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Rivaroxaban for prevention of cardiovascular events following an episode of decompensated heart failure

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LAY SUMMARY

Chronic heart failure is a long term condition with no cure where the heart is unable to pump blood around the body properly, usually because the heart has become too weak or stiff. Symptoms of heart failure include breathlessness, tiredness and swollen legs and ankles. Heart failure has many different causes including coronary artery disease, where the blood supply to the heart is blocked or interrupted by the build-up of fatty substances in the coronary arteries. Sometimes in chronic heart failure there can be an episode of worsened symptoms which will require immediate or additional treatment called acute decompensated heart failure.

Rivaroxaban is an oral medicine which prevents the development of blood clots by blocking the formation of a molecule called thrombin which is a key part of the process of blood clot formation. Rivaroxaban has the potential to reduce thrombin and blood clot formation in people with heart failure and coronary artery disease. This is potentially important as patients with heart failure after an episode of acute decompensation have been seen to have increased levels of thrombin. No other drug is currently licenced for use in this group of patients which targets thrombin.

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TARGET GROUP

Prevention of cardiovascular events - risk of death, myocardial infarction or stroke, in patients with chronic heart failure and significant coronary artery disease following an episode of decompensated heart failure) – add on therapy

TECHNOLOGY

DESCRIPTION

Rivaroxaban is a highly selective direct factor Xa inhibitor with oral bioavailability. Inhibition of factor Xa interrupts the intrinsic and extrinsic pathway of the blood coagulation cascade, inhibiting both thrombin formation and development of thrombi. Rivaroxaban does not inhibit thrombin (activated factor II) and no effects on platelets have been demonstrated.[1]

In the phase III clinical trial to assess the effectiveness and safety of Rivaroxaban in reducing the risk of death, myocardial infarction or stroke in participants with heart failure and coronary artery disease following an episode of decompensated heart failure (COMMANDER HF - NCT01877915), rivaroxaban is administered as one 2.5mg tablet taken orally (by mouth) twice daily (once in the morning and once in the evening).[2]

Rivaroxaban is currently licenced in the EU for:[3]

- Prophylaxis of venous thromboembolism following knee replacement surgery
- Prophylaxis of venous thromboembolism following hip replacement surgery
- Initial treatment of deep vein thrombosis
- Initial treatment of pulmonary embolism
- Continued treatment of deep vein thrombosis (following initial treatment)
- Continued treatment of pulmonary embolism (following initial treatment)
- Prophylaxis of recurrent deep vein thrombosis
- Prophylaxis of recurrent pulmonary embolism
- Prophylaxis of stroke and systemic embolism in patients with non valvular atrial fibrillation and with at least one of the following risk factors: congestive heart failure, hypertension, previous stroke or transient ischemic attack, age > 75 years or diabetes mellitus
- Prophylaxis of atherothrombotic events following an acute coronary syndrome with elevated cardiac biomarkers (in combination with aspirin alone or aspirin and clopidogrel)

The most common side effects of rivaroxaban (affecting between 1 in 10 people and 1 in 100 people) include anaemia, dizziness, headache, eye haemorrhage, hypotension, haematoma, epistaxis, haemoptysis, gingival bleeding, gastrointestinal (GI) haemorrhage, GI and abdominal pains, dyspepsia, nausea, constipation, diarrhoea, vomiting, pruritus, rash, ecchymosis, cutaneous and subcutaneous haemorrhage, pain in the extremities, urogenital tract haemorrhage, renal impairment, fever, peripheral oedema and decreased strength and energy.[1]

Rivaroxaban (in combination with aspirin) is currently in pre-registration in the EU for the prevention of major cardiovascular events in patients with coronary artery disease (CAD) and/or peripheral artery disease (PAD). [4]

INNOVATION and/or ADVANTAGES

If licensed, rivaroxaban will offer an additional treatment option for patients with chronic heart failure and significant coronary artery disease. Current therapies target the renin–angiotensin–aldosterone and the β-adrenergic system and no anti-thrombotic medication has yet been licensed for use in HF patients. As thrombin plays a role in the pathophysiological processes which occur in coronary artery disease patients after acute decompensation of HF, rivaroxaban has the potential to target the reduction of thrombin in this context.[5]

DEVELOPER

Bayer AG

PATIENT GROUP

BACKGROUND

Heart failure (HF) occurs when the heart is unable to pump blood around the body properly, usually because the heart has become too weak or stiff. It is a long term condition which usually progresses over time. There are many potential causes of heart failure including coronary heart disease, cardiomyopathy, arrhythmias, damage to the heart valves and congenital heart disease.[6] HF can be acute, developing suddenly with severe symptoms (often following a heart attack) or chronic, where symptoms develop slowly over time and gradually worsen.[7] There is no cure for chronic HF and the condition worsens over time.[8]

Patients with heart failure have three potential outcomes: remaining stable with no acute decompensation or fatal events, sudden cardiac death or an episode of acute decompensation.[9] About 75% cases of acute decompensation occur in those with chronic heart failure, with the remaining 25% in those with new onset heart failure.[9] An episode of acute decompensation in people with chronic HF can be defined as an acute or gradual exacerbation of signs and symptoms of HF at rest which requires additional or immediate therapy. The most common symptom of acute decompensation is shortness of breath however this is a symptom common to many other conditions and so diagnosis of acute decompensation will also include the presence of other more specific symptoms such as orthopnoea, paroxysmal nocturnal dyspnoea and presence of a third heart sound.

There are many potential causes or triggering factors for an episode of acute decompensation, the most common being low adherence to HF treatment (including water and sodium restriction and inadequate use of medication) and others including infection, pulmonary embolism, use of medications such as anti-inflammatories, tachy- and bradyarrhythmias. It is important to establish the cause of an acute decompensation episode as this will guide treatment and can indicate prognosis. Signs and symptoms can also be used to classify patients into four subtypes which also guides treatment. These subtypes are based on the presence or ('wet') or absence ('dry') of congestion (characterised by shortness of breath, cough and edema) and by the either inadequate ('cold') or adequate ('warm') levels of perfusion (characterised by prolonged capillary filing time, cold extremities and syncope). These characteristics make up the four subgroups of acute decompensation: profile A (dry-warm), profile B (wet-warm – the most common subtype), profile C (wet-cold – having the worst prognosis) and profile L (dry-cold).[10]

The cost of hospitalisation due to acute decompensation has been estimated at approximately 60% of the total cost of HF treatment.[10]

CLINICAL NEED and BURDEN OF DISEASE

The prevalence of heart failure in the UK according to the Heart Failure Register in 2015/16 is 530,133 people.[11] According to the HES for 2016/17, there was 81,393 admissions and 169,756 finished consultant episodes with a primary diagnosis of Heart Failure (ICD-10: I50). The majority of patients hospitalised with HF will have be having an acute decompensation episode due to chronic HF.[12]

HF generally has poor prognosis with 30-40% patients diagnosed with HF dying within a year and 10% mortality rate after that.[13] The mortality rate of patients hospitalized for acute decompensation and discharged within 90 days is approximately 10% with 25% of people readmitted during this period.[10]

The 5-year survival rate for those on general practitioners (GP) heart failure registers is 58%.[13]

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal guidance. Ivabradine for treating chronic heart failure (TA267). November 2012.
- NICE technology appraisal guidance. Clopidogrel and modified-release dipyridamole for the prevention of occlusive vascular events (TA210). December 2010.
- NICE guideline in development. Chronic heart failure in adults: diagnosis and management. Expected publication date 05 September 2018.
- NICE clinical guideline. Acute heart failure: diagnosis and management (CG187). October 2014.
- NICE clinical guideline: Myocardial infarction: cardiac rehabilitation and prevention of further cardiovascular disease (CG172). November 2013.
- NICE clinical guideline. Chronic heart failure in adults: management (CG108). August 2010.
- NICE quality standard. Chronic heart failure in adults (QS9). June 2011. Last updated February 2016.
- NICE quality standard. Acute heart failure (QS103). December 2015.
- NICE quality standard. Secondary prevention after a myocardial infarction (QS99). September 2015.
- NICE public health guideline. Cardiovascular disease: identifying and supporting people most at risk of dying early (PH15). September 2008.

NHS ENGLAND and POLICY GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for cardiology: Implantable Cardioverter Defibrillator (ICD) and Cardiac Resynchronisation Therapy (CRT) (Adult) A09/S/a.

OTHER GUIDANCE

American Heart Association and American College of Cardiology Foundation. AHA/ACCF Secondary Prevention and Risk Reduction Therapy for Patients with Coronary and Other Atherosclerotic Vascular Disease: 2011 Update. November 2011.[14]

CURRENT TREATMENT OPTIONS

Chronic HF is a long term condition which cannot be cured, so the aim of treatment is to control and relieve symptoms. This is usually done using a combination of lifestyle changes, medications, implantable devices (to control heart rhythm) and surgery:[15] [16]

- Lifestyle changes: including smoking cessation, eating healthily, moderating alcohol consumption, reducing salt intake and regular exercise.
- Medication: multiple medications may be taken at the same time to control symptoms. Medications will be chosen according to the cause of heart failure, symptoms present and any intolerances to medications.
    - *First line:*
        - Angiotensin-converting enzyme (ACE) inhibitors: used to relax blood vessels making it easier to pump blood around the body e.g. Ramipril, captopril, enalapril, Lisinopril, perindopril
        - Beta blockers: slow the heart e.g. bisoprolol, carvedilol, nebivolol
    - *Alternative first line or Second line:*
        - Hydralazine with nitrate: to relax and open the blood vessels given to patients who cannot take and ACE inhibitor or ARB
        - Angiotensin Receptor Blockers (ARBs): to relax blood vessels and reduce blood pressure e.g. candesartan, losartan, telmisartan, valsartan
        - Aldosterone antagonists: used to reduce fluid levels without reducing potassium levels e.g. spironolactone, eplerenone. Also recommended after acute myocardial infarction
        - Sacubitiril valsartan: a combination of an ARB and neprilysin inhibitor for people with severe heart failure whose heart can only pump a reduced amount of oxygenated blood around the body despite taking other medication
        - Ivbradine: slows the heart in people who cannot take beta blockers or in combination with beta blockers if they are not effective enough
    - *Third or subsequent line*
        - Digoxin: strengthens heart muscle contractions and slows the heart rate. Recommended for people who have symptoms despite treatment with ACE inhibitors. ARBs, beta-blockers and diuretics
    - *Prescribed where needed:*
        - Diuretics: used to reduce fluid levels to relieve swelling and breathlessness e.g. frusemide, bumetanide
        - Calcium channel blockers: used for treatment of comorbid hypertension/angina in HF patients e.g. amlodipine
        - Anticoagulants – used in patients with HF in sinus rhythm and history of thromboembolism, left ventricular aneursm or intracardiac thrombus

        - Aspirin – prescribed in patients with HF and atherosclerotic arterial disease (including coronary heart disease)
        - Inotropic agents – used for the short term treatment of acute decompensation of chronic heart failure e.g. dobutamine, milrinone or enoximone
- Implantable devices: used to control the hearts rhythm.
    - Pacemakers – a device which continuously monitors the heart rate and sends electric impulses to the heart to keep it beating regularly and at the right speed. It is implanted under local anaesthetic.
    - Cardiac resynchronisation therapy – this is a special type of pacemaker which makes the left ventricle contract at the same time as the rest of the heart
    - Implantable cardio converter defibrillators (ICDs) – used for people who have or are at high risk of developing an abnormal heart rhythm. ICDs constantly monitor the heart rhythm and delivers a small controlled electrical shock (defibrillation) if the heart starts to beat dangerously fast. If the heart fails it will deliver a larger shock.
    - CRT-Ds – devices which combine cardiac resynchronisation and defibrillation for patients who require both.
- Surgery – for those whose HF cannot be managed by medication alone
    - Heart valve surgery – for patients with damaged or diseased heart valves. Surgery involves valve replacement or valve repair depending on what is wrong with the valve and how serious the problem is.
    - Angioplasty or bypass – for patients with HF due to coronary heart disease. There are two types of procedure which make it easier for the heart to pump blood around the body:
        - Coronary angioplasty – where a tiny balloon is used to stretch narrowed or blocked arteries
        - Coronary artery bypass graft – where a blood vessel from another part of the body is used to divert blood around the narrowed or clogged part of an artery
    - Left ventricular assist devices – mechanical pumps which can help if the left ventricle is not working. This may be used as permanent treatment for those who cannot have a heart transplant or as a temporary treatment until heart transplant
    - Heart transplant – this is necessary in cases of severe heart failure which cannot be managed with medication or other types of surgery

EFFICACY and SAFETY	
Trial	COMMANDER HF, NCT01877915, EudraCT-2013-000046-19, UKCRN-18984; Rivaroxaban vs placebo; phase III
Sponsor	Janssen Research & Development LLC (sponsor) and Bayer (collaborator)
Status	Ongoing – not recruiting
Source of Information	Trial registry[2]
Location	19 European countries (incl UK), USA, Canada, 2 countries in South America, 5 countries in Asia, Australia, Mexico, Russian Federation and South Africa
Design	Randomised, placebo-controlled, double blind, parallel group

Participants	n=5070; aged 18-95 years; previous episode of decompensated heart failure requiring emergency or unscheduled treatment; symptomatic heart failure evidence of significant coronary artery disease
Schedule	Participants are randomised in a 1:1 ratio to one of two treatment arms: 1. Rivaroxaban 2.5mg tablet taken orally (by mouth) twice daily (morning and evening) until the global treatment end date (GTED) (defined as the date when 1200 primary efficacy outcome event have occurred) in combination with the standard of care for heart failure and coronary heart disease (prescribed by the patients physician) throughout the study. 2. One matched placebo tablet taken orally twice daily (morning and evening) until GTED in combination with the standard of care for heart failure and coronary heart disease (prescribed by the patients physician) throughout the study.
Follow-up	Active treatment till global treatment end date (GTED) (defined as the date when 1200 primary efficacy outcome event have occurred) – estimated study duration for participants is approximately 29 months.
Primary Outcomes	• Time to the first occurrence of any of the following: death from any cause, myocardial infarction, or stroke [Time Frame: Day 1 up to approximately Month 54] • Time to the first occurrence of either fatal bleeding or bleeding into a critical space with potential for permanent disability [Time Frame: Day 1 up to approximately Month 54]
Secondary Outcomes	• Time to the first occurrence of either death due to a cardiovascular cause or re-hospitalization for worsening of heart failure [Time Frame: Day 1 up to approximately Month 54]. If both events occur (re-hospitalization and death) they will be separately counted as per outcome measures below. • Time to death due to a cardiovascular cause [Time Frame: Day 1 up to approximately Month 54] • Time to rehospitalization for worsening of heart failure [Time Frame: Day 1 up to approximately Month 54] • Time to rehospitalization for cardiovascular events [Time Frame: Day 1 up to approximately Month 54] • Bleeding requiring hospitalization [Time Frame: Day 1 up to approximately Month 54]
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Estimated study primary completion date 14 May 2018. Estimated study completion date 18 May 2018.

ESTIMATED COST and IMPACT

COST

Rivaroxaban is already marketed in the UK; a pack of 56 x 2.5mg tablets costs £50 (NHS indicative price, Drug tariff part VIIIA Category C).[3]

IMPACT – SPECULATIVE

IMPACT ON PATIENTS AND CARERS

☒ Reduced mortality/increased length of survival

☒ Reduced symptoms or disability

☒ Other: *reduced risk of further cardiovascular episodes and resulting impact on patient and healthcare.*

☐ No impact identified

IMPACT ON HEALTH and SOCIAL CARE SERVICES

☐ Increased use of existing services

☒ Decreased use of existing services

☐ Re-organisation of existing services

☐ Need for new services

☒ Other: *potentially reduced need for future acute services due to reduced risk of cardiovascular event occurrence*

☐ None identified

IMPACT ON COSTS and OTHER RESOURCE USE

☐ Increased drug treatment costs

☐ Reduced drug treatment costs

☐ Other increase in costs

☒ Other reduction in costs: *potentially reduced need for interventional procedures and treatment for cardiovascular events*

☐ Other

☐ None identified

OTHER ISSUES

☐ Clinical uncertainty or other research question identified

☒ None identified

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