Management of acute intradialytic cardiovascular complications: Updated overview (Review)

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Abstract. An increasing number of patients require renal replacement therapy through dialysis and renal transplantation. Chronic kidney disease (CKD) affects a large percentage of the world’s population and has evolved into a major public health concern. Diabetes mellitus, high blood pressure and a family history of kidney failure are all major risk factors for CKD. Patients in advanced stages of CKD have varying degrees of cardiovascular damage. Comorbidities of these patients, include, on the one hand, hypertension, hyperlipidemia, hyperglycemia, hyperuricemia and, on the other hand, the presence of mineral-bone disorders associated with CKD and chronic inflammation, which contribute to cardiovascular involvement. Acute complications occur quite frequently during dialysis. Among these, the most important are cardiovascular complications, which influence the morbidity and mortality rates of this group of patients. Chronic hemodialysis patients manifest acute cardiovascular complications such as intradialytic hypotension, intradialytic hypertension, arrhythmias, acute coronary syndromes and sudden death. Thus, proper management is extremely important.

Key words: chronic kidney disease, hemodialysis, intradialytic hypotension, high blood pressure, arrhythmia, unstable angina, acute coronary syndrome, sudden death

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1. Introduction

Chronic kidney disease (CKD) represents a public health concern as it affects over 50 million people worldwide, and is more and more commonly encountered, especially due to the increased incidence of high blood pressure (HBP) and diabetes mellitus (DM). Over 1 million CKD patients require renal replacement therapy (RRT) through dialysis and renal transplantation (1). DM, HBP and a family history of kidney failure are all major risk factors for CKD (2-4). Official data in the USA reported over 661,000 patients with advanced stage CKD, out of which 468,000 receive RRT through dialysis and 193,000 have a functional kidney transplant (5-7). The acute complications occur quite frequently during dialysis, and are caused by complex mechanisms, which are insufficiently known (8). Among these, the most important are cardiovascular complications, which influence the morbidity and mortality rates in this group of patients (8).

2. Acute cardiovascular complications of hemodialysis

Advanced stage CKD is associated with the increased risk of cardiovascular affection. Thus, in the case of chronic dialysis patients, cardiovascular disease is identified in a large percentage of patients. An important role in its onset, in addition to factors such as mineral bone disease and patient comorbidities (e.g., HBP, hyperlipidemia, hyperglycemia, homocysteine, hypeuricemia), is chronic inflammation (9-12).

Research particularly describe a smaller total antioxidant capacity (TAC) in healthy controls than in diabetic hemodialysis patients; oxidative stress is one of the main factors leading to the onset of CKD in this group of patients (13).

Acute intradyalitic cardiovascular complications besides chronic cardiovascular affection are identified in chronic hemodialysis patients. These are summarized in Table I and are: intradialytic hypotension (IDH), HBP, arrhythmias, acute coronary syndrome (unstable angina/myocardial infarction) and sudden death (1).

3. Intradialytic hypotension

IDH is quite commonly encountered. It has an impact on the quality of lives of these patients, on the cost of dialysis and is associated with mortality. There is no clear definition of IDH; two factors are taken into account in clinical practice: The decrease in systolic pressure under 90 mmHg (14) or the symptomatic intradialytic decrease in systolic pressure by more than 20 mmHg compared to the value from the beginning of dialysis (15). Studies have demonstrated the strong association between the decrease in systolic pressure under 90 mmHg during dialysis in over 30% of treatments and an increase in mortality (15).

Epidemiology. IDH reporting differs according to the defining criteria. Thus, IDH episodes can vary between 5 and 30% of all hemodialysis treatments (16-18). A study that analyzed a number of 44,801 hemodialysis treatments performed on 1,137 patients found IDH present in 75% (16).

Risk factors and physiopathological particularities. There are several groups of risk factors for IDH onset, and they concern the patient, the dialysis machine or the medical manoeuvres (iatrogenic factors). Hemodialysis patients with direct or indirect cardiovascular affection, that is to say elderly patients undergoing dialysis for a long time, diabetic patients, patients with low arterial pressure prior to dialysis, patients with systemic infections, arrhythmias, valvulopathy, myocardial infarction, hemorrhage, or patients with hypoalbuminemia are predisposed to IDH (16,17,19,20) (Fig. 1).

Dialysis parameters, such as acetate dialysis, the dialysate composition and temperature (20-22), the ultrafiltration rate and the total ultrafiltration volume (23), the rapid reduction in plasma osmolality, incorrect determination of the dry weight, antihypertensive medication before dialysis and food ingestion pre- or intradialysis can also represent risk factors for IDH onset.

IDH may occur in the case of patients with acute hemodialysis, air embolism or allergic reaction to the dialysate (17,18,20,24). Table II summarizes the factors leading to IDH.

Intradialytic ultrafiltration causes the decrease in venous return, with the subsequent decrease in cardiac flow. This phenomenon is emphasized in patients with cardiac damage in whom the ventricular allure or the myocardial contractility do not increase to compensate (25,26). Several studies have shown that the optimal ultrafiltration rate is 10 ml/kg/h; an ultrafiltration rate higher than 13 ml/kg/h is associated with an increased IDH risk and an elevation in mortality (27).

The decrease in blood volume in hemodialysis patients takes place along with peripheral vasodilation (25,28-30). There are several mechanisms which may produce this phenomenon, such as the release of adenosine in response to tissue ischemia, the increase in the synthesis of the vasodilating endogenous substances (nitric oxide) and the inadequate decrease in the vasopressin plasma levels (31-37).

Clinical presentation. IDH patients can be asymptomatic or can suffer from dizziness, muscle cramps, nausea, vomiting and dyspnea at rest. Vagal symptoms such as yawning, ‘sighing’ or hoarseness can occur before a decrease in BP (17).
**Management.** IDH management involves two aspects: Emergency treatment and the prevention of relapses.

**Emergency IDH treatment.** In emergency IDH treatment, the rate of ultrafiltration is decreased/stopped, the patient is placed in the Trendelenburg position, and oxygen ($O_2$) is administered (38,39). If blood pressure does not increase following these techniques, hyperosmolar solutions or albumin is administered in bolus; these include isotonic saline solutions (40,41) (Fig. 2).

**IDH management to prevent relapse.** The general measures for the prevention of IDH relapses involve a re-evaluation of the dry weight (42-46), avoiding intradialytic food ingestion, avoiding the administration and diminishing salt intake. Patients should also be advised regarding caffeine consumption as studies have shown that 3 or more coffees daily increase the risk of a higher diastolic BP, potassium and interdialytic weight gain (IDWG). IDWG in hemodialysis patients and caffeine may alter the cardiovascular response even in healthy people (47-49).

The composition of the dialysate ($Ca \geq 2.25 mEq/l; Mg \geq 1.0 mEq/l$ and Na) (50-54) and the dialysate temperature (low dialysate temperature increases hemodynamic stability) (55-68) must be reassessed, as complementary measures to diet adjustment.

Patients exhibiting recurrent IDH may be administered midodrine (2.5 or 5 mg) 15-30 min prior to dialysis (63,69-73). Sertraline, vasopressine and carnitine can also be administered (74,75).

The evaluation of the cardiac function and the treatment of anemia with erythropoiesis-stimulating agents (which increase cardiac flow) should be performed in patients with recurrent IDH. It should also be mentioned that chronic dialysis patients who are prone to recurrent IDH should have a longer hemodialysis session, and another RRT method, such as hemodiafiltration or peritoneal dialysis, respectively, should be considered (76) (Fig. 3).

**4. Intradialytic hypertension**

Intradialytic hypertension (HBP) has been defined as an increase in intradialytic systolic pressure by ≥10 mmHg compared to pre-dialysis systolic pressure and it has been confirmed to be associated with increased mortality in dialysis patients (77). Some patients develop HBP during the last part of the dialysis session, a moment when the hydric excess has been ultrafiltered. The frequency of intradialytic HBP varies, even in the same patient, and the mechanisms are not clear; there are proofs related to the alteration of the nitric oxide/endothelin-1 balance and/or endothelial dysfunction (78,79).

**Epidemiology.** Intradialytic HBP occurs in 10-15% of hemodialysis patients (80). The frequency of intradialytic HBP episodes varies; a study undertaken during a 6-month period showed that 90% of the patients experienced at least one HBP episode (77). The 5-year analysis of a large number of hemodialysis treatments (n>100,000) showed an increase in intradialytic systolic pressure by at least 10 mmHg in 10% of the cases; the same study concluded that the mortality risk occurs once the intradialytic pressure begins to increase, irrespective of value, and rises with a higher BP value (81). Other studies have demonstrated that an increase in systolic pressure by 5 or 10 mmHg during dialysis is associated with an increase in patient mortality (80).

**Risk factors and physiopathological particularities.** Studies have shown that the onset of intradialytic HBP is associated both with a volume overload between dialysis sessions and with elevated values of intradialytic pressure (82,83). Patients with IDH generally have a smaller dry weight than most hemodialysis patients, have a smaller IDWG and lower pre-dialysis blood pressure (81). These patients do not have clinical signs of hyperhydration, which causes the prescription of a smaller ultrafiltration volume than the one needed, without the lowering of the arterial pressure (80). The intensive intradialytic ultrafiltration for several weeks resulted in the decrease in intradialytic pressure, emphasizing the fact that the expansion of the extracellular volume, even in the absence of clinical signs of volemic overload can mediate HBP (82,84).
The intradialytic osmolar changes contribute to the arterial pressure changes, irrespective of the calculated ultrafiltration rate (85).

The composition of the dialysate in establishing blood pressure values plays an important role, alongside volume overload in the chronic dialysis patients. In this respect, the clinician focuses on the sodium, potassium and calcium concentrations of the dialysate (86–88).

Sodium. A retrospective study undertaken on 113,255 hemodialysis patients over 5 years, highlighted the fact that patients with intradialytic HBP have a series of common characteristics, such as malnutrition markers, the lack of correct feeding or hydration, and lower pre-dialysis values of urea and creatinine, serum albumine, and normalized protein appearance (nPNA); they have smaller interdialysis body weight and weight gain compared to most dialysis patients (81). Sodium in the dialysate represents a key element in modulating intradialytic blood pressure values; it has been found that the sodium concentration in the dialysate is higher compared to the serum concentration of pre-dialysis sodium in intradialysis HBP patients (increased sodium gradient) (86).

Potassium. In patients who received a low-level potassium dialysate, blood pressure values were decreased after the

Table II. Intradialytic hypotension: Etiologic factors (24).

| Intradialytic hypotension | Hemorrhage |
|---------------------------|------------|
| Decline in circulating volume | The decrease in vascular filling rate |
| Reaction to dialysate | Excessive ultrafiltration |
| Cardiac factors | Myocardial infarction |
| Organic cardiac disease | Arrhythmias |
| Cardiac tamponade | Patient-related factors |
| Hemolysis | Neuroathry |
| Defective vasoconstriction | Hypertensive medication |
| | Insufficient norepinephrine plasma level |
| | Decrease in RAAS sensitivity |
| | Splanchnic vasodilation secondary to food ingestion |
| | Tissue ischemia |
| | Sepsis |
| | Anemia |
| | Inflammation |
| | Hemodialysis-related factors |
| | Vasodilation secondary to acetate dialysate |
| | Low calcium concentration in the dialysate |
| | Complement activation |
| | Generation of cytokines |

RAAS, renin-angiotensin-aldosterone system.

Figure 3. Recommended measures for the prevention of IDH. IDH, Intradialytic hypotension.
first hour of the dialysis session (87); low-level potassium dialysate is also associated with rhythm disorders in dialysis patients (89).

Calcium. Calcium levels in the dialysate influence myocardial contractility and vascular tone (90). A high calcium level in the dialysate is associated with vascular hyperactivity and possibly with intradialysis HBP (88,91). Literature data show that intradialysis hypertension is associated with an increase in vascular resistance and less with extracellular volume overload (78,92). An increase in vascular resistance is likely related to the method of dialysis per se but, on the other hand, patients with interdialysis HBP have certain common comorbidities, including ischemic coronary disease, heart failure, a history of vascular accident, and peripheral vascular disease (81).

Dialysis patients with intradialysis HBP have endothelial dysfunction, with an imbalance between vasoconstrictor substances [endothelins 1 (ET-1) and asymmetric dimethylarginine (ADMA)] and vasodilator substances [nitric oxide (NO)]. Studies have shown that ET-1 diminishes or increases during dialysis along with blood pressure (78,93,94) and that patients with intradialysis HBP have high levels of ET-1 post dialysis and a low NO/ET-1 ratio (95,96).

The direct involvement of the stimulation of the sympathetic nervous system in intradialysis HBP has not been demonstrated; recent research has shown that blood pressure increases during dialysis when the cardiac rhythm increases and the baroreflex activity is suppressed, indicating an increased activity of the sympathetic nervous system (80).

Clinical presentation. Patients experiencing an increase in intradialysis blood pressure can be asymptomatic or can complain of headaches, profuse perspiration, thoracic discomfort, dispnea, palpitations or anxiety (78).

Management. There is no optimal therapeutic approach for HBP. Taking into account the association of HBP with volemic overload, it is necessary to accurately establish the dry weight (97).

Considering the role of ET-1 in causing IDH, carvedilol may play a beneficial role, since it is an inhibitor of ET-1 release. A pilot study, which lasted for 12 weeks, found that administration of carvedilol (50 mg twice/day) was associated with a decreased frequency of HBP episodes from 77 to 28% during hemodialysis sessions (98). Similarly, a reduction in sodium concentration in the dialysate under the patient’s serum sodium level can trigger a decrease in blood pressure values during dialysis sessions (99).

5. Arrhythmias

Definition. Hemodialysis patients quite frequently present with hydroelectrolytic and acid base imbalances both during and between treatment sessions, which can cause heart rhythm disorders (100).

Epidemiology. In 2013, United States Renal Data System (USRDS) reported a mortality rate of 198/1,000 patients/year, 40% of the deaths having a cardiovascular cause. Among the cardiovascular causes, 26% were cardiac arrhythmias (101). In addition, atrial fibrillation (AFi) was the most commonly found heart abnormality in clinical practice and affected more hemodialysis patients than the general population (102), with percentages varying between 14% (103) and 27% (104). The Framingham Study reported an incidence of 0.2% per year for AFi in the general population, for 20 years. In comparison, the AFi incidence in the hemodialysis patients reaches 1.25 episodes/100 patient-year (105).

Risk factors and physiopathological particularities. Chronic hemodialysis patients have a higher risk to develop arrhythmias, taking into account the special context of the disease: The presence of certain structural and functional myocardial defects (interstitial fibrosis, decrease in coronary perfusion reserve, endothelial dysfunction), rapid hydroelectrolytic and blood pressure dynamic changes, as well as the use of certain drugs (100).

Intradialytic arrhythmias are generated by hydroelectrolytic and acid base disorders which occur quite frequently in the dialysis patients; all of these, along with the composition of the dialysate, create an ‘arrhythmogenic environment’ (106). On the other hand, dialysis patients present cardiovascular comorbidities, such as myocardial ischemia and secondary anemia, which increase the risk for intradialytic arrhythmias (107).

A range of acid-base (pH) and electrolytic (especially in potassium, calcium and magnesium) changes, causing prolongation of the QT interval and associated with an increased risk of arrhythmias occur in the dialysis patients, both during and post-dialysis (108). Dialysis patients can develop atrial fibrillation during dialysis. The risk factors for the onset of AFi in these patients include ischemic coronary disease, old age, enlarged left atrium, the value of systolic pressure before the beginning of dialysis and the presence of peripheral vascular disease (104,105).

Clinical presentation. The clinical picture is influenced by the rapidity of the onset of rhythm disorder, the cardiac rhythm and the pre-existing cardiovascular pathology. Patients can be totally asymptomatic when the rate of ventricular contractions is within normal limits or can suffer from cardiac failure to collapse. If the ventricular rhythm is rapid, patients complain of palpitations, precordial pain, dizziness, nausea, and syncope. Cardiorespiratory arrest and sudden cardiac death (SCD) may also occur in very severe cases (100).

Management. It is important to reduce structural myocardial changes, especially hypertrophy of the left ventricle, which predisposes to ischemia and arrhythmias. It is also necessary to optimize the dialysis parameters to ensure hemodynamic and electrolytic balance, to evaluate the drug treatment and its impact on the incidence and seriousness of malignant arrhythmias and SCD (100).

AFi treatment aims mainly to maintain the ventricular rate by administering antiarrhythmic medication or cardioversion, to improve symptomatology and to increase effort tolerance. AFi treatment also focuses on lowering the CVA risk, discontinuing the anticoagulant treatment, increasing the quality of life and the survival rate. An accepted alternative, although
often secondary to antiarrhythmic medication is the strategy to simply control the rate of ventricular response of AFi by using node blocking agents in association with continuous anticoagulation (109).

Class 1A and IC arrhythmic medications can ensure the rapid conversion of AFi to the sinus rhythm; for example, propafenone can be administered successfully both for paroxystic AFi and for the prevention of relapses. Taking into account that it is eliminated through the liver, it can be safely used to treat dialysis patients (102). As in most cases, caution is necessary when administered to patients with concomitant liver disease (110).

Digoxin is sometimes administered also in patients with AFi and cardiac failure. Taking into consideration that digoxin half-time is extended; this can cause arrhythmias in the presence of arrhythmogenic factors such as hypopotassemia or class 1A arrhythmic medication. Digoxin toxicity causes bradycardia, different degrees of atrioventricular block, junctional tachycardia, ectopic ventricular activity and ventricular tachycardia. Oral administration of digoxin in dialysis patients at doses of 0.125 mg 3 or 4 times a week seems safe and efficient. A 0.125 mg/day dose may easily lead to toxic levels and 0.25 mg/day can be life threatening. For these reasons, digoxin administration in dialysis patients should be carried out with extreme care (100).

There are few studies that show that angiotensin-converting enzyme (ACE) inhibitor treatment in dialysis patients is associated with a lower number of AFi episodes as compared to this incidence in the general population.

AFi hemodialysis patients run the risk of bleeding and thrombosis (104). Because of their renal pathology, chronic hemodialysis patients have a high risk of bleeding, thus treatment with oral anticoagulants increases the risk by 3- to 10-times in this group of patients compared to the general population (111-113). On the other hand, the rate of thromboembolic events is much higher in these patients. Randomized studies have shown that oral anticoagulant prophylaxis is more efficient than aspirin in reducing the CVA risk associated with AFi in dialysis patients, although it increases the risk of bleeding and/or vascular calcifications (114). Until new data become available, treatment with oral anticoagulants and monitoring are recommended in hemodialysis patients with chronic AFi (105).

Implantable cardioverter defibrillator (ICD) implantation in dialysis patients who were resuscitated after a cardiopulmonary arrest significantly improved the survival rate (the risk of death decreases by 42%) (115). On the other hand, a meta-analysis of the existing data in the literature showed that the mortality rate in ICD dialysis patients is 2.7% higher than in non-dialysis patient (116). The use of ICD in dialysis patients has a series of adverse effects. It is associated with an increased risk of bleeding and infection. Positioning the ICD on the same side with the vascular approach is associated with a higher rate of stenosis and occlusion of the subclavian vein. Factors that should be taken into consideration in these patients include: Performing hemostasis with special care, avoiding post-implantation anticoagulation, placing of intravascular leads on the contralateral side of dialysis access and the use of high-output devices with left-sided prepectoral generator placement (116).

6. Acute coronary syndrome

Definition. CKD is associated with a high death risk of cardiovascular pathology (117-121). Most often patients with CKD have an acute myocardial infarction as the initial manifestation of ischemic heart disease, without previous signs of stable angina (122).

Epidemiology. Cardiovascular diseases account for about 45% of the death in dialysis patients (123,124). Among these, approximately 10% are caused by ischemic coronary disease/coronary heart disease (CHD). Dialysis patients have a higher CHD incidence with a rate of death through myocardial infarction higher than the general population (125). The data reported by the 2018 Annual Data Report of the United States Renal Data System (USRDS) showed a 15.3% prevalence of acute myocardial infarction in the hemodialysis population (https://adr.usrds.org/2020/end-stage-renal-disease/8-cardiovascular-disease-in-patients-with-esrd) Similarly, in 2016, the adjusted mortality rate was 166 in 1,000 patients-year for hemodialysis patients; 37% of the deaths had cardiovascular causes, and 11% were due to myocardial infarction and CHD (125).

Risk factors and physiopathological particularities. There are several types of CHD risk factors in the dialysis patients. In this respect, CHD onset can be favored by ‘traditional’ risk factors or by uremia-related risk factors. The ‘traditional’ risk factors include: DM (54%), low serum high-density lipoprotein (HDL) cholesterol (33%), HBP (96%), HVS diagnosed by electrocardiographic criteria (22%), sedentary life style (80%), old age (125), and smoking (126-128).

CKD is an independent CHD risk factor (129-131). Uremia and hemodialysis as treatment methods increase oxidative stress and the production of proinflammatory factors (132), and so creates a favorable environment for the fast development of atherosclerosis (133-139).

Chronic hemodialysis patients exhibit the increased production of nitric oxide (NO) inhibitors, which cause vasoconstriction and HBP and augment the risk of acute cardiovascular events. ADMA, an endogenous NO inhibitor, is significantly elevated in chronic hemodialysis patients and is an important predictor for cardiovascular mortality in these patients (140-142). The amplification of oxidative stress in these patients represents an extra aggravating factor (143) and can be evaluated by determining the activity of certain antioxidant enzymes (144).

Hemodialysis patients present extensive vascular and valvular calcifications, associated with mineral and bone abnormalities. These patients have been found to have increased phospho-calcium product, secondary hyperparathyroidism and increased calcium intake through the treatment with calcium-based phosphorus binders. In chronic hemodialysis patients, calcium is identified at the levels of vascular media and the intima, in atheroma plaque (145,146). The calcification of the vascular media is associated with an increase in arterial stiffness, but not with atherosclerosis or the narrowing of the arterial lumen. Even in the absence of atherosclerosis or luminal narrowing, coronary media calcification can cause a decrease in diastolic filling, while the peripheral medial calcification increases cardiac afterload (145,146).
Clinical presentation. Hemodialysis patients are most often asymptomatic or have atypical symptoms which can delay the diagnosis and choice of therapeutic approach (147,148). Angina can occur during dialysis, and is precipitated by the exchange of fluids and by the episodes of IDH. Myocardial ischemia and the effort angina are covered in this group of patients because they are generally sedentary, or the level of their effort is very low. Patients with serious coronary lesions can suffer from acute coronary syndrome (ACS)-unstable angina, non-ST elevation myocardial infarction, or ST elevation myocardial infarction. The classic diagnostic triad (angina, increased biological markers and EKG changes) cannot be found in hemodialysis patients (147). EKG can show left ventricle hypertrophy in HD patients, which can mask the ST segment depression. The cardiac lesion markers (creatine kinase MB isoform and troponin I) can be elevated in dialysis patients in the absence of myocardial necrosis, as a reflection of cellular apoptosis or small vessel disease (149).

Management. The prognosis of CKD and ACS patients are unfavorable, in spite of the present medical therapies and the revascularization techniques (150). Platelet antiagregants in ACS patients decrease the mortality risk, although they increase minor bleeding. Thus, clopidogrel administered to non-ST-segment elevation patients to prevent relapses (CURE Trial) proved beneficial (151,152). The PLATO Study (Platelet Inhibition and Patient Outcomes) showed that ticagrelor, an oral purinergic receptor inhibitor cleared by extrarenal mechanisms, reduced mortality and major cardiovascular events, being more efficient than clopidogrel in CKD and ACS patients (153). A recent meta-analysis showed that antiplatelet agents reduce the probability of myocardial infarction in CKD patients, but have unclear effects on vascular accidents and mortality and can increase the risk of bleeding (152).

Glycoprotein IIb/IIIa inhibitors or clopidogrel, in association with the standard ACS treatment, have a minimal or no effect on mortality, myocardial infarction or coronary revascularization and can heighten the risk of major bleeding in CKD and ACS patients or in patients with high-risk coronary artery intervention. Aspirin is essential in CKD and ACS patient treatment (154). The benefits of antiplatelet agent treatment are not known in CKD and ACS patients (154).

Statins decrease the risk of cardiovascular events and cardiovascular death in dialysis patients (155). The results reported in studies performed to date do not explain the impact of the treatment with statins in CKD and ACS patients (154).

The therapy of cardiovascular revascularization, including percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG) is used also in dialysis patients. Studies have demonstrated that SCA dialysis patients treated with PCI can have a lower mortality risk compared to those patients who only receive medication (156). Comparing various strategies of coronary revascularization, dialysis patients who received CABG surgery have a prolonged long-time survival vs. the ones who received PCI (157-159). Several studies have aimed to ascertain whether dialysis patients benefit from aggressive SCA therapy more than from conservative therapy.

7. Sudden death

Definition. Sudden death refers to the sudden arrest of cardiac activity, with hemodynamic collapse, generally caused by sustained ventricular arrhythmia (ventricular tachycardia or ventricular fibillation). These events occur in patients with preexisting cardiac diseases, particularly ischemic coronary disease (160).

Epidemiology. Data reported by DOOPS (Dialysis Outcomes and Practice Patterns) show a high SCD prevalence among hemodialysis patients in the US (33% of all deaths) compared to other countries, such as Japan (23%), Australia/New Zealand (19%), and Canada (18%) (161). Hemodialysis patients who suffered sudden cardiac arrest and were resuscitated present smaller chances of long-term survival (8%) (162,163).

Risk factors and physiopathological particularities. Hemodialysis patients have a particularity concerning the predisposition for SCD, because of the myocardial affection and due to the risk factors for fatal arrhythmias (164). In the general population, the main SCD physiopathologic mechanism is the rupture of atheroma plaques, with acute secondary ischemia and reduction in the left ventricle ejection fraction. The association of ventricular fibrillation causes cardiac arrest and death takes place in about 80% of cases (165,166). The mechanism is different for hemodialysis patients. Thus, these patients present with arterial wall stiffening, valvular and vascular calcifications, affecting especially the vascular media, not the intima (167). A study on 1,200 patients showed that a reduction in left ventricle ejection fraction occurs in only 13% of the cases (168). On the other hand, it seems that hemodialysis patients with SCD and left ventricular hypertrophy present diastolic dysfunction. Studies show that left ventricular hypertrophy (LVH) is a risk factor for sudden death in this group of patients (169). More than 70% of SCD patients had LVH (170,171).

In chronic hemodialysis patients there is a series of factors which trigger arrhythmias: Low content calcium of the dialysate, aggressive ultrafiltration, hyperkalemia and rapid potassium elimination, especially in patients who receive hemodialysis three times a week, during the session following the longest interdialysis pause (Monday and Tuesday) (164). The use of a high bicarbonate concentration in the dialysate causes metabolic alkalosis, associated with hypocalcemia, hemodynamic instability and the elongation of the QT interval (164).

Another risk factor for SCD is the overexpression of angiotensin II. There is a range of angiotensin II mechanisms of action, such as stimulation of fibrosis and inflammation, increased activity of the sinus node and of the His-Purkinje system, alteration of Ca²⁺, K⁺ and Na⁺ exchange at the cell level, increased sympathetic nervous system activity, and aldosteron release (109).

Clinical presentation. SCA patients lose consciousness within seconds or minutes because of insufficient cerebral irrigation. These patients do not generally have warning symptoms or they may have unspecified signs, such as discomfort in the thorax, palpitations, dyspnea and fatigability. Ventricular
tachyarrhythmias are the most common and are associated with cardiorespiratory arrest, both in the general population and in dialysis patients (172). Studies have shown that the indexed left ventricular mass is the most powerful predictor for ventricular arrhythmia in CKD patients (173). A study of 75 chronic hemodialysis patients who had a portable defibrillator showed that 79% of cardiac arrests were caused by ventricular tachycardia or ventricular fibrillation (174).

There are studies showing that supraventricular rhythm disorders can lead to cardiorespiratory arrest in hemodialysis patients. SCD patients can suffer from bradycardia (26.3%), asystole (15.8%) and electromechanical dissociation (15.8%) (175). There are few data regarding fatal supraventricular arrhythmias, which do not respond to the classical resuscitation measures, electrical defibrillation included. In order to obtain more knowledge in this respect, the Monitoring in Dialysis Study reports on the use of implantable loop recorders employed to analyze the type and frequency of arrhythmias on the traces obtained in a 6-month period (176). The final results of the study have not been published yet, but the preliminary results for 66 enrolled patients show the presence of atrial arrhythmias (57.4%), bradycardia (15%) and of ventricular arrhythmia in only 9.1% of the cases, mainly in the postdialysis period (177).

Management

Primary prevention of SCD. Taking into consideration the frequency and the importance of this phenomenon, identifying the risk factors for SCD proves to be significant. SCD risk occurs in the first three months following the onset of hemodialysis and builds up directly proportional with the period of dialysis, which means both new and old patients can be considered at risk (164). In addition, at risk for SCD are hemodialysis patients who suffer from large IDWG, extreme variations in serum potassium (hypo/hyperpotassemia), uncorrected mineral or bone deficiencies or malnutrition (89,178).

SCD hemodialysis patients are generally diabetics, with preexisting cardiac pathology and a history of cardiac arrhythmias (179-181). There are studies that emphasize the strong association between SCD and inflammatory markers including interleukin (IL)–6 (181), C reactive protein (CRP) (182) and adiponectin (183), but also between SCD and nutrition markers: Serum albumin (182) and predialysis serum creatinine (89).

Medication. Several drugs have proven useful in lowering the risk of SCD. In this respect, β adrenergic blockers were found to reduce SCD risk following myocardial infarction (184). A study of 200 hemodialysis patients assessed the efficiency of lisinopril vs. atenolol in reducing left ventricle hypertrophy and reported a significantly lower number of hospital admissions for cardiovascular events and cardiac failure in a group of patients who were treated with atenolol (185). Patients treated with atenolol had fewer episodes of arrhythmia and cardiorespiratory arrest. On the other hand, the HEMO study did not show an association between β-blockers and the decrease in SCD risk (186). However, the initiation of treatment with β-blockers in hemodialysis patients to prevent SCD cannot be recommended, based on present data.

There is no clear evidence that treatment with cholesterol-lowering medication (statin therapy) or renin-angiotensin-aldosterone system blockers, which is beneficial in the general population in lowering cardiovascular risk, would prove equally beneficial in hemodialysis patients (164).

Adjusting the hemodialysis prescription. The parameters of dialysis can be adjusted so as to prevent SCD. Thus, a low potassium level in the dialysate (<2 mEq/l) in patients with predialysis serum potassium within a normal limit increases the risk of SCD (89,107,161). A study on 30 hemodialysis patients who received potassium modeling vs. a fixed potassium dialysate demonstrated a decrease in ventricular arrhythmias, which suggests that the gradual elimination of potassium excess has a protective effect compared to its linear elimination, the latter one with aritrogenous effect. Unfortunately, potassium modeling is not widely available in hemodialysis centers (164).

The decrease in the Ca²⁺ level in the dialysate is associated with elongation of the QT interval and ventricular arrhythmias (187,188). Research has shown that exposure to low-calcium dialysate (<2.5 mEq/l) is associated with an increase in the risk of SCD by 40% (189). On the other hand, other studies have shown that the use of high-calcium dialysate is correlated with an increase in mortality, by acceleration of the vascular calcification and by increasing the myocardium vulnerability to arrhythmias (190-192).

In addition to the role of calcium in the dialysate, further studies are necessary to explain the role of vitamin D analogues, of phosphate binders and of calcimetics in SCD. Furthermore, it is necessary to control the phosphate serum levels, taking into account that the relationship between hyperphosphatemia and mortality has been demonstrated, probably because of myocardial calcifications and hemodynamic changes in microcirculation (193).

In addition to the electrolytic exchanges in hemodialysis patients, the relationship between cardiovascular mortality and high rate of ultrafiltration has been demonstrated (194). An ultrafiltration rate over 10 ml/kg/h is associated with increased mortality (195). It is necessary to train the patient to respect dietary recommandations (to limit salt and fluid intake), to increase the frequency and duration of the dialysis sessions and to maintain a small gradient between serum sodium and the sodium in the dialysate (196). The temperature in the dialysate influences blood pressure and coronary circulation, a decrease in the dialysate temperature causing a decrease in IDH and myocardial ischemic injury, and the risk of cardiovascular death (197).

8. Conclusion

Acute intradialytic cardiovascular complications are commonly encountered in clinical practice and influence the quality of life, such as morbidity and the mortality rate of dialysis patients. In order to have detailed knowledge concerning the risk factors and the pathogenic mechanisms and to ensure an optimal management of these complications, more studies must be conducted.

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Authors’ contributions

DT, MDT, DGB, AT, OS, IA V , AM, PCC, CIC, ME, RIP and DI designed the review and wrote the manuscript and performed the literature search and selected the included studies. DT, MDT, DGB, AT, OS, IA V , AM, PCC, CIC, ME, RIP and DI critically revised the manuscript. All authors read and approved the final manuscript. The contributions of all the authors toward this review are greatly valued and appreciated.

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Competing interests

The authors declare that they have no competing interests.

References

1. Ozkan G and Ulusoy S: Acute Complications of Hemodialysis. In: Technical Problems in Patients on Hemodialysis. Penido MG (ed). Intech, 2011. https://www.intechopen.com/books/technical-problems-in-patients-on-hemodialysis/acute-complications-of-hemodialysis. Accessed December 7, 2011.

2. Balan DG, Stroescu AE B, Tanasescu MD, Diaconescu A, Raducu L, Mihaia A, Tanase M, Stanescu II and Ionescu D: Nutritional intervention in patients with diabetic renal diseases. A brief presentation. Rev Chim 69: 3178-3182, 2018.

3. Balcaniu-Stroescu AE, Tanasescu MD, Diaconescu AC, Raducu L, Balan DG, Mihaia A, Tanase M, Stanescu II and Ionescu D: Diabetic nephropathy: A concise assessment of the causes, risk factors and implications in diabetic patients. Rev Chim 69: 3118-3121, 2018.

4. Mandita A, Timofte D, Balcaniu-Stroescu AE, Balan DG, Raducu L, Tanasescu MD, Diaconescu AC, Dragos D, Cosconel CI, Stoicescu SM, et al: Treatment of high blood pressure in patients with chronic renal disease. Rev Chim 70: 993-995, 2019.

5. National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK): Kidney Disease Statistics for the United States. https://www.niddk.nih.gov/health-information/health-statistics/ kidney-disease. Accessed November 2, 2019.

6. Saha M and Allon M: Diagnosis, treatment, and prevention of hemodialysis emergencies. Clin J Am Soc Neph 12: 375-369, 2017.

7. United States Renal Data System (USRDS): 2009 Annual Report United States Renal Data System. https://www.usrds.org/.

8. Bregman H, Daugirdas JT and Ing TS: Complications during hemodialysis. In: Handbook of Dialysis. Daugirdas JT and Ing TS (eds). Little, Brown, New York, NY, p149, 1994.

9. Paparelo J, Kshirsagar A and Battle D: Comorbidity and cardiovascular risk factors in patients with chronic kidney disease. Sempol Nephrol 22: 494-506, 2002.

10. Olariu L, Dumitriu B, Craciun L, Buse E, Rosoiu N, Bojinca M and Papacocea T: The in vitro influence of a pharmaceutically active small fish extract on apoptosis and proliferation mechanisms amplified by inflammatory conditions. Farmacia 67: 140-145, 2019.

11. Balcaniu-Stroescu AE, Tanasescu MD, Diaconescu AC, Raducu L, Constantin AM, Balan DG, Tarmure V and Ionescu D: Cardiovascular comorbidities, inflammation and serum albumin levels in a group of hemodialysis patients. Rev Chim Buchar 69: 926-930, 2018.

12. Timofte D, Mandita A, Balcaniu-Stroescu AE, Balan DG, Raducu L, Tanasescu MD, Diaconescu AC, Dragos D, Cosconel CI, Stoicescu SM, et al: Hyperuricemia and cardiovascular diseases-clinical and paraclinical correlations. Rev Chim Buchar 70: 1045-1046, 2019.

13. Totan A, Balcaniu-Stroescu AE, Melescanu Imre M, Miricescu D, Balan DG, Stanescu II, Ionescu D, Timofte D, Tanasescu MD and Greabu M: XOR-Possible correlations with oxidative stress and inflammation markers in the context of diabetic kidney disease. Rev Chim Buchar 70: 1396-1398, 2019.

14. Sars B, van der Sande FM and Kooman PJ: Intradialytic Hypotension: Mechanisms and outcome. Blood Purif 49: 158-167, 2020.

15. Flythe JE, Xue H, Lynch KE, Curhan GC and Brunelli SM: Association of mortality risk with various definitions of intradialytic hypotension. J Am Soc Nephrol 26: 724-734, 2015.

16. Sands JJ, Usvyat LA, Sullivan T, Segal JH, Zabetakis P, Kotanko P, Maddux FW and Diaz-Buxo JA: Intradialytic hypotension: Frequency, sources of variation and correlation with clinical outcome. Hemodial Int 18: 415-422, 2014.

17. Reilly RF: Attending rounds: A patient with intradialytic hypotension. Clin J Am Soc Nephrol 9: 798-803, 2014.

18. Assimon MM and Flythe JE: Definitions of intradialytic hypotension. Semin Dial 30: 464-472, 2017.

19. Masani NN, Miyawaki N and Maesaka JK: A patient with an uncommon etiology of intradialytic hypotension. Semin Dial 18: 435-439, 2005.

20. Roy PN and Danziger RS: Dialysate magnesium concentration predicts the occurrence of intradialytic hypotension. J Am Soc Neph 7: 1496, 1996.

21. Van der Sande FM, Cheriex EC, van Kuikj WH and Leunissen KM: Effect of dialysate calcium concentrations on intradialytic blood pressure course in cardiac-compromised patients. Am J Kidney Dis 32: 125-131, 1998.

22. Alappan R, Cruz D, Abu-Alfa AK, Mahnensmith R and Perazella MA: Treatment of severe intradialytic hypotension with the addition of high dialysate calcium concentration to midodrine and/or cool dialysate. Am J Kidney Dis 37: 294-299, 2001.

23. Lin CJ, Chen CY, Wu PC, Pan CF, Shih HM, Huang MY, Chou LH, Tang JS and Wu CJ: Intelligent system to predict intradialytic hypotension in chronic hemodialysis. J Formos Med Assoc 117: 888-893, 2018.

24. Seabra VF and Jaber BL: Acute complications during hemodialysis. In: Comprehensive Clinical Nephrology, Floege J, Johnson RJ and Feehally J (eds). Elsevier, Philadelphia, PA, p306-1307, 2010.

25. Kooman JP, Katzarski K, van der Sande FM, Leunissken KM and Kotanko P: Hemodialysis: A model for extreme physiology in a vulnerable patient population. Semin Dial 31: 500-506, 2018.

26. Barth C, Boer W, Garzoni D, Kuenzi T, Ries W, Schaefer R, Schneditz D, Tsobanelis T, van der Sande FM, Cheriex EC, van Kuikj WH and Leunissen KM: Effect of dialysate calcium concentrations on intradialytic blood pressure course in cardiac-compromised patients. Am J Kidney Dis 32: 125-131, 1998.

27. Aronoff GR: The effect of treatment time, dialysis frequency, and there a critical relative blood volume? Nephrol Dial Transplant 18: 1353-1360, 2003.

28. Barth C, Boer W, Garzoni D, Kuenzi T, Ries W, Schaefer R, Schneditz D, Tsobanelis T, van der Sande FM, Leunissen KM and Kotanko P: Hemodialysis: A model for extreme physiology in a vulnerable patient population. Semin Dial 31: 500-506, 2018.

29. Kooman JP: Attending rounds: A patient with intradialytic hypotension: Frequency, sources of variation and correlation with clinical outcome. Hemodial Int 18: 415-422, 2014.

30. Reilly RF: Attending rounds: A patient with intradialytic hypotension. Clin J Am Soc Nephrol 9: 798-803, 2014.

31. Assimon MM and Flythe JE: Definitions of intradialytic hypotension. Semin Dial 30: 464-472, 2017.

32. Masani NN, Miyawaki N and Maesaka JK: A patient with an uncommon etiology of intradialytic hypotension. Semin Dial 18: 435-439, 2005.

33. Roy PN and Danziger RS: Dialysate magnesium concentration predicts the occurrence of intradialytic hypotension. J Am Soc Neph 7: 1496, 1996.

34. Van der Sande FM, Cheriex EC, van Kuikj WH and Leunissen KM: Effect of dialysate calcium concentrations on intradialytic blood pressure course in cardiac-compromised patients. Am J Kidney Dis 32: 125-131, 1998.

35. Alappan R, Cruz D, Abu-Alfa AK, Mahnensmith R and Perazella MA: Treatment of severe intradialytic hypotension with the addition of high dialysate calcium concentration to midodrine and/or cool dialysate. Am J Kidney Dis 37: 294-299, 2001.

36. Lin CJ, Chen CY, Wu PC, Pan CF, Shih HM, Huang MY, Chou LH, Tang JS and Wu CJ: Intelligent system to predict intradialytic hypotension in chronic hemodialysis. J Formos Med Assoc 117: 888-893, 2018.

37. Seabra VF and Jaber BL: Acute complications during hemodialysis. In: Comprehensive Clinical Nephrology, Floege J, Johnson RJ and Feehally J (eds). Elsevier, Philadelphia, PA, p306-1307, 2010.

38. Kooman JP, Katzarski K, van der Sande FM, Leunissen KM and Kotanko P: Hemodialysis: A model for extreme physiology in a vulnerable patient population. Semin Dial 31: 500-506, 2018.

39. Barth C, Boer W, Garzoni D, Kuenzi T, Ries W, Schaefer R, Schneditz D, Tsobanelis T, van der Sande FM, Leunissen KM and Kotanko P: Hemodialysis: A model for extreme physiology in a vulnerable patient population. Semin Dial 31: 500-506, 2018.
31. Assa S, Hummel YM, Voors AA, Kuipers J, Westerhuis R, de Jong PE and Franssen CFM: Hemodialysis-induced regional left ventricular systolic dysfunction: Prevalence, patient and dialysis-related factors, and prognostic significance. J Clin Am Soc Nephrol 7: 1615-1623, 2012.

32. Seong EY, Zheng Y, Winkelmayer WC, Montez-Rath ME and Chang TI: The relationship between intradialytic hypotension and hospitalized mesenteric ischemia: A case-control study. Clin J Am Soc Nephrol 15: 1517-1525, 2020.

33. Magder SA: The highs and lows of blood pressure: Toward meaningful clinical targets in patients with shock. Crit Care Med 42: 1241-1251, 2014.

34. Charytan DM, Skali H, Shah NR, Veeranna V, Cheezum MK, Taqueti VR, Kato T, Bibbo CR, Hainer J, Dorbala S, et al: Coronary flow reserve is predictive of the risk of cardiovascular death regardless of chronic kidney disease stage. Kidney Int 93: 501-509, 2018.

35. Burkhart D, Bartosova M, Schaefer B, Grabe N, Lahrmann B, Naser H, Freise C, Schneider A, Lingnau A, Degenhart P, et al: Reduced microvascular density in omental biopsies of children with chronic kidney disease. PLoS One 11: e0166050, 2016.

36. Mitsides C, Cornelis T, Broers NJ, Diederen NM, Brenchley P, van der Sande FM, Schalkwijk CG, Kooman JP and Mitra S: Extracellular overhydration linked with endothelial dysfunction and inflammation in chronic kidney disease. PLoS One 12: e0183281, 2017.

37. Amann K, Wiest G, Zimmer G, Grettz N, Ritz E and Mall G: Reduced capillary density in the myocardium of uremic rats-a stereological study. Kidney Int 48: 237-243, 1995.

38. Mancini E, Perazzini C, Gusella L, uczella F, Limido A, Mancini E, Perazzini C, Gesualdo L, Aucella F, Limido A, et al: Intra-dialytic blood oxygen saturation (SO2): Association with dialysis hypotension (the SOGLIA Study). J Nephrol 30: 811-819, 2016.

39. Campos I, Chan L, Zhang H, Deziel S, Vaughn C, Meyring-Wösten A and Kotanko P: Intradialytic hypoxemia in chronic hemodialysis patients. Blood Purif 41: 177-187, 2016.

40. Knoll GA, Grabowski JA, Dervin GF and O'Rourke K: A randomized, controlled trial of albumin versus saline for the treatment of intradialytic induced blood volume changes. Kidney Int 55: 1457-1462, 1999.

41. Nette RW, Krepel HP, van den Meiracker AH, Weimar W and Schneditz D: Effect of controlled extracorporeal blood cooling on ultrafiltration rate changes during hemodialysis. J Am Soc Nephrol 8: 956-964, 1997.

42. Cruz DN, Mahnensmith RL, Brickel HM and Perazella MA: Midodrine and cold dialysate are effective therapies for symptomatic intradialytic hypotension. Am J Kidney Dis 33: 920-926, 1999.

43. Yu AW, Ing TS, Zabaneh RI and Daugirdas JT: Effect of dialysate temperature on central hemodynamics and urea kinetics. Kidney Int 48: 237-243, 1995.

44. Schneditz D, Ronco C and Levin N: Temperature control by the blood temperature monitor. Semin Dial 16: 477-492, 2003.

45. Pérgola PE, Habiba NM and Johnson JM: Body temperature regulation during hemodialysis in long-term patients: Is it time to change dialysis temperature prescription? Am J Kidney Dis 44: 155-165, 2004.

46. Pizzarelli F: From cold dialysis to isothermic dialysis: A twenty-five year voyage. Nephrol Dial Transplant 22: 1007-1012, 2007.

47. Mustafa RA, Bdair F, Akb EA, Garg AX, Thiessen-Philbrook H, Salameh H, Kirs S, Ghinad N, Al-Jaishi A, Patel P, et al: Effect of lowering the dialysate temperature in chronic hemodialysis: A Systematic review and meta-analysis. Clin J Am Soc Nephrol 11: 442-457, 2016.

48. Flynn JJ III, Mitchell MC, Caruso FS and McElligott MA: Midodrine treatment for patients with hemodialysis hypotension. Clin Nephrol 45: 261-267, 1996.

49. Montagac RH, Clavel P, Delhotal-Landes B, Flouvat B, Poulsen S and Schilling F: Use of midodrine (Gutron) to treat permanent hypotension in a chronic hemodialysis patient. Clin Nephrol 56: 162-168, 2001.

50. Perazella MA: Pharmacologic options available to treat symptomatic intradialytic hypotension. Am J Kidney Dis 38 (4 Suppl 4): S26-S36, 2001.

51. Prakash S, Garg AX, Heidenheim AP and House AA: Midodrine appears to be safe and effective for dialysis-induced hypotension: A systematic review. Nephrol Dial Transplant 19: 2553-2558, 2004.

52. Low PA, Gilden JL, Freeman R, Sheng KN and McElligott MA: Efficacy of midodrine vs. placebo in neurogenic orthostatic hypotension. A randomized, double-blind multicenter study. Midodrine Study Group. JAMA 277: 1046-1051, 1997.

53. Dheenan S, Venkatesan S, Grubb BP and Henrich WL: Effect of serum thalidomide on dialysis hypotension. Am J Kidney Dis 31: 624-630, 1998.
Sabry AA: Is there a role for endothelin-1 in the hemodynamic
El-Shafey EM, El-Nagar GF, Selim MF, El-Sorogy HA and
of nitric oxide and endothelin. Kidney Int 61: 697‑704, 2002.
Welbourne TC, Levi M, Shah V, Blandon P, Zager P and
pressure waveform. Nephrol Dial Transplant 24: 3788‑3794,
Desmeules S and Agharazii M: Effects of acute variation of
Hypertension 13: 213‑218, 1989.
and Borow KM: Physiological mechanisms for calcium‑induced
within hemodialysis clinics. Kidney Int 79: 218‑227, 2011.
Gabutti L, Bianchi G, Soldini D, Marone C and Burnier M:
Dolson GM, Ellis KJ, Bernardo MV, Prakash R and Adrogué HJ:
sodium gradient on intradialytic hypertension: An observational
Pola A, Carli O, Valzorio B and Cancarini G: Role of dialysis
and Toto R: Probing the mechanisms of intradialytic hypertension: A pilot study targeting endothelial cell dysfunction. Clin J Am Soc Nephrol 7: 1300‑1309, 2012.
Inrig JK, Molina C, D’Silva K, Kim C, Van Buren P, Allen J and Toto R: Effect of low versus high dialysate sodium concentration on blood pressure and endothelial‑derived vaso‑regulators during hemodialysis: A randomized crossover study. Am J Kidney Dis 65: 464‑473, 2015.
Corra‑Cavieiras R, Martin‑Malo A, Pedrini L, Basci A, Canaud B, Angiotensin II‑induced sudden arrhythmic death and electrical remodeling. Am J Physiol Heart Circ Physiol 293: H1242‑H1253, 2007.
and mortality in a cohort of long‑term hemodialysis patients. Am Heart J 140: 886‑890, 2000.
Voroneanu L and Covic A: Arrhythmias in hemodialysis patients. J Nephrol 22: 716‑725, 2009.
United States Renal Data System (USRDS): USRDS 2013 Annual Data Report: Atlas of End‑Stage Renal Disease in the United States. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2013. https://www.usrds.org/atlas13.aspx Accessed June 25, 2020.
Zebe H: Atrial fibrillation in dialysis patients. Nephrol Dial Transplant 15: 765‑768, 2000.
Vazquez E, Sanchez‑Perales C, Borrego F, Garcia‑Cortes MJ, Lozano C, Guzman M, Gil JM, Borrego MJ and Perez V: Influence of atrial fibrillation on the morbido‑mortality of patients on hemodialysis. Am Heart J 140: 886‑890, 2000.
Genovessi S, Vincenti A, Rossi E, Pogliani D, Acquistapace I, Stella A and Valsecchi MG: Atrial fibrillation and morbidity and mortality in a cohort of long‑term hemodialysis patients. Am J Kidney Dis 51: 255‑262, 2008.
Abbott KC, Trespalacios FC, Taylor AJ and Agodua LY: Atrial fibrillation in chronic dialysis patients in the United States: Risk factors for hospitalization and mortality. BMC Nephrol 4: 1, 2003.
Hecking E, Bragg‑Gresham JL, Rayner HC, Pisoni RL, Andreucci VE, Combe C, Greenwood R, McCullough, Feldman H, Young EW, et al: Haemodialysis prescription, adherence and nutritional indicators in five European countries. Results from the dialysis Outcomes and practice patterns Study (DOPPS). Nephrol Dial Transplant 19: 100‑107, 2004.
Karnik JA, Young BS, Lew NL, Herget M, Dubinsky C, Lasarus JM and Chterow GM: Cardiac arrest and sudden death in dialysis units. Kidney Int 40: 350‑355, 1996.
Voroneanu L and Covic A: Arrhythmias in hemodialysis patients. J Nephrol 22: 716‑725, 2009.
Fischer R, Dechend R, Gapelyuk A, Shagdarsuren E, Gruner K, Băicuş C: Role of adenosine A1 receptor antagonist improves remodeling. Am J Physiol Heart Circ Physiol 293: H1242‑H1253, 2007.
and mortality in a cohort of long‑term hemodialysis patients. Am J Kidney Dis 51: 255‑262, 2008.
Abbott KC, Trespalacios FC, Taylor AJ and Agodua LY: Atrial fibrillation in chronic dialysis patients in the United States: Risk factors for hospitalization and mortality. BMC Nephrol 4: 1, 2003.
114. Routledge HC, Chowdhry S and Townsend JV: Heart rate variability: A therapeutic target? J Clin Pharm Ther 27: 85-92, 2002.
115. Herzog CA: Don't forget the defibrillator in the dialysis unit. N Engl J Med 351: 1285-1295, 2004.
116. Sakhaja R, Keebler M, Lai TS, McLaughlin Gav, Thakur R and Bhatt DL: Meta-analysis of mortality in dialysis patients with an implantable cardioverter defibrillator. Am J Cardiol 103: 735-741, 2009.
117. Anavel A, McMurray JJ, Velazquez EJ, Solomon SD, Keber L, Rouleau JL, White HD, Nordlander R, Maggioni A, Dickstein K, et al: Relation between renal dysfunction and cardiovascular outcomes after myocardial infarction. N Engl J Med 351: 1285-1295, 2004.
118. Go AS, Chertow GM, Fan D, McCulloch CE and Hsu C: Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med 351: 1296-1305, 2004.
119. Collins AJ, Foley RN, Herzog C, Chavers BL, Gilbertson D, Ishani A, Kasiske B, Liu J, Mau LW, McBean M, et al: United States renal data system 2008 annual data report abstract. Am J Kidney Dis 53 (1 Suppl): S1-S374, 2009.
120. Ix JH, Shlipak MG, Liu HH, Schiller NB and Whooley MA: Association between renal insufficiency and inductive ischemia in patients with coronary artery disease: The heart and soul study. J Am Soc Nephrol 14: 3233-3238, 2003.
121. Sarnak MJ, Levey AS, Schoolwerth AC, Coresh J, Cuddon B, Harlan LL, Keefe BJ, Kelepouris E, Klag MJ, et al: Kidney disease as a risk factor for development of cardiovascular disease: A statement from the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. Circulation 108: 2154-2169, 2003.
122. Go AS, Bansal N, Chandra M, Lathon PV, Fortmann SP, Iribarren C, Hsuy CY and Hlatky M; ADVANCE Study Investigators: Chronic kidney disease and risk for presenting with acute myocardial infarction versus stable exertional angina in adults with coronary heart disease. J Am Coll Cardiol 58: 1600-1607, 2011.
123. Collins AJ, Foley RN, Herzog C, Chavers BM, Gilbertson D, Ishani A, Kasiske BL, Lui J, Mau LW, McBean M, et al: Excerpts from the US renal data system 2009 annual data report. Am J Kidney Dis 55 (1 Suppl 1): S1-S420, A6-A7, 2010.
124. United States Renal Data System (USRDS): USRDS 2013 annual data report: atlas of chronic kidney disease and end-stage renal disease in the United States, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD. 2013. https://www.usrds.org/atlas13.aspx. Accessed August 19, 2016.
125. Herzog CA and Passman R: Evaluation of sudden cardiac arrest and sudden cardiac death in dialysis patients. UpToDate, 2020. https://www.uptodate.com/contents/evaluation‑of‑sudden‑cardiac‑arrest‑and‑sudden‑cardiac‑death‑in‑dialysis‑patients. Accessed March 24, 2020.
126. Munter P, He J, Hamm L, Loria C and Whelton PK: Renal insufficiency and subsequent death resulting from cardiovascular disease in the United States. J Am Soc Nephrol 13: 745-753, 2002.
127. Di Benedetto A, Marcelli D, Andrella C, Aice G, D'Isa S, Capobianco F, Pacchiano G, D'Amato R, Kelepouris E, Klag MJ, et al: Kidney disease as a risk factor for development of cardiovascular disease: A statement from the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. Circulation 108: 2154-2169, 2003.
128. Shah DS, Polkinghorn KR, Pellicano R and Kerr PG: Are traditional risk factors valid for assessing cardiovascular risk in end-stage renal failure patients? Nephrology (Carlton) 13: 667-671, 2008.
129. Levey AS, Coresh J, Balk E, Kausz AT, Levin A, Steffes MW, Hogg R, Perrone RD, Lau J and Eknoyan G; National Kidney Foundation: National kidney foundation practice guidelines for chronic kidney disease: Evaluation, classification, and stratification. Ann Intern Med 139: 137-147, 2003.
130. Antman EM, Anbe DT, Armstrong PW, Bates ER, Green LA, Hedges JR, Hochman JS, Krumholz H, Kushner FG, Lamas GA, et al: ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction-executive summary: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 1999 Guidelines for the Management of Patients With Acute Myocardial Infarction). Circulation 110: 588-636, 2004.
131. Van der Velde M, Matsushita K, Coresh J, Astor BC, Woodward M, Levey A, de Jong P, Gansevoort RT; Chronic Kidney Disease Prognosis Consortium, van der Velde M, et al: Lower estimated glomerular filtration rate and higher albuminuria are associated with all-cause and cardiovascular mortality: A collaborative meta-analysis of high-risk population cohorts. Kidney Int 79: 1341-1352, 2011.
132. Hörl WH, Cohen JJ, Harrington JT, Madras NE and Zisman CJ: Atheroembolism and uremic retention solutes. Kidney Int 66: 1719-1731, 2004.
133. Becker BN, Himmelfarb J, Henrich WL and Hakim RM: Reassessing the cardiac risk profile in chronic hemodialysis patients: A hypothesis on the role of oxidant stress and other non-traditional cardiac risk factors. J Am Soc Nephrol 8: 475-486, 1997.
134. Harper SJ and Bates DO: Endothelial permeability in uremia. Kidney Int Suppl 63: S84-S44, 2003.
135. Stenmark P, Pecotis-Filho R and Lindholm B: Coronary artery disease in end-stage renal disease: No longer a simple plumbing problem. J Am Soc Nephrol 14: 1927-1939, 2003.
136. Büzello M, Törnig J, Faulhaber J, Ehmke H, Ritz E and Amann K: The apolipoprotein e knockout mouse: A model documenting accelerated atherogenesis in uremia. J Am Soc Nephrol 14: 313-316, 2003.
137. Bro S, Benzon JF, Falk E, Andersen CB, Olgaard K and Nielsen LB: Chronic renal failure accelerates atherogenesis in apolipoprotein E-deficient mice. J Am Soc Nephrol 14: 2466-2474, 2003.
138. Vervloet M and Cozzolino M: Vascular calcification in chronic kidney disease as a risk factor for cardiovascular disease. A collaborative meta-analysis of high-risk population cohorts. Kidney Int 91: 93-98, 2011.
139. Juonala M, Viikari JS, Althán F, Marniemi J, Kahonen M, Taittonen L, Laitinen T and Raitakari OT: Brachial artery flow-mediated dilation and asymmetrical dimethylarginine in the cardiovascular risk in young Finns study. Circulation 116: 1367-1373, 2007.
140. Zoccali C, Bode-Büger S, Mallamaci F, Benedetto F, Tripepi G, Malatino L, Cataliotti A, Bellanuova I, Fermo I, Froligh J and Büger R: Plasma concentration of asymmetrical dimethylarginine and mortality in patients with end-stage renal disease: A prospective study. Lancet 358: 2113-2117, 2001.
141. Nuhu F and Bhandari S: Oxidative stress and cardiovascular complications in chronic kidney disease, the impact of anaemia. Pharmaceuticals (Basel) 11: 103, 2018.
142. Papacocca T, Buraga L, Papacocca R, Badarau AI, Buraga M, Cioccari C, Mihai G, Stoian I and Adam D: Antioxidant enzymes-potential targets in intracerebral haemorrhage. Farmacia 62: 1118-1125, 2014.
143. Vervoort M and Cozzolino M: Vascular calcification in chronic kidney disease: Different bricks in the wall? Kidney Int 91: 808-817, 2017.
144. Jablonski K and Chonchol M: Vascular calcification in end-stage renal disease. Hemodial Int 17 (Suppl 1): S1-S21, 2013.
145. Sosnov J, Lessard D, Goldberg RJ, Warzebski J and Gore JM: Differential symptoms and outcomes of acute myocardial infarction in patients with kidney disease: A community-wide perspective. Am J Kidney Dis 47: 387-384, 2006.
146. Herzog CA, Littrell K, Arko C, Frederick PD and Blaney M: Clinical characteristics of dialysis patients with acute myocardial infarction in the United States: A collaborative project of the United States Renal Data System and the National Registry of Myocardial Infarction. Circulation 116: 1465-1472, 2007.
147. Freda BJ, Tang WH, Van Lente F, Peacock WF and Francis GS: Cardiac troponins in renal insufficiency: Review and clinical implications. J Am Coll Cardiol 40: 2065-2071, 2002.
148. Bonello L, De Labriolle A, Roy P, Steinberg DH, Okabe T, Pinto Slottow TL, Xue Z, Torguson R, Suddath WO, Satler LF, et al: Impact of optimal medical therapy and revascularization on outcome of patients with chronic kidney disease and on dialysis who presented with acute coronary syndrome. Am J Cardiol 102: 535-540, 2008.
151. Keltai M, Tonelli M, Mann JF, Sitkei E, Lewis BS, Hawken S, Mehta SR and Yusuf S: CURE Trial Investigators: Renal function and outcomes in acute coronary syndrome: Impact of dialysis. Eur J Cardiovasc Prev Rehabil 14: 312-318, 2007.

152. Palmer SC, Di Micco L, Razavian M, Craig JC, Perkovic V, Pellegrini F, Copetti M, Graziano G, Tognoni G, Jardine M, et al: Effects of antiplatelet therapy on mortality and cardiovascular and bleeding outcomes in patients with chronic kidney disease: A systematic review and meta-analysis. Ann Intern Med 156: 445-450, 2012.

153. James S, Budaj A, Aylward P, Buck KK, Cannon CP, Cornell JJ, Harrington RA, Horro R, Katus H, Keltai M, et al: Ticagrelor versus clopidogrel in acute coronary syndromes in relation to renal function: Results from the Platelet Inhibition and Patient Outcomes (PLATO) trial. Circulation 122: 1056-1067, 2010.

154. Huang CC and Chen CJW: Contemporary management of coronary artery disease and acute coronary syndrome in patients with chronic kidney disease and end-stage renal disease. Acta Cardiol Sin 29: 132-141, 2013.

155. Strippoli GF, Navaneethan SD, Johnson DW, Perkovic V, Pellegrini F, Nicolucci A and Craig JC: Effects of statins in patients with chronic kidney disease: Meta-analysis and meta-regression of randomised controlled trials. BMJ 336: 645-651, 2008.

156. Chou MT, Wang JJ, Sun YM, Sheu MJ, Chu CC, Weng SF, Chu CC, Lai CH and Chien CT: Coronary artery disease and mortality among dialysis patients with acute coronary syndrome: Taiwan National Cohort Study. Int J Cardiol 167: 2719-2723, 2012.

157. Herzog CA, Ma JZ and Collins AJ: Comparative survival of dialysis patients in the United States after coronary angioplasty, coronary artery stenting, and coronary artery bypass surgery: Kidney Int Suppl 106: 2207-2211, 2002.

158. Szczec A, Reddan DN, Owen WF, Racz M, Jones RH and Hannan EL: Differential survival after coronary revascularization procedures among patients with renal insufficiency. Kidney Int 60: 292-299, 2001.

159. Koyanagi H, Kimura K, Ito Y, Takahashi R, Toriyama T, National Cohort Study. Int J Cardiol 167: 2719-2723, 2012.

160. Podrid PJ: Pathophysiology and etiology of sudden cardiac arrest. UpToDate, 2020. 

161. Panda S, Raju R, Nityananda S, Charytan D: Autopsy findings of new-onset atrial fibrillation in hemodialysis patients: A pilot study. Int J Nephrol 2014: 661393.

162. Han CD, Zimetbaum P, Herzog CA and Tumlin JA: MiD Investigators and Committees: Arrhythmia and sudden death in hemodialysis patients: Protocol and baseline characteristics of the Monitoring in Dialysis Study. Clin J Am Soc Nephrol 11: 721-734, 2016.

163. Roy-Chaudhury P, Tumlin JA, Koplan BA, Costea AI, Kher V, Williamson D, Pokhriyal S and Charytan DM: MiD investigators and committees: Primary outcomes of the Monitoring in Dialysis Study indicate that clinically significant arrhythmias are common in hemodialysis patients and related to dialytic cycle. Kidney Int 93: 941-951, 2018.

164. Ganesh SK, Stack AG, Levin NW, Hulbert-Shearon T and Port FK: Association of elevated serum PO(4), Ca x PO(4) product, and parathyroid hormone with cardiac mortality risk in chronic hemodialysis patients. J Am Soc Nephrol 12: 2151-2158, 2001.

165. Podrid PJ: Pathophysiology and etiology of sudden cardiac arrest. UpToDate, 2020. https://www.uptodate.com/contents/pathophysiology-and-etiology-of-sudden-cardiac-arrest

166. Adou M, Thumma J, Fuller DS, Tentori F, Li Y, Morgenstern H, Mendeksohn D, Tomo T, Ethier J, Port F and Robinson BM: Modifiable practices associated with sudden death among hemodialysis patients in the dialysis outcomes and practice patterns study. Clin J Am Soc Nephrol 7: 765-774, 2012.

167. Pun PH, Lehrich RW, Smith SR and Middleton JP: Predictors of survival after cardiac arrest in outpatient hemodialysis clinics. Clin J Am Soc Nephrol 2: 491-500, 2007.

168. Kasuga H, Kimura K, Ito Y, Takahashi R, Toriyama T, Nishiyama T and Hosoda S: Comparison of clinical outcomes of coronary artery bypass grafting and percutaneous transluminal coronary angioplasty in renal dialysis patients. Ann Thorac Surg 61: 1793-1796, 1996.

169. Widlar JJ: Cardiac arrest in dialysis patients. Approaches to alter an abysmal outcome. Kidney Int Suppl 63: S197-S200, 2003.

170. Pun PH, Smarz TR, Honeycutt EF, Shaw LK, Al-Khatib SM and Middleton JP: Chronic kidney disease is associated with increased risk of sudden cardiac death among patients with coronary artery disease. Kidney Int 76: 652-658, 2009.

171. Diacoumi C: Treatment of diabetes in patients with heart failure. In: Proceedings of the 3rd International Conference on Interdisciplinary Management of Diabetes Mellitus and its Complications-Diabetes mellitus as cardiovascular disease. INTERDIAB, Bucharest, pp70-177, 2017.

172. Paredes MS, Plantinga LC, Kao WHL, Meoni LA, Jaar BG, Fine JD, Powe NR, Cornwell VS and Williams K: The association of sudden cardiac death with inflammation and other traditional risk factors. Kidney Int 74: 1335-1342, 2008.

173. Drechsler CR, Krane V, Winkler K, Dekker FW and Wanner C: Changes in adiponectin and the risk of sudden death, stroke, myocardial infarction, and mortality in hemodialysis patients. Kidney Int 76: 567-575, 2009.

174. Domanski MJ, Zipes DP and Schron E: Treatment of sudden cardiac death. Current understandings from randomized trials and future research directions. Circulation 95: 2694-2699, 1997.

175. Agarwal R, Sinha AD, Pappas MK, Abraham TN and Tegegne GG: Hypertension in hemodialysis patients treated with atenolol or lisinopril: A randomized controlled trial. Nephrol Dial Transplant 29: 672-681, 2014.

176. Tangri N, Shastri S, Tighiouart H, Beck GJ, Cheung AK, Ekowayan G and Sarnak MJ: β-Blockers for prevention of sudden cardiac death in patients on hemodialysis: A propensity score analysis of the HEMO Study. Am J Kidney Dis 58: 939-945, 2011.

177. Beaubien ER, Pylypchuk GB, Akhtar J and Biem HJ: Value of corrected QT interval dispersion in identifying patients initiating dialysis at increased risk of total and cardiovascular mortality. Am J Kidney Dis 39: 834-842, 2002.

178. Di Iorio B, Torraca S, Piccopo C, Sirico ML, Micco LD, Pota A, Tartaglia D, Berardino L, Morrone LF and Russo D: Dialysate bath and QTc interval in patients on chronic maintenance hemodialysis: Pilot study of single dialysis effects. J Nephrol 25: 653-660, 2012.
189. Pun PH, Horton JR and Middleton JP: Dialysate calcium concentration and the risk of sudden cardiac arrest in hemodialysis patients. Clin J Am Soc Nephrol 8: 797-803, 2013.

190. Timofte D, Ionescu D, Medrihan L, Mandita A, Rasina A and Damian L: Vascular calcification and bone disease in hemodialysis patients: assessment, association and risk factors. Nephrol Dialysis Transplantation 22: 325-326, 2007.

191. Timofte D, Dragos D, Balcangiu-Stroescu AE, Tanaseascu MD, Balan DG, Raducu L, Tulp A, Stiru O and Ionescu D: Abdominal aortic calcification in predialysis patients: Contribution of traditional and uremia-related risk factors. Exp Ther Med 20: 97-102, 2020.

192. Kim ED and Parekh RS: Calcium and sudden cardiac death in end-stage renal disease. Semin Dial 28: 624-635, 2015.

193. Di Lullo L, Rivera R, Barbera V, Bellusi A, Cozzolino M, Russo D, De Pascalis A, Banerjee D, Flocchini F and Ronco C: Sudden cardiac death and chronic kidney disease: From pathophysiology to treatment strategies. Int J Cardiol 217: 16-27, 2016.

194. Flythe JE and Brunelli SM: The risks of high ultrafiltration rate in chronic hemodialysis: Implications for patient care. Semin Dial 24: 259-265, 2011.

195. Flythe JE, Kimmel SE and Brunelli SM: Rapid fluid removal during dialysis is associated with cardiovascular morbidity and mortality. Kidney Int 79: 250-257, 2011.

196. Mendoza JM, Bayes LY, Sun S, Doss S and Schiller B: Effect of lowering dialysate sodium concentration on interdialytic weight gain and blood pressure in patients undergoing thrice-weekly in-center nocturnal hemodialysis: A quality improvement study. Am J Kidney Dis 58: 956-963, 2011.

197. Jefferies HJ, Burton JO and McIntyre CW: Individualised dialysate temperature improves intradialytic haemodynamics and abrogates haemodialysis-induced myocardial stunning, without compromising tolerability. Blood Purif 32: 63-68, 2011.