IN VIVO 39: 1182-1189 (2025)
doi: 10.21873/invivo.13922

Chronic Kidney Disease Following Cardiac Arrest Manifesting as Dyspnoea and Peripheral Oedema in Cardiovascular Multimorbidity: Case Analysis and Brief Literature Review

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Abstract

Background/Aim: Chronic kidney disease (CKD) contributes significantly to morbidity, mortality, and healthcare costs. CKD is not only an independent risk factor for cardiovascular disease (CVD) but also a severe complication for patients with CVD, impacting substantially their prognosis and quality of life.

Case Report: A 79-year-old male with a complex medical history, including asthma, hypertension, myocardial infarction, ischaemic heart disease, and recent atrial fibrillation, presented with new-onset exertional breathlessness and peripheral oedema following cardiac arrest and pacemaker insertion. Investigations, including medication reviews conducted shortly after in an outpatient setting, revealed severe renal impairment with creatinine levels at 250 μmol/l (reference range for adult males: 59-104), representing an initial acute kidney injury (AKI) that did not resolve and resulted in the diagnosis of stage 4 CKD (eGFR 25 ml/min/1.73 m^2). The patient was treated with furosemide, dapagliflozin, and adjusted doses of ramipril and edoxaban. Following treatment, the patient's symptoms ameliorated and renal function slightly improved (eGFR 27 ml/min/1.73 m^2).

Conclusion: This case highlights the importance of individualised treatment for patients with CKD alongside complex cardiovascular multi-morbidity. The administration of dapagliflozin and furosemide, together with careful adjustments to ramipril, were instrumental in stabilising the patient's renal function and alleviating symptoms. This case demonstrates how a multifaceted approach, continuous monitoring, and patient education are essential for achieving optimal outcomes in patients with CKD and cardiovascular comorbidities.

Keywords: Chronic kidney disease, CKD, acute kidney injury, AKI, cardiovascular disease, CVD, shortness of breath, peripheral oedema, cardiac arrest, pacemaker, differential diagnosis.

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Received November 26, 2024 | Revised December 5, 2024 | Accepted December 6, 2024

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Introduction

Chronic kidney disease (CKD) is a progressive disorder characterised by a gradual loss of kidney function, affecting up to 15% of adults (1). CKD is associated with diminished quality of life and reduced life expectancy (1) and is frequently accompanied by comorbidities, such as diabetes and cardiovascular disease (2). While CKD is an independent risk factor for cardiovascular disease (CVD) (3, 4), CVD can also lead to acute kidney injury (AKI) and precipitate or worsen CKD (5), mainly due to decreased renal perfusion (6, 7). This relationship with comorbidities complicates the management of CKD and worsens patient outcomes, highlighting the need for integrated strategies that address both renal and cardiovascular conditions. Traditional therapies for CKD include the use of renin-angiotensin system inhibitors (RASIs) including angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs), both of which help to slow the progression of renal disease and provide cardiovascular protection (8). Recent advancements in the treatment of CKD include the use of sodium-glucose cotransporter 2 (SGLT2) inhibitors, which have shown benefits in reducing the progression of CKD (9) and mitigating cardiovascular risks (10). Although the underlying mechanisms are not fully understood (11), these trials have shown that SGLT2 inhibitors reduce the risk of cardiovascular-related death and kidney failure and improve survival in CKD patients, regardless of their CVD status (12).

This report presents the case of a man with a complex cardiovascular history who developed exertional breathlessness and peripheral oedema following a recent cardiac arrest and pacemaker insertion. Subsequent investigation revealed severe renal impairment, likely due to inadequate perfusion and post-cardiac arrest.

Case Report

Case presentation. A 79-year-old male patient with a complex medical history presented with new exertional breathlessness and peripheral oedema after a recent cardiac arrest and pacemaker insertion. His medical history included ongoing asthma, hypertension, hypercholesterolaemia since 1988, inferior myocardial infarction in 1988, ongoing angina since 1995 as well as osteoarthritis of the knees since 2001. He sustained a traumatic head injury and cerebral haemorrhage in 2014. In 2019, he was diagnosed with squamous cell carcinoma and identified as pre-diabetic. Recent developments in 2023 included atrial fibrillation (AF), complete atrioventricular block, type 2 diabetes (T2DM), cardiac arrest, and pacemaker insertion. The patient had an extensive medication history involving multiple changes and adjustments over time due to evolving health conditions. His current medications included rosuvastatin (20 mg once daily OD) and ezetimibe (10 mg OD) for hypercholesterolaemia as a means of secondary prevention of cardiovascular events, ramipril (10 mg OD) for blood pressure (BP) control, Bisoprolol (5 mg OD) for AF and BP control, edoxaban (60 mg OD) for AF, glyceryl trinitrate [400 mcg pro re nata (PRN)] for angina, monomil XL (120 mg OD) for angina, nicorandil [10 mg twice daily (BD)] for angina, tamsulosin (400 mcg OD) for a prostatic disorder, lansoprazole (15 mg OD) for gastrointestinal protection, salbutamol (100 mcg PRN), and beclometasone dipropionate (100 mcg BD) inhalers for asthma.

Investigations/Differential diagnoses. Outpatient investigations and laboratory monitoring revealed several abnormal results, including a serum BNP of 3,802 ng/l (normal <400), haemoglobin level of 122 g/l (normal 130-170), sodium 143 mmol/l (normal 133-146), potassium 3.3 mmol/l (normal 3.5-5.3), creatinine 250 μmol/l (adult males 59-104), urea 10 mmol/l (normal 2.5-7.8), estimated glomerular filtration rate eGFR of 25 ml/min/1.73 m^2 (normal >90), and urine albumin-to-creatinine ratio (uACR) of 35 mg/mmol (normal <3). The patient's laboratory results and clinical presentation indicated severe renal impairment consistent with CKD stage 4. This was likely secondary to unresolved AKI triggered by cardiac arrest, which

resulted in inadequate renal perfusion. This is supported by the fact that the patient had a normal eGFR prior to the cardiac arrest.

Management plan/Follow-up. The overall management of the patient's AKI and subsequent CKD was informed by the broader clinical picture and guidelines. The management plan included the initiation of furosemide (40 mg OD) to address the oedema and fluid overload associated with CKD. At the time of the AKI, the ramipril dose was reduced to 2.5 mg OD initially, with a further reduction to 1.25 mg OD, due to eGFR of less than 30 ml/min and the new diagnosis of CKD stage 4. This reduction was crucial to minimise the risk of renal hypoperfusion following cardiac arrest, which could worsen AKI, and to reduce the risk of hyperkalaemia while enabling diuretic use without compromising BP. The goal was to titrate ramipril to the maximum tolerated dose, once the patient stabilised. Once the patient was on the maximally tolerated ramipril dose, dapagliflozin (10 mg OD) was initiated to slow the progression of newly diagnosed CKD stage 4 and to improve cardiovascular outcomes. The edoxaban dose was reduced to 30 mg OD due to the patient's renal impairment, in accordance with guidelines for anticoagulant dosing in patients with reduced renal function (13).

The initial consultation at the patient's home included blood tests and a discussion of treatment options. After the patient stabilised, a baseline kidney function test was performed before initiating dapagliflozin treatment. BP and kidney function were re-checked after four weeks, noting that creatinine levels could increase during the initial treatment period (14). The patient was monitored for side effects and symptoms of urinary tract infections (UTIs). Additionally, patient education on how to recognise UTIs and adherence to lifestyle modifications were emphasised by ensuring that the patient was on fluid restriction and educated about fluid balance. It is important to clarify that items, such as ice cream, soup, and gravy are considered fluids, as these are often overlooked in a patient's total fluid intake. Dietary advice and a referral to a dietitian were provided, as some patients may need guidance on managing potassium, phosphate, calorie, and salt intake according to their individual care needs. Following the initiation of dapagliflozin, monitoring of renal function was scheduled for every six months, with more frequent evaluation in the event of clinical deterioration, if there were new risk factors for AKI, or if abnormal laboratory results were observed (14).

All required blood tests were completed before starting furosemide. Dosing was confirmed and the patient agreed to start treatment. The medication was initiated and titrated according to response, starting at 40 mg once daily, aiming for a maintenance dose of 20-40 mg daily. If oedema persisted, the dose could be increased to 80-120 mg daily (15). The amount of peripheral oedema and BP were monitored closely. After initiating furosemide, renal function tests were repeated 1-2 weeks post-commencement and after any dose adjustment, then every six months if stable, with an earlier review if side effects, low blood pressure, or increased oedema occurred. Concurrent BP checks ensured no significant reduction. The patient was educated on 'sick day rules' and advised to pause furosemide, ramipril, and dapagliflozin for 2-3 days if acutely unwell with diarrhoea and vomiting and to have renal function rechecked before restarting if these symptoms persisted (15).

The ramipril dose was initially reduced from 10 mg to 5 mg daily, followed by a further reduction to 2.5 mg daily. BP was monitored daily for seven days and reassessed two weeks after the dose reduction to inform subsequent adjustments. Renal function was checked before reductions and routinely every six months. A detailed consultation was conducted with the patient following the blood test results; this acted as a guide and rationale for ramipril dose reduction due to the new diagnosis of CKD stage 4. The patient demonstrated adherence and expressed willingness to proceed with the recommended adjustments. It was further explained that furosemide might also contribute to a reduction in BP, thereby necessitating close monitoring over the ensuing weeks. The patient diligently attended follow-up appointments and submitted home BP readings as instructed.

The patient's eGFR and creatinine clearance (CrCl) initially decreased within the first month of dapagliflozin treatment but later stabilised, showing a slight improvement to an eGFR of 27 ml/min/1.73 m^2. Continued monitoring ensured stable renal function and BP. Furosemide remained effective at a daily dose of 40 mg, with a gradual reduction in oedema. Following dapagliflozin and furosemide initiation, the patient's BP dropped excessively, prompting a reduction of ramipril to a daily dose of 1.25 mg. This adjustment proved beneficial and less nephrotoxic, allowing the furosemide dose to remain unchanged. For both CKD and heart failure (HF), the goal is to titrate ACEIs or ARBs to the maximum tolerated dose particularly when there is proteinuria to achieve a BP <130/80 mm Hg. In this case, the dose was reduced to mitigate the impact on the AKI and allow diuretic use without compromising the patient's BP, which remained stable at the lower dose. The patient is currently undergoing evaluation for a potential HF diagnosis. Close monitoring of the patient's BP continued, and the plan was to gradually up-titrate to the maximum tolerated dose of ramipril once the patient stabilised.

Discussion

CKD represents a significant complication in CVD patients as the interplay between CKD and cardiovascular comorbidities complicates management and adversely influences patient outcomes. This highlights the need for comprehensive strategies that address both the renal and cardiovascular systems, aiming to optimise patient outcomes and improve quality of life. This case report underscores the necessity for a multifaceted approach to managing CKD occurring alongside cardiovascular comorbidities through medication adjustment, continuous monitoring, and lifestyle modification.

The patient experienced severe renal impairment, consistent with CKD stage 4, likely due to unresolved AKI following cardiac arrest, which caused inadequate renal perfusion (6, 7). While the decline in renal function had coincided with the use of medications like RASIs and beta-blockers, which can exacerbate renal stress, renal impairment more commonly follows circulatory compromise and contrast media exposure, both of which contributed to AKI in our patient. Although this is considered a common clinical scenario, it occurs less frequently than previously believed (16). A systematic review and meta-analysis by Coca et al. (17) demonstrated that AKI increases the risk of developing CKD by eightfold and the risk of progressing to end-stage kidney disease by threefold, consistent with the CKD stage 4 observed in our patient. Research shows that even when serum creatinine returns to baseline, the risk of advanced CKD remains high, with long-term kidney function often deteriorating (18). Therefore, rather than being thought of as separate conditions, AKI and CKD are part of a continuum (19). AKI significantly increases both short-term mortality and long-term risks, often leading to CKD stage 5 or kidney failure (19, 20), underscoring the importance of early detection and timely intervention of AKI. Patients at risk for AKI should be closely monitored, particularly when presenting with worsening symptoms or upon initiating new medications. Risk factors for CKD after AKI include high baseline serum creatinine, AKI severity, recovery pattern, recurrent AKI episodes, male sex, older age, prior cardiovascular disease, T2DM, low haematocrit, hypoalbuminemia, and proteinuria (21).

While RASIs have long been the primary medications used to slow the decline of renal function in CKD (8), recent trials have shown that SGLT2 inhibitors not only reduce CKD progression (9) and lower cardiovascular death risk but also improve survival rates overall, regardless of CVD status (12). According to NICE guidelines, dapagliflozin is recommended for patients with an eGFR of 25-75 ml/min/1.73 m^2, T2DM, or a uACR of ≥22.6 mg/mmol on the highest tolerated dose of RASIs (22), or when these are contraindicated (23). The patient was on the maximally tolerated ramipril dose and met these criteria, thus dapagliflozin was initiated. Dapagliflozin is advantageous due to its single standard dosage for all indicated conditions, taken once daily (14) and also because it does not require de-prescription if the eGFR drops below 15 ml/min post-initiation (11). However, due to increased

urinary glucose, there is a heightened risk of UTIs. The patient was closely monitored for symptoms, with urine samples sent for culture if clinically indicated.

Patients with advanced CKD require very close monitoring when starting new medications. ACEIs, SGLT2 inhibitors, beta blockers, and mineralocorticoid receptor antagonists (MRAs), commonly used for HF, can impact BP and renal perfusion. Therefore, to minimise adverse outcomes while maximising the cardiovascular and renal benefits of these treatments, medications should be introduced cautiously, using low starting doses, a stepwise approach for up-titration, and close monitoring. Studies have shown that premature and rapid medication titration while offering quicker benefits, should be balanced with the need to avoid compromising renal function, particularly when baseline kidney function is poor (24, 25). Aggressive medication initiation can cause rapid drops in BP or renal perfusion, potentially exacerbating kidney injury and worsening renal outcomes, especially in CKD patients.

In CKD, furosemide is recommended for fluid retention as it can excrete up to 20% of sodium and remains effective even at low GFR levels (26). Literature indicates that patients with renal failure may initially require high doses of loop diuretics, provided the impairment is not due to nephrotoxic or hepatotoxic drugs, with careful monitoring to avoid hypokalaemia (15). Thiazide diuretics, by contrast, are less effective at lower GFRs and guidelines recommend switching to a loop diuretic when CrCl drops below 30 ml/min (27). Therefore, a thiazide was considered but not started for our patient. Furosemide, which is rapidly absorbed, reaches peak plasma concentrations within 30 minutes to 2 hours (28), although absorption can be slowed by nephrotic syndrome (29). Its renal action peaks at 1 hour orally and within 5 minutes intravenously (30). Approximately half of the furosemide dose is excreted unchanged in the urine, a process delayed in patients with kidney failure (31). Consideration should be given therefore to patients with high-grade proteinuria, as excessive albumin in the glomerular filtrate can reduce free furosemide levels, thereby diminishing its effectiveness (32, 33). In terms of safety, an analysis of real-world prescribing data and adverse drug event reports also revealed that furosemide is linked to a lower incidence of serious and fatal adverse effects compared to bumetanide (34). Furosemide also helps reduce BP by decreasing fluid volume, but it can cause hypotension, necessitating close monitoring and dose adjustments. There is limited evidence on how diuretics reduce BP in hypertension (35), although renal function appears important for their antihypertensive effect (36). Non-pharmacological interventions for our patient included fluid restriction to no more than 1.5 l daily, evenly distributed throughout the day (37). The patient was also advised to elevate his legs when sitting and may have been prescribed compression stockings to increase lymphatic and venous return, thereby reducing oedema (38).

For adults with proteinuric CKD, RASIs are the recommended first-line treatment for hypertension (27). The British National Formulary and NICE recommend a maximum daily dose of ramipril at 5 mg for renal impairment with CrCl between 30-60 ml/min. If CrCl is below 30 ml/min, the starting dose should be 1.25 mg daily, with potential titration up to but not exceeding 5 mg daily (39). However, the Renal Drug Handbook advises that ramipril dosing for patients with a GFR of 20-50 ml/min is similar to those with normal renal function, while for GFR <20 ml/min, the recommended starting dose is 1.25 mg daily, with adjustments based on the patient's response (40). In the case of our patient, his dose was reduced to 2.5 mg initially, then to 1.25 mg. Reducing or discontinuing ACEIs is not standard practice and should generally be avoided (41, 42). However, it may be clinically warranted if there is suspicion that they are contributing to AKI, even though the likelihood of ACEIs being the primary cause is low (43). In the landmark trials that highlighted the benefits of RASIs in reducing the progression of both diabetic and non-diabetic patients with CKD, there were no reports of elevated rates of AKI associated with these medications (44). Yet, temporarily pausing ACEI therapy can be considered in particular cases where AKI progression is a concern.

The patient was on bisoprolol fumarate 5 mg, which works synergistically with ramipril for optimal BP control (45). There is no significant drug-drug interaction between these medications; however, monitoring was essential to avoid hypotension (46). Bisoprolol is also associated with the lowest incidence of serious adverse effects compared to other beta-blockers (34). Both the UK Renal Association and NICE guidelines recommend a target BP of <140/90 (47, 48). However, the SPRINT study, which included participants with CKD, showed that lowering systolic blood pressure below 120 mm Hg in patients with high cardiovascular risk compared to 140 mm Hg reduced major CV events and mortality. Yet, the intensive treatment group had higher rates of adverse effects (49). Masked uncontrolled hypertension should be considered in CKD, necessitating home and ambulatory BP monitoring for accurate diagnosis (27).

Personalised non-pharmacological interventions, such as lifestyle changes, were also recommended for our patient. Patients with hypertension and CKD should aim for 150 minutes of moderate-intensity physical activity per week, adjusted as necessary. Salt intake should be limited to less than 5 g per day, though this can be challenging for CKD patients, especially the elderly such as our patient (50). However, universal dietary sodium restriction is not recommended as it has minimal impact on BP management in CKD (51).

Conclusion

This case underscores the need for a tailored management of CKD in patients with a complex cardiovascular history. Effective management using dapagliflozin and furosemide led to partial stabilisation of renal function and alleviated the patient's symptoms. However, this improvement was not fully sustained, highlighting the importance of close monitoring and gradual adjustments to the treatment plan. This case also emphasises the importance of understanding dapagliflozin's benefits in CKD treatment and treatment pathways for hypertension in CKD including careful adjustments to ramipril dosage and the effective use of loop diuretics like furosemide to manage fluid overload. This case enhances our understanding of the multifaceted approach required in managing CKD in the context of cardiovascular multimorbidity. It emphasises the necessity for continuous monitoring, patient education and regular follow-ups.

Data Availability

All data relevant to the study are included in the article.

Conflicts of Interest

The Authors have no conflicts of interest to declare in relation to this case report.

Authors' Contributions

KH: Patient management, assessment, data collection and manuscript contribution. KM: Manuscript drafting, study supervision and assurance of scientific rigour. KH, KE, AI, DA, RD, and KM: Critical discussion and clinical review.

Acknowledgements

The Authors would like to express deep gratitude to Dr Alexander Hamilton for his thoughtful feedback, constructive suggestions and valuable time in reviewing earlier drafts of this manuscript. His contributions have significantly strengthened the clarity and quality of the work. This publication was supported by the University of Exeter. For the purpose of open access, the Authors have applied a Creative Commons Attribution (CC BY) licence to any Author Accepted Manuscript version arising from this submission.

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