Royal Brompton & Harefield NHS
NHS Foundation Trust

Acute Heart Failure:

Current recommendations and future directions

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Declaration of interests

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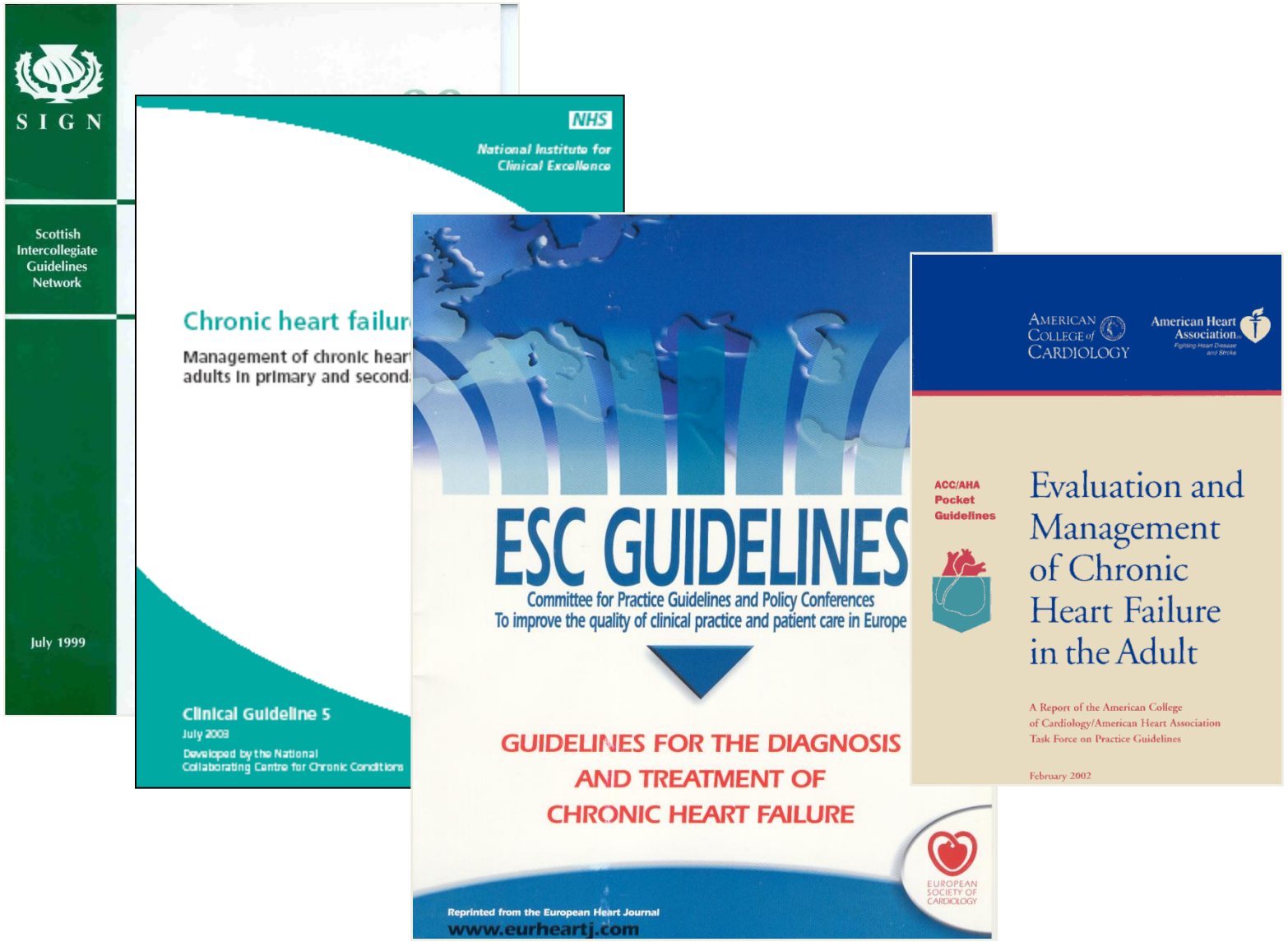
- Non-Executive Director of the National Institute for Health and Care Excellence (NICE), but opinions are my own

National & international guidelines



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)

Developed with the special contribution of the Heart Failure Association (HFA) of the ESC

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Ponikowski P et al. Eur Heart J 2016 (July 14); 37: 2129 – 200

What is new in acute HF treatment?

In the management of a patient with suspected acute HF:

1) try to shorten all diagnostic and therapeutic decisions

2) In parallel, identify coexisting life-threatening clinical conditions and/or precipitants, and

3) introduce guideline-recommended specific management.

Ponikowski P et al. Eur Heart J 2016 (July 14); 37: 2129 – 200

Initial management of a patient with acute HF

Patient with suspected AHF

Urgent phase after first medical contact

1. Cardiogenic shock ? — yes

Circulatory support
- pharmacological
- mechanical

no

2. Respiratory failure ? — yes

Ventilatory support
- oxygen
- NIPPV(CPAP, BiPAP)
- mechanical ventilation

no

Immediate phase (initial 60-120 minutes)

Immediate stabilization and transfer to ICU/CCU

Identification of acute aetiology:

C acute **C**oronary syndrome
H **H**ypertensive emergency
A **A**rrhythmia
M acute **M**echanical cause
P **P**ulmonary embolism

yes → Immediate initiation of specific treatment

Follow detailed recommendations in the specific ESC guidelines

no → **Diagnostic work-up to confirm AHF**
Clinical evaluation to select optimal management

www.escardio.org/guidelines

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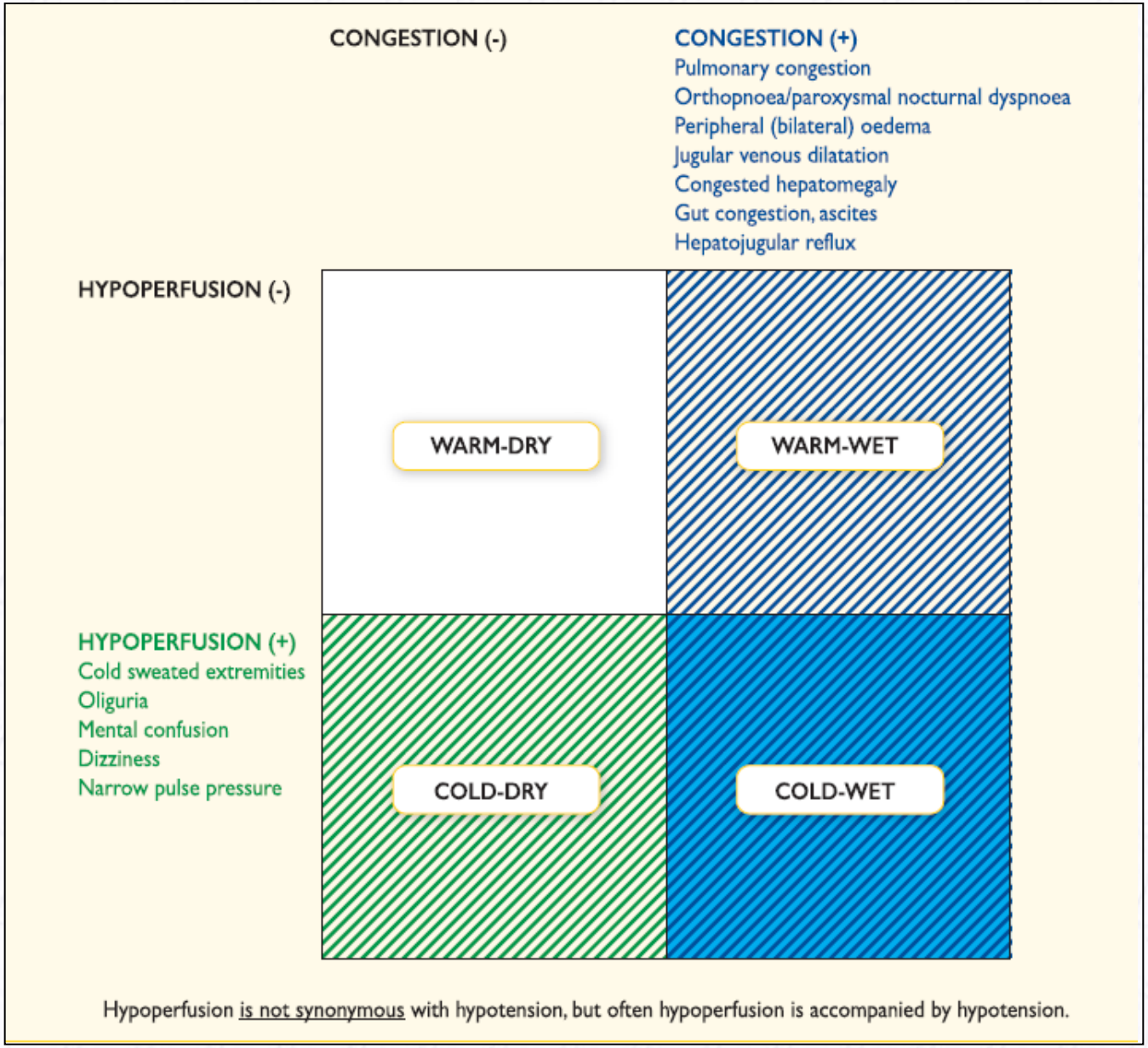

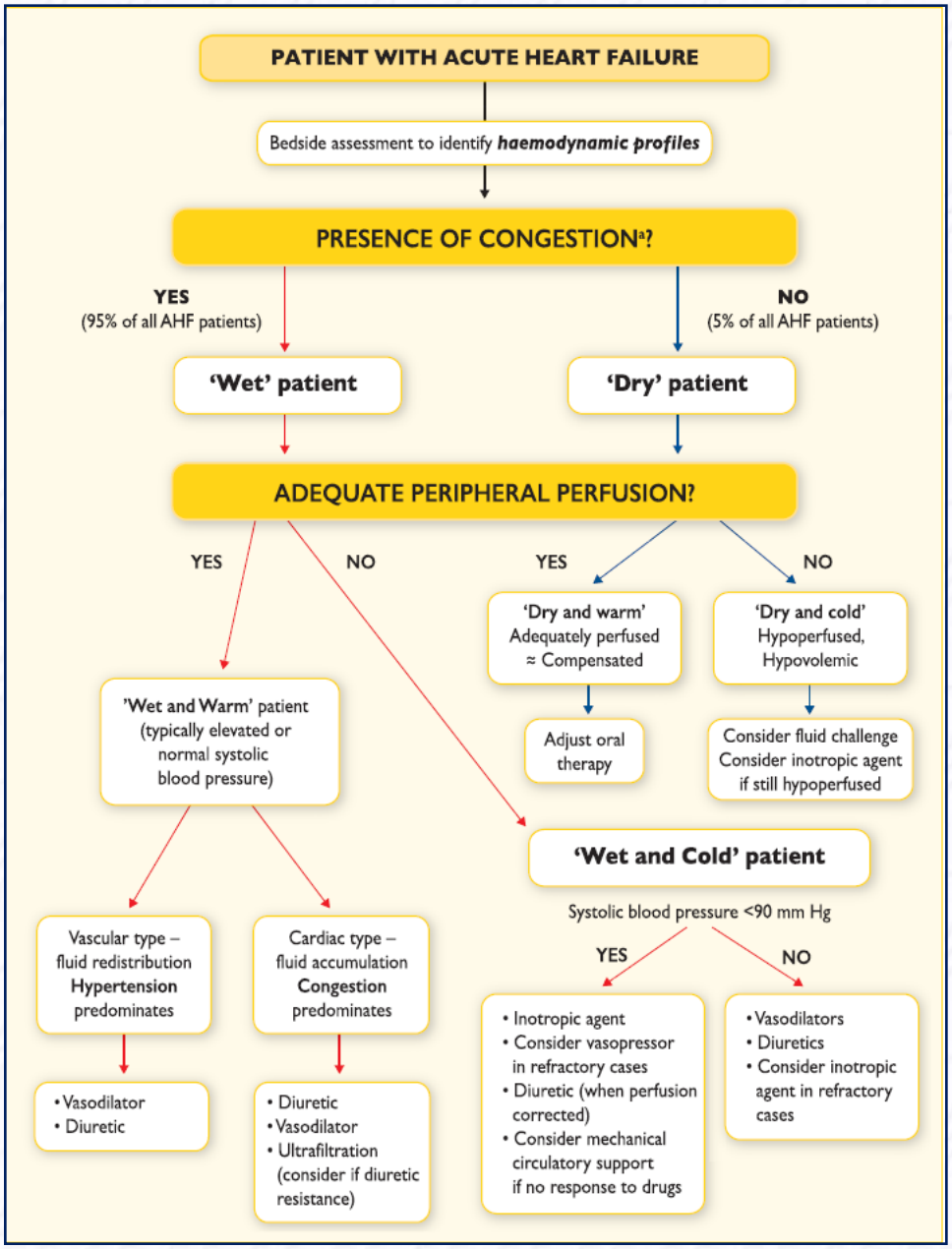

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Recommendations for the management of patients with acute heart failure: pharmacotherapy

Recommendations	Class [a]	Level [b]
Diuretics		
Intravenous loop diuretics are recommended for all patients with AHF admitted with signs/symptoms of fluid overload to improve symptoms. It is recommended to regularly monitor symptoms, urine output, renal function and electrolytes during use of i.v. diuretics.	I	C
In patients with new-onset AHF or those with chronic, decompensated HF not receiving oral diuretics the initial recommended dose should be 20–40 mg i.v. furosemide (or equivalent); for those on chronic diuretic therapy, initial i.v. dose should be at least equivalent to oral dose.	I	B
It is recommended to give diuretics either as intermittent boluses or as a continuous infusion, and the dose and duration should be adjusted according to patients' symptoms and clinical status.	I	B
Combination of loop diuretic with either thiazide-type diuretic or spironolactone may be considered in patients with resistant oedema or insufficient symptomatic response.	IIb	C
Vasodilators		
i.v. vasodilators should be considered for symptomatic relief in AHF with SBP >90 mmHg (and without symptomatic hypotension). Symptoms and blood pressure should be monitored frequently during administration of i.v. vasodilators.	IIa	B
In patients with hypertensive AHF, i.v. vasodilators should be considered as initial therapy to improve symptoms and reduce congestion.	IIa	B
Inotropic agents – dobutamine, dopamine, levosimendan, phosphodiesterase III (PDE III) inhibitors		
Short-term, i.v. infusion of inotropic agents may be considered in patients with hypotension (SBP <90 mmHg) and/or signs/symptoms of hypoperfusion despite adequate filling status, to increase cardiac output, increase blood pressure, improve peripheral perfusion and maintain end-organ function.	IIb	C
An intravenous infusion of levosimendan or a PDE III inhibitor may be considered to reverse the effect of beta-blockade if beta-blockade is thought to be contributing to hypotension with subsequent hypoperfusion.	IIb	C
Inotropic agents are not recommended unless the patient is symptomatically hypotensive or hypoperfused because of safety concern.	III	A
Vasopressors		
A vasopressor (norepinephrine preferably) may be considered in patients who have cardiogenic shock, despite treatment with another inotrope, to increase blood pressure and vital organ perfusion.	IIb	B
It is recommended to monitor ECG and blood pressure when using inotropic agents and vasopressors, as they can cause arrhythmia, myocardial ischaemia, and in the case of levosimendan and PDE III inhibitors also hypotension.	I	C
In such cases intra-arterial blood pressure measurement may be considered.	IIb	C
Thrombo-embolism prophylaxis		
Thrombo-embolism prophylaxis (e.g. with LMWH) is recommended in patients not already anticoagulated and with no contra-indication to anticoagulation, to reduce the risk of deep venous thrombosis and pulmonary embolism.	I	B
Other drugs		
For acute control of the ventricular rate in patients with atrial fibrillation: a. digoxin and/or beta-blockers should be considered as the first-line therapy.[d] b. amiodarone may be considered.	IIa IIb	C B
Opiates may be considered for cautious use to relieve dyspnoea and anxiety in patients with severe dyspnoea but nausea and hypopnea may occur.	IIb	B

Recommendations regarding renal replacement therapy in patients with acute heart failure

Recommendations	Class [a]	Level [b]	Ref [c]
Ultrafiltration may be considered for patients with refractory congestion, who failed to respond to diuretic-based strategies.	IIb	B	578–580
Renal replacement therapy should be considered in patients with refractory volume overload and acute kidney injury.	IIa	C	

Goals of treatment in acute heart failure

Immediate:

- Improve organ perfusion & haemodynamics
- Restore oxygenation
- Alleviate symptoms
- Limit cardiac & renal damage
- Prevent thrombo-embolism
- Minimize ICU length of stay

ED/ICU/CCU

Intermediate:

- Identify aetiology and relevant co-morbidities
- Titrate therapy to control symptoms and congestion and optmize blood pressure
- Initiate and up-titrate disease-modifying pharmacological therapy
- Consider device therapy in appropriate patients

In-hospital

Pre-discharge and long-term management:

- Develop a careful plan that provides:
  a. schedule for up-titrating and monitoring of pharmacological therapy
  b. need and timing for review for device therapy
  c. who will see the patient and when
- Enrol in disease management programme, educate, initiate lifestyle adjustments
- Prevent early readmission
- Improve symptoms, QoL and survival

Consecutive phases of AHF management

Pre-discharge management and criteria for discharge

Develop a careful plan that provides:

a. schedule for up-titrating and monitoring of pharmacological therapy

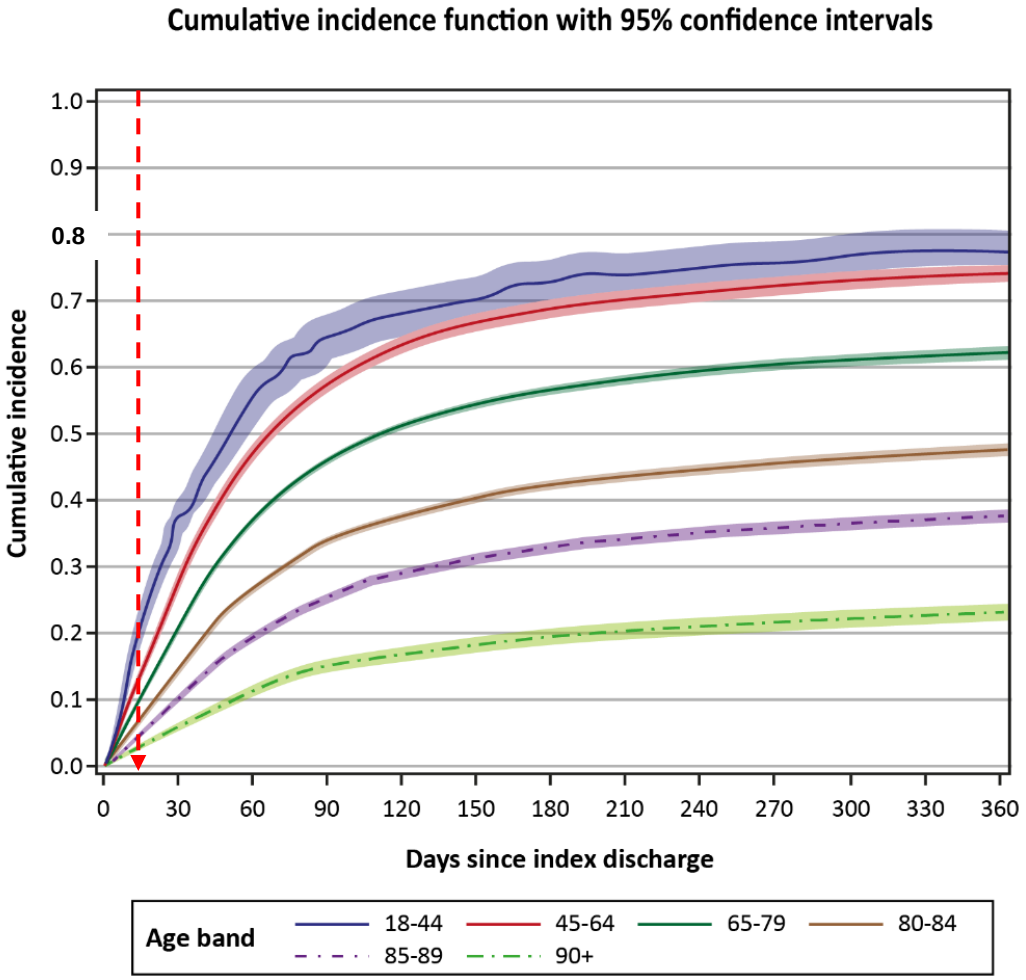
b. need and timing for review for device therapy

c. who will see the patient and when

Patients should be:

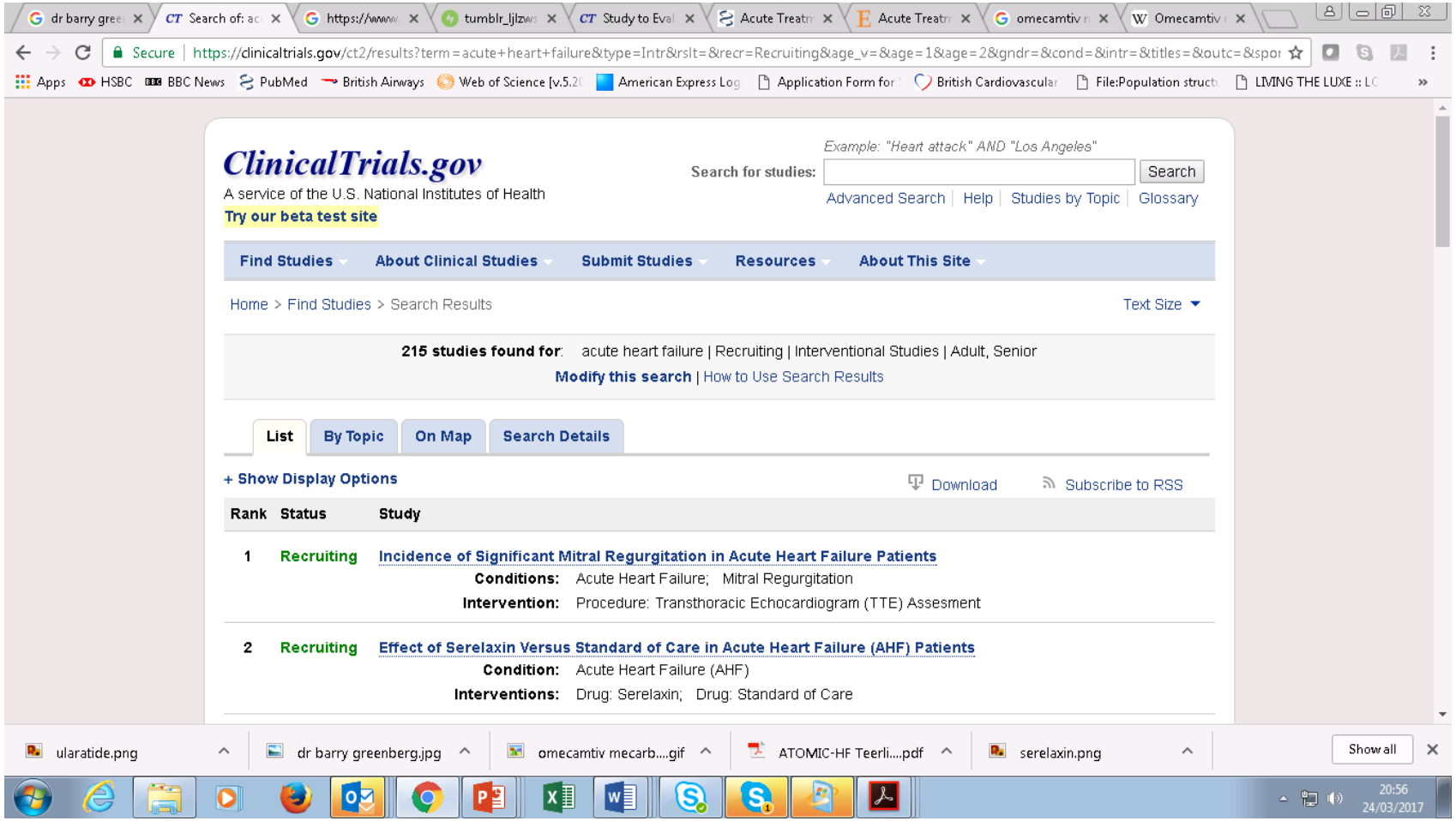
- enrolled in a disease management program
- seen by their **general practitioner within 1 week of discharge**
- seen by the hospital cardiology team within 2 weeks of discharge (if feasible)

Cardiology follow-up after discharge in NHS hospitals in England (2009-11)



Bottle A et al. BMJ Open 2016; 6: e010669

Future directions



Serelaxin

NOVARTIS

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http://www.novartis.com

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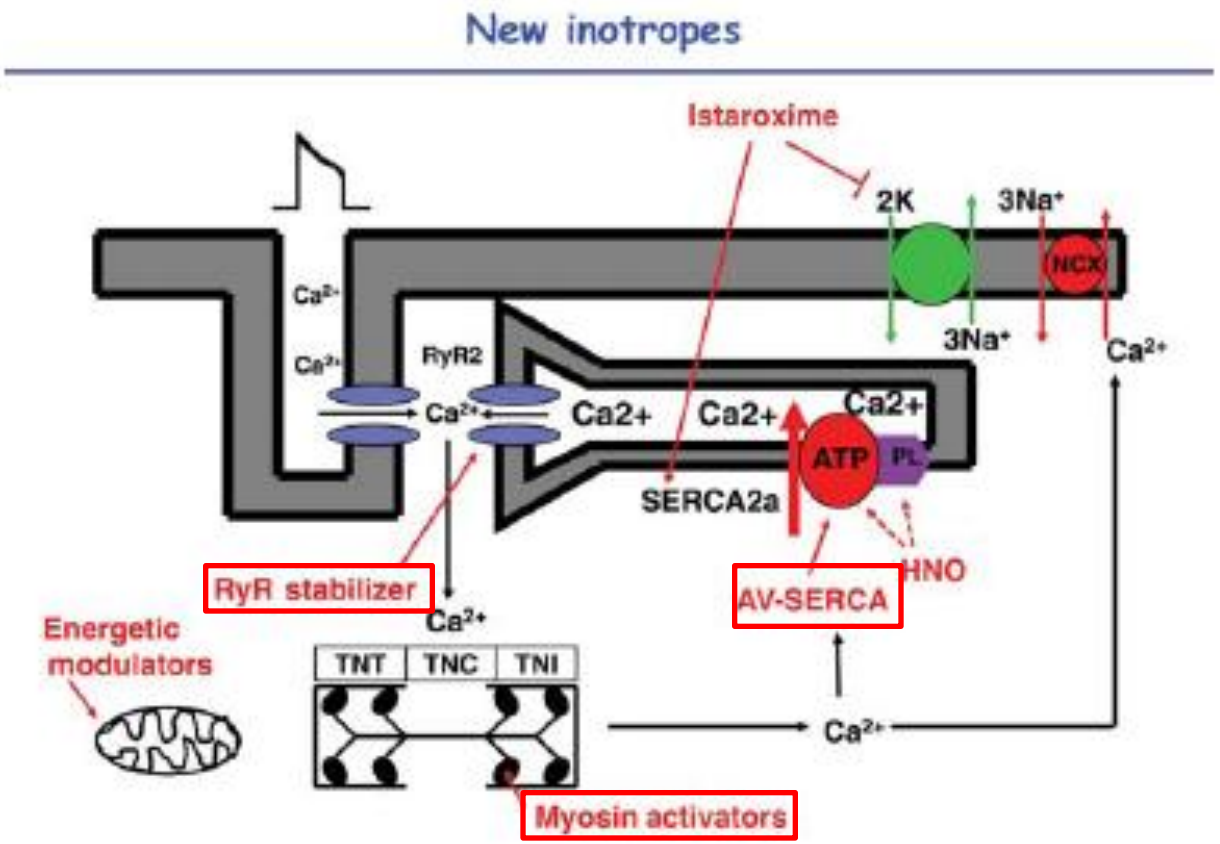
Novartis provides update on Phase III study of RLX030 (serelaxin) in patients with acute heart failure

- *Phase III RELAX-AHF-2 study did not meet primary endpoints of reduced cardiovascular death or worsening heart failure in patients with acute heart failure*
- *Novartis remains committed to improving and extending the lives of patients with cardiovascular disease and will continue to invest in ways to improve their outcomes*

Basel, March 22, 2017 – Novartis today announced results from the global Phase III RELAX-AHF-2 study investigating the efficacy, safety and tolerability of RLX030 (serelaxin) in patients with acute heart failure (AHF).

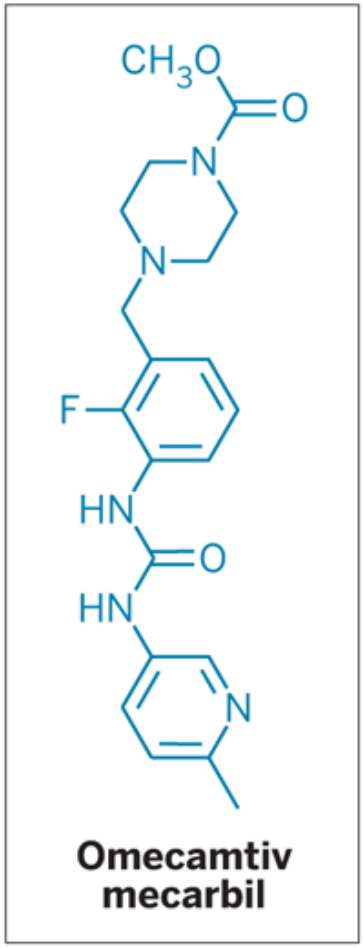
RELAX-AHF-2 did not meet its primary endpoints of reduction in cardiovascular death through Day 180 or reduced worsening heart failure through Day five when added to standard therapy in patients with AHF.

New inotropes



Hasenfuss & Teerlink. EHJ 2011; 32: 1838 - 45

ATOMIC-HF

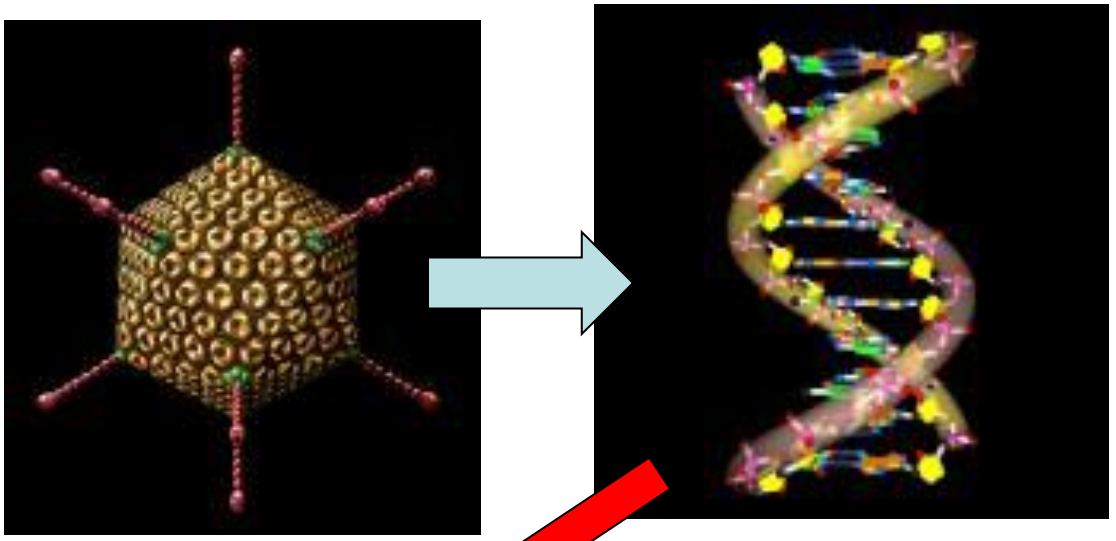


Omecamtiv mecarbil

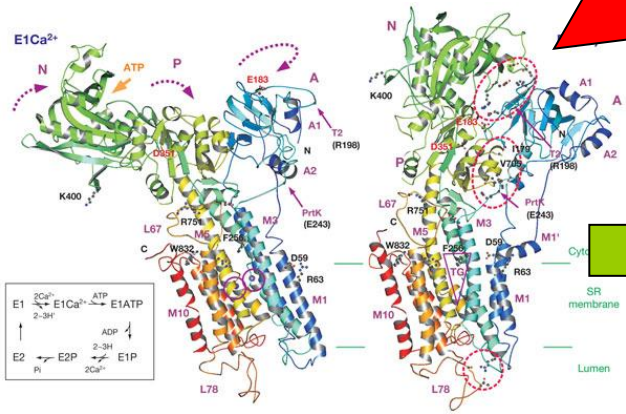
- “in patients with AHF, intravenous omecamtiv did NOT meet the primary endpoint of dyspnoea improvement, but it was generally well tolerated, increased systolic ejection time, and may have improved dyspnoea in the high dose group”

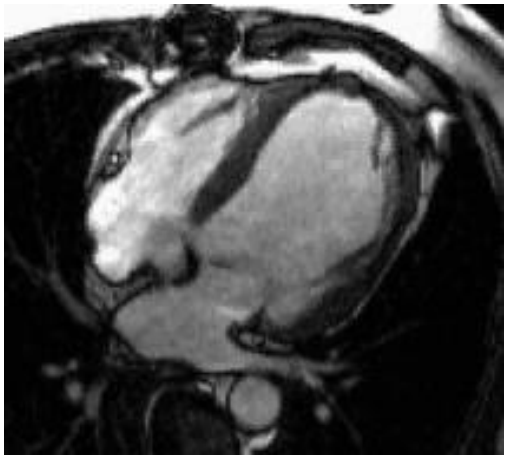
Teerlink JR et al. JACC 2016; 67: 1444-55

SERCA2a Gene Therapy



SERCA2a protein

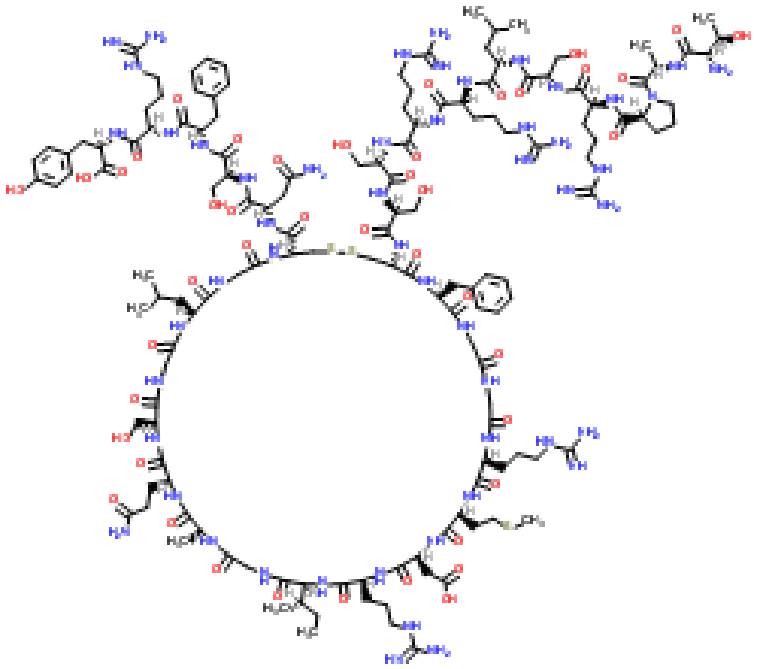




- “A lot of us were very optimistic and hopeful that CUPID2 would meet its endpoint,” says Barry Greenberg of the University of California, San Diego (UCSD), who chaired the CUPID2 executive clinical steering committee. “There was a very logical and appropriate scientific rationale and the study was done very well,” he says. “But it just didn't work out.”

Greenberg B et al. Lancet 2016; 387: 1178 – 86

Ularatide – TRUE-HF



- NEW ORLEANS, LA, Nov 2016 — Early intravenous treatment with a synthetic natriuretic peptide (ularatide) decongested patients with acute decompensated heart failure (ADHF) and made them feel better in the first 48 hours but did nothing to improve long-term survival, in a large randomized trial[1].
- Nor did the drug protect the myocardium from damage as measured by troponin levels, which was an important prospective end point in TRUE-AHF.

http://www.medscape.com/viewarticle/871899

Mini-LVAD

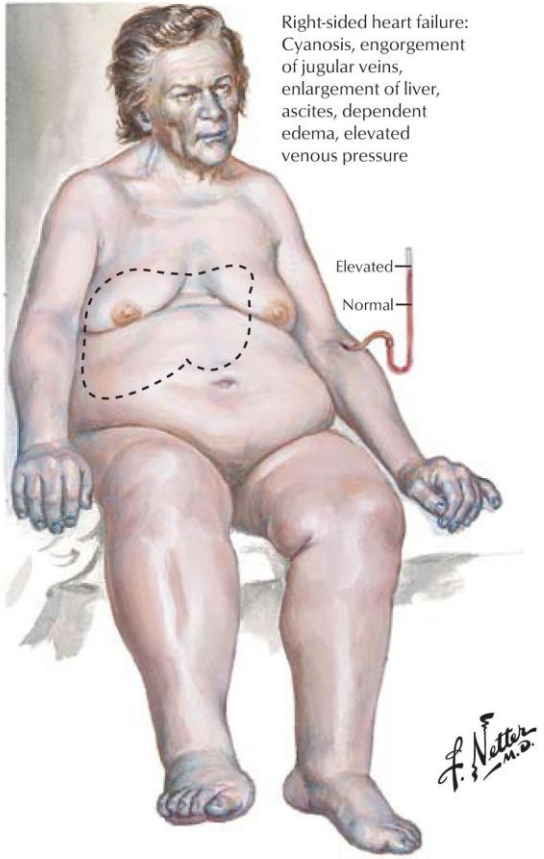
- “medium-term outcomes (of rotary blood pumps as destination therapy) now compete favourably with cardiac transplantation, although...candidates are fundamentally different...

- “The debate is rarely between cardiac transplant or lifetime LVAD – it should focus on the choice between pump versus palliative care for the thousands of patients of all age groups who are ineligible for transplantation..”

And they may well be getting smaller and smaller and smaller and smaller

Future Cardiology 2013; 9: 199-213

Fluid retention



UNLOAD

- 200 patients admitted with at least 2 signs of hypervolaemic HF
- Randomised to UF or IV diuretics (bolus or infusion, at physician discretion)
- Primary endpoint: dyspnoea relief and weight loss at 48 hours.

Costanzo MR et al. 1) JACC 2007; 49: 675 – 83, 2) J Cardiac Failure 2010; 16: 277 - 84

The results of this analysis from the UNLOAD trial show that despite the lack of a statistical difference in weight and fluid loss by UF and IV diuretics administered by continuous infusion, UF was associated with fewer rehospitalizations. Additional prospective, randomized studies are needed to confirm or refute the hypothesis that removal of *isotonic* rather than *hypotonic* fluid is a key factor in producing sustained clinical benefit in congested HF patients

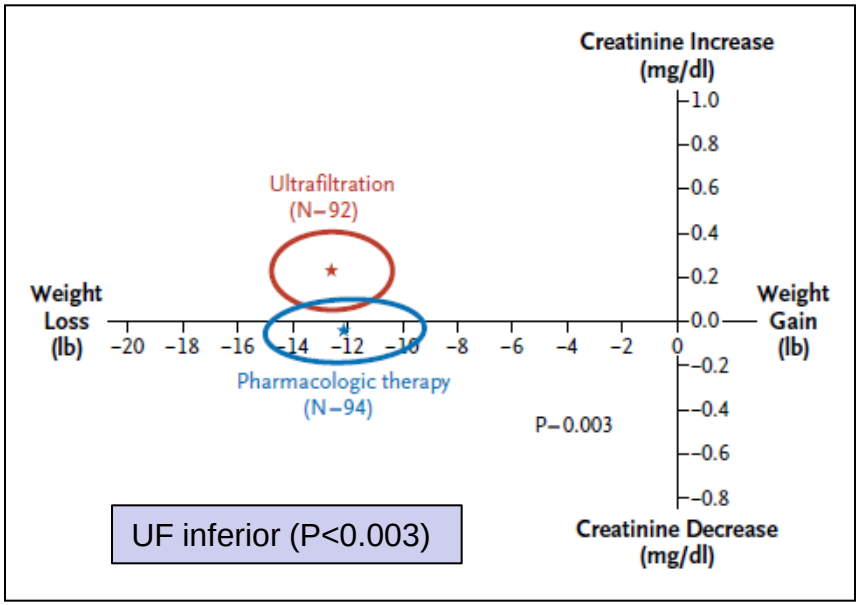
Costanzo MR et al. J Cardiac Failure 2010; 16: 277 - 84

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

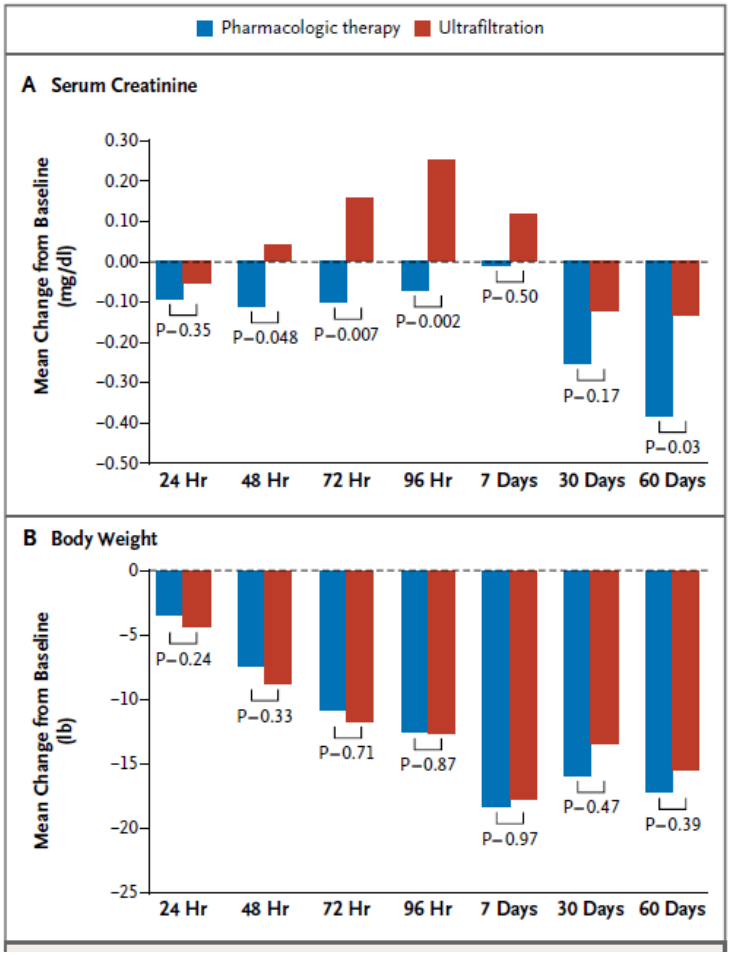
Ultrafiltration in Decompensated Heart Failure with Cardiorenal Syndrome

- 188 patients
- Acute decompensated HF admission + persistent congestion + worsening renal function [≥ 26 µmol/l in the 12 weeks before or 10 days after admission]
- Strategy: stepped drug therapy versus ultrafiltration
- Primary endpoint:
  - bivariate change from baseline in serum creatinine and body weight at 96 hours from randomisation
- 60 day follow-up



Bart BA et al. N Engl J Med 2012; 367: 2296 - 304

CARESS-HF



- Serious adverse events higher in UF group (72% vs 57% P=0.03)
- No difference in deaths or hospitalisations out to 60 days

Bart BA et al. N Engl J Med 2012; 367: 2296 - 304

Conclusions

- New guidance from ESC on AHF is pragmatic and focused on reducing delay and identifying aetiologies that require specific management
- Transition to the more chronic phase is key
- Early follow-up is essential
- Much disappointment in trying to identify new treatments
- Mechanical approaches to circulatory and renal support being examined closely
- Put effort into doing what we do know more consistently and efficiently