CHANGE PAGE

Consider β blockers for patients with heart failure

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ß blockers remain underused in chronic heart failure despite important benefits, but the difficulty in starting treatment is probably overestimated

The clinical problem

Chronic systolic heart failure is a major public health problem that is associated with high mortality, poor quality of life, and frequent hospitalisation.[1] The sympathetic nervous system is a key activated neurohormonal system that drives progression of this disorder; blocking this system with β adrenergic blocking drugs can improve clinical outcomes.[2] However, the underuse of β blockers is well documented,[3 4] whether by cardiologists or by other specialists, such as geriatricians, general physicians, and general practitioners, who manage many, if not most, patients with heart failure. We propose that in patients with systolic chronic heart failure such doctors need to consider starting β blockers and titrating the dose up as tolerated.

The evidence for change

There is a wealth of evidence on the clinical usefulness of β blockers in systolic heart failure (although evidence is lacking about their use in patients with heart failure with preserved ejection fraction). In fact, the number of patients with systolic chronic heart failure assessed in placebo controlled trials for β blockers exceeds that of patients in trials for angiotensin converting enzyme inhibitors, which also improve morbidity or mortality in heart failure. Three major randomised controlled trials of β blockers in mild to moderate systolic chronic heart failure were stopped early because of overwhelming evidence of mortality benefits and concern that patients receiving placebo should not be denied active therapy.[5-7] The benefits of β blockers have been further extended to those with advanced disease,[8] and a small but significant clinical benefit has been reported in patients with heart failure aged over 70.[9] Patients with asymptomatic systolic dysfunction showed favourable anti-remodelling effects with β blockers, but data on clinical outcomes are lacking in these patients (table).[10]

More than 15 years after evidence from these studies began to accumulate, surveys, registries, and epidemiological studies indicate that these drugs remain vastly underused in everyday clinical practice. For example, in the Euroheart survey, 49% of 11 304 patients with heart failure were prescribed β blockers and even fewer the optimum combination of angiotensin converting enzyme inhibitors, β blockers and diuretics.[3] A few of the patients who do not receive β blockers may represent those with a genuine contraindication to these drugs. Nevertheless, the number of patients receiving β blockers is clearly suboptimal in this and other such surveys of prescribing. The same is true of trials in heart failure that involve specialists in the field.[11] It is not unreasonable to assume even lower numbers of patients prescribed β blockers by other clinicians (for example, general practitioners, general physicians, and geriatricians), although we lack substantive data. Thus, β blockers are probably even more underused than the available data suggest.

Barriers to change

The main barrier to change in practice has been the prior, longstanding contraindication of β blockers in systolic heart failure. This contraindication was based on the concept that sudden withdrawal of sympathetic drive to the failing myocardium may result in worsening, rather than improvement, in the overall disorder. However, clinical trials have clearly shown that this is not the case, although some care is needed when starting or increasing the dose of the drugs, including regular monitoring and observation of patients. This caveat has been sufficient to put β blockers in the "too hard basket", particularly for non-cardiologist practitioners, the perception being that these drugs result in frequent adverse events and require extreme clinical vigilance. However, observational data from clinical practice have shown overall very good tolerability during initiation and upward dose titration even in elderly patients and those with relative contraindications to the treatment (diabetes, fixed airflow obstruction, mild hypotension, and concomitant therapies such as digoxin and amiodarone).[12-14]

SOURCES AND SELECTION CRITERIA

In compiling this article, I made a search of Embase and PubMed for the terms "beta-blockers" and "heart failure."

Effect of β blockers in patients with systolic chronic heart failure

Study	β blocker	Target dose (mg/day)	Patient population	No of patients	Main findings	Size of drug effect
CIBIS II[6]	Bisoprolol	10	Mild-moderate systolic chronic heart failure (LVEF <35%)	2647	Significantly reduced all-cause mortality	HR 0.66 (95% CI 0.54 to 0.81)
COPERNICUS[8]	Carvedilol	50	Severe systolic chronic heart failure (LVEF <25%)	2289	Significantly reduced all-cause mortality	HR 0.65 (95% CI 0.52 to 0.81)
MERIT-HF[7]	Metoprolol CR/XL	200	Mild-moderate systolic chronic heart failure (LVEF <40%)	3951	Significantly reduced all-cause mortality	HR 0.66 (95% CI 0.53 to 0.81)
REVERT[10]	Metoprolol CR/XL	50/200*	Asymptomatic left ventricular systolic dysfunction (LVEF <40%)	164	Dose dependent improvement in left ventricular structure and function	LVESVI reduced by 14 (SD 3) ml/m^2 LVEF increased by 6% (SD 1%)†
SENIORS[9]	Nebivolol	10	Elderly (>70 years) with heart failure (no ejection fraction cut-off)	2128	Significantly reduced all-cause mortality and cardiovascular hospitalisation	HR 0.86 (95% CI 0.74 to 0.99)
US Carvedilol[5]	Carvedilol	50	Mild-moderate systolic chronic heart failure (LVEF <35%)	1094	Significantly reduced all-cause mortality	HR 0.35 (95% CI 0.20 to 0.61)

LVEF = left ventricular ejection fraction. HR = hazard ratio (95% confidence interval). LVESVI = left ventricular end-systolic volume index.
*Dose ranging study (2 doses of metoprolol CR/XL studied).
†Data shown for 200 mg/day dose.

An additional barrier to change may be concern that the populations of patients with chronic heart failure in the main outcome trials do not represent those seen in everyday clinical practice.[15]

How should we change our practice?

For patients with systolic heart failure of any severity (those with ventricular function objectively determined by, for example, echocardiography), treating doctors should start one of the four β blockers that are proven to be efficacious in heart failure (bisoprolol, carvedilol, extended release metoprolol, and nebivolol). Such patients should be clinically stable, relatively euvolaemic, and without major absolute contraindication to this treatment—for example, reversible air flow obstruction, high degree atrioventricular block, or severe hypotension.

The drugs should be started at low doses in appropriately selected patients and can then be titrated up slowly to the target dose (for example, at fortnightly intervals). Patients should be monitored appropriately through this process (volume status, heart rate and rhythm, blood pressure, renal function, and so on). The responsibility for prescribing β blockers falls not just on cardiologists but on all practitioners involved in managing this disorder.

Competing interests: I have received research grants and have been on advisory boards and study steering committees for Roche, GlaxoSmithKline, and Merck.

KEY POINTS

β blockers are essential therapy in systolic chronic heart failure, with important mortality benefits, but they remain underused because of concerns about difficulties in starting treatment

Recent evidence suggests that despite these concerns all practitioners, including non-cardiologists, should consider patients with heart failure for β blockers; even elderly patients and those with relative contraindications tolerate the drugs well

β blockers should be started at low doses in selected patients and titrated up slowly to target dose if possible, with monitoring throughout this process

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GUIDELINES

Recognition and assessment of coeliac disease in children and adults: summary of NICE guidance

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This is one of a series of *BMJ* summaries of new guidelines, which are based on the best available evidence; they highlight important recommendations for clinical practice, especially where uncertainty or controversy exists. The supporting evidence statements and further information about the guidance and the Guideline Development Group are in the full version on bmj.com.

Why read this summary?

Coeliac disease is an autoimmune condition that can be diagnosed at any age. Although it has been traditionally associated with mainly gastrointestinal signs and symptoms, its non-gastrointestinal features have been increasingly recognised.

Given its varied clinical manifestations and the historical belief that it is relatively uncommon,[1 2] concern has been raised that coeliac disease—and its possible long term consequences—is being underdiagnosed. It has also been shown to be more prevalent in people with other autoimmune conditions.[3] This article summarises the most recent recommendations from the National Institute for Health and Clinical Excellence (NICE) on the recognition and assessment of coeliac disease.[4]

Recommendations

NICE recommendations are based on systematic reviews of best available evidence. When minimal evidence is available, recommendations are based on the Guideline Development Group's experience and opinion of what constitutes good practice. Evidence levels for the recommendations are in the full version of this article on bmj.com.

Who should be offered serological testing for coeliac disease?

- Offer testing to children and adults with any of the following signs and symptoms:
  - -Chronic or intermittent diarrhoea
  - -Failure to thrive or faltering growth (in children)
  - -Persistent and unexplained gastrointestinal symptoms including nausea or vomiting
  - -Prolonged fatigue
  - -Recurrent abdominal pain, cramping, or distension
  - -Sudden or unexpected weight loss
  - -Unexplained iron deficiency anaemia or other unspecified anaemia.
- Offer testing to children and adults with any of the following conditions:
  - -Autoimmune thyroid disease
  - -Dermatitis herpetiformis
  - -Irritable bowel syndrome
  - -Type 1 diabetes.
- Offer testing to children and adults who have first degree relatives with coeliac disease.
- Consider offering testing to children or adults with any of the following: Addison's disease, amenorrhoea, aphthous stomatitis, autoimmune liver conditions, autoimmune myocarditis, chronic thrombocytopenia purpura, dental enamel defects, depression or bipolar disorder, Down's syndrome, epilepsy, low trauma fracture, lymphoma, metabolic bone disease (such as rickets or osteomalacia), microscopic colitis, persistent or unexplained constipation, persistently raised liver enzymes with unknown cause, polyneuropathy, recurrent miscarriage, reduced bone mineral density, sarcoidosis, Sjögren's syndrome, Turner's syndrome, unexplained alopecia, unexplained subfertility.
- Do not use serological testing for coeliac disease in infants before gluten has been introduced into the diet.

Advice to patients

- Inform people that testing for coeliac disease is accurate only if the person is eating a diet that contains gluten at the time of testing.
- Inform people that when following a normal gluten containing diet they should eat some gluten (for example, bread, chapattis, pasta, biscuits, or cakes) in more than one meal every day for a minimum of six weeks before testing.
- If a person is reluctant or unable to reintroduce gluten into their diet before testing refer them to a gastrointestinal specialist and inform them that it may be difficult to confirm a diagnosis of coeliac disease on intestinal biopsy.
- Inform people and their parents or carers that a delayed diagnosis of coeliac disease, or undiagnosed coeliac disease, can result in:
  - -Continuing ill health
  - -Long term complications, including osteoporosis and increased risk of fracture, unfavourable pregnancy outcomes, and a modest increased risk of intestinal malignancy
  - -In children, growth failure, delayed puberty, and dental problems.

Serological tests

- All tests should be undertaken in laboratories with clinical pathology accreditation.

- Do not use IgG or IgA antigliadin antibody (AGA) tests in the diagnosis of coeliac disease.
- When clinicians request serology, laboratories should:

  -Use IgA tissue transglutaminase antibody (tTGA) testing as the first choice of test
  -Use IgA endomysial antibody (EMA) testing if the result of the IgA tissue transglutaminase antibody test is equivocal
  -Check for IgA deficiency if serology is negative (if the laboratory detects a low optical density on the IgA tTGA test, very low IgA tTGA results, or low background on the IgA EMA test)
  -Use IgG tissue transglutaminase antibody or IgG endomysial antibody tests (or both) for people with confirmed IgA deficiency
  Communicate clearly the results in terms of values, interpretation, and recommended action.

Referral for intestinal biopsy

- Offer anybody with positive serological results a referral to a gastrointestinal specialist for intestinal biopsy to confirm or exclude coeliac disease.
- If serology tests are negative but coeliac disease is still clinically suspected, offer referral to a gastrointestinal specialist for further assessment.

Overcoming barriers

Coeliac disease was previously thought to be uncommon, and the best serological tests for diagnosing this condition are unclear. This guideline emphasises the variety of symptoms and signs that can arise from coeliac disease and the many conditions that may coexist with it. It aims to raise awareness of coeliac disease and increase appropriate diagnosis, thus enabling effective treatment and improvement of the health and quality of life of people with the disease.

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DRUG POINT

Hypoglycaemia induced by second generation antipsychotic agents in schizophrenic non-diabetic patients

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We report three cases of hypoglycaemia in non-diabetic non-obese Japanese inpatients who had schizophrenia and were being treated with a second generation antipsychotic. The clinical findings of hypoglycaemia emerged typically 2-3 hours after meals in all patients during escalation of the dose of second generation antipsychotic. No other antipsychotic or concomitant drug with a metabolic effect was coadministered.

Case 1—A 27 year old woman who took 400 mg of quetiapine a day complained of dizziness, tremor, and palpitations on day 112 of her inpatient stay. These symptoms worsened with a 600 mg daily dose of quetiapine (day 132). At this point, her blood glucose three hours after lunch was 3.2 mmol/l. Her symptoms (tremor, irritability) resolved after oral sugar intake. An oral glucose tolerance test during quetiapine treatment (600 mg a day, day 154), found further evidence of hypoglycaemia (table). We replaced quetiapine with perospirone (day 167), and her hypoglycaemia symptoms resolved clinically but asymptomatic hypoglycaemia was still present upon repeat oral glucose tolerance test.

Case 2—A 53 year old man received an oral glucose tolerance test on two successive risperidone doses at 6 mg a day (day 43 of admission) and 8 mg a day (day 86). His plasma glucose was markedly low (2.5 mmol/l) two hours after the test, with 8 mg daily risperidone (table). Although he complained of tremor and palpitations after meals while taking 8 mg of risperidone a day, these symptoms were absent with 6 mg a day, and no biochemical evidence showed hypoglycaemia after an oral glucose tolerance test. Hypoglycaemic symptoms and abnormal oral glucose tolerance test results resolved after risperidone was reduced to 3 mg a day and coprescription of 18 mg of aripiprazole a day.

Case 3—A 32 year old woman received an oral glucose tolerance test while taking two successive doses of olanzapine—10 mg a day (day 74 of admission) and 20 mg a day (day 115). With 10 mg a day she did not have clinical symptoms of hypoglycaemia or low plasma glucose during oral glucose tolerance testing.

Results of the 75 g oral glucose tolerance test in three Japanese patients with schizophrenia

Case	Antipsychotic treatment	Days since last change in antipsychotic dose		Concentration of glucose (mmol/l) and insulin (pmol/l) before and after oral glucose tolerance test				
				0 min	60 min	90 min	120 min	180 min
1	Quetiapine 600 mg/day	22	Glucose	4.5	13.2	14.2	9.2	3.7*
			Insulin	67	1619	2380	1671	75
	Perospirone 36 mg/day	22	Glucose	5.9	12.8	12.6	9.4	3.3*
			Insulin	22	380	701	388	37
2	Risperidone 6 mg/day	12	Glucose	4.7	8.8	7.8	6.9	—
			Insulin	14	463	309	201	—
	Risperidone 8 mg/day	23	Glucose	5.2	7.0	5.6	2.5*	—
			Insulin	67	412	342	87	—
	Risperidone 3 mg/day and aripiprazole 18 mg/day	19	Glucose	4.7	7.6	7.3	6.9	—
			Insulin	32	448	503	369	—
3	Olanzapine 10 mg/day	74	Glucose	4.3	4.7	4.6	5.7	—
			Insulin	45	522	189	539	—
	Olanzapine 20 mg/day	16	Glucose	4.5	5.0	2.3*	5.9	—
			Insulin	54	858	91	328	—

Oral glucose tolerance tests were performed at 6 am in each patient in a fasting state. In case 1 glucose and insulin levels were monitored up to 180 minutes because of previous hypoglycaemia-like symptoms three hours after lunch. The Pharmaceuticals and Medical Devices Agency in Japan lists hypoglycaemia with possible relation to quetiapine (eight cases), risperidone (four cases), olanzapine (three cases), and perospirone (one case). *Reference ranges for plasma glucose 3.9-6.1 mmol/l and insulin 23-126 pmol/l. Plasma glucose less than 3.9 mmol/l is considered evidence of hypoglycemia.

Taking 20 mg a day she exhibited irritability after meals, marked hypoglycaemia during testing, and a higher peak insulin response with an unstable time course (table). This is consistent with increased insulin release by olanzapine in vitro and in vivo.[1,2]

Hypoglycaemia is a serious medical condition and can cause seizures, permanent neurological damage, or death. Although the risk of hyperglycaemia induced by second generation antipsychotics is known, this case series shows hypoglycaemia associated with use of second generation antipsychotics after verification with oral glucose tolerance testing. Because hypoglycaemia generates symptoms of adrenergic stimulation, such as irritability and anxiety, recognition of the possible link between second generation antipsychotics and hypoglycaemia can prevent missed cases in the future and improve differential diagnosis of exacerbation of schizophrenia.

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From our archive

Effect of large doses of histamine on gastric secretion of HCl

In the routine histamine test of gastric secretion the dose of histamine advised has been determined arbitrarily as being generally sufficient to provoke an acid response and generally free from liability to cause untoward symptoms. It is thus a compromise, and fails to take account of individual variations in susceptibility. This defect can be overcome by utilizing the group of synthetic drugs known as the antihistamines.

These compounds have been shown to antagonize all histamine effects save that on gastric secretion. This interesting anomaly has been well demonstrated by the work of Halpern (1948). He has shown that, although guinea-pigs could be protected against the systemic effects of as much as 1,500 lethal doses of histamine, many animals died within a day or two as a result of gastric perforation.

The purpose of this paper is to describe the parietal cell response in man to large doses of histamine, the systemic effects of the drug being prevented by the use of an antihistamine. It will be shown that in this way it is possible to give a maximum stimulus to the parietal cells. An augmented histamine test of gastric secretion, based on this principle of maximum stimulation, is described and an analysis made of the results of 148 such tests performed on normal subjects and on patients with peptic ulcer.

Kay AW. Effect of large doses of histamine on gastric secretion of HCl. *BMJ* 1953;2:77-80

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