Spotlight on

Hyperkalaemia in heart failure

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Executive summary

People with heart failure (HF) are susceptible to hyperkalaemia (an excess of potassium in the blood). Potassium is important for normal bodily function, but too much can cause complications of the heart and may be life-threatening.[1-3] Hyperkalaemia can be caused by impaired kidney function,[3] which is common in people with HF,[4 5] and can also arise as a result of taking certain guideline-recommended HF medications.[6-8] Prevalence of hyperkalaemia in people with HF has been shown to be as high as 40% in the two years following HF diagnosis.[3]

Hyperkalaemia worsens quality of life and clinical outcomes, and increases healthcare costs. The development of hyperkalaemia is associated with increased risk of death and often leads to the discontinuation or reduction in dose of life-saving HF medications, which could indirectly impact clinical outcomes.[9-12] The presence of hyperkalaemia in HF is associated with higher costs, mainly due to longer hospitalisations.[2 13]

Hyperkalaemia is one of the leading barriers to the effective use of medications in HF. People with HF and healthcare professionals may face a dilemma in choosing between the significant cardiac benefits that guideline-recommended HF medications provide and maintaining potassium levels within a safe range. In one study, almost half of all people who developed hyperkalaemia discontinued their HF medication,[14] which was associated with worse outcomes.[15]

Management of hyperkalaemia among people with HF is often insufficient. The temporary withdrawal or reduction in dose of HF medications should be minimised and medications should be reintroduced as soon as possible while monitoring potassium levels in the blood, to reduce the risk of complications.[16 17] Other strategies for managing hyperkalaemia in HF include implementing dietary restrictions that are often difficult to adhere to and using traditional potassium binders to excrete potassium, which can have serious adverse effects.[2]

New treatments may allow for the continued adherence to life-saving HF medications, but further research is required. The 2016 European Society of Cardiology guidelines for HF highlight the potential of two new potassium binders to reduce blood potassium levels and prevent recurrent hyperkalaemia in people with HF.[16] Further research is warranted, however, to determine their ability to reduce hyperkalaemia while simultaneously allowing for HF medications to be adjusted to the dose of maximum benefit, and to improve patient outcomes, before guidelines can recommend their widespread use in therapy.[1 18]

There is a clear need to properly address hyperkalaemia as an essential contribution to clinical management of HF. Governments preparing strategic improvement programmes in HF – itself a major cause of hospitalisations – must ensure that HF care pathways and delivery models are ready to reduce the burden of hyperkalaemia on people with HF, the healthcare system and society in general.

Key actions to improve diagnosis and management of hyperkalaemia in HF

1. Raise awareness and improve diagnosis of hyperkalaemia in HF	Healthcare professionals working in HF must be alert to the causes, as well as subtle signs and symptoms of hyperkalaemia in people living with HF.
2. Encourage collaboration between healthcare professionals to optimise HF medications while reducing the risk of hyperkalaemia	Specialists with experience in managing hyperkalaemia should support non-specialist healthcare professionals to optimise life-saving HF medications while minimising the risk of hyperkalaemia through consistent monitoring of potassium levels in the blood.
3. Support clinical research to improve the prevention and treatment of hyperkalaemia	Future research should investigate the efficacy, long-term safety, and cost-effectiveness of recently developed potassium binders in the prevention and treatment of hyperkalaemia in HF.
4. Develop guidance for all healthcare professionals in the management of hyperkalaemia across HF types	Evidence gathered in ongoing and future research should be translated into new guidance to support all healthcare professionals in the management of hyperkalaemia across all types of HF.

1 What are hyperkalaemia and heart failure?

Hyperkalaemia is common in people living with heart failure

Hyperkalaemia is a condition that affects many people with heart failure (HF),[1] potentially contributing to poorer clinical outcomes.[17 19 20] It is therefore crucial that healthcare professionals detect and manage hyperkalaemia to ensure optimal management of HF.[16]

HF occurs when the heart is unable to pump enough blood

HF occurs when the heart becomes too weak or stiff to pump enough blood to the body.[16 21] Signs and symptoms include breathlessness, extreme fatigue, reduced exercise capacity and fluid retention resulting in weight gain and/or swelling. HF is designated as either acute or chronic. Acute HF occurs when there is a sudden and rapid onset or exacerbation of symptoms, requiring immediate medical attention, while chronic HF involves symptoms appearing slowly and gradually worsening. Quality of life and survival rates in HF remain poor.[22]

HF places a high burden on people, healthcare systems and society as a whole

More than 15 million people in Europe, or 2% of the population, are estimated to be living with HF.[23] These numbers are expected to rise in the coming years due to an ageing population and increased survival rates of other cardiovascular conditions.[24] HF is often associated with other health conditions (comorbidities), with estimates suggesting that up to 75% of people living with HF have at least one other illness.[25] Comorbidities may aggravate HF and create additional challenges to clinical management.[16]

European guidelines distinguish three types of HF

The European Society of Cardiology (ESC) HF guidelines differentiate between three types of HF based on the left ventricular ejection fraction,[16] which is the proportion of oxygenated blood pumped out by the left ventricle to the rest of the body with each heartbeat.[26] The three types are HF with reduced ejection fraction (HFrEF), HF with mid-range ejection fraction (HFmrEF) and HF with preserved ejection fraction (HFpEF).[27] HFrEF is better understood than other types of HF, in terms of both its development and treatment options.

Potassium is essential to the normal functioning of the body

Potassium is crucial for maintaining normal cell function such as enabling nerves to transmit information and muscles (such as the heart) to contract.[28] The body fulfils its need for potassium through dietary intake;[19] in a healthy person, a diet rich in potassium is associated with lower blood pressure and reduced risk of heart disease and stroke.[29] The human body has developed many mechanisms for maintaining a narrow, optimal range of potassium in the blood,[30] and the kidneys are the main organ responsible for this via elimination of excess potassium in urine.[31] In some people, particularly people with kidney dysfunction, these processes are impaired and potassium levels in the blood rise, leading to hyperkalaemia.

There are different classes of hyperkalaemia based on potassium levels

There is no universally accepted definition of hyperkalaemia,[1 32] but it is commonly described in the literature as a blood potassium level of more than 5 mmol/L. Hyperkalaemia can be subclassified as mild (5.0–5.5 mmol/L), moderate (5.5–6.0 mmol/L) or severe (above 6.0 mmol/L).[17 19] It can be further categorised as acute or chronic according to the onset and number of episodes experienced. Acute hyperkalaemia is a singular event that is often severe in nature, while chronic hyperkalaemia is defined as more than one incidence of potassium levels above 5.0 mmol/L in one year.[19 33]

There are several causes of hyperkalaemia

Several factors can lead to hyperkalaemia, including:[30 34]

- impaired potassium elimination (due to advanced age or disease-related decline in kidney function)
- certain medications (including some of those used in the treatment of HF)
- a lack of aldosterone (a hormone that helps the kidneys to regulate potassium levels)
- a diet high in potassium
- cells releasing too much potassium into the blood.

People at the highest risk of developing hyperkalaemia include those with HF, chronic kidney disease and diabetes.[35]

Hyperkalaemia can have a negative impact on health

Hyperkalaemia is a potentially life-threatening disorder.[20 36] As potassium levels are not routinely measured in the general population, the true prevalence of hyperkalaemia is unknown,[2] but estimates indicate that it impacts between 1% and 10% of people hospitalised for any cause.[5] Most people with mild or even moderate hyperkalaemia are asymptomatic.[36] If symptoms do appear, they are usually minor and non-specific. For example, a person with mild or moderate hyperkalaemia may experience muscle weakness, heart palpitations or a slow, weak pulse.[1 30] Severe hyperkalaemia manifests more evidently – it may result in a significant reduction in heart rate, which can reduce the heart's ability to pump blood and may lead to sudden death.[37] If severe hyperkalaemia is not treated quickly, the risk of death may be as high as 30%.[6]

2 Interaction of hyperkalaemia with heart failure

As the prevalence of HF rises, more people are at risk of developing hyperkalaemia

Estimates of the prevalence of hyperkalaemia in HF differ,[22 38] which may be due to the varying definitions of hyperkalaemia used in different study settings.[9] A comprehensive registry-based study in Northern Denmark, from 2000 to 2012, reveals a worrying burden of hyperkalaemia among people with HF. The analysis showed that almost 40% of people with HF developed hyperkalaemia within two years of diagnosis, and that repeated episodes of hyperkalaemia were common.[3] As the number of people developing HF is increasing worldwide,[39] a significant amount of people are at risk of developing hyperkalaemia. The prevalence of hyperkalaemia may also be rising due to the increased presence of comorbidities among people living with HF.[17]

Hyperkalaemia worsens clinical outcomes for HF

Hyperkalaemia, particularly when severe, is associated with increased mortality in people with HF[6 11 12 38] (see *Figure 1*). The extent to which hyperkalaemia is implicated in other clinical outcomes is difficult to assess, as the condition is often asymptomatic.[1]

HF medications essential to improve clinical outcomes may lead to hyperkalaemia

Several medications that are crucial to reduce morbidity and mortality in HF are also known to raise potassium levels in the blood (see *Box 1*).[11 34 40 41] As a result, medication is one of the most common causes of hyperkalaemia in people with HF.[1] This is particularly true for medications that impair the elimination of potassium by the kidneys.[2 34 42] A combination of such medications cumulatively increases the risk of hyperkalaemia.[10 43 44]

Box 1. Which classes of heart failure medication may increase potassium levels in the blood?[16 44]

- Angiotensin-converting enzyme inhibitors (ACE inhibitors)
- Angiotensin receptor blockers (ARBs)
- Mineralocorticoid receptor agonists (MRAs)
- Angiotensin receptor neprilysin inhibitors (ARN inhibitors)
- Beta blockers

Note: The link to increased potassium levels should not deter anyone from using the aforementioned HF medications. People with HF should always seek the guidance of a qualified healthcare professional with any questions regarding medication.

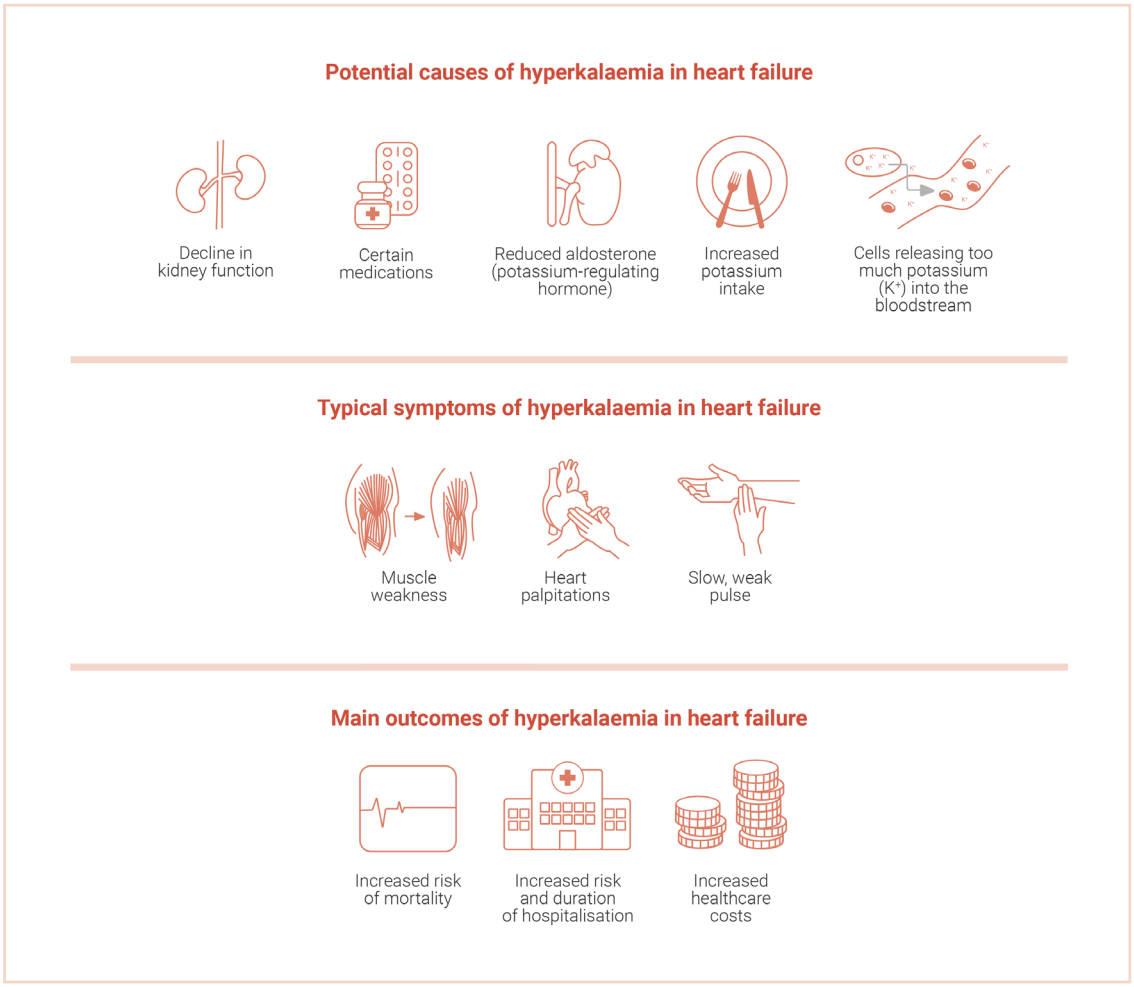
HF comorbidities may lead to, or worsen, hyperkalaemia

People with HF often have comorbidities;[16] for example, kidney dysfunction is estimated to be present in 40–50% of people with HF.[45] As the kidneys are the main organ responsible for eliminating potassium, a reduction in their ability to function properly is likely to lead to hyperkalaemia. Other HF comorbidities may also be linked to hyperkalaemia, including diabetes.[17] In the literature, it has been suggested that the risk of moderate or severe hyperkalaemia is higher in people with HFpEF and HFmrEF than those with HFrEF, due to the increased burden of comorbidities in these people.[1 38 46] However, some experts have noticed a higher prevalence of hyperkalaemia among the HFrEF population in clinical practice.[41 47] Reasons for this may include the prescription of guideline-recommended HF medications that can induce hyperkalaemia among this population.

Hyperkalaemia in HF is associated with high expenditure

The economic burden of hyperkalaemia is high, especially in people with HF. Most studies investigating hyperkalaemia-related costs are from the United States, where elevated potassium levels have been associated with increased duration of hospitalisation and emergency department visits.[2] This has a direct bearing on the overall cost of HF. A study from Europe analysing data from 2005–2011 estimated that hyperkalaemia in HF increased total healthcare costs by over €6,000 in the first six months after the occurrence of elevated potassium levels, mostly due to the need for hospitalisation.[13] It also found that a large proportion of people with HF experienced subsequent elevations in potassium levels after the first incident, with a shorter time between occurrences.

Figure 1. Causes, symptoms and outcomes of hyperkalaemia in heart failure



3 Diagnosis and management of hyperkalaemia in heart failure: facts and challenges

> ***'One of the biggest barriers in terms of policy development for hyperkalaemia in HF is that we cannot agree on a definition across specialties and healthcare providers. It is challenging to write standardised guidelines and care pathways if we cannot agree on what blood potassium level constitutes hyperkalaemia.'***
>
> Ms Louise Clayton, UK

Hyperkalaemia can be asymptomatic, which may delay diagnosis

It is important to diagnose and treat hyperkalaemia to prevent fatal complications. However, as hyperkalaemia is often asymptomatic, it may be difficult to diagnose.[36] Hyperkalaemia may only be discovered through blood analysis undertaken when a person with HF is hospitalised for another reason.[1]

Monitoring of potassium levels following medication initiation rarely meets guideline recommendations

Despite guidelines recommending the regular measurement of potassium levels following the commencement of HF medications,[10] surveillance of potassium levels remains insufficient. While potassium levels are routinely measured at first diagnosis of HF,[9 47] consistent monitoring of potassium levels outside of specialist settings may be insufficient.[41 47] A study from Sweden found that out of 4,036 people commencing HF treatment, only 24% were adequately monitored during the initial weeks to detect and potentially avoid adverse events.[48] Suboptimal monitoring was especially prevalent when treatment was initiated in a primary care setting rather than a hospital.[48] Studies have shown that the benefits of HF medications outweigh the risks even if medication induces hyperkalaemia, provided an appropriate surveillance strategy is in place.[8] Experts suggest that barriers to optimal management of hyperkalaemia in HF include variations in blood potassium monitoring under specialist care compared with non-specialist care, along with a lack of communication between healthcare professionals regarding the importance of repeated blood analysis.[41 47]

Hyperkalaemia is an obstacle to optimal HF treatment as it may prompt reduction or discontinuation of medication

In efforts to address hyperkalaemia in HF, healthcare professionals often reduce or discontinue HF medications that may contribute to its development.[1 8 14 41] For example, in Sweden, almost half of all people who developed hyperkalaemia discontinued their HF medication, while 10% reduced their prescribed dose.[14] When medication was stopped, 76% of people did not resume treatment in the year following the development of hyperkalaemia. Similarly, in the UK, the development of hyperkalaemia in people with newly diagnosed HF increased the likelihood of medication discontinuation.[49] This is particularly concerning given that a dose-reduction or complete termination of these medications may increase the risk of cardiovascular complications and death in people with HF.[15]

> ***'The fear of hyperkalaemia prevents certain healthcare professionals from up-titrating key HF medications to the recommended doses, which reduces their effectiveness.'***
>
> Dr Dimitri Richter, Greece

Acute hyperkalaemia requires management in hospital

Although there are effective treatment strategies for acute hyperkalaemia,[6] it must be treated in a hospital setting as therapeutics are administered intravenously.[41 50] Acute management aims to shift potassium from the blood into cells and remove excess potassium from the body to quickly restore normal levels and prevent lethal complications.[15 31 51] In serious, life-threatening situations, excess potassium can be removed from the blood using dialysis, a procedure that removes waste products and excess fluid from the blood when the kidneys do not function correctly.[50 52]

Few options exist for ongoing management of chronic hyperkalaemia

There are limited options available for the ongoing management of people with HF at risk of repeated episodes of hyperkalaemia.[2 50] Current options for the chronic management of hyperkalaemia have various drawbacks. Reducing or discontinuing HF medications is associated with adverse outcomes,[15] while instigating dietary counselling to restrict potassium intake often leads to intolerable dietary restrictions that may adversely affect nutrition in people living with HF.[1 2 50] Traditional potassium binders may be used to eliminate potassium; they are typically administered in hospital due to the increased risk of side effects (such as nausea, vomiting, diarrhoea and worsening hypertension).[17 52 53] In addition, traditional binders may also reduce potassium to unsafe levels, leading to a condition known as hypokalaemia,[17] which can increase the risk of adverse cardiovascular events.[31 46] As such, there is a substantial unmet need for novel strategies that consistently maintain potassium levels within a safe range while allowing for the continuation of life-saving HF medications.

> ***'Once a person with HF is admitted to hospital with hyperkalaemia, they lose confidence in their HF drugs and sometimes the prescriber. It induces anxiety.'***
>
> Ms Louise Clayton, UK

Further research is needed to understand hyperkalaemia in HF

Most trials investigating hyperkalaemia in HF have been conducted in people with HFrEF.[54-56] Very few trials include people with HFpEF,[7 57] or are conducted solely in the HFpEF population.[58] Consequently, there is a need for evidence-based recommendations for minimising the risk of hyperkalaemia in people living with HFpEF.[1] In addition, further studies are required to determine the level of potassium in the blood above the normal range that should be of concern and trigger intervention.[1] There is currently a lack of agreement on the exact level of potassium at which the treating physician should consider altering medications, which is an additional concern in the management of HF and hyperkalaemia.[41 47 59]

4 Best practice in management of hyperkalaemia in heart failure

> ***'HF specialists and HF clinics are experienced in the management of hyperkalaemia. People with HF, especially HFrEF, may have physical difficulties that make it harder for them to attend HF clinics and access specialist care. It is very important that HF clinics and specialist care are accessible by all people with HF to appropriately manage hyperkalaemia.'***
>
> Dr Dimitri Richter, Greece

Hyperkalaemia prevention strategies should be in place for people living with HF

Hyperkalaemia may be preventable, and therefore prevention strategies in the management of HF should be a priority. This includes making sure that healthcare professionals are aware of the medications and other risk factors that can increase potassium levels, such as a history of kidney dysfunction, and advise people to restrict potassium intake via diet and health supplements.[34 40 44]

Measurement of potassium levels in the blood is the gold standard for diagnosing hyperkalaemia

Clinical guidelines recommend the measurement of blood potassium levels for the diagnosis and management of hyperkalaemia.[10 16] An electrocardiogram (ECG), which measures the heart's rhythm and electrical activity, should be performed in a person with suspected hyperkalaemia because the most lethal complication of hyperkalaemia is cardiac abnormalities.[36] However, an ECG may not be sensitive enough to diagnose mild to moderate degrees of hyperkalaemia.[20] In fact, there are reports of normal ECG readings even in cases of severe hyperkalaemia.[32] Furthermore, if abnormalities are present, they may be difficult to attribute to hyperkalaemia alone.[60 61]

Clinical management of HF should include regular screening for hyperkalaemia

Blood potassium levels should be regularly monitored, especially in people with worsening kidney function.[44] Clinical guidelines recommend that HF medications which are more likely to lead to hyperkalaemia should only be initiated if blood potassium levels are below 5.0 mmol/L.[10 32] These medications should be started at low doses, with close monitoring of kidney function and potassium levels.[5 16 40] In general, potassium levels should be measured at regular intervals after treatment initiation or dose increase, with the actual schedule for revision varying with the class of medication.[1] If hyperkalaemia develops and is mild, it may be possible to continue the HF medication, as long as the serum potassium level is carefully monitored.[31] However, according to ESC guidelines, if blood potassium levels exceed 6.0 mmol/L, HF medications may be stopped temporarily.[16]

Management of hyperkalaemia in HF should be multidisciplinary and include the person with HF in decision-making

Hyperkalaemia complicates the management of HF due to a need for adjustment of doses of medications that are typically part of a complex therapeutic regimen.[52] While HF medications may lead to an initial decrease in kidney function and consequent hyperkalaemia, medications should not be stopped unless this decrease is significant – clinical decision-making may require consultation with a kidney specialist (nephrologist).[10 62] Consequently, people with HF and hyperkalaemia would benefit from monitoring by a multidisciplinary team with continuity across care settings, including primary care.[47 63] Experts state that the person with HF also has a role to play in the management of hyperkalaemia.[47] In other chronic conditions, such as chronic kidney disease, people may be sent their blood results, which helps them to become more independent and confident in their own treatment.[64] Empowering people with HF in this way may encourage them to participate in clinical decisions regarding the management of hyperkalaemia.[47]

'With better planning and communication between healthcare settings, we could avoid a lot of hospitalisations for hyperkalaemia. For people at an increased risk of developing hyperkalaemia, we should have better care plans in place with primary care teams to improve management of the condition.'

Ms Louise Clayton, UK

New therapeutics promoting the elimination of excess potassium may enable the long-term continuation of life-saving HF medications

Recently approved potassium binders may enable core HF medications to be used at optimum doses in people at risk of hyperkalaemia.[65-67] Clinical trials have shown that these novel potassium binders may decrease blood potassium levels in people with HF at high risk of developing hyperkalaemia, but their impact on patient outcomes has yet to be established.[52 68-72] Experts have indicated that some HF teams have used the new potassium binders in some patients.[47] However, despite the promising findings, the value of new potassium binders has yet to be widely recognised, and high costs may be a barrier to their widespread use.[17 73] According to the Heart Failure Association of the ESC, regulatory approval for local use of these novel potassium binders is incomplete in some countries,[72] but they have been approved for use in others, including the UK and Sweden.[74-77]

> ***'The development of medications that can effectively treat hyperkalaemia in HF in an outpatient setting is urgently needed.'***
>
> Dr Dimitri Richter, Greece

5 The way forward

Hyperkalaemia is a preventable condition that increases the burden of HF

Hyperkalaemia is common in HF and linked to poorer outcomes – it increases hospitalisations and mortality, and may limit the use of guideline-based HF medications. However, awareness of hyperkalaemia among some healthcare professionals is limited, diagnosis may be delayed and current treatment strategies are insufficient. This results in a significant burden on people with HF, the healthcare system and society.

Concerted action is required to improve the diagnosis and management of hyperkalaemia in people living with HF

We propose actions to improve the understanding and management of hyperkalaemia in HF, so the additional challenges posed by high potassium levels in people living with HF can be addressed.

1. Raise awareness and improve diagnosis of hyperkalaemia in HF

Healthcare professionals working in HF should be aware of the potential causes of hyperkalaemia in people living with HF, and recognise signs and symptoms of hyperkalaemia – which may be subtle – to improve diagnosis. Efforts to train the healthcare workforce on hyperkalaemia should start during formal education and should target both specialist and non-specialist professionals who may interact with people living with HF.

2. Encourage collaboration between healthcare professionals to optimise HF medications while reducing the risk of hyperkalaemia

Healthcare professionals involved in the management of HF should consistently monitor blood potassium levels, especially in people who also have reduced kidney function. HF medications may temporarily reduce kidney function but can bring long-term benefits to people with HF. Discontinuation of medications may not be necessary – strict monitoring of potassium levels and/or temporarily pausing the medication may be sufficient. Ideally, clinical decision-making regarding potassium levels should involve a multidisciplinary team including HF specialists, general practitioners, kidney specialists and the person with HF.

3. Support clinical research to improve the prevention and treatment of hyperkalaemia

The low number of therapeutic options for chronic hyperkalaemia carries a high cost, given the relatively high prevalence of the condition in people with HF and its link with poorer outcomes. Recently developed potassium binders are promising, but additional evidence may be needed to further clarify their ability to use life-saving HF medications at optimal doses and improve patient outcomes. Comparative studies between these new potassium binders and medications already in use should be conducted to determine whether they improve survival and quality of life.

4. Develop guidance for all healthcare professionals in the management of hyperkalaemia across HF types

As a result of the gaps in research, the 2016 ESC guidelines for HF only briefly discuss management of hyperkalaemia which includes the short-term withdrawal of HF medications. Healthcare professionals thus face the challenge of achieving a balance between optimising life-saving HF medications and minimising hyperkalaemia-associated risk without the support of evidence-based recommendations. Evidence gathered in ongoing and future research should be translated into new guidance, for both specialists and non-specialists, to support the management of hyperkalaemia in all types of HF – including HFpEF, which has been largely overlooked in clinical trials.

The time has come to recognise and improve the management of hyperkalaemia in people with HF

We hope this report and the actions proposed may lead to positive changes in policy, prevention, diagnosis and management of hyperkalaemia in HF – ultimately improving the lives of the millions of people living with HF across Europe.

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About the Heart Failure Policy Network

The Heart Failure Policy Network (HFPN) is an independent, multidisciplinary group of healthcare professionals, patient advocacy groups, policymakers and other stakeholders from across Europe whose goal is to raise awareness of unmet needs surrounding heart failure and its care. All members provide their time for free. All Network content is non-promotional and non-commercial. The Secretariat is provided by The Health Policy Partnership Ltd, an independent health policy consultancy based in London.

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