



National Prescribing Service Limited



Case study 52 report: Optimising chronic heart failure therapy

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The information contained in this material is derived from a critical analysis of a wide range of authoritative evidence. Any treatment decision based on this information should be made in the context of the clinical circumstances of each patient. Declarations of interest have been sought from all commentators.

Case study 52

Optimising chronic heart failure therapy

Scenario

Harry is a 75-year-old retired naval officer diagnosed with systolic heart failure by echocardiogram 10 months ago. He presents with increased breathlessness on ordinary physical activity (mild chronic heart failure, NYHA II grading of symptoms).

He has a history of hypertension (18 years), stable ischaemic heart disease (10 years), gout (5 years) and depression (6 months) following the recent death of his wife. He has no other significant medical history. His body mass index is 23 kg/m².

His current medications (all once daily) are enalapril 10 mg, frusemide 80 mg, aspirin 100 mg, simvastatin 40 mg, isosorbide mononitrate 120 mg, allopurinol 100 mg, fluoxetine 20 mg and glyceryl trinitrate spray when required.

Harry was an active sailor; before being diagnosed with heart failure he could sail for two hours without symptoms but now he gets breathless after a short while. Before his symptom of breathlessness appeared, he did not have any other physical activity except sailing every two weeks. Harry drinks about 1 litre of water daily and tries to reduce his salt intake but finds this difficult.

The echocardiogram revealed a left ventricular ejection fraction of 30% and no valvular abnormalities. Serum biochemistry (urea, creatinine, electrolytes) two weeks ago were normal. On examination, his pulse rate is 79 and regular, blood pressure is 140/85 mmHg. His jugular venous pulse is not raised and there is no peripheral oedema. His weight is 68 kg, unchanged from his visit 3 weeks ago.

1. a) Given Harry's current condition, what target dose should be recommended for enalapril (currently 10 mg daily for past 8 years), and why?

Target dose _____ mg Frequency _____ Why? _____

- b) How should enalapril be titrated to reach target dose?

What dose increment? _____ mg How often? _____

- c) What should be monitored during ACE inhibitor titration?

2. a) What are the potential benefits and harms of beta-blocker therapy in chronic heart failure?

Potential benefits

Potential harms

- b) In chronic heart failure, what should be monitored during beta-blocker initiation?

- c) What advice should be given to a patient on the initiation or continuation of beta-blocker therapy for chronic heart failure?

3. a) Is a beta blocker recommended for Harry? Why/ why not?

Yes No

Why/ why not? _____

b) If yes, please list which beta blocker and dosage.

c) How should the beta blocker be titrated to reach target dose?

What dose increment? _____ How often? _____

4. To help Harry with self-management of his heart failure, please answer the following questions:

a) Which symptoms and signs would suggest his condition is worsening?

b) If he develops such symptoms, what should he do?

c) What over-the-counter/complementary medicine(s) should be avoided? List 3 examples.

Summary of results

At the time of publication, 1187 responses had been received. This report summarises responses from 200 general practitioners.

Case synopsis

Harry, a 75-year-old retired naval officer with systolic heart failure, presented with increased breathlessness with ordinary physical activity. He has a history of hypertension, stable ischaemic heart disease, gout and depression. His current medications (all once daily) are enalapril 10 mg, frusemide 80 mg, aspirin 100 mg, simvastatin 40 mg, isosorbide mononitrate 120 mg, allopurinol 100 mg, fluoxetine 20 mg and glyceryl trinitrate spray when required. Echocardiogram revealed a left ventricular ejection fraction of 30% and no valvular abnormalities. (See page 3 for more details.)

ACE inhibitor use and titration

- 79.5% of respondents recommended increasing the enalapril dose to a target daily dose of 40 mg; 20.5% recommended increasing to 20 mg.
- Main reasons for titrating enalapril to a higher target dose were to improve survival rates (46.0%), maximise CHF benefits (24.5%), reduce likelihood of worsening CHF (22.0%), reduce morbidity (18.5%), and control hypertension (9.0%).
- When titrating ACE inhibitor to target doses, respondents would monitor renal function, blood pressure, potassium levels, adverse effects (e.g. cough), electrolytes and/or urea and volume depletion/weight changes.

Beta blocker use and titration

- Improvements in mortality and morbidity (81.0% and 75.0%, respectively) were cited by most respondents as benefits of beta-blocker therapy. The main harms suggested by respondents were hypotension (91.0%) and bradycardia (75.5%).
- When initiating a beta blocker, most respondents established the need to monitor blood pressure, pulse rate, signs or symptoms of worsening CHF, weight gain and respiratory symptoms.
- Respondents would provide the following advice when initiating or continuing beta-blocker therapy:
 - be aware of possible postural hypotension (70.0%)
 - expect heart to beat slower (29.5%)
 - beta blocker may cause lethargy/tiredness (20.5%)
 - transient worsening of symptoms possible (19.5%)
 - breathlessness may increase (17.5%)
 - titrate slowly (11.0%)
 - the benefits of treatment (8.0%)
 - see GP if symptoms deteriorate (7.5%).

Appropriateness of beta-blocker therapy for Harry

- 82.0% of respondents would add a beta blocker, mainly to improve symptoms of CHF (56.1%), because Harry is haemodynamically stable or has no contraindications (26.8%), to reduce mortality (26.2%), treat moderate CHF (12.2%) and reduce his blood pressure (11.6%). Reasons for not adding a beta blocker included the need to maximise ACE inhibitor dose first (80.6%) and that Harry was haemodynamically unstable (16.7%).

- The beta blocker of choice for Harry was carvedilol (61.6% of respondents), bisoprolol (30.5%), metoprolol succinate controlled release (7.3%) and metoprolol tartrate immediate release (0.6%).
- The target daily dose was:
 - carvedilol 50 mg (95.0% of respondents who selected carvedilol)
 - bisoprolol 10 mg (94.0% of respondents who selected bisoprolol)
 - metoprolol controlled release 190 mg (91.7% of respondents who selected metoprolol controlled release).

Identifying and managing worsening CHF

- Respondents provided many examples of signs and symptoms of worsening CHF; main examples were breathlessness, tiredness, weight gain, fluid retention and worsening exercise tolerance.
- In response to worsening CHF, respondents recommended that Harry should consult his GP, go to hospital if acute, assess and reduce fluid intake, and/or increase his diuretic dose.

Over-the-counter/complementary medicines to avoid

- Over-the-counter/complementary medicines to be avoided in CHF included conventional NSAIDs, oral decongestants (e.g. pseudoephedrine, ephedrine, cough and cold preparations), sodium-containing preparations, St John's wort, liquorice, potassium-containing preparations and aspirin.

Results in detail

ACE inhibitor use and titration

- Given Harry's worsening CHF, 79.5% of respondents recommended increasing the enalapril dose to a target daily dose of 40 mg; 20.5% recommended increasing to 20 mg.
- 87.5% (n = 175) selected a twice-daily regimen, 11% (n = 22) a once-daily regimen, and the remainder (n = 3) were flexible, with either a once- or twice-daily regimen.
- To reach target dose, dosage increments suggested were 20 mg (50.5%), 2.5 mg (26.0%) or 5 mg (18.5%). Most respondents would titrate enalapril to target dose every two weeks, if tolerated.

Reason for ACE inhibitor titration

Reason for titrating to target ACE inhibitor dose	% of respondents* (n = 200)
Better survival rates	46.0
Reduce morbidity/beneficial to condition	43.0
Reduce worsening symptoms of CHF	22.0
Control hypertension	9.0
Provide 24-hour cover, as enalapril has a short duration of action	7.0
Enhance cardiac function	5.0

*Respondents may have more than one response

Monitoring ACE inhibitor titration

Monitoring parameters during ACE inhibitor titration	% of respondents* (n = 200)
Blood pressure	71.5
Renal function	69.0
Potassium levels	39.5
Adverse effects (e.g. cough)	20.5
Urea and electrolytes	18.0
Electrolytes	18.0
Volume depletion/weight changes	6.5

*Respondents may have more than one response

Practice points ¹⁻⁴

- ACE inhibitors improve symptoms, reduce mortality and risk of hospitalisation in CHF.
- Enalapril can be prescribed once or twice daily although enalapril was given in two divided doses in clinical trials in which mortality and morbidity were reduced. ⁵ In these trials, target doses were 10–20 mg twice daily, with the upper dose range higher than recommended in the product information.
- Check blood pressure, blood chemistry (urea, creatinine and electrolytes) at least 1–2 weeks after initiation and at least 1–2 weeks after each dose titration.
- If a patient presents with symptomatic hypotension, reconsider the need for nitrates, calcium-channel blockers and other vasodilators. Decrease the dose of diuretic before that of the ACE inhibitor if there are no signs or symptoms of congestion.



Beta blocker use and titration

Suggested benefits and harms of beta-blocker therapy

Potential benefits of beta blocker	% of respondents (n = 200)*	Potential harms of beta blocker	% of respondents (n = 200)*
Improve mortality	81.0	Hypotension	91.0
Improve morbidity	75.0	Bradycardia	75.5
Improve CHF symptomst	25.0	Exacerbation of CHF	34.0
Improve cardiac function	12.0	Exacerbation of asthma	21.0
Reduce hypertension	8.0	Lethargy	13.0
Control arrhythmia	5.0		

*Respondents may have more than one response

Monitoring beta blocker titration

Monitoring parameters	% of respondents* (n = 200)
Blood pressure	91.5
Pulse rate	75.5
Signs/symptoms of worsening CHF	24.0
Weight gain	9.0
Respiratory symptoms	8.0

*Respondents may have more than one response

Advice to patient on initiation or continuation of beta-blocker therapy

Advice to patient	% of respondents* (n = 200)
Be aware of possible postural hypotension	70.0
Expect heart to beat slower	29.5
Beta blocker may cause lethargy/tiredness	20.5
Transient worsening of symptoms possible	19.5
Breathlessness may increase	17.5
Titrate slowly	11.0
Explain benefits of treatment	8.0
See GP if symptoms deteriorate	7.5

*Respondents may have more than one response

Practice points¹⁻⁴

- Monitor heart rate, blood pressure and clinical status (signs and symptoms of congestion, weight gain) when initiating beta blockers.
- If heart rate is < 50 beats per minute and symptoms are worsening, halve the beta-blocker dose; if symptoms deteriorate significantly, stop the beta blocker (rarely necessary) and seek specialist input.
- Check blood chemistry 1–2 weeks after initiation and 1–2 weeks after final dose titration.



Appropriateness of beta-blocker therapy for Harry

- Respondents were asked if a beta blocker was indicated for Harry: 82.0% (n = 164) said yes and 18.0% said no (n = 36). Of those who said yes, 6.1% stated that enalapril would have to be further titrated before adding the beta blocker. Main reasons for adding or not adding a beta blocker are listed below.

Reason for adding a beta blocker	% of respondents (n = 164)*	Reason for not adding a beta blocker	% of respondents (n = 36)*
Improve CHF symptoms	56.1	Need to maximise ACE inhibitor dose before initiating beta blocker	80.6
Haemodynamically stable/ no contraindications	26.8	Haemodynamically unstable	16.7
Reduce mortality	26.2		
Treat moderate CHF	12.2		
Reduce blood pressure	11.6		
Stabilise ischaemic heart disease	5.5		

*Respondents may have more than one response

- When a beta blocker was recommended, 61.6% chose carvedilol, 30.5% bisoprolol, 7.3% metoprolol succinate (controlled release) and 0.6% metoprolol tartrate (immediate release). Main target doses were:
 - carvedilol 50 mg (95.0%)
 - bisoprolol 10 mg (94.0%)
 - metoprolol succinate (controlled release) 190 mg (91.7%)
 - metoprolol tartrate (immediate release) 150 mg (100.0%).
- To reach target dose for beta blockers, most respondents suggested doubling the dose every 2 weeks if tolerated.



Practice points

- In Australia, carvedilol, bisoprolol and metoprolol succinate controlled release are the only beta blockers licensed for CHF. Metoprolol succinate controlled release has been shown to perform better than placebo, while metoprolol tartrate immediate release was less effective in reducing mortality when compared with carvedilol.² Evidence is inconclusive as to whether a class effect exists for beta blockers in CHF, so best evidence of benefit lies with carvedilol, bisoprolol and metoprolol succinate controlled release.
- Patients need not be taking high doses of ACE inhibitors before being considered for beta blocker treatment, because most patients enrolled in trials of beta blockers in heart failure were not taking high doses of ACE inhibitors.⁶
- Recommended target doses and titration regimens for beta blockers in CHF are shown below.^{1,2}

Beta blocker	Starting dose	Titration regimen	Target dose
bisoprolol	1.25 mg daily	Double dose every 1–2 weeks if patient is stable	10 mg daily
carvedilol	3.125 mg twice daily	Double dose every 2–4 weeks if patient is stable	25 mg twice daily
metoprolol succinate controlled release	23.75 mg daily. If NYHA class III-IV heart failure, half tablet daily (i.e. half of 23.75 mg) for 1 week then one tablet daily for 1 week	Double dose every 2–4 weeks if patient is stable	190 mg daily

Identifying and managing worsening CHF

Symptoms and signs suggestive of worsening CHF

Symptoms and signs of worsening CHF	% of respondents (n = 200)*
Increased breathlessness	94.5
Fluid retention (peripheral/ankle oedema)	57.0
Weight gain	52.5
Tiredness	37.0
Worsening exercise tolerance	25.0
Paroxysmal nocturnal dyspnoea	10.5
Orthopnoea	9.5
Palpitations	9.0
Chest pain	8.0
Symptoms of asthma	7.0
Cough	6.0

*Respondents may have more than one response

Management of worsening CHF

- With worsening CHF, respondents recommended that Harry consults his GP (79.0%), go to a hospital if acute (18.0%), increase diuretic dose (14.0%) and/or assess and reduce fluid intake (11.0%).

Over-the-counter/complementary medication to avoid in CHF

Over-the-counter/complementary medicines to avoid	% of respondents (n = 200)*
Conventional NSAIDs	91.5
Oral decongestants (e.g. pseudoephedrine, ephedrine, cough and cold preparations)	29.5
Sodium-containing preparations (e.g. urinary alkalinisers, antacids)	17.5
St John's wort	17.5
Licorice	10.0
Potassium-containing preparations	6.5
Aspirin	5.0

*Respondents may have more than one response



Practice points

- The detrimental effects of conventional NSAIDs in CHF are well known.⁷
- Pseudoephedrine can increase blood pressure or combination with other sympathomimetic amines (e.g. ephedrine, phenylephrine) may result in excess sympathetic stimulation and adverse effects.¹ Preparations containing sodium or potassium may influence the electrolyte balance of CHF patients and should be used with caution. Excessive use of laxatives may also deplete potassium levels.⁸

- The data on interactions between complementary and prescription medications vary widely in quality and reliability.⁸ Coupled with the unpredictable strength and quality of complementary medications and recent reports of adulteration, it is challenging to elucidate the clinical significance of these reported interactions. See tables below for reported cardiac effects and potential drug–herb interactions.
- Encourage patients to discuss use of complementary products and remain vigilant for potential interactions with prescription medications, especially those with narrow therapeutic index (e.g. digoxin).

Selected herbal medicines with cardiac effects*

Complementary medication	Known effect(s)
Dandelion	Sodium retention
Dong quai, aescin	Anticoagulant: increased risk of bleeding
Ephedra (ma huang), yohimbe bark	Sympathomimetic
Gingko, garlic, danshen	Antiplatelet: increased risk of bleeding
Ginseng	Hypertension
Gossypol	Hypokalaemia
Liquorice [†] (glycyrrhizin)	Fluid retention

*Adapted from SIGN 2007², Amabile and Spencer 2004⁷, Aggarwal and Ades 2001⁹, and Awang 2002¹⁰

[†]Most liquorice is flavoured with anise, but true liquorice-containing herbs contain glycyrrhizin¹¹

Potential digoxin – complementary medication interaction*

Observed effects	Complementary medication	Recommendation
Increased digoxin effects	Siberian ginseng	Monitor digoxin level when Siberian ginseng is initiated or stopped
Decreased digoxin effect	St John's wort	Monitor digoxin level when St John's wort is initiated or stopped

*Source: Williamson 2003⁸, Aggarwal and Ades 2001⁹, Izzo et al 2005¹², and Gardiner et al 2008¹³

- Useful complementary medication websites for health professionals include <http://nccam.nih.gov/> or <http://herbmed.org/> (free, for 45 herbs only)

Commentary 1

Overview

Heart failure is increasingly common as our patients become older and suffer a more complex mix of conditions.

Within our practice lifetimes, new therapies have considerably reduced the impact this disease has on individuals and communities.

A basic understanding of the pathophysiology of heart failure, including Starling's hypothesis¹⁴ and the destructive neurohormonal feedback cycles mediated by renin–angiotensin, adrenaline and kinins, helps management principles.¹⁵

Briefly, the approach to management should include:

- assessment of immediate risk and appropriate emergency measures
- early institution and up-titration of proven therapies, especially ACE inhibitors (or angiotensin II-receptor antagonists if ACE inhibitors not tolerated) and beta blockers
- investigation, diagnosis and management of reversible causes
- management of comorbidities and associated diseases
- ongoing education support and review.

This case study

Harry presents with increasing symptoms but no signs of CHF — as commonly seen with frusemide, which can relieve symptoms but have little effect on disease progression or mortality. The slow onset of symptoms suggests a measured rather than emergency approach to treatment.

Harry has the known risks of longstanding ischaemic heart disease and hypertension (currently inadequately treated) and is in the dangerous situation of recent widowhood.

His echocardiogram excludes structural heart problems (and effusions) and provides a baseline for therapeutic response.

It would also be useful to know Harry's thyroid status, his chest X-ray (to exclude contributing lung disease) and if alcohol may be contributing to his plight.

Harry's management needs optimising with an evidence-based treatment regimen. During (or after) this process, when symptomatically stable, Harry should have his coronary artery disease reassessed and appropriate medical and surgical interventions. Blood pressure and cholesterol levels should be reduced as far as practicable.

Regular support from his GP, cardiac rehabilitation centre, community-based CHF support projects and phone-based advice would be particularly important to Harry, given his vulnerable psychosocial situation. The more he understands about his disease, his therapies and their implications, the more he can take part in his treatment and the better the outcome. In addition to medication, he needs a graded exercise program, dietary advice and emotional support.

Comments on responses

Most respondents seem to follow the recommendations that ACE inhibitors and beta blockers should be introduced and slowly titrated to accepted targets while monitoring for adverse events. This reduces both morbidity and mortality.

ACE inhibitor

The accepted dose of enalapril has been 10–20 mg bd.^{16,17} Increments of 5 mg per dose are practical and should be made at approximately 2-week intervals, provided the patient is stable.

The need to monitor for symptomatic hypotension, hyperkalaemia, renal failure and cough are well recognised.

Beta blockers

Beta blockers are indicated for patients with NYHA class II–IV heart failure who are

haemodynamically stable and euvolaemic (preferably already taking a diuretic and ACE inhibitor).¹⁸ Their use has been shown to prolong life, reduce symptoms and improve wellbeing.

Potential harms are hypotension, bradycardia (potential heart block) and worsening heart failure. These are most likely at initiation of therapy or on increasing doses. Consequently, therapy should be initiated carefully and slowly in co-operation with a well-informed patient who must understand the risks and potential benefits.

Monitoring dizziness and breathlessness is vital. Weight charts showing sudden or sustained gain can give early warning of fluid retention. A postural blood pressure drop can be a warning, as can bradycardia or ECG evidence of conduction defects.

Beta-blocker therapy has benefit on top of ACE inhibitor therapy and can be initiated before target doses of ACE inhibitors are achieved. Thus, up-titration of both drugs can occur simultaneously. Hypotension that may occur can be managed by slowing the increase of doses, by reducing the dose of one or both drugs or by reducing doses of other medication with a hypotensive effect that may no longer be necessary. In Harry's case the doses of frusemide and isosorbide mononitrate could be reduced in

the absence of fluid overload or angina. Harry certainly appears an appropriate patient for beta-blocker therapy. Agents approved in Australia for use in CHF are carvedilol, bisoprolol and controlled-release metoprolol succinate. Doses mentioned by respondents seem appropriate.¹⁸ A 2-week interval between incremental doses in stable patients is a general guide.

Worsening CHF

Worsening symptoms of CHF have also been correctly identified. These patients need ready access to their GPs and hospitals but can also be helped by other support services such as community heart-support nurses (available in some communities) or by telephone support services. Well-informed patients can monitor their diuretic use if symptoms worsen. They should also be warned to seek early help if concurrent illnesses (e.g. respiratory infections) intervene.

Over-the-counter medications that promote fluid retention (NSAIDs), promote arrhythmias or hypertension (decongestants) or produce electrolyte imbalance (sodium- or potassium-containing agents) are correctly identified. It should also be noted that excess alcohol contributes to heart failure in many of our patients.

Commentary 2

General comments on the case study

This is a fairly straightforward case of a patient with heart failure and clinical deterioration.

His history demonstrates well-known CHF risk factors of hypertension and ischaemic heart disease. Furthermore, he has gout, possibly as a consequence of frusemide. Given that he needs this medication for volume control, we need to keep this adverse event in mind and manage empirically when it occurs. He is also depressed, a common comorbid association of systolic CHF, but also clearly reactive to the death of his wife. It would be interesting to know what his body mass index was before his heart failure admission, as a BMI of 23 may be indicative of a degree of cardiac cachexia in this patient if it was higher before heart failure development.

Evidence on ACE inhibitor, beta blocker, statin and aspirin use in CHF

Harry's medications reflect a patient with background ischaemic heart disease and hypertension as well as gout and diabetes. Clearly Harry is taking a suboptimal dose of ACE inhibitor, as enalapril 20-40 mg/day was the dose range used in landmark studies such as CONSENSUS¹⁷ and SOLVD.¹⁶ He is not taking a beta blocker and there does not appear to be any major contraindication to him receiving this medication. Indeed, a beta blocker may be useful symptomatically in a patient with concomitant ischaemic disease, if indeed this is currently active.

The use of statins and aspirin are not controversial in a patient with ischaemic heart disease but the recent CORONA study¹⁹ showed that there was no further benefit to be obtained by use of a statin in patients with an ischaemic cardiomyopathy. Furthermore, aspirin even at low doses may cause salt and water retention, which led to increased hospitalisation for heart

failure in studies of such as WATCH²⁰ and WASH.²¹ Nevertheless, in patients with known ischaemic heart disease it is recommended that aspirin be continued indefinitely at low dose.

Fluoxetine is a safe antidepressant drug in the setting of heart failure.²²

The presentation is one of worsening heart failure symptoms, but in the context of a physical examination does not demonstrate any evidence of volume overload clinically. Indeed, his weight was unchanged compared with previous review, which supports this.

This scenario provides the perfect setting in which to further block key neurohormonal systems such as the renin-angiotensin-aldosterone system and sympathetic nervous systems. Conventional approach (among many that could be considered) would be to increase his enalapril to 10 mg twice daily and, if symptoms persist, to then cautiously introduce a low-dose beta blocker (one of the three proven to be of benefit in systolic heart failure — carvedilol, bisoprolol or extended-release metoprolol). CIBIS III²³ suggested that beta blockers could be used before ACE inhibitors. The main goal of therapy is to have patients on both classes of drugs and at target doses as soon as this can be safely achieved. During up-titration of beta blockade, patients should be carefully followed clinically, including assessment of heart rate, blood pressure, postural symptoms, evidence of volume overload and measurement of renal function and potassium.

Further therapy beyond this depends on his clinical status. If he has NYHA class III symptoms despite adequate doses of ACE inhibitor and beta blocker, consideration could be given for introduction of either spironolactone or an angiotensin II-receptor blocker. Consideration also should be given to the potential benefit of device therapies such as implantable cardioverter defibrillator and (if QRS duration is prolonged) biventricular pacing to help co-ordinate cardiac contraction.

Comment on the GP responses

In general the GP responses were correct. With regard to ACE inhibitor use, the GPs clearly understand the importance of up-titrating enalapril to target dose, and the benefits to be derived from this. Monitoring of ACE inhibition with this increase in dose is also appropriately considered.

There is more evidence of need for caution with use and up-titration of beta blockers. For example, many GPs would not add a beta blocker on the grounds that the patient was haemodynamically unstable; however, we are given information that blood pressure was adequate, that there was no volume overload

and that weight had not changed from the previous visit. Therefore, instability, as claimed, was really not there. Most respondents not adding a beta blocker would not do so because of the need to maximise ACE inhibitor dose first. This is a reasonable argument before up-titrating ACE inhibition but should not be used to permanently defer the introduction of beta blockade.

Respondents would avoid over-the-counter aspirin but, as mentioned above, while associated with salt and water retention in heart failure, low-dose aspirin clearly has a role in thromboembolic prophylaxis in the patient with proven ischaemic heart disease.

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