# Patient with congestive heart failure

Patient S. V. is a 54 years old female. She is a postmenopausal housewife and her family history is not being recorded. She is a non-smoker and does not drink alcohol at all. She has no-known drug allergic. The past medical history showed us that Madam S. V. is having, rheumatoid arthritis (RA), hypertension (HPT) for 10 years and diabetes mellitus (DM) for 7 years. She was admitted to the hospital on few weeks ago due to congestive heart failure.

Madam S. V.’s drugs history include:

T. furosemide

40mg od

Oedema & HF

T. perindopril

4mg od

HF & HPT

T. spironolactone

25mg od

HF

T. Losec (Omeprazole)

20mg bd

Duodenal ulceration

P. Calcium lactate

1 puff od

Calcium supplement

T. Rocatriol

0. 25mg bd

Vitamin D supplement

T. Metformin

500mg bd

DM

T. folate

5mg od

Folate deficiency

T. Methotrexate

20mg/week

RA

## Clinical data

The abnormal result of FBC may due to folate deficiency that caused by side effect of methotrexate. Besides that, patient was having high neutrophil number for his differential count which is 8. 7 k/µL (normal range 1. 9-8. 7 k/µL). This may due to the long-term use of corticorsteroid. Patient's total carbon dioxide in the blood was two times higher than normal range (23-27 Vol%). Prothrombin time and INR of the patient was low: PT = 11. 1 sec (normal range = 11. 9-14. 5 sec), INR = 0. 82 (normal range 2-4). However, the reason is unknown.

## Diagnosis

ECG and chest X-ray were carried out and the results showed that patient was having sinus tachycardia and cardiomegaly. Cardiovascular system of patient also had been checked. It found that the patient was having a 3rd heart sound. Hence, the patient was diagnosed with congestive heart failure (CHF).

## Clinical progress

DAY 1

Patient is admitted to the hospital at 10. 30am by ambulance. She is weak but conscious and alert. The patient complains that she is shortness of breath (SOB) and her sleep has been interrupted due to SOB. It can also be considered as paroxysmal nocturnal dyspnoea (PND) which is sudden, severe SOB at night that awakes a person from sleep, often coughing and wheezing.

At the same time, she also experiences from chest discomfort and swelling leg. Besides that, the patient also shows the symptoms of cushing's

syndrome such as moonface and hirstuism. The blood pressure (BP) and pulse rate (PR) of Madam S. V. are found to be quite high as well, which is 118/87mm/Hg and 146b/min respectively.

Test ordered include FBC, RP, LFT, ABG, Coagulation test, U&E, CXR, ECG and random glucose test.

Nebulizer is given to patient once she is admitted. She is also on high flow mask oxygen 15L/min at the same time to ease the problem of SOB. Salfasalazine 1g bd is added to patient. The management plan is to carry out lung function test, continue to on the face mask for oxygen supply, revise all test results, restrict fluid and continue with old medications.

DAY 2

Patient still complain of minimal SOB and minimal chest pain. Another new complain, headache, has been recorded. Her BP and PR have been slowly decreased but they are still not within the normal range.

T. bisoprolol 2. 5mg od is added for a better control of HPT and HF. Management plan include restrict fluid < 800cc/day, strict I/O charting and off oxygen face mask.

DAY 3

Patient is no longer complaining for anything. She has no chest pain and SOB anymore. Her PR has back to normal range. However her BP is still slightly higher than normal range. Management plan is same as day 2. Sulphasalazine since the condition of RA is improved.

DAY 4

Patient is feeling well, comfortable and tolerating orally. Her BP and PR are within the normal range. The management plan is to perform a CRX report, patient can be discharged if normal result is obtained and continue old medications.

## Pharmaceutical care issues

There are few things need to be taken care of in this case. Firstly, the patient is having the problem of nausea and vomiting and no action is taken to solve this problem. Antiemetic drug (H1 receptor antagonist, cyclizine; D2 receptor antagonist, halopiridol) should be given. At the same time, underlying cause of nausea and vomiting has to be identified if possible. This may caused by side effect of perindopril.

Secondly, patient is having cushing's syndrome due to long-term usage of steroids for her rheumatoid arthritis. However, there is no any record about the steroids intake for patient in clinical notes. Hence, we have to ask GP or patient to make sure that whether she has stopped taking steroids or still continue with it. According to CSM, long-term corticosteroids therapy should be withdrew gradually. Abrupt discontinuation of corticosteroids therapy may cause severe symptoms because normal production of steroids by the body has been affected. The dose may be reduced rapidly down to physiological doses (prednisolone 7. 5mg daily). Then, the progress of dose reducing can be slowed down. The patient is hirudism which is one of the symptoms of cushing's syndrome. This problem can be overcome by local measures such as shaving, or depilation such as using wax or cream (eg: eflornithine).

The dose of T. folate for patient which is 5mg once daily is indicated for treatment of megaloblastic anemia. However, the FBC test result does not show any symptoms of megaloblastic anemia. The dose of T. folate should be 5mg once daily if it is indicated for folate deficiency induced by mehtotrexate. Blood film should be carried out to make sure that whether the patient is having megaloblastic anemia or not. FBC, serum folate and serum B12 are reliable indicator of folate status. Real indication of T. folate has to be clarified with doctor before dispense the drug.

Oedema problem never been improved since the day patient been admitted into the hospital. Restrict fluid intake and strict I/O charting is carried out. However, patient is not compliance to it. Some simple self-care techniques can be taught to patient to reduce the build up of fluid. Counsel the patient about the importance of following Strict I/O chart. Dose of furosemide can be increased if oedema doesn’t improve.

The blood pressure of patient is still not stable yet. Patient has to be counseled to improve her diet and lifestyle. It is also necessary to monitor BP of patient regularly. Increasing dose of Î²-blocker can be considered if BP is not reducing. However, due to its negative inotropic effect, Î²-blocker should be started in very low dose and increase gradually.

Lastly, upon discharge, ensure all appropriate medications are prescribed and patient is counseled appropriately. We have to tell patient that Perindopril is added in and ensure patient’s compliance with medication. Patient should be told to avoid alcohol and cranberry juice and consult GP if anything goes wrong.

# Disease overview

## Incidence

Heart failure (HF) affects 0. 3-2% of general population. In 2001, officially there are 11500 deaths are recorded in the UK due to HF. The incidence rate increase by double each decade from age 45. It affects 3-5% of those over 65 years and 8-16% of those over 75 years. The Rotterdam study shows that prevalence is higher in men compared to women.

## Pathophysiology

Heart failure can be defined as inability of the heart to supply sufficient blood flow to meet the body’s needs. HF can result from any disorder that reduces ventricular filling (diastolic dysfunction) and myocardial contractility (systolic dysfunction). The leading causes of HF are coronary artery disease and HPT. As cardiac function decreases after myocardiac injury, the heart relies on few compensatory mechanisms. Although those compensatory mechanisms can initially maintain the cardiac function, they are responsible for HF symptoms and contribute to disease progression. An initiating event such as acute MI can cause the HF state becomes a systemic disease whose progression is largely mediated by neurohormones and autocrine/paracrine factors such as agiotensin II, norepinephrine, aldosterone, natriuretic peptides, and so on. Some drugs may exacerbate HF due to their inotropic, cardiotoxic and sodium-/water- retention properties.

## Diagnosis

A complete history, physical examination and appropriate lab testing are essential in initial evaluation of patients suspected from having HF. The signs and symptoms are the key for early detection. Breathlessness, angina,

fatigue and wheeze are common signs and symptoms. Patient complains that she is having SOB and PND.

Electrocardiogram (ECG) and B-type natriuretic peptides (BNP) are essential tests for every patient with suspected HF. ECG is carried out once the patient is admitted into the hospital. Madam S. V. was detected to have sinus tachycardia by ECG which is one for the common ECG abnormalities in HF. Others common ECG abnormalities include sinus bradycardia, atrial fibrillation, ventricular arrhythmias and so on. Plasma BNP is not measured in this case.

Chest X-ray (CXR) is also an essential component of diagnostic work-out in HF. It is very useful for detection of cardiomegaly, pulmonary congestion and pleural fluid accumulation. It also demonstrates the presence of any pulmonary disease or infection that will lead to dyspnoea. Via CXR, patient is detected from having cardiomegaly which is also one of the abnormalities for HF.

Echocardiography (ECHO) should be performed shortly if one or both ECG and BNP get an abnormal result. ECHO is widely available and safe and provides essential information on aetiology of HF. However, ECHO is not carried out in this case. Some other tests such as FBC, RP, LFT, ABG, U&E and random glucose test have been carried out to exclude others possible conditions.

# Pharmacology basis of drug therapy

## Diuretics

The most important function of diuretic drug is to act by decreasing Na+ reabsorption. Diuretic drugs can inhibit Na+ reabsorption by actions on different transport mechanism, which are located at different sites in nephron. All diuretics are acting on the luminal surface of the nephron. They are protein bound in blood and reach the tubular fluid by secretion into proximal convoluted tubule utilizing the organic acid transport mechanism. They are mostly used to control symptoms of breathlessness and fluid retention. However, they do not alter disease progression or prolong survival. Thus they are not considered mandatory therapy for patients without fluid retention.

Loop diuretics for example furosemide is most widely used if compared to other thiazide. It produces diuresis with NaCl loss. It also has vasodilator action which is partly mediated via prostaglandin. This will increase blood flow in the medulla and hence contributes to their natriuretic effect. Unlike thiazides, loop diuretics maintain their effectiveness in the presence of impaired renal function, although higher doses may be necessary. Thizide diuretics are relatively weak diuretics and used alone infrequently in HF. However, thiazide like metolazone can be used in the combination with loop diuretic to promote effective diuresis.

## Angiotensin-Converting Enzyme Inhibitors (ACEIs)

ACE is binding to the plasma membrane and can also exist as a soluble enzyme. The ACEIs act by substrate competition by binding in the Leu-His binding pocket on ACE. Thus, action of angiotensin-I is inhibited. They also

decrease the concentration of angiotensin II and aldosterone and attenuating many of their deleterious effects, including reducing ventricular remodelling, myocardial fibrosis, vasoconstriction and sodium and water retention. In addition, they also very helpful in reducing blood pressure due to arterial vasodilation. However, they will inhibit the breakdown of bradykinin which contributes to strong hypotensive action and cough.

There are currently 11 ACEIs available for clinical use with similar structure and properties, including captopril, enalapril, lisinopril and others. ACEIs are indicated in all grades I to IV of heart failure which stated in NYHA. Potassium sparing diuretics should be stopped before starting ACEI. ACEIs may increase the risk of renal failure in patient with high dose diuretics, elderly, those with existing renal dysfunction and patients with grade IV HF. Hence regular renal function monitoring is required once patient has stabilized on drug.

## Î²-blockers

Î²-blockers can be either selective for Î²1-adrenoceptor which is cardioselective such as atenolol, bisoprolol and metoprolol or non-selective which can act on both Î²1-and Î²2-adrenocepors such as propranolol and timolol. Blockade of Î²1-receptors will decrease rate and force of contraction of heart. Meanwhile, Î²2-adrnoceptor blockade inhibits adrenaline-induced vasodilatation mediated by these receptors. Via these mechanisms, heart rate and cardiac output can be reduced. Beneficial effects of Î²-blockers may result from antiarrhythmic effects, slowing ventricular remodelling, decrease myocyte death, improving LV systolic function, decreasing heart rate, and ventricular wall stress.

The use of Î²-blockers is not suitable for patients who have unstable HF. Patients should receive a Î²-blocker even if symptoms are mild or well controlled with ACEI and diuretic therapy. Because of negative inotropic effects of Î²-blockers, they should be started in very low doses with slow upward dose titration to avoid any symptomatic worsening. Î²-blockers may worsen HF in the short term, but if use with caution they may be very useful in preventing long-term deterioration.

## Aldosterone antagonists

Aldosterone antagonists such as spironolactone and eplerenone also can be called as potassium sparing diuretics. They act on aldosterone-sensitive portion of nephron (last part of distal convoluted tubule and first part of collecting tubule. They block the mineralcorticoid receptor and inhibit Na+ reabsoption and K+ excretion.

Spironolactone can be added to ACEI, diuretic and digoxin to improve morbidity and mortality in patient with severe HF. Eplerenone is more specific compared to spirinolactone as inhibitor of aldosterone receptors and has been shown to reduce morbidity and mortality in patient with left ventricular dysfunction post-MI. However, the diuretic effects of aldosterone antagonists are minimal. Combination of aldosterone antagonist with thiazide or loop diuretics will potentiate the effect of thiazide or loop diuretics. This is a more effective alternative compared to potassium supplement.

## Angiotensin receptor blockers (ARBs) and Digoxin

ARBs may be used as an alternative to ACEIs (eg: losartan) when patient is intolerant to ACEIs or may be used as adjunct therapy (eg: valsartan and cadesartan) in patient who remains symptomatic despite the dose of ACE and Î²-blockers have been optimised. However, ARB is not given to the patient since she is well tolerated to ACEIs.

Digoxin is one of the main drugs for HF treatment. However, digoxin is not recommended in this case. Digoxin can only been given if patient's HF is worsening or patient is having atrial fibrillation at the same time. Hence, it is reasonable to exclude digoxin from treatment in this case.

## Evidence for treatment of the conditions

## Diuretics

Diuretic is a very important drug for heart failure treatment especially for symptoms of fluid retention. A meta-analysis which includes 18 randomised controlled trials (RCT), n= 982, had been carried out to study the role of diuretics (loop diuretics and thiazides) in patient with congestive heart failure (CHF). 8 trials were placebo-controlled and another 10 were comparison between diuretics and other drugs such as ACEIs, digoxin and ibopamine. The results had shown that diuretics reduce the risk of deterioration of disease and mortality compared to placebo group. When compared to active controls, diuretics also showed significant improvement in patient's exercise capacity. The beneficial effects of diuretics are further supported by Cochrane database which also indicated that diuretics cause significant reduction rate and improvement in patient's morbidity.

Another study also proved that the withdrawal of furosemide will cause increase in volume load and right ventricular pressure. There will lead to deterioration of CHF which include impaired quality of life, weight gain and walking distance reduced. Higher dose of furosemide will have more desirable effects such as increasing general well-being and reducing symptoms of disease. However, the inappropriate high dose of furosemide will lead to hypotension. The risk of hypotension will be increased if patient on ACEIs or vasodilators at the same time with diuretics. According to NICE guidelines, low dose should be prescribed for the initiation of therapy and titrated up according to patient's condition.

Furosemide is the most commonly used loop diuretic. However, some patients are more responsive to other loop diuretic such as torasemide. This may due to its longer duration of action and high absorption. Some pharmacoeconomic analyses also proved that torsemide reduces hospitalisation for patient with CHF. Hence, overall treatment costs are reduced although torasemide is more expensive than furosemide. Patients that treated with torasemide have improved their quality of life. The data also suggest torasemide to be used as first-line treatment for patients with CHF and for those who are not response to furosemide.

Besides that, according to a double-blind study, n= 1663, additional of aldosterone antagonist, spironolactone with furosemide had significantly reduced mortality and morbidity rate of patients with severe HF Hence from the evidences above, we can conclude that furosemide 40mg od is rationale to be given to patient to treat the symptoms of her CHF.

## Angiotensin-Converting Enzyme Inhibitors (ACEIs)

The patient is taking perindopril 4mg od for her HF. A clinical trial has been carried out to compare the effectiveness between ACEIs and placebo in patients with symptomatic CHF. The overall results showed the significant reduction in total rate of mortality and risk hospitalisation.

The benefits of ACEIs are further supported by five long-term randomised trials which had recruited 12763 patients with heart failure or left-ventricular systolic dysfunction (LVSD) to compare the effectiveness between ACEIs and placebo. Results showed that mortality rate has been reduced by 23%, readmission rate of heart failure reduced by 35% and re-infarction rate had been reduced by 26% for the patients who assessed ACEIs compared to placebo group. The benefits of ACEIs were observed at the beginning of therapy and it persisted long term.

In SOLVD investigation, n= 4228, ACEIs (enalapril) reduced the rate of hospitalisations and also incidence of heart failure in patients with reduced left ventricular ejection fractions compared to placebo group. Some randomised controlled trials proved that ACEIs also improve the exercise capacity and quality of life in majority of the patients. Not all the patients with heart failure due to left-ventricular systolic dysfunction experienced the improvement of exercise capacity. However, ACEIs alone is not enough for the treatment of heart failure with pulmonary oedema. Diuretic is needed to maintain sodium balance and prevent any fluid retention. ACEIs are more often to be prescribed compared to vasodilators and angiotensin receptor blockers due to more evidence supports.

ACEIs will cause hyperkalaemia, cough and deterioration of renal function. Hence, renal function and serum potassium level need to be checked before the treatment is initiated. The SOLVD data, a randomised, double-blind and placebo controlled trial with 3379 patients, proved that enalapril caused 33% increased in deterioration of renal function compared to control group (P = 0. 03). There is another study (n= 191) showed that 44% of patients taking ACEIs suffered from persistent cough compared to controls which is only 11. 1% (P <0. 001). NICE guideline indicates that ACEIs is cost effective. This may due to low rate of hospitalisation.

The studies above showed that ACEIs are rationale to be used as first-line treatment HF.

## Î²-blockers

Î²-blockers should be included in the treatment of HF even though the patient is already well controlled by diuretics and ACEIs. The European Journal of Heart Failure suggested that Î²-blockers should be prescribed to all patients with stable HF and when left-ventricular ejection fraction â‰¤ 40%. A lot of meta-analyses showed that Î²-blockers play a role in increasing life expectancy in patients with HF due to LVSD.

In a meta-analysis which includes 21 trials (n= 5894), Î²-blockers showed a significantly reduction of overall and cardiovascular mortality by 34-39%in patients with severe HF. Another meta-analysis of 16 clinical studies also showed the reduction of 24% for patients who were taking Î²-blockers for their HF treatment rather than placebo. An interesting meta-analysis had been carried out to test the efficacy of Î²-blockers in the patients with

diabetes mellitus (DM) and CHF. The result of this meta-analysis showed that Î²-blockers had reduced the mortality rate of patient with DM and CHF. However, the reduction was not significant (P= 0. 11) compared to CHF patients without DM.

Most of the survival benefits for patient with NYHA class II and III are well documented. There is a meta-analysis had proven that Î²-blockers are having the same improvement of survival rate among the patients with severe HF compared to patients with NYHA class II and III. However, further studies need to be carried out to evaluate overall benefits versus risks of treatment in NYHA class IV. There are three main studies, nâ‰ˆ9000, had been carried out to compare the efficacy between Î²-blockers (bisoprolol, metoprolol succinate CR, carvedilol) and placebo. Almost 90% of patients involve in there three randomised trials were on ACEIs or ARB. Most of them also took diuretics and digoxin. All trials showed the improvement of mortality rate (RRR= 34%), risk of hospitalisation (RRR= 28-36%) and self-reported well being. So far, there are no significant differences between selective and non-selective Î²-blockers and those with or without vasodilating properties.

In one randomised controlled trial (COMET), n= 3029, carvedilol was used to compared with the efficacy and clinical outcome of metoprolol tartate. The result has shown that carvedilol reduced the mortality rate significantly among the patients compared to short-acting metoprolol tartate (P= 0. 0017). However, there is no any clinical trial about comparison between carvedilol and long-acting metoprolol succinate. There is little economic evidence can be found for Î²-blockers. NICE guidelines suggested that Î²-blockers are cost effective due to reduction of hospitalisation rate.

Bisoprolol 2. 5mg od had been added to the patient on second day since patient was admitted. The evidences above do support that the usage of Î²-blocker should be included in patient with HF.

## Aldosterone antagonists

Spironolactone is the most common aldosterone antagonist used in treatment of HF. In a double-blind study (RALES), 1663 patients with severe HF (NYHA class III and IV), left ventricular ejection fraction â‰¤ 35% and being treated with diuretics, ACEIs or digoxin were recruited to test the effectiveness of spironolactone on their morbidity and mortality. The result showed 30% reduction in mortality rate and 35% reduction of frequency of hospitalisation compared to placebo group. Addition of spironolactone to ACEIs, diuretics or digoxin had reduced the mortality rate in patients with severe HF. Additional of spironolactone may lead to hyperkalaemia. However the problem of hyperkalaemia can be solved by closing monitoring the potassium level of patients. Another study also showed that spironolactone reduced 30% mortality rate in patients with HF when it has been added to Î²-blockers and digoxin.

A selective aldosterone antagonist, eplerenone, has fewer side effects compared to spironolactone. A randomised controlled trial (EPHESUS), n= 6633, proved that morbidity and mortality rate among patients with left ventricular dysfunction after acute myocardial infarction had been reduced with the addition of eplerenone compared to placebo group. There is no relevant economic evidence of aldosterone antagonist. Eplerenone is mostly used when patients cannot tolerate with spironolactone.

Hence, spironolactone 25mg od is appropriate to used as adjunct to diuretics, ACEIs or maybe Î²-blockers for patient in this case. Since the patient does not suffer any side-effects from spironolactone, it is not necessary to change to eplerenone.

## Conclusion

As a conclusion, patient’s CHF has been appropriately treated by following the guidelines and also supported by numerous of clinical studies. From the clinical process, we can see that the condition of patient was gradually improved day by day. A Î²-blocker, bisoprolol was added in the second day in order to achieve a better control of patient’s HF and also HPT. According to guidelines, the dose of bisoprolol should be initiated with 1. 25mg, not 2. 5mg. The potassium levels need to be monitored regularly due to the concomitant use of perindopril and spironolactone which may cause hyperkalaemia. ARB and digoxin are not prescribed to the patient because she is well tolerated with ACEIs and she does not have AF. Other treatment for HF such as vasodilators (hydrazine and ISDN) will only be considered when all of the treatment options above have failed to this patient. Non pharmacological treatment such as life-style modification, healthy diet, restrict fluid intake and salt intake also play a very important in controlling patient’s HF and HPT for long-term.