Heart Failure Diagnosis and Medical Management

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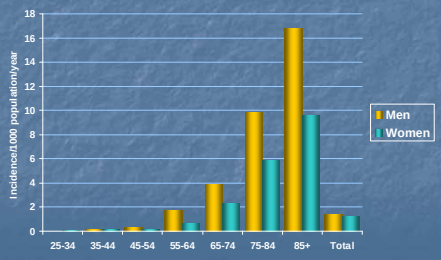
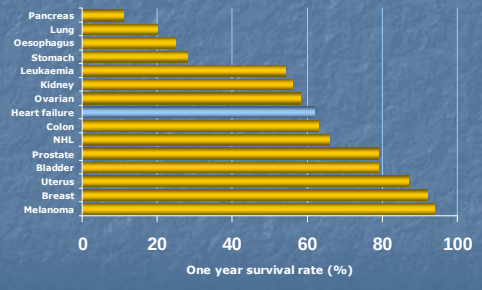
Heart Failure - the size of the problem

- HF effects 1-2% of adult UK population
- Incidence of 5-10 cases per 1000 population per year



Heart Failure Prognosis



Heart Failure in Primary Care

- On average -
  - A GP will look after 30 patients with HF
  - Suspect a new diagnosis in 10 patients per year
- Patients on GP heart failure registers represent the "prevalent pool"
- 5 year survival of 58% cp to 93% in age-sex matched population
- Regular review is vital

Chronic Heart Failure

"Heart failure is a complex **syndrome** that can result from any structural or functional cardiac disorder that impairs the pumping ability of the heart"

Stages in the Development of Heart Failure

	Stage	Patient Description
A	High risk for developing heart failure (HF)	▪ Coronary artery disease ▪ Hypertension ▪ Diabetes mellitus, obesity ▪ Family history of cardiomyopathy
B	Asymptomatic HF	▪ Previous myocardial infarction ▪ Left ventricular systolic dysfunction ▪ Asymptomatic valvular disease
C	Symptomatic HF	▪ Known structural heart disease ▪ Shortness of breath and fatigue ▪ Reduced exercise tolerance
D	Refractory end-stage HF	▪ Marked symptoms at rest despite maximal medical therapy (e.g., those who are recurrently hospitalised or cannot be safely discharged from hospital without specialised interventions)

American Heart Association

Heart Failure Diagnosis - why is it so difficult?

- Shortness of breath on exertion
- Fatigue (exercise intolerance)
- Orthopnoea
- Paroxysmal nocturnal dyspnoea
- Fluid retention

…symptoms are non-specific and present in many other conditions!

Masquerading as Heart Failure

- Obesity
- Venous insufficiency
- Drug induced ankle swelling (di-hydropyridines)
- Chest, renal or hepatic disease
- Angina
- Hypoalbuminaemia
- Pulmonary embolic disease
- Depression/anxiety
- Severe anaemia or thyroid disease

Heart Failure Diagnosis - why is it so difficult?

- Most specific signs are
  - Laterally displaced apex beat
  - Elevated JVP
  - Third heart sound
- Less specific signs are
  - Basal crackles
  - Peripheral oedema
  - Hepatic engorgement
  - Tachycardia

....signs are insensitive and may not be present!

Heart Failure - Baseline Investigations

- FBC, U+E, TFT, LFT, Lipids & glucose
- CXR, PEFR, Spirometry

- ECG
  - Abnormal in 90% of cases
  - Normal makes HF unlikely

Echocardiography

- Most commonly used test to confirm a diagnosis of HF
- Provides information on structure and function of chambers, valves and pericardium
- BUT, Echo is far from perfect: -
  - Assessment of LV function can be difficult and is often subjective
  - What is diastolic dysfunction?
  - Limited Echo views (obese, COPD etc)
  - Delay to diagnosis and treatment

B-type Natriuretic Peptide

- BNP – cardiac hormone secreted by ventricles
- Synthesised in response to cardiac stretch (ventricular dilatation)
- Splits into two:
  - Biologically active BNP
  - Inactive fragment (NT-proBNP)
- BNP has advantageous physiological effects
  - Natriuresis
  - Vasodilatation
  - Inhibition of RAAS and SNS

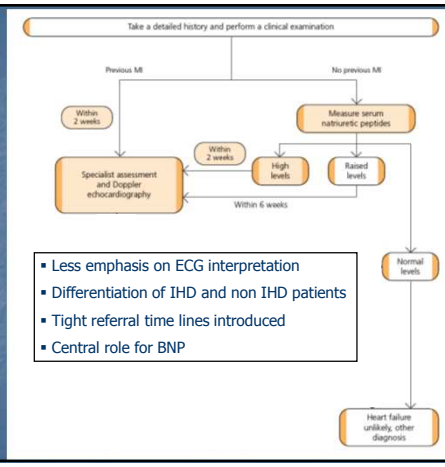
Measurement of BNP in Chronic Heart Failure

- Diagnosis - excellent "rule out" test (high negative predictive value)
- Prognosis – high BNP associated with increased risk of hospitalisation and death

Take home message 1

BNP has excellent negative predictive value – if it's negative you don't have heart failure

BNP is not 100% specific - it can be elevated in other conditions (LVH, ischaemia, renal failure, sepsis, COPD etc)

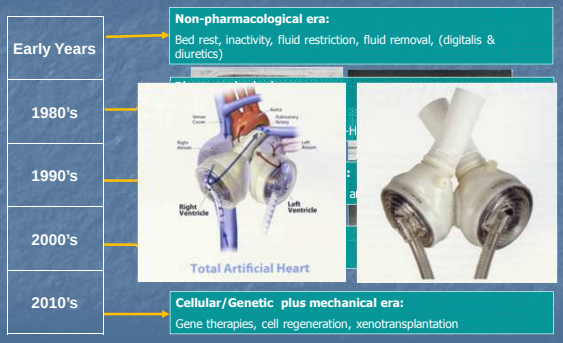


- Less emphasis on ECG interpretation
- Differentiation of IHD and non IHD patients
- Tight referral time lines introduced
- Central role for BNP

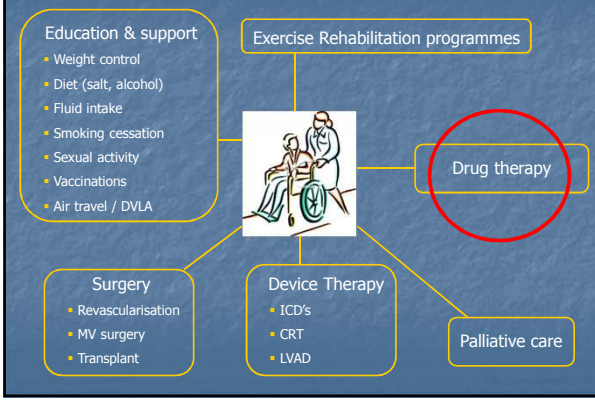
Heart Failure Diagnosis

- Heart failure is not a complete diagnosis
- Requires more than stating whether syndrome present or not
- The following should be considered:
  - Underlying cardiac condition
  - Severity of the syndrome
  - Estimation of prognosis
  - Precipitating and exacerbating factors
  - Aetiology
  - Any co-morbidities relevant to the management

Heart Failure Management Timeline



Modern Management of Heart Failure



Drug therapy in heart failure

Diuretics

- 1920 Organomercurial diuretics first used
- 1958 Thiazide diuretics introduced

- Useful in the acute setting and in the overloaded patient
- Rapid relief of congestive symptoms
- Exacerbate RAA system due to diuresis and natriuresis
- No evidence for mortality benefit
- No effect on disease progression

" Diuretics should be routinely used for the relief of congestive symptoms and fluid overload in patients with heart failure"

NICE 2003

Take home message 2

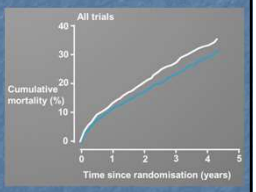
Diuretics provide symptom relief in fluid overloaded patients

They should be increased and DECREASED according to fluid status.

ACE Inhibitors (1)

- First ACE inhibitor - Captopril synthesised in 1977
- Undisputable evidence of reduction in mortality in chronic HF

- Review of data from 5 RCT's
- Compared with placebo. ACEi reduce
  - Mortality (p<0.0001)
  - Readmission (p<0.0001)
  - Reinfarction (p<0.0001)
- Benefit occurs early (30 days)



Flather *et al.*, Lancet 2000

ACE Inhibitors (2)

..... in symptomatic heart failure patients:

- CONSENSUS 1987 (First ACEi trial) - Enalapril 20mg bd
- SOLVD 1990
- ATLAS 1999 (High v Low dose Lisinopril)

..... in post infarct heart failure:

- SAVE 1991 (Captopril 50mg tds)
- AIRE 1993 (Ramipril 5mg bd)
- TRACE 1995 (Trandolapril 4mg od)

..... and in asymptomatic patients with LV dysfunction:

- SOLVD 1990 (prevention arm)
- TRACE 1995
- SAVE 1991

ACE inhibitors (3)

Practical advice

- start with low dose
- aim for trial target dose or highest tolerated dose
- Remember, some ACEi is better than none
- Symptomatic low BP (stop other vasodilators ± diuretics)
- Monitor creatinine and electrolytes
- Rise in creatinine of 30% is probably acceptable

Take home message 3

ACE inhibitors are first line therapy for heart failure due to LV systolic dysfunction

All patients should be offered one

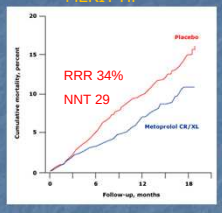
Beta Blockers in Heart Failure

- More patients in trials with beta-blockers than ACE inhibitors

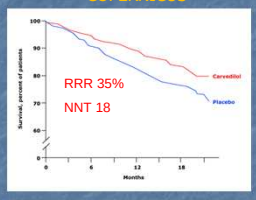
Name	Drug	Year	n
MDC	Metoprolol tartrate 100-150mg/day	1993	383
MERIT-HF	Metoprolol succinate 200mg od	1999	3991
US Carvediolol HF Program	Carvedilol 25-50mg bd	1996	1094
CIBIS II	Bisoprolol 10mg 0d	1999	2647
COPERNICUS	Carvedilol 25-50mg bd	2000	2289

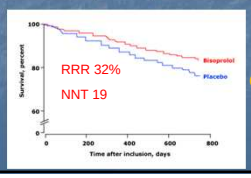
Beneficial effects of Beta Blockers

MERIT-HF



COPERNICUS





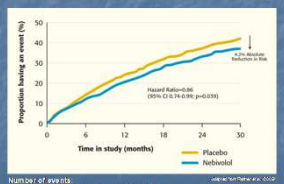
CIBIS II

Beta blockers and the elderly

SENIORS Trial (2005)

- First HF outcome trial restricted to elderly (mean age 76 yrs)
- Nebivolol (Long acting, cardioselective, vasodilating properties)

SENIORS' - all cause mortality or CV hospital admission (primary outcome)[1]



Nebivolol initiated at 1.25mg. Target 10mg od.

Beta blockers in heart failure

"offer beta blockers licensed for heart failure to all patients with heart failure due to LV systolic dysfunction"

This should include:

- Older people
- PVD
- Diabetes mellitus
- erectile dysfunction
- COPD without reversibility

Which beta-blocker and what dose?

- Beta-blockers are NOT all equal
- 3 licensed in UK (Carvedilol, Bisoprolol & Nebivolol)
  - Bisoprolol (ß1 selective).
  - Carvedilol (Mixed α1, ß1, ß2 antag)
  - Nebivolol (ß1 selective & Vasodil. ? via NO)
- Switch patients if already on non evidence based beta-blocker to one with heart failure licence
- What dose? - "Start low, go slow"
- Aim for trial doses (or max tolerated)
- Some probably better than none!

Beta blockers in heart failure

Practical advice (1)

- Initiate slowly, in stable patients (i.e. no congestion)
- B blocker or ACEi first?
  - CIBIS III - Mild-moderate HF
  - bisoprolol or enalapril first
  - No difference in mortality / hospitalisation
- What if increasing congestion?
  - Double diuretic, if no better halve ß blocker (?stop in short term)
- What if profound fatigue/bradycardia?
  - Unusual. Halve dose, reassess

Beta blockers in heart failure

Practical advice (2)

- Inform patients –
  - Primary aim of Rx is to prevent worsening heart failure & improve survival
  - If symptoms do improve, it can take weeks – months
  - Temporary deterioration of symptoms in 20 - 30%

Take home message 4

In combination with ACE inhibitors - Beta blockers are first line therapy for heart failure due to LVSD

All patients should be considered for beta-blocker treatment

Take home message 5

There are very few patients who are truly intolerant of beta blockers

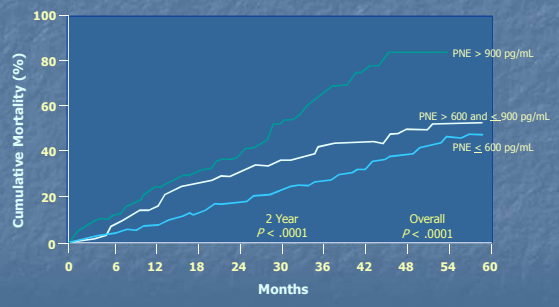
The risk and intolerability of beta blockers is often exaggerated at the detriment of those patients who derive the greatest benefit[1]

Every effort should be made to up-titrate beta blockers

[1]Erdmann *et al.* Eur Heart J Suppl 2009;11(Suppl A):A21-5.

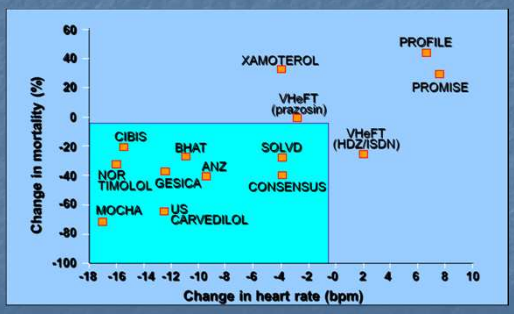
How do Beta blockers have their beneficial effect?

Heart Failure Mortality and Plasma Norepinephrine Level



Francis G et al. *Circulation.* 1993;87(suppl VI):VI-40 - VI-48.

Heart rate and heart failure



Kjekshus J. Gullestad L. *Eur Heart J.* Suppl 1999, Vol 1(Suppl H):H64-H69

Beta blocker trials meta-analysis

- For every 5bpm reduction in heart rate there was an 18% reduction in the risk of CV death.
- Survival benefit in beta blocker trails statistically associated with magnitude of HR reduction rather than the dose of beta blocker

McAlister FA *et al.* Ann Intern Med 2009;150:784-94

Question:
Do Beta-blockers work purely by lowering heart rate or is it their diverse effects on the sympathetic nervous system that are important?

Answer:
Don't know, and probably never will!

Heart rate as a therapeutic target

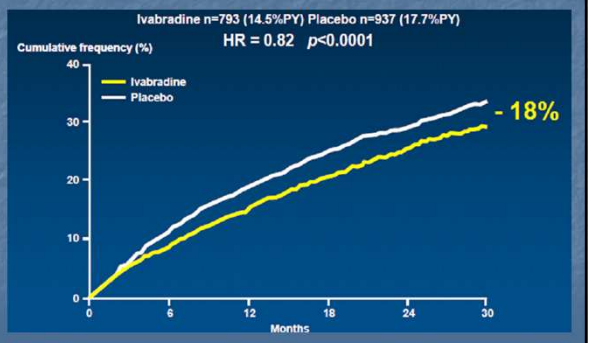
- Resting heart rate is a risk factor for morbidity and mortality in general population, IHD and chronic heart failure
- SHIFT trial – Lancet 2010[1]
- Ivabradine – selective I_f channel inhibitor in SAN
- No effect on SNS (Beta receptor)
- Does pure heart rate reduction with Ivabradine lead to improved CV outcomes?

[1]Bohm *et al.* Lancet 2010; 376: 886-894

SHIFT
Systolic Heart failure treatment with I_f inhibitor ivabradine Trial

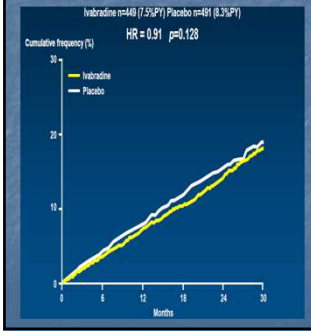
- Moderate to severe heart failure symptoms
- LVSD (EF ≤35%)
- Heart rate ≥70bpm
- Sinus rhythm
- HF admission in last 12 months
- Good background medical treatment

SHIFT Primary composite endpoint

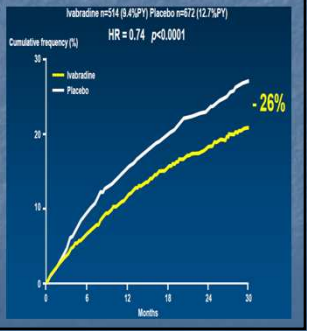


SHIFT
Systolic Heart failure treatment with I_f inhibitor ivabradine Trial

CV Mortality



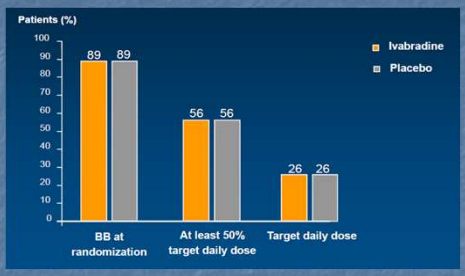
CV Hospitalisations



SHIFT Conclusions

- Benefits of pure heart rate reduction in heart failure proven
- Heart rate is a therapeutic target in heart failure
- Ivabradine reduced hospitalisations for HF by 26% (NNT=27)
- The effect was most dramatic for those with the highest heart rate

Background β-blocker treatment

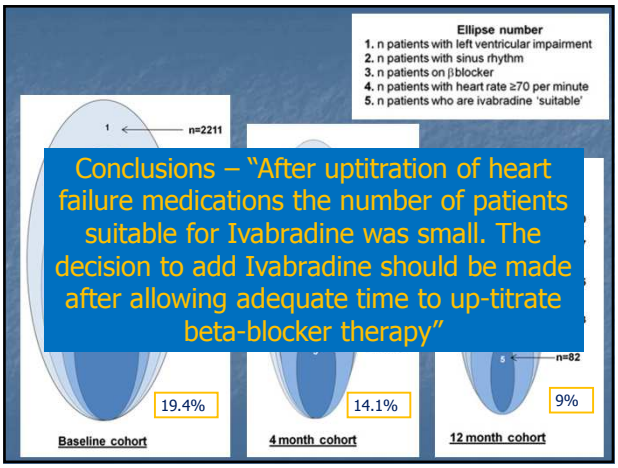


Would these benefits have occurred if the dose of beta-blocker had been closer to the recommended trial dose?

Role of Ivabradine in a real life heart failure clinic

- Retrospective analysis of heart failure clinic database
- Aim – To quantify the proportion of patients attending a community HF clinic with LVSD who might benefit from Ivabradine therapy
- Examined data at baseline, 4 and 12 months

Clark AL *et al.* Heart. 2011 Dec;97(23):1961-6. Epub 2011 Sep 13.



Conclusions – "After uptitration of heart failure medications the number of patients suitable for Ivabradine was small. The decision to add Ivabradine should be made after allowing adequate time to up-titrate beta-blocker therapy"

Take home message 6

Heart rate is an independent risk factor for CV events in heart failure

Heart rate should be a therapeutic target

Check the pulse and aim for a resting heart rate of < 70bpm

Take home message 7

B-blockers are first line treatment for heart rate reduction – increase to maximum tolerated dose

If β-blockers contraindicated (definite reversible airways disease) or has intolerable side effects and in SR, and HR > 70bpm consider Ivabradine

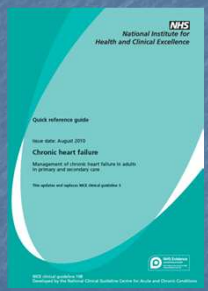
Ivabradine is safe and effective at reducing heart failure hospitalisations (Licence awaited)

What if the patient is still symptomatic?

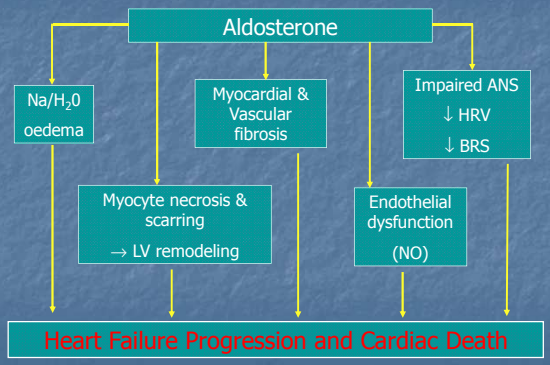
Heart Failure – second line treatment

"Seek specialist advice and consider adding one of the following if patient remains symptomatic despite optimal Rx with ACEi and ß blocker"

- Aldosterone antagonists
- ARB
- Nitrates & Hydralazine



Aldosterone & Heart Failure

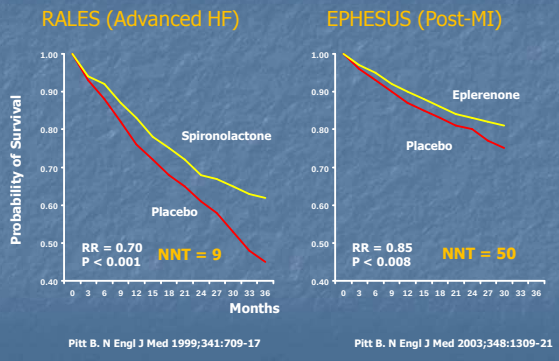


Aldosterone Antagonists

- Spironolactone
  - RALES trial 1999 (25mg od)
  - NYHA III/IV – On ACEi, diuretic ± digoxin
  - LVEF ≤ 35%
- Eplerenone
  - EPHESUS trial 2003 (25-50mg od)
  - 3-14 days post MI
  - LVEF ≤ 40% with clinical heart failure

Pitt B et al. *NEJM* 1999; 341:709-17, Pitt B et al. *NEJM* 2003; 348:1309-1321

Aldosterone Antagonists in HF



Aldosterone antagonists

Spironolactone or Eplerenone?

- Licensed for different indications
- No evidence for beneficial effect of Spironolactone in heart failure post MI
- No evidence for beneficial effect of Eplerenone in CHF
- 10% incidence of gynaecomastia with Spironolactone
- Similar problems with hyperkalaemia
- Eplerenone significantly more expensive

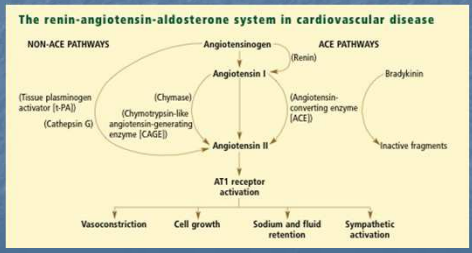
Take home message 8

Aldosterone antagonists are effective 2nd line heart failure treatments proven to reduce mortality in moderate-severe heart failure

Careful monitoring of renal function and Potassium is required

Angiotensin Receptor Blockers

- ACEi fail to block RAAS completely
- ARB's prevent binding of angiotensin II to type 1 receptor



Angiotensin Receptor Blockers

- Chronic Heart Failure Trials
  - ELITE II 2000 (non inferiority to ACEi, better tolerated)
  - VALHeFT 2002 (ARB + ACEi ↓ hospitalisations, but not mortality)
- Post MI heart failure trials
  - OPTIMAAL 2002 (ACEi better at reducing mortality)
  - VALIANT 2003 (ARB similar to ACEi at reducing mortality)

CHARM Trial

7,601 patients with heart failure (NYHA II-IV)

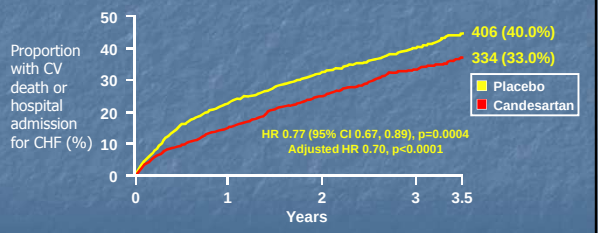
3 Individual component randomized trials with the ARB candesartan (4 or 8 mg/day, titrated to target dose of 32 mg) or placebo

CHARM-Alternative	CHARM-Added	CHARM-Preserved
n=2028	n=2548	n=3025
LVEF ≤40% ACE-inhibitor intolerant	LVEF ≤40% ACE-inhibitor treated	LVEF >40% ACE-inhibitor treated/not treated

Primary outcome for each trial: CV death or CHF hospitalisation
Primary outcome for overall programme: All-cause death

CHARM-Alternative

Primary outcome CV death or CHF hospitalisation



CHARM-Added

Primary outcome CV death or CHF hospitalisation

Angiotensin Receptor Blockers - Summary

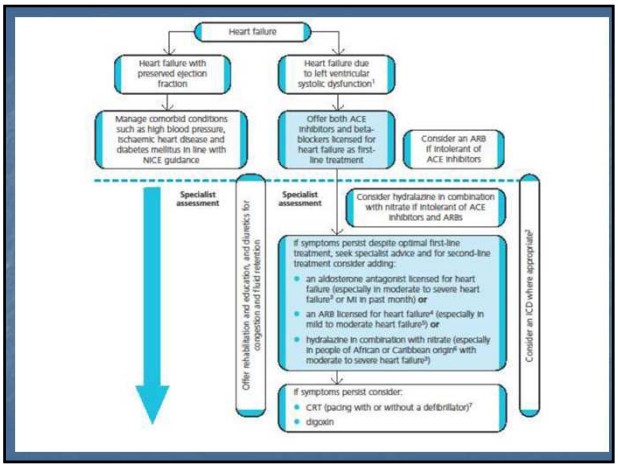
- ARB's are very well tolerated
- Consider an ARB if intolerant of ACE inhibitors
- If patients symptomatic on ACEi and B blocker . Seek specialist attention and consider adding an ARB licensed for HF to reduce mortality and HF hospitalisation.
- 3 licensed for heart failure in UK, Candesartan, Losartan, Valsartan
- No direct comparison –
  - Losartan cheapest
  - Candesartan probably has superior evidence base
- Monitor renal function and K^+ as per ACE inhibitors

Take home message 9

ACE inhibitors are first line in treatment of heart failure

ARB with heart failure licence are good alternatives if patient is intolerant of ACEi

Rarely, and with Specialist input – ARB can be added to ACEi to improve outcomes



Drugs to avoid in Heart Failure

- Anti-inflammatory medication (NSAIDS, COX 2 inhibitors)
- Class 1 antiarrhythmic agents (e.g. flecainide, lignocaine)
-

Digoxin

- Oldest established drug treatment for HF
- Extract of Foxglove (*Digitalis purpurea*)
- 1785 William Withering
- Narrow therapeutic window
- Arrhythmias and GI side effects common

DIG Trial 1997 (Digoxin 250µg od.)

- No mortality benefit
- Significant reduction in hospitalisations due to worsening HF

Digoxin

- Digoxin is recommended for:
  - i. Patients with AF and any degree of heart failure
  - ii. Worsening or severe heart failure due to LV systolic dysfunction despite ACE inhibitor, beta-blocker and diuretic therapy

NICE, 2003