIG	37 months	24%	17
Angiotensin receptor blocker[8]	Val--HeFT	23 months	23%	18
Angiotensin receptor blocker[9]	CHARM	40 months	27%	19
PA pressure monitoring[10]	CHAMPION	18 months	33%	**4**

PA pressure monitoring led to lower NNT
to prevent one hf--related hospitalization vs. other therapies


From: 12-09-2016 To: 07-06-2017
Date Range: 30 days 90 days 180 days All
PA Metrics and Events
PA Systolic
PA Systolic Trend
PA Mean
PA Mean Trend
PA Diastolic
PA Diastolic Trend
Heart Rate from PA Sensor
Medications
Hospitalizations
Notes
Suspect Readings
mmHg
100
80
60
40
20
0
12-2016
01-2017
02-2017
03-2017
04-2017
05-2017
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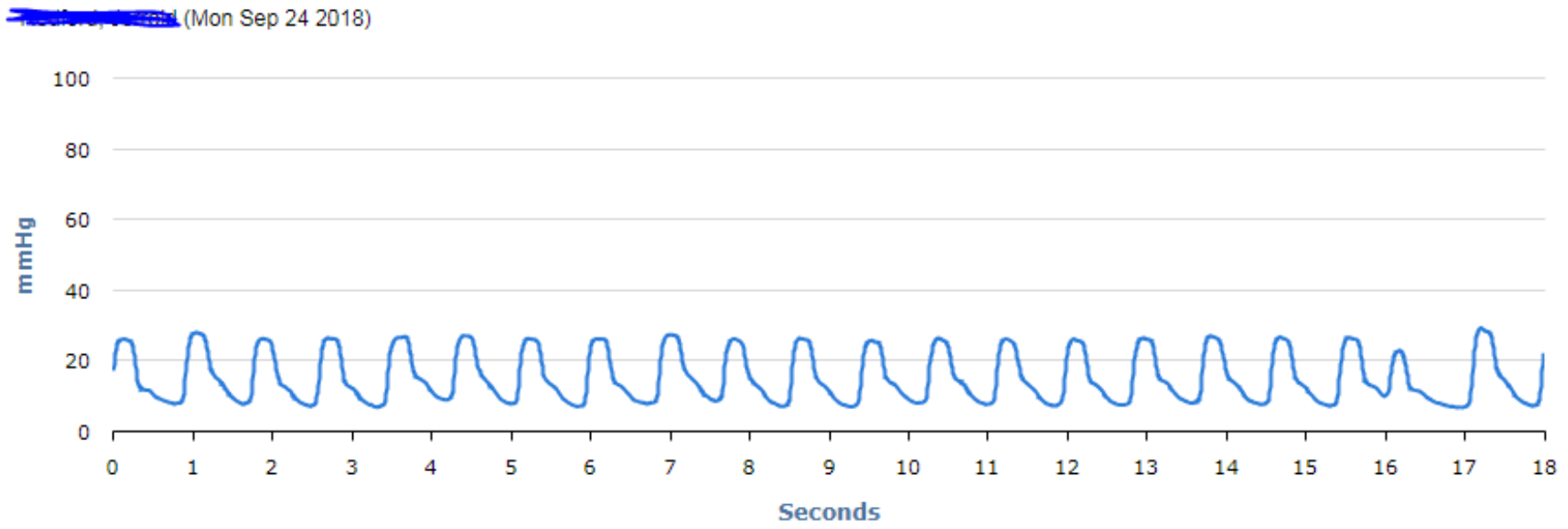
11-2017
01-2018
03-2018
05-2018
07-2018
09-201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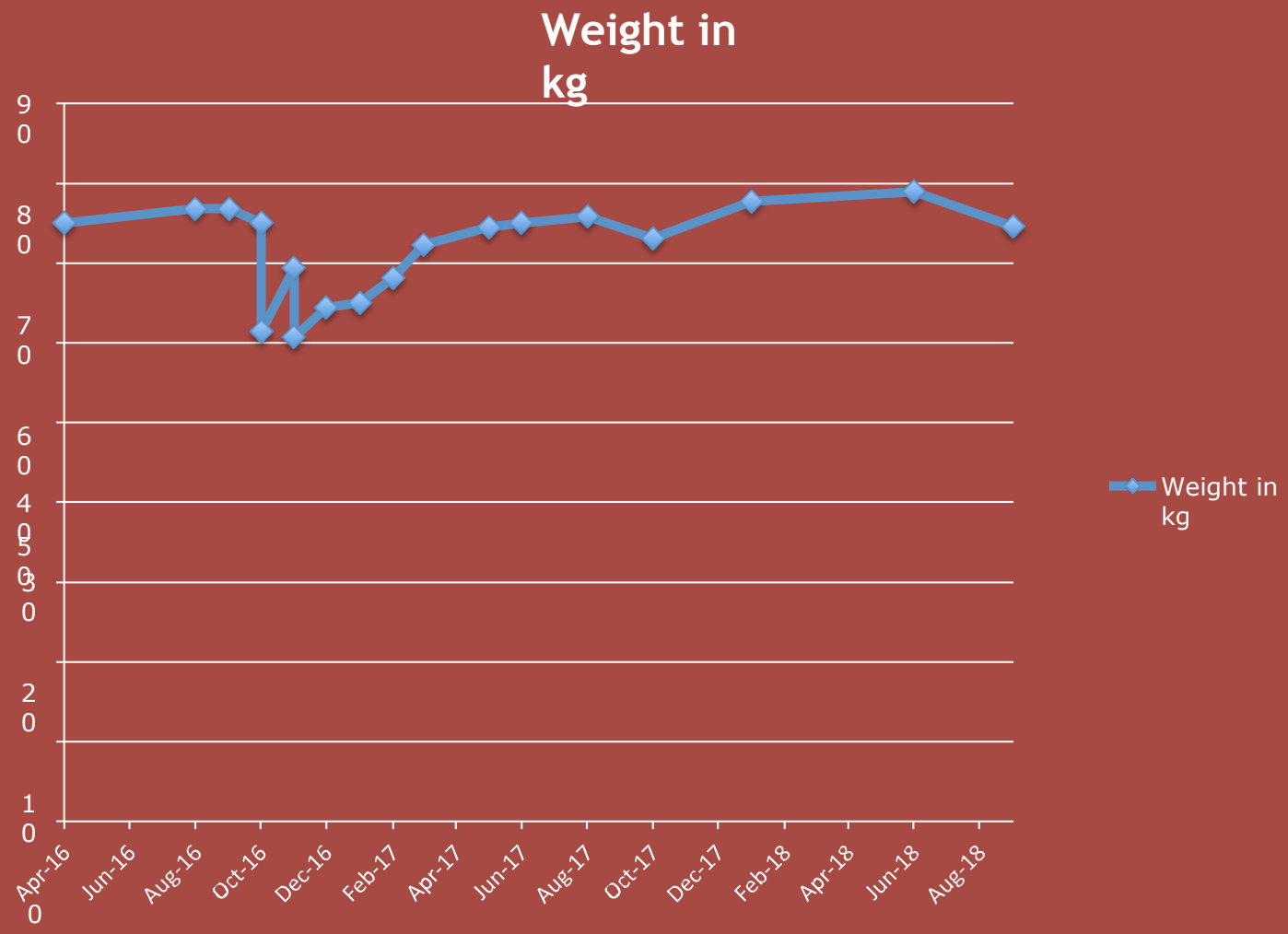
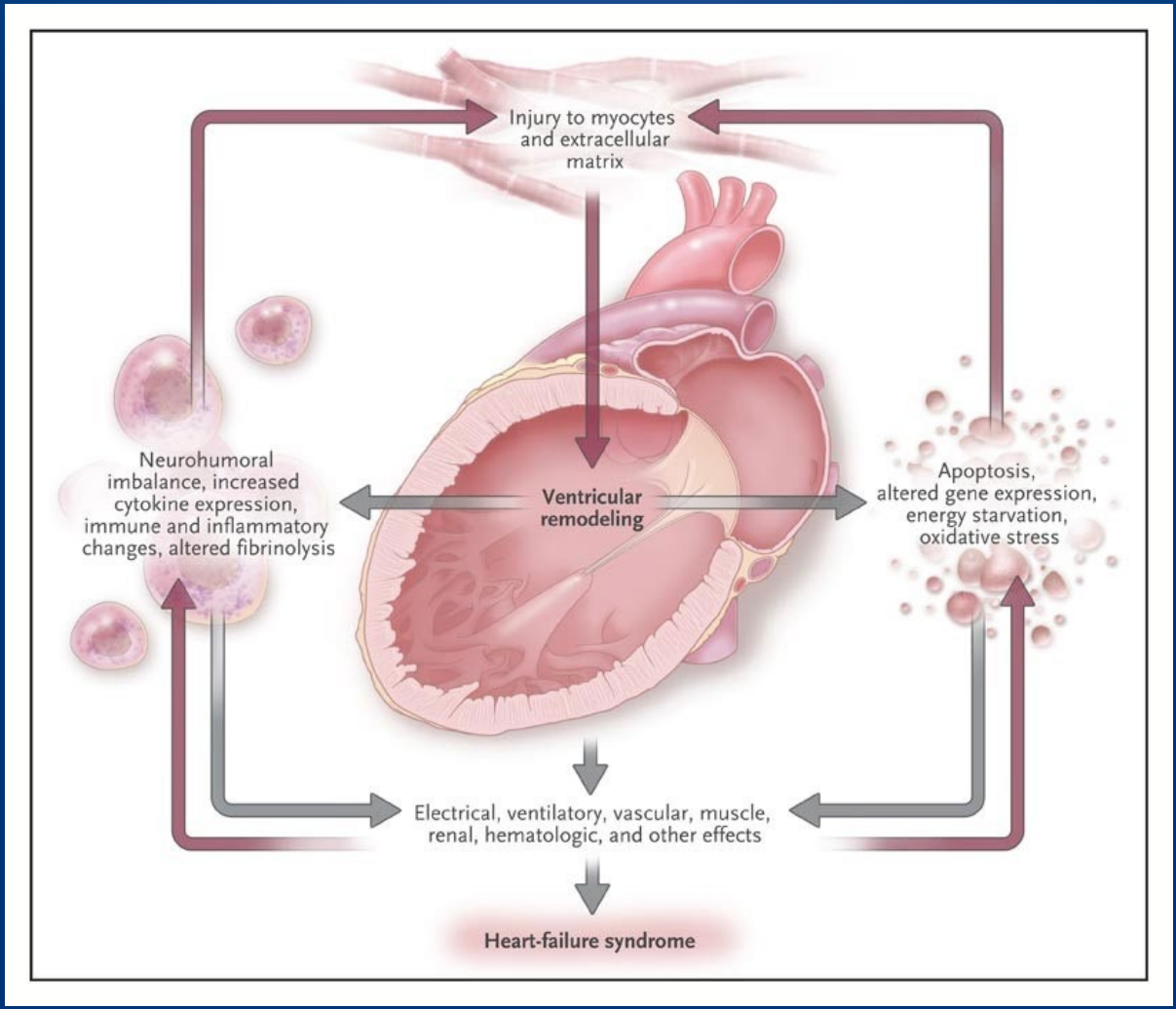
100
80
60
40
20
0
mmHg
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18
Seconds


Weight in kg
90
80
70
60
50
40
30
20
10
0
Apr-16
Jun-16
Aug-16
Oct-16
Dec-16
Feb-17
Apr-17
Jun-17
Aug-17
Oct-17
Dec-17
Feb-18
Apr-18
Jun-18
Aug-18
Weight in kg

HFrEF

- EF<40% with symptomatic heart failure
- Includes “recovered” ejection fraction
- Excludes pts with tachycardia--induced cardiomyopathy

Pathophysiology of Systolic Heart Failure



McMurray J. N Engl J Med 2010;362:228-238

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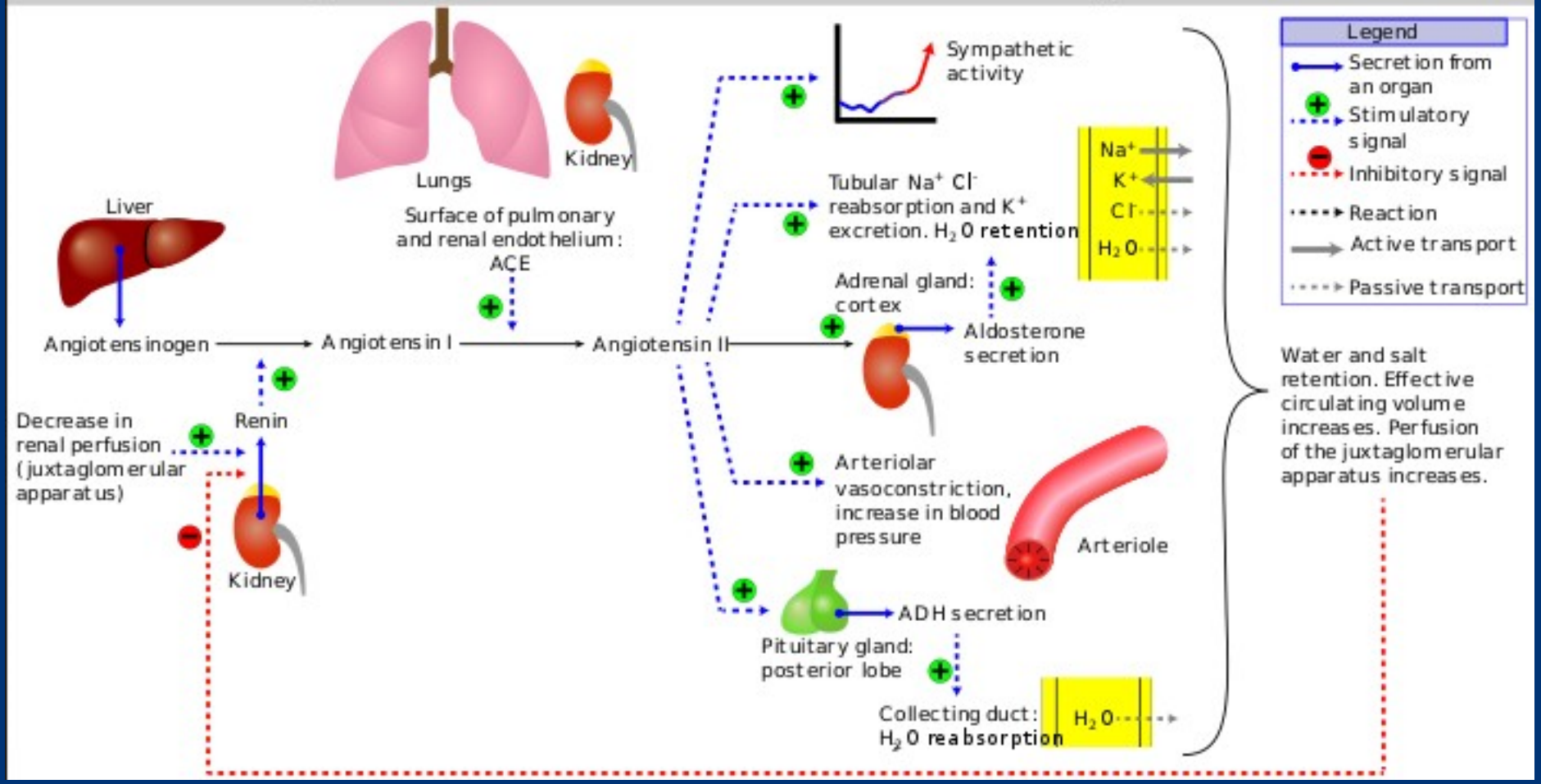
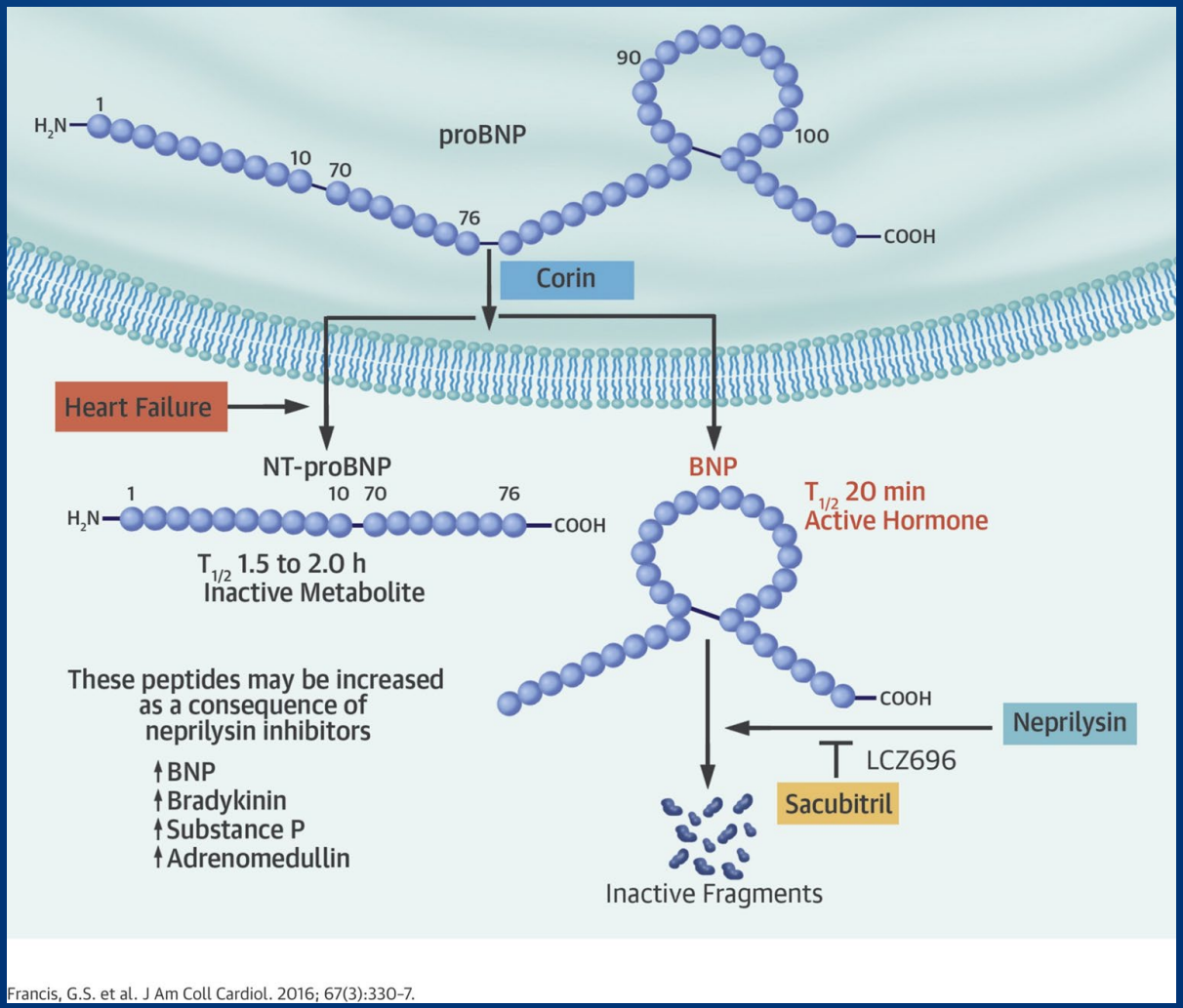
Renin-angiotensin-aldosterone system





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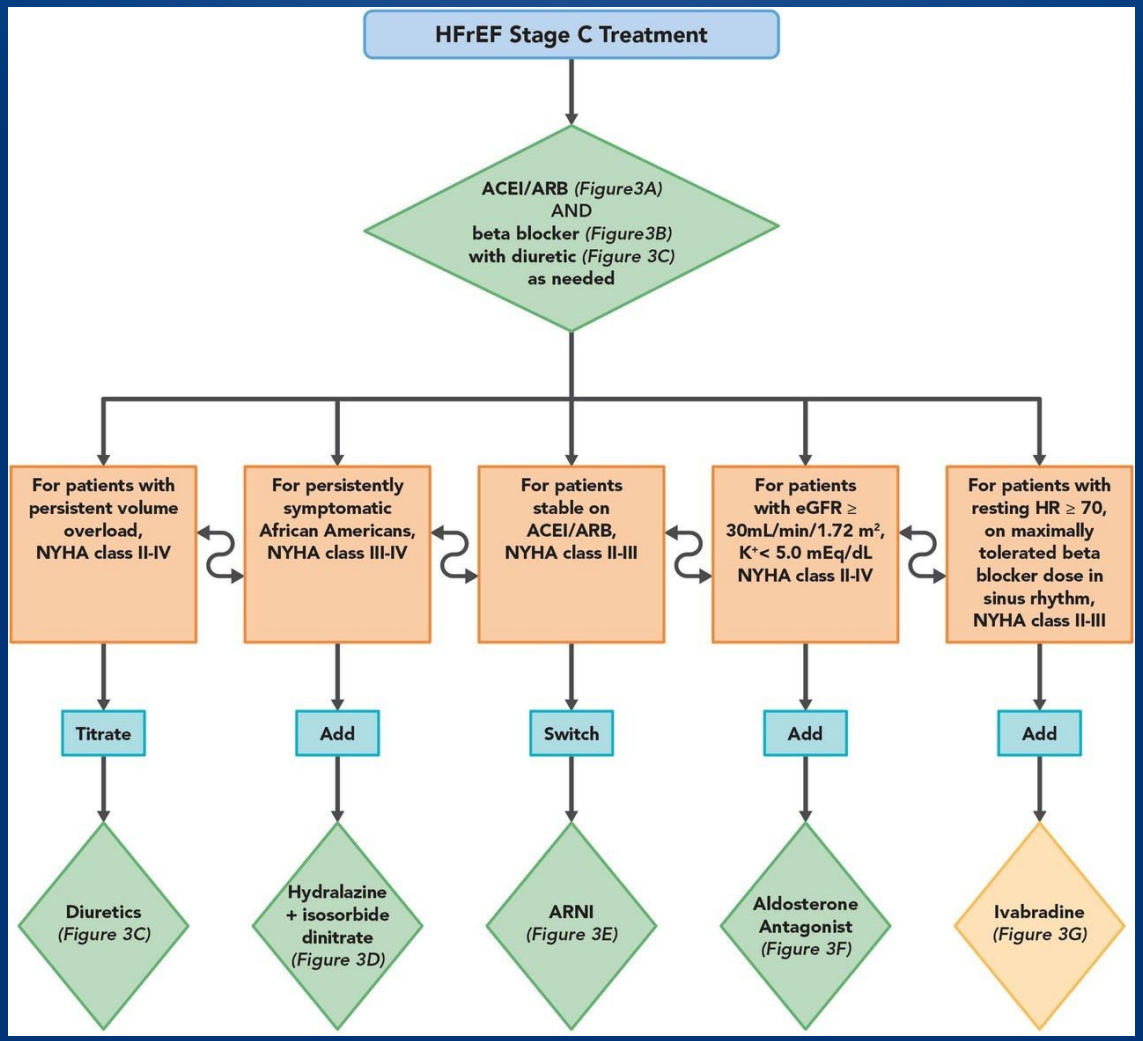
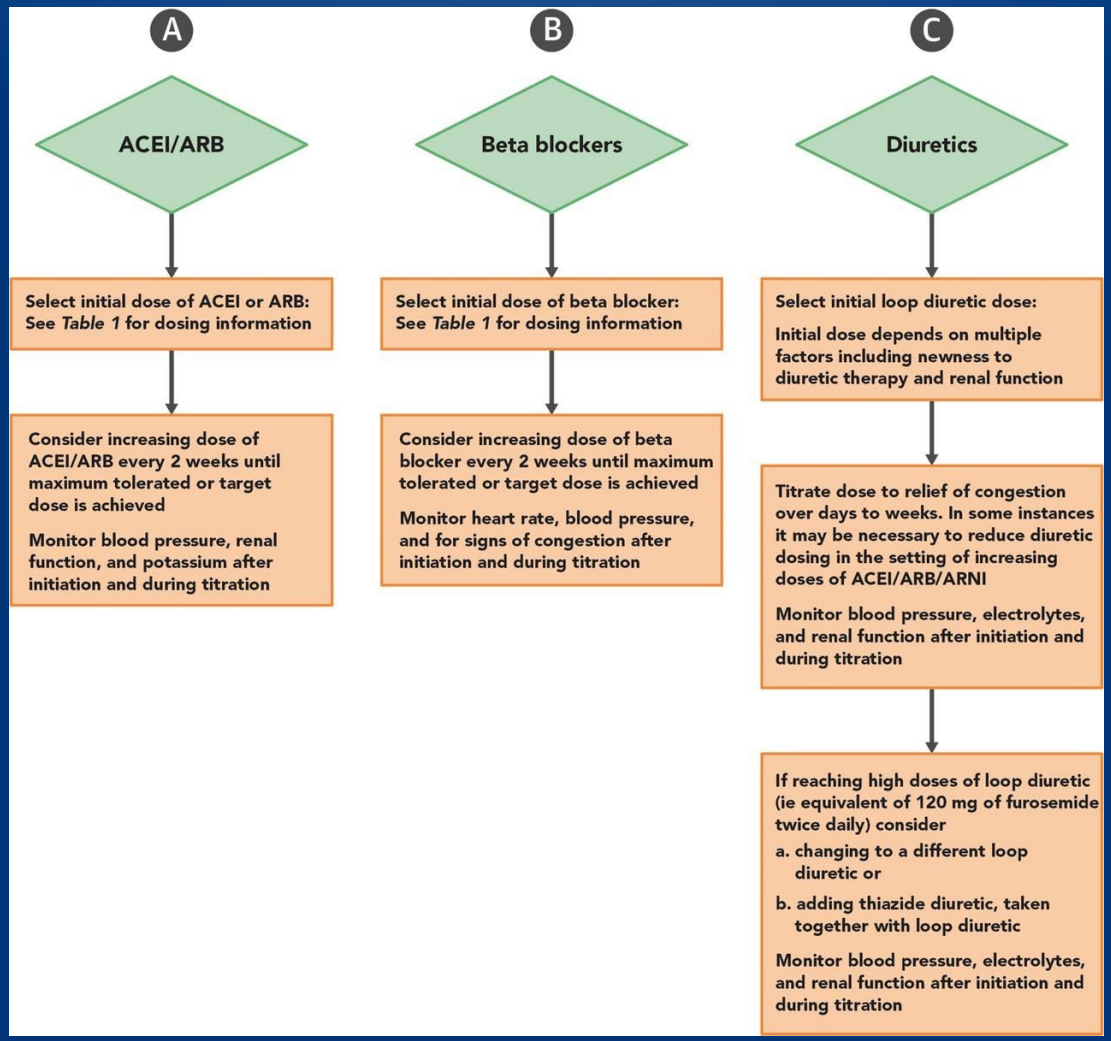
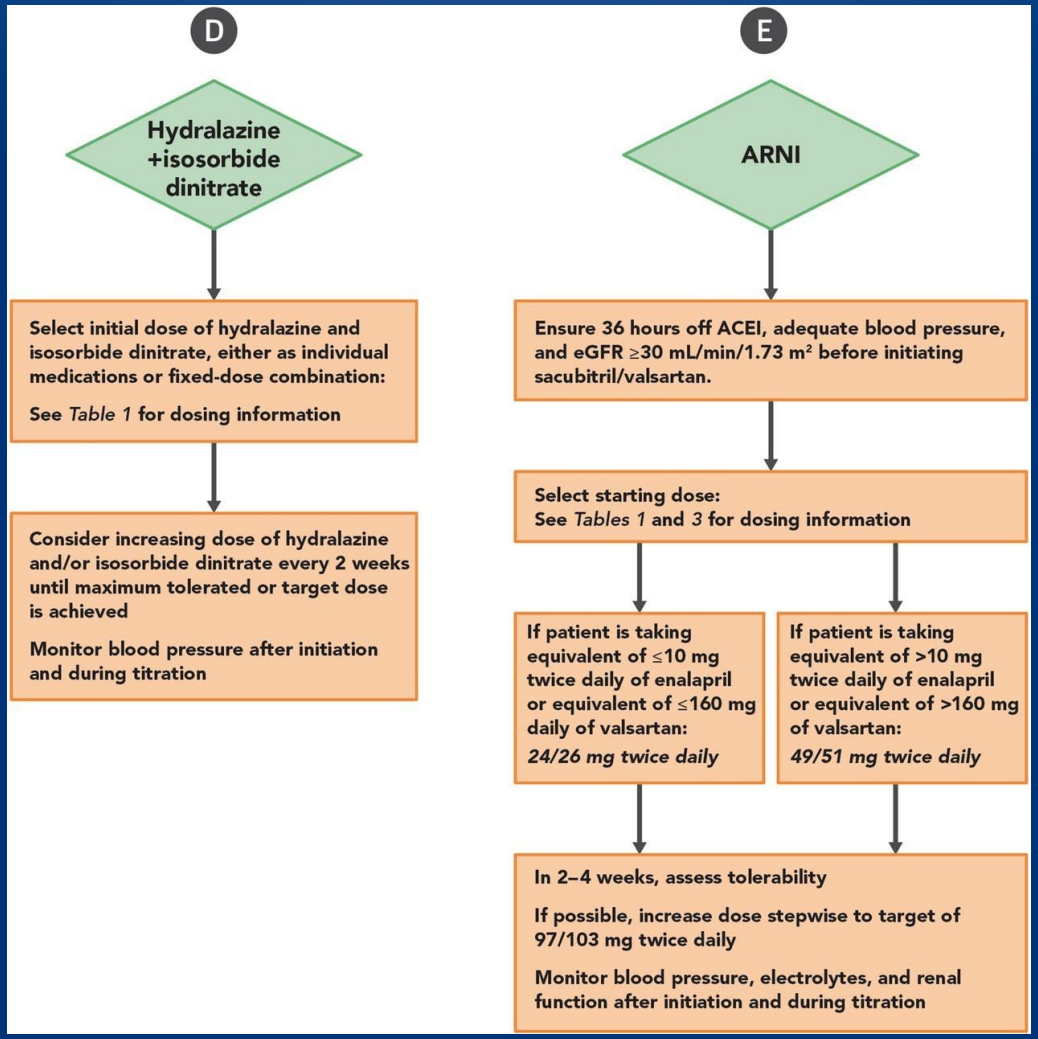
J Am Coll Cardiol. 2016;67(3):330-337.
doi:10.1016/j.jacc.2015.10.073



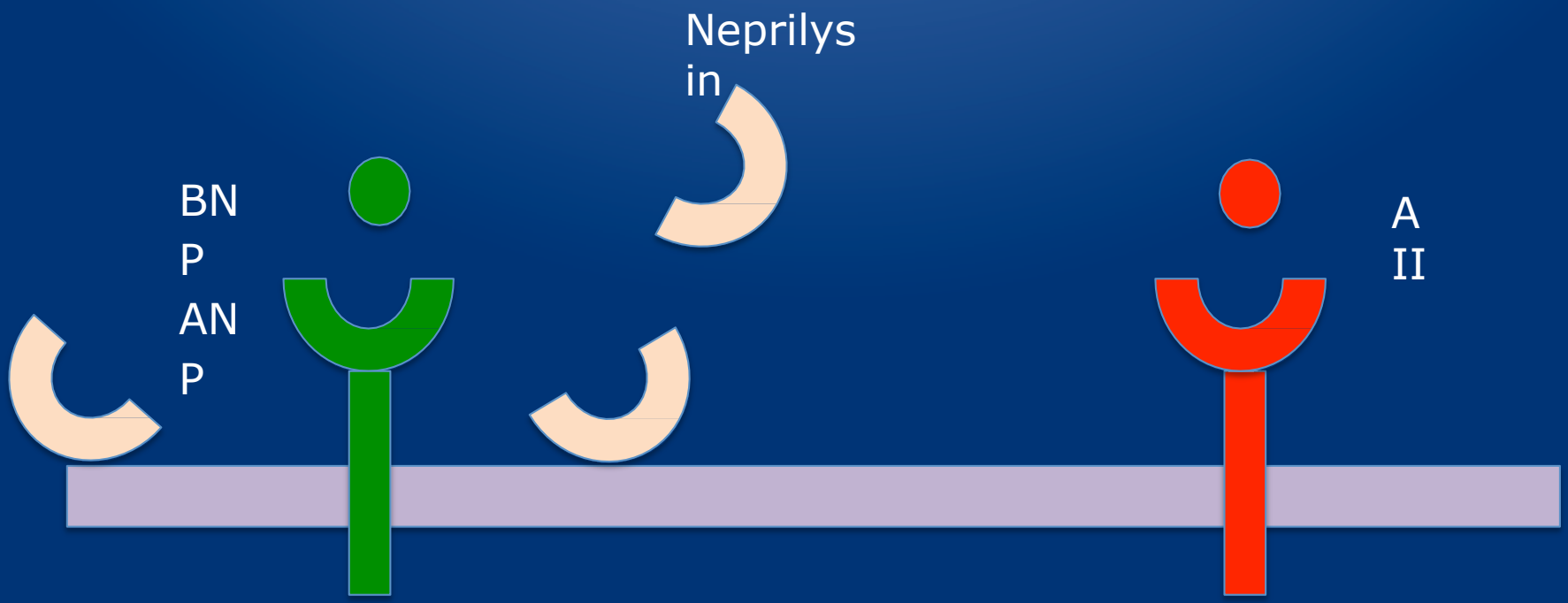
Clyde W. Yancy et al. JACC 2018;71:201-230



Clyde W. Yancy et al. JACC 2018;71:201-230

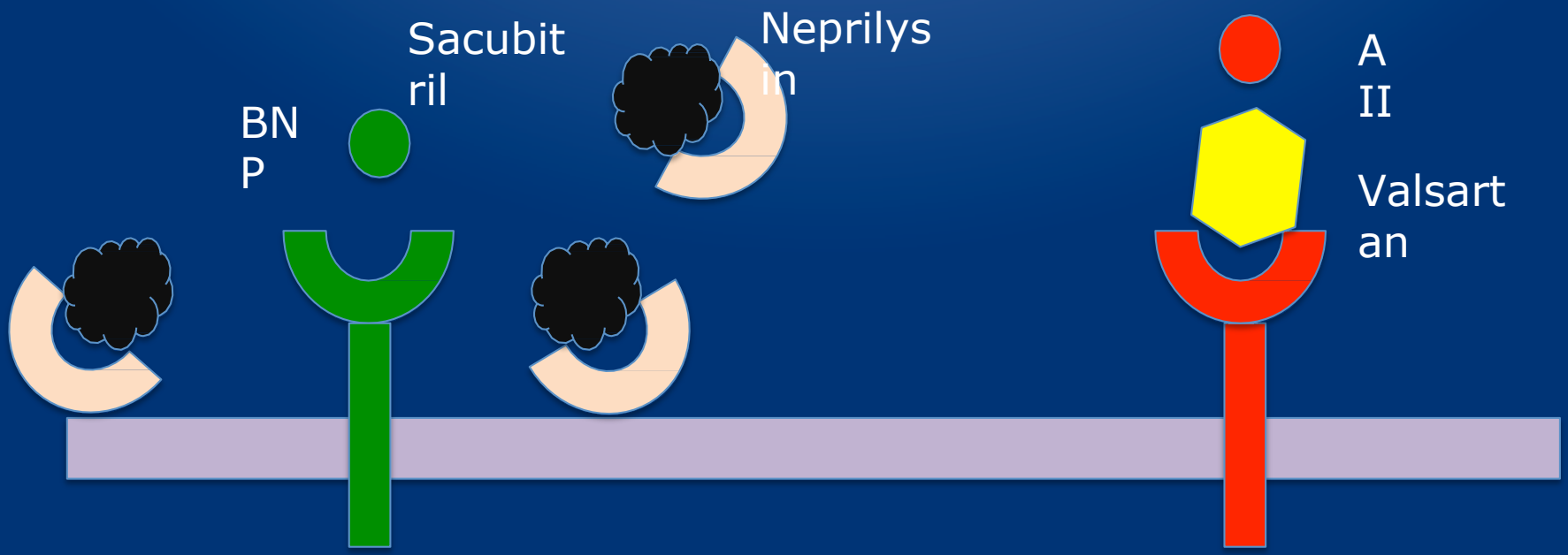


Clyde W. Yancy et al. JACC 2018;71:201-230



Vasodilation Natriuresis Diuresis
Decrease fibrosis
Decrease hypertrophy

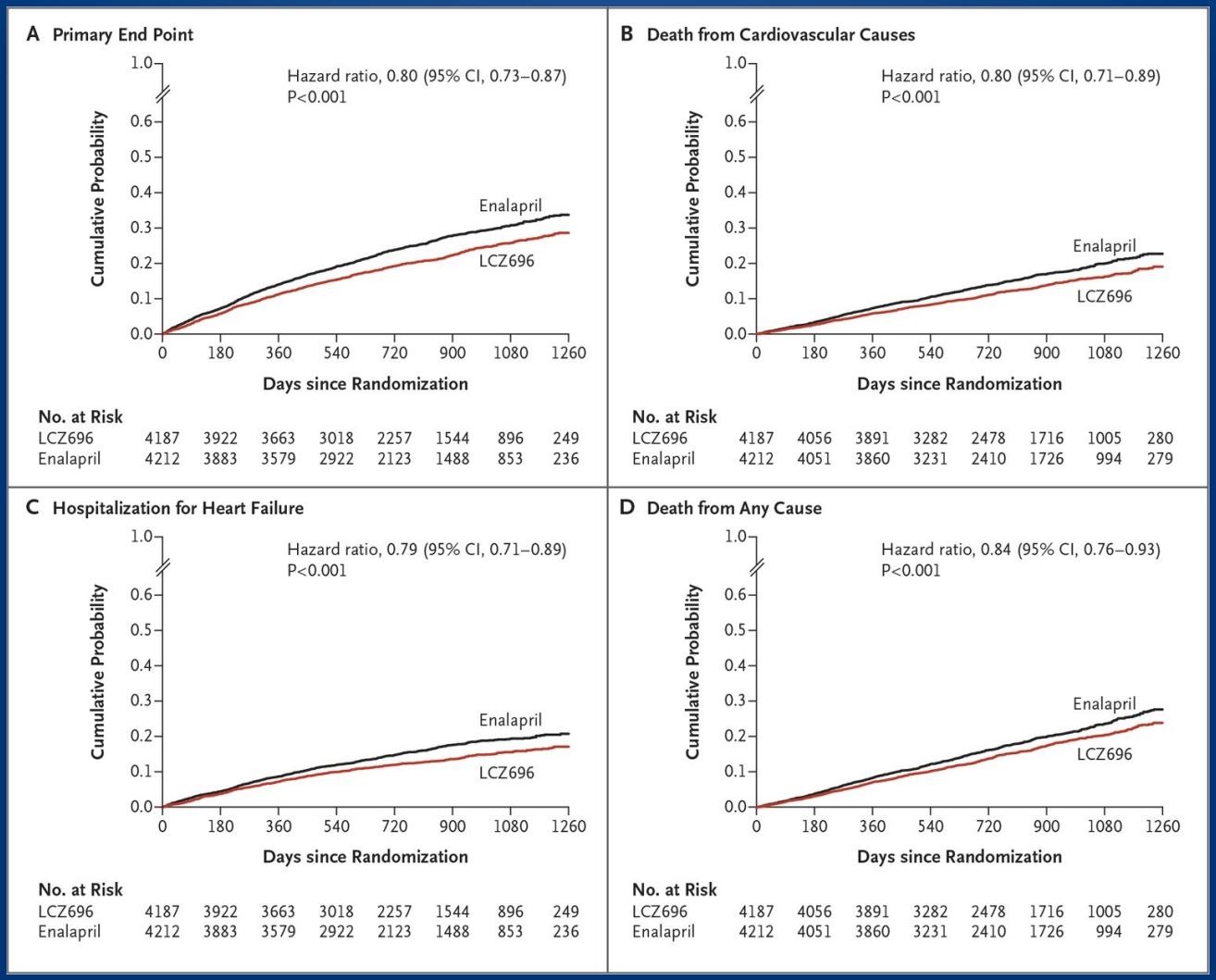
Vasoconstriction
Na retention
Water retention
Increase fibrosis
Increase hypertrophy



Vasodilation
Natriuresis
Diuresis
Decrease
fibrosis
Decrease
hypertrophy

Vasoconstrict
ion Na
retention
Water
retention
Increase
fibrosis
Increase
hypertrophy

Kaplan–Meier Curves for Key Study Outcomes, According to Study Group.



McMurray JJV et al. N Engl J Med 2014;371:993-1004

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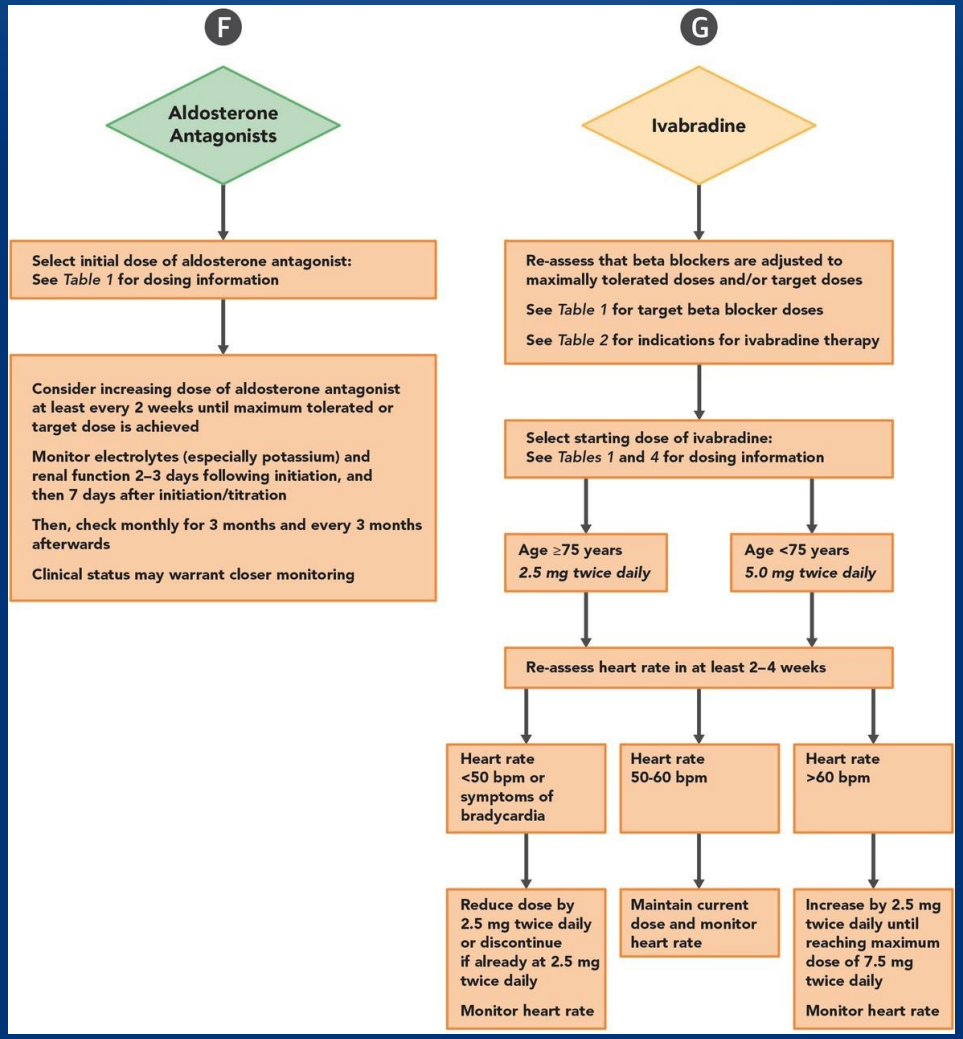


Clyde W. Yancy et al. JACC 2018;71:201-230

TABLE 1 Starting and Target Doses of Select Guideline-Directed Medical Therapy for HF (3,15)

	Starting dose	Target dose
Beta Blockers		
Bisoprolol	1.25 mg once daily	10 mg once daily
Carvedilol	3.125 mg twice daily	25 mg twice daily for weight <85 kg and 50 mg twice daily for weight ≥85 kg
Metoprolol succinate	12.5-25 mg/d	200 mg daily
ARNI		
Sacubitril/valsartan	24/26 mg-49/51 mg twice daily	97/103 mg twice daily
ACEI		
Captopril	6.25 mg 3× daily	50 mg 3x daily
Enalapril	2.5 mg twice daily	10-20 mg twice daily
Lisinopril	2.5-5 mg daily	20-40 mg daily
Ramipril	1.25 mg daily	10 mg daily
ARB		
Candesartan	4-8 mg daily	32 mg daily
Losartan	25-50 mg daily	150 mg daily
Valsartan	40 mg twice daily	160 mg twice daily
Aldosterone antagonists		
Eplerenone	25 mg daily	50 mg daily
Spironolactone	12.5-25 mg daily	25-50 mg daily
Vasodilators		
Hydralazine	25 mg 3× daily	75 mg 3× daily
Isosorbide dinitrate*	20 mg 3× daily	40 mg 3× daily
Fixed-dose combination isosorbide dinitrate/ hydralazine†	20 mg/37.5 mg (one tab) 3× daily	2 tabs 3× daily
Ivabradine		
Ivabradine	2.5-5 mg twice daily	Titrate to heart rate 50-60 bpm. Maximum dose 7.5 mg twice daily

Stage C HFrEF Titration of Medical Therapy over months

- Adjust doses q2wks—at the fastest!
  - Check creatinine/potassium each step of ACEi/ARB/ ARNI 1--2 weeks later; 3 d later for MRA
  - Watch for worsened failure each step of BB
  - Reassess/reduce diuretic dose (recheck lytes 3 d later if increase dose)
- Achieve GDMT/max tolerated doses 3--6 mo aQer dx—at the fastest!
- Reassess LV 3 mo aQer achieve stable GDMT/max doses

What doesn't work for Stage C HFrEF

- Digoxin
- Diltiazem, verapamil
- Combination of ACEi with and ARB
- Tekturna with ACEi or ARB
- Ultrafiltration, nesiritide, tolvaptan
- Inotropes may be needed for inpatients, not indicated for ongoing treatment

HFrEF Treatment, Stage C

- Medical treatment
- Devices
  - ICD
  - CRT, CRT--D
- Revascularization
  - CABG
  - PCI?
- PVI for AF
- Surgery/intervention for secondary MR

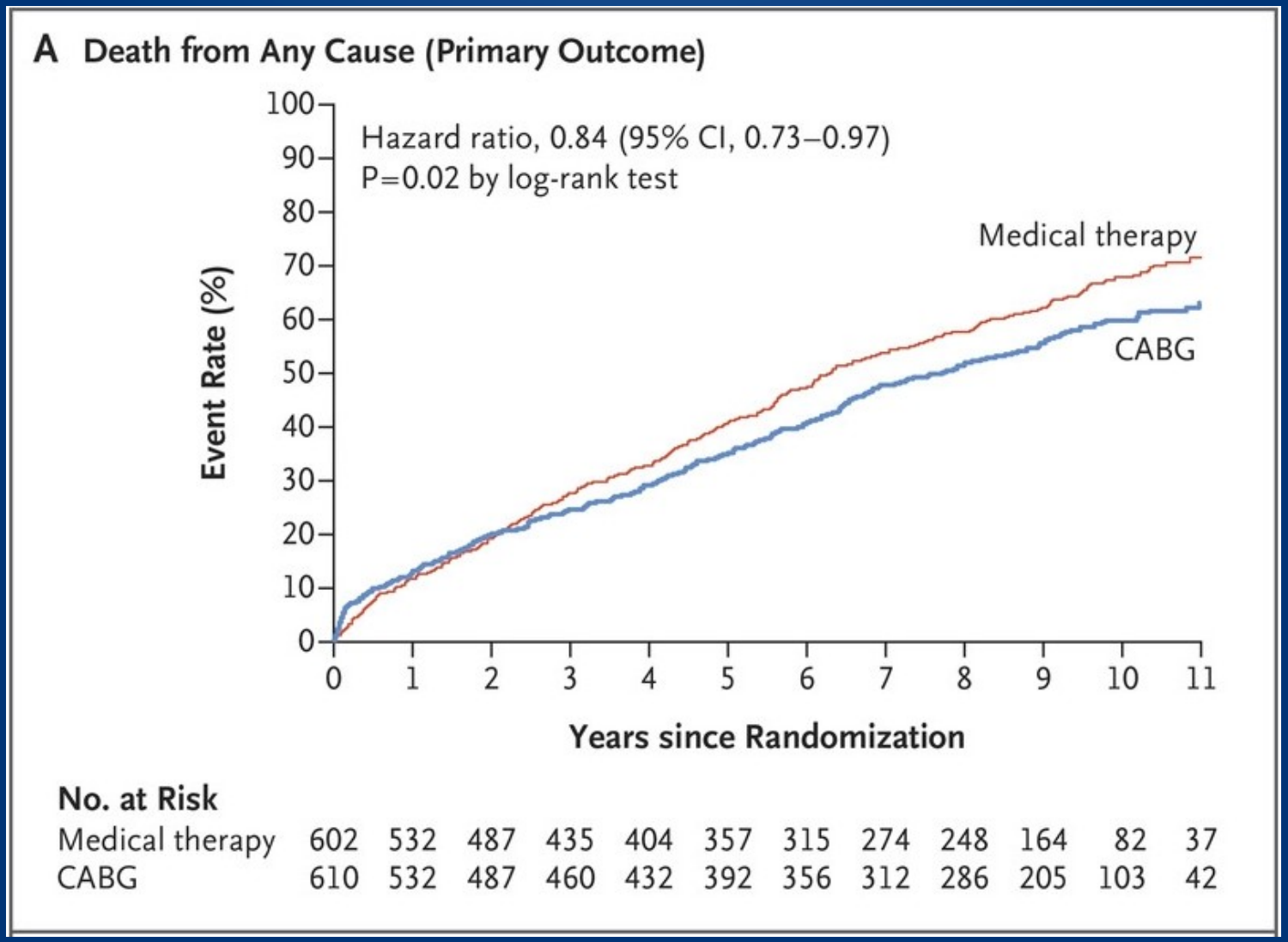
HFrEF Treatment, Stage D

- Continue feasible prior treatment
- LVAD
  - Bridge to transplant
  - Destination therapy
- Transplant
- Hospice/palliative care
  - Decongestion
    - Diuretics
    - Thoracentesis/paracentesis
  - Inotropes

HFrEF Treatment, Stage C

- Medical treatment
- Devices
  - ICD
  - CRT, CRT--D
- Revascularization
  - CABG
  - PCI
- Surgery/intervention for secondary MR
- PVI for AF

CABG in



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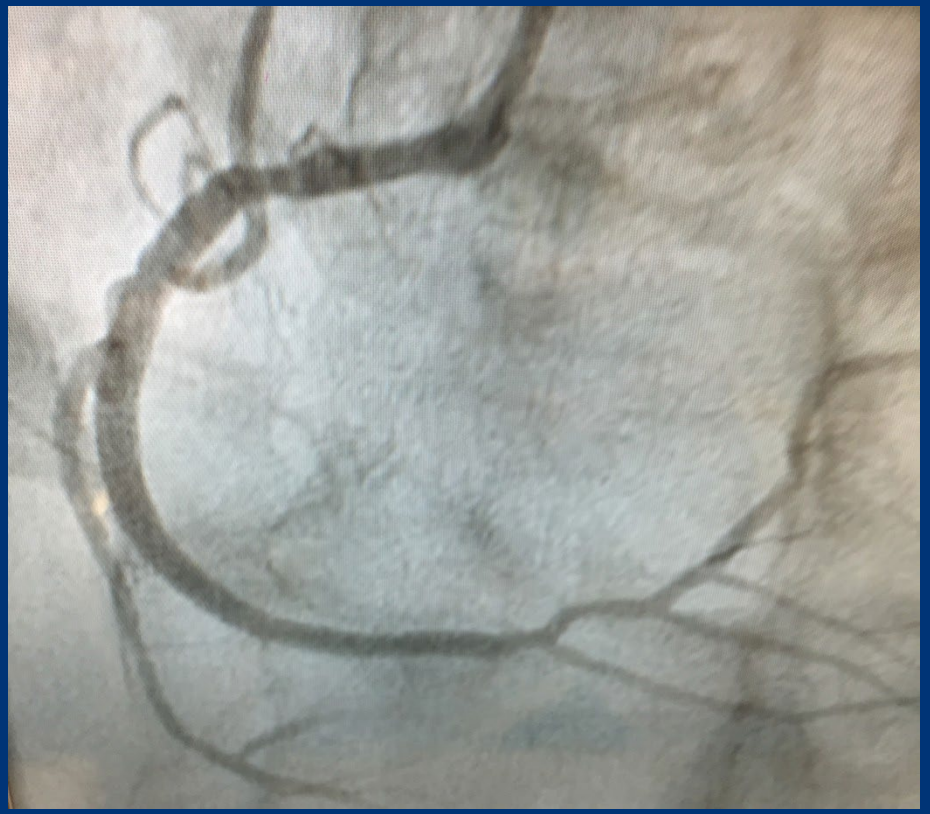
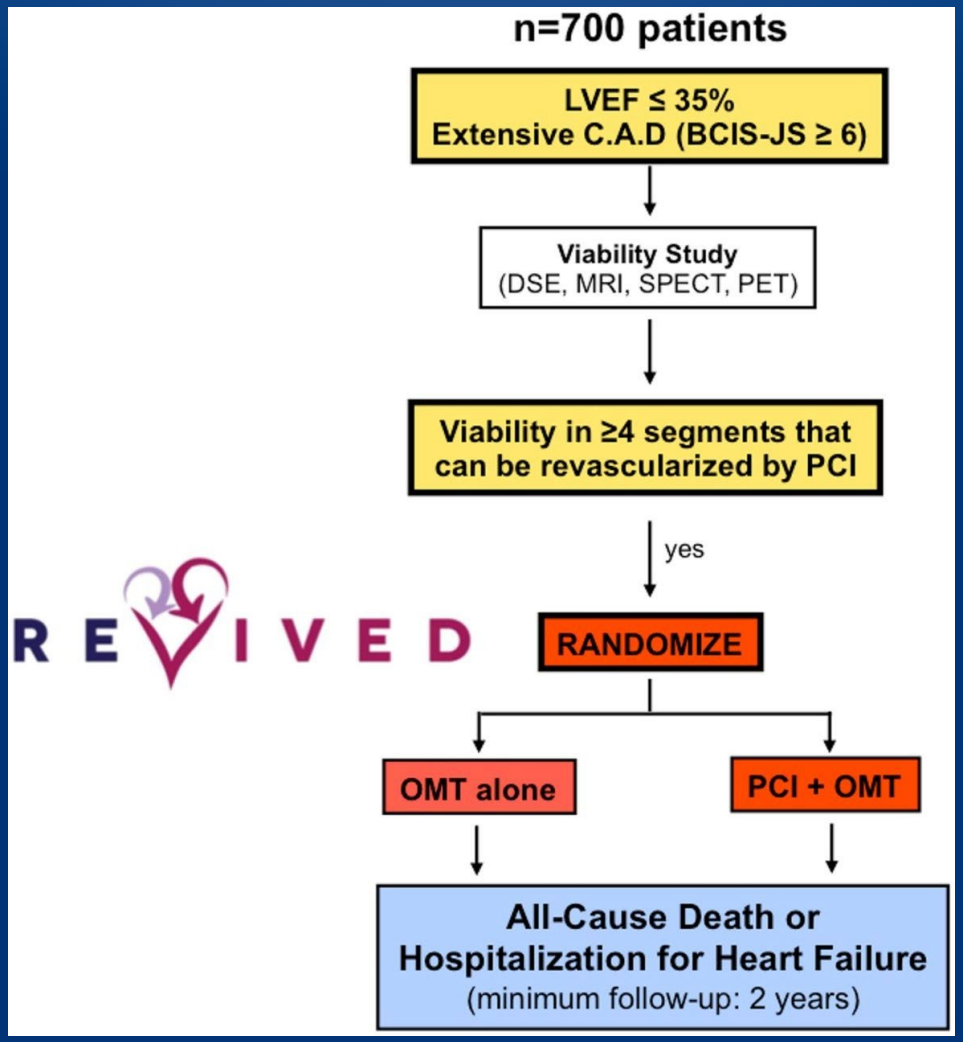


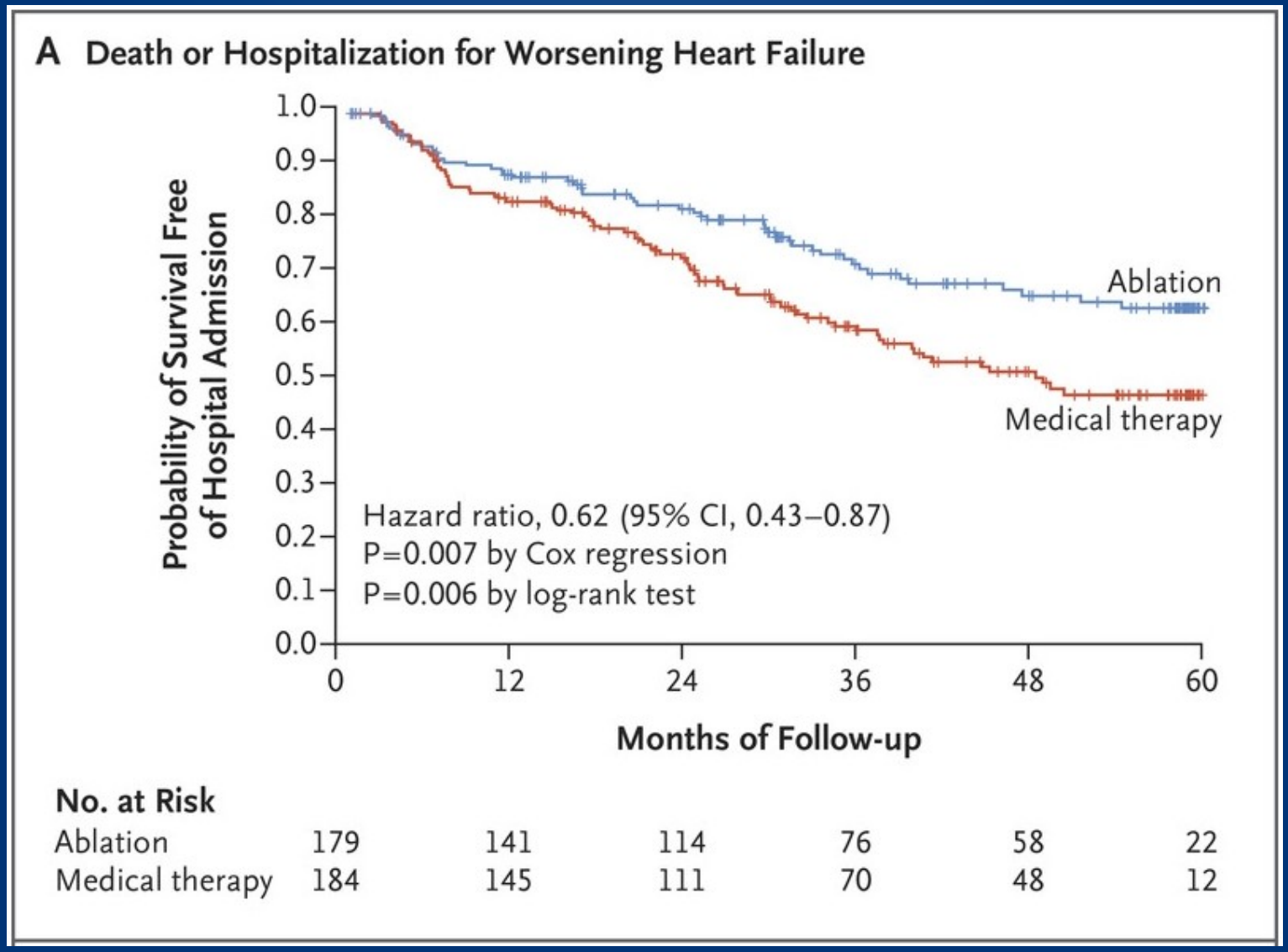


Divaka Perera et al. JCHF 2018;6:517-526

HFrEF Treatment, Stage C

- Medical treatment
- Devices
  - ICD
  - CRT, CRT--D
- Revascularization
  - CABG
  - PCI?
- PVI for AF
- Surgery/intervention for secondary MR

PVI for HFrEF



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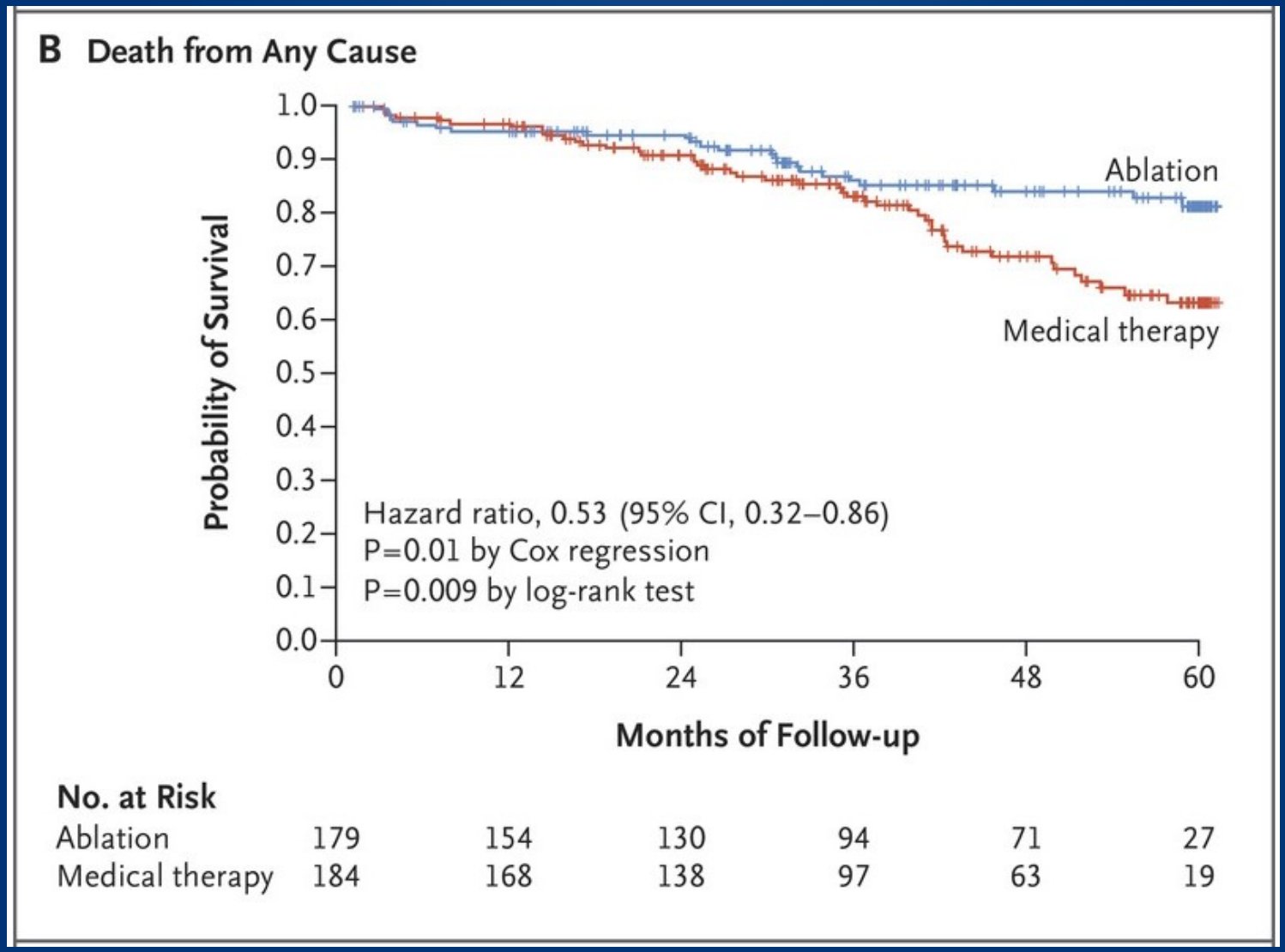
PVI for HFrEF



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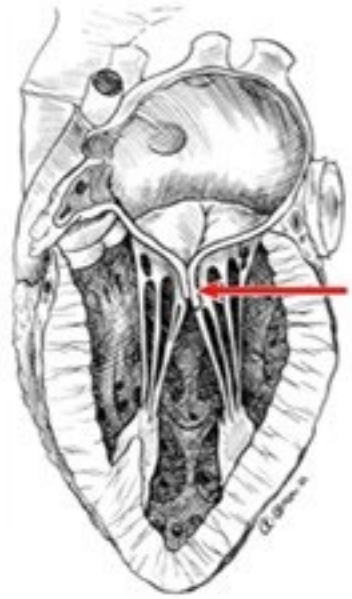
HFrEF Treatment, Stage C

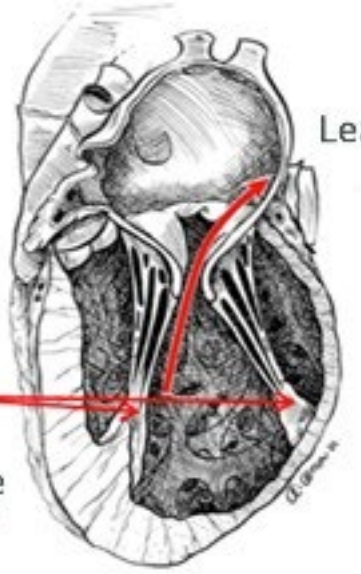
- Medical treatment
- Devices
  - ICD
  - CRT, CRT--D
- Revascularization
  - CABG
  - PCI?
- PVI for AF
- Surgery/intervention for secondary MR

Normal Mitral Valve



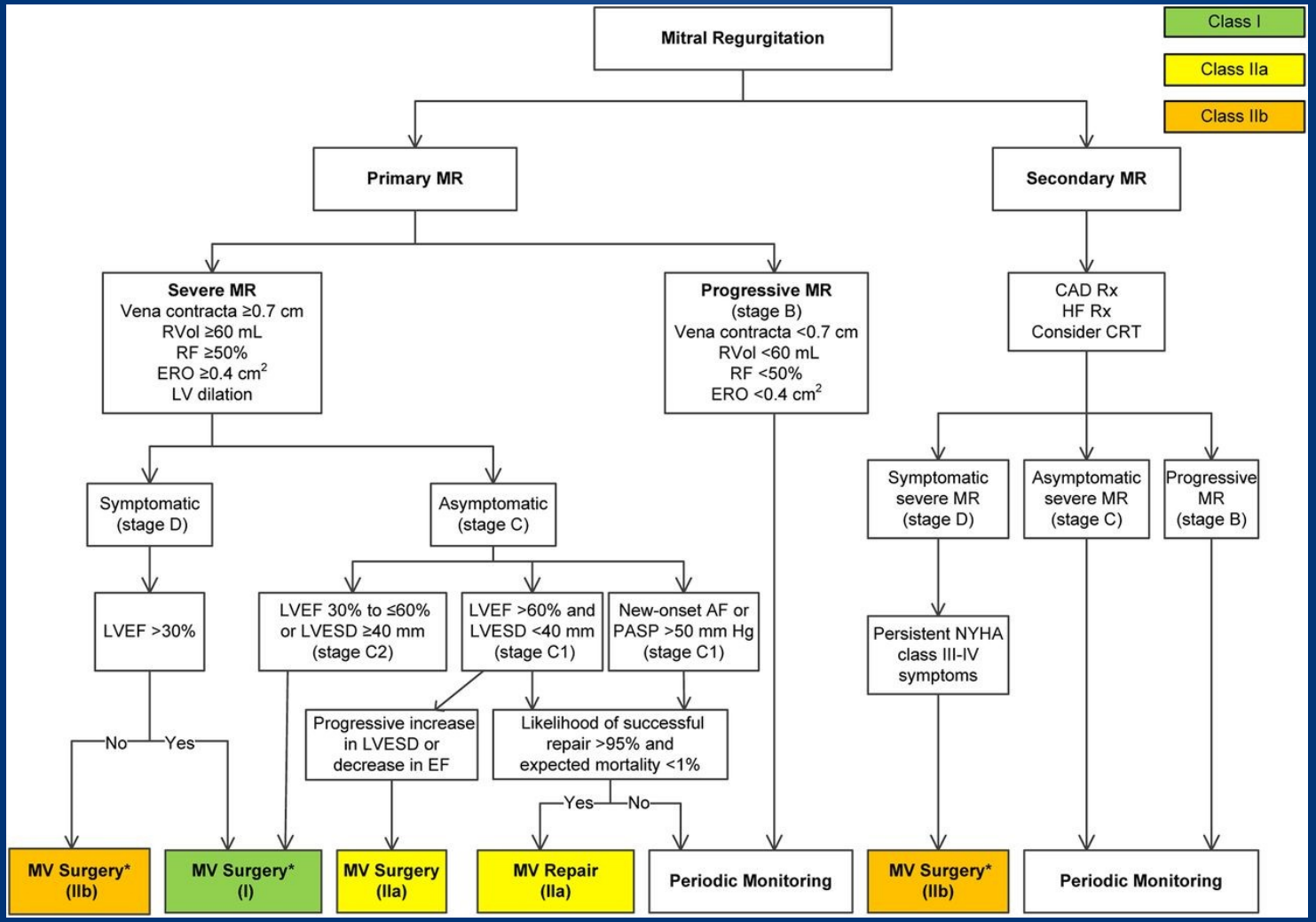
No leakage

Functional Mitral Valve Regurgitation



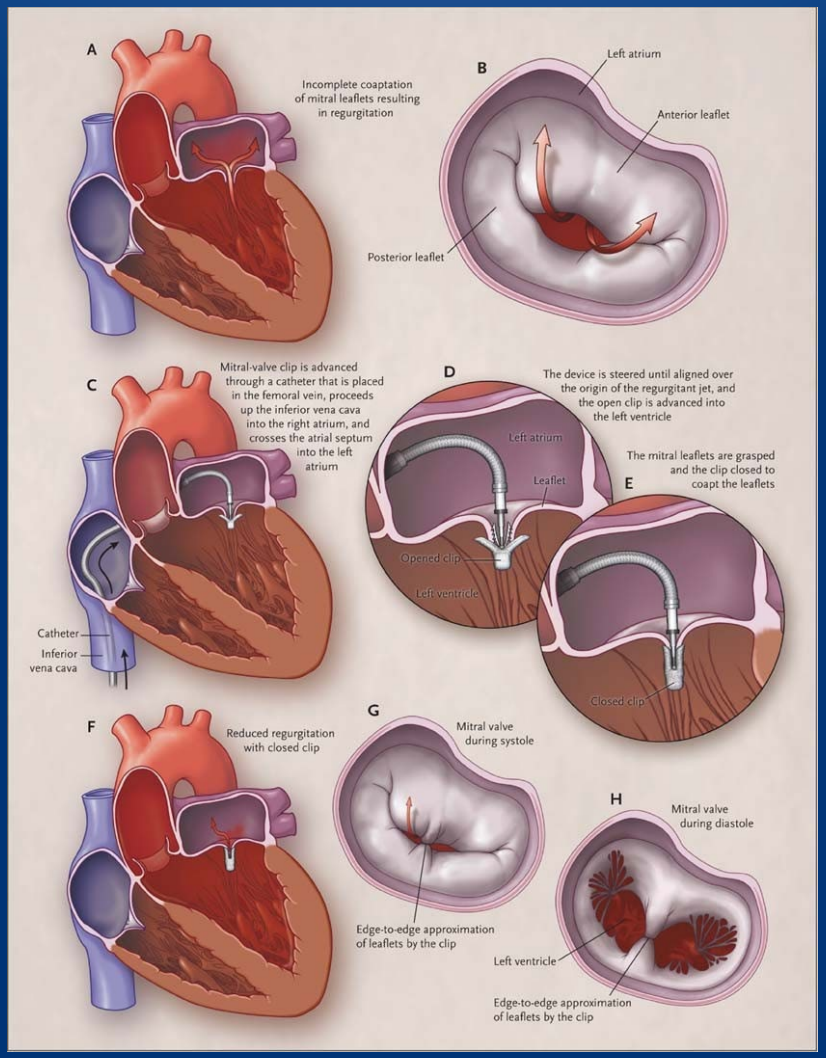
Leakage into atrium

Papillary muscles are displaced due to dilation of ventricle



Rick A. Nishimura et al. JACC 2017;70:252-289

Percutaneous Repair of a Mitral Valve.



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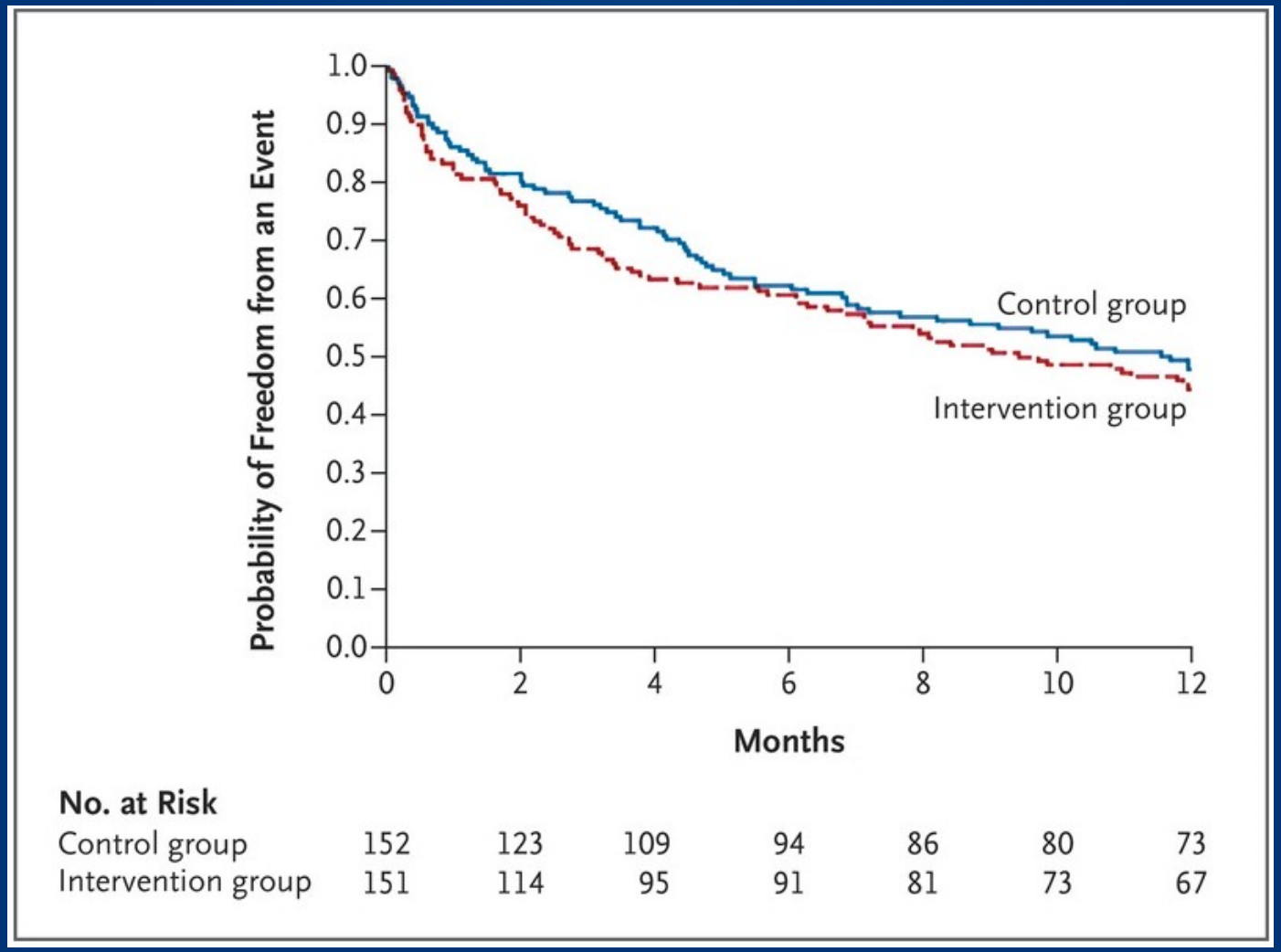
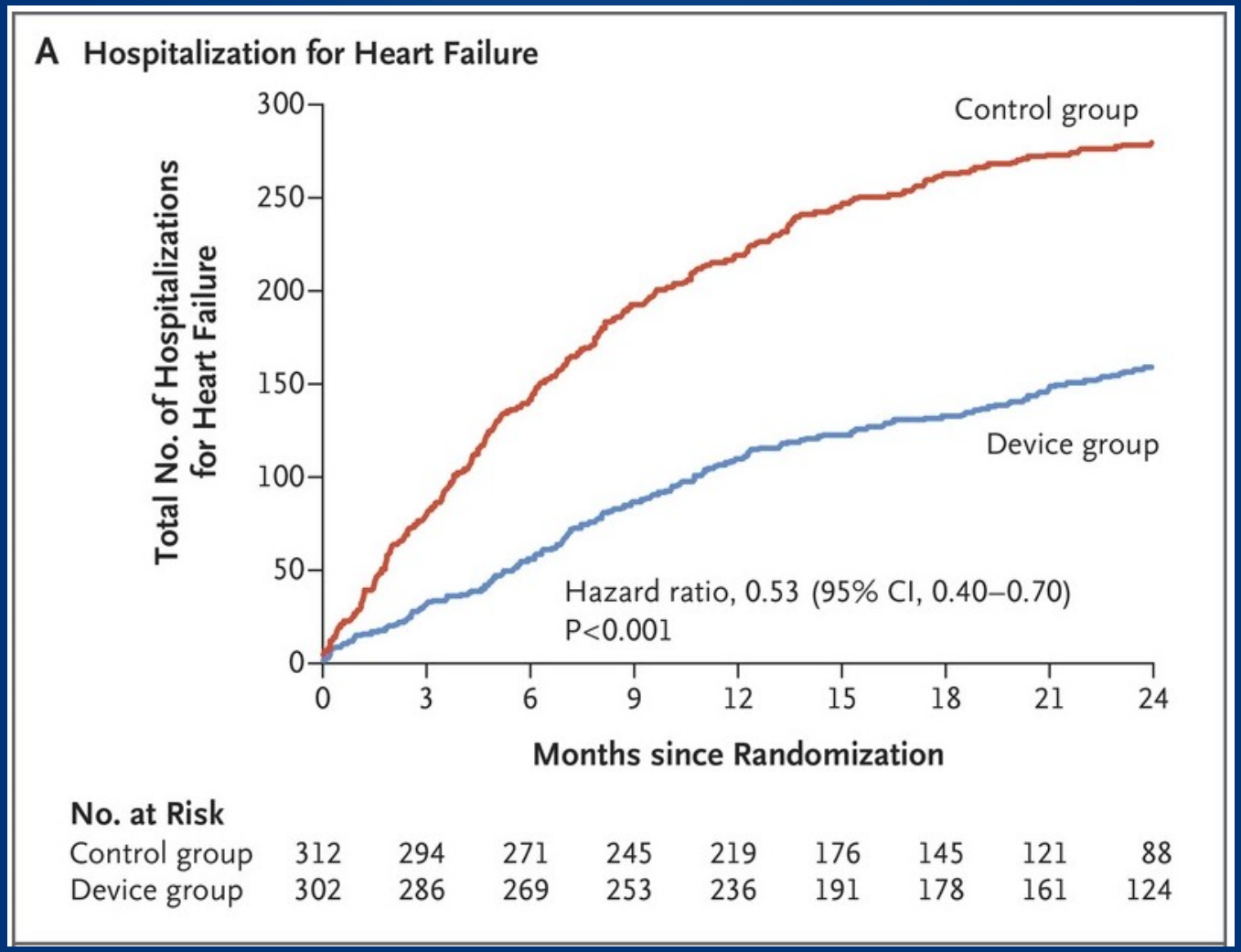
Transcatheter Mitral Valve Repair



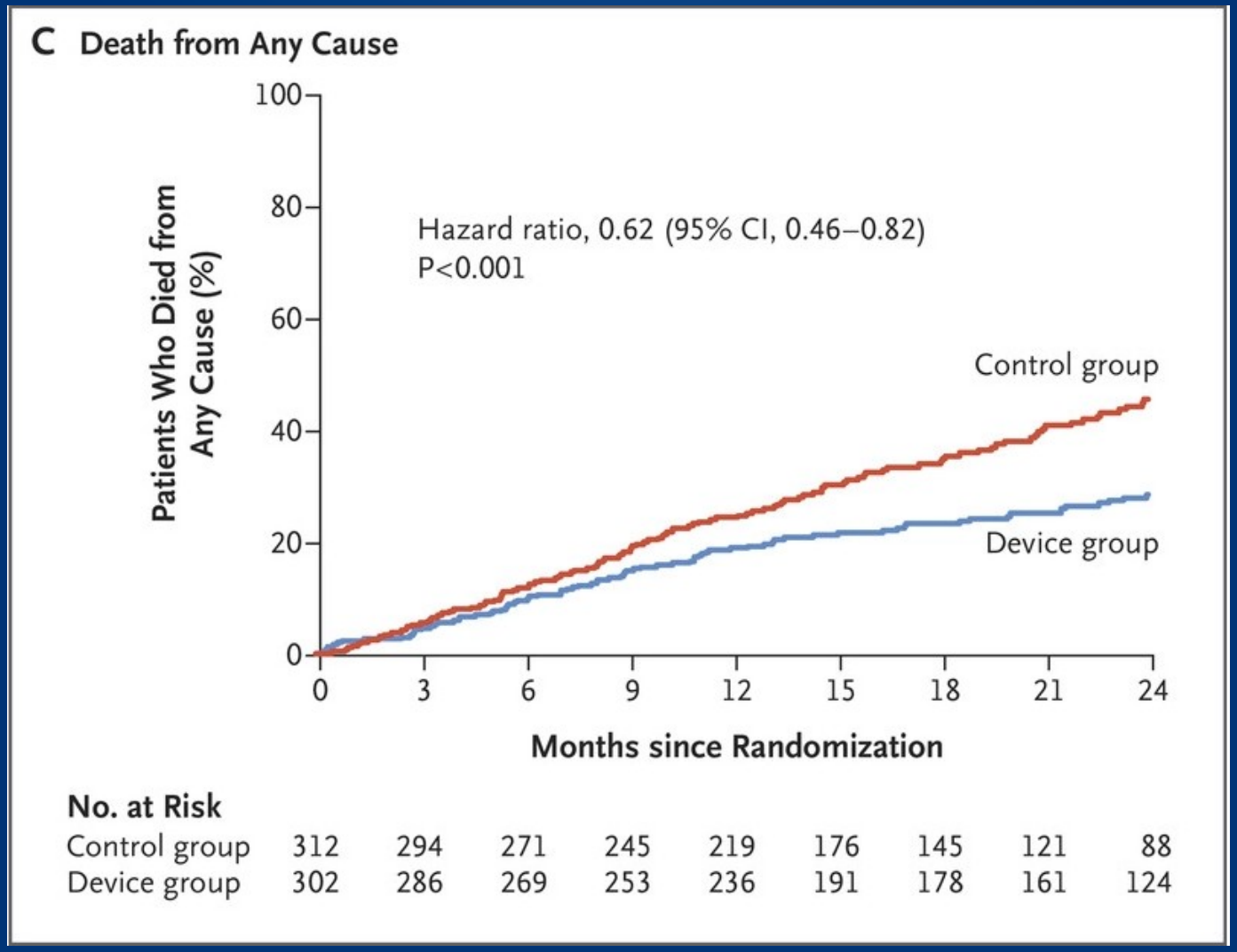
NEJM Aug 2018

Transcatheter Mitral Valve Repair



NEJM Sept 2018

Transcatheter Mitral Valve Repair



NEJM Sept 2018