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ΠΡΟΓΡΑΜΜΑ ΜΕΤΑΠΤΥΧΙΑΚΩΝ ΣΠΟΥΔΩΝ
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(MSc in Heart Failure - Cardio-oncology - Cardiac Rehabilitation)

Μεταπτυχιακή Διπλωματική Εργασία

«Από του στόματος αντιπηκτική αγωγή στους ασθενείς με καρδιακή ανεπάρκεια και τελικού σταδίου νεφρική ανεπάρκεια»

υπό

Ιωάννου Μαρίας

Ειδικευόμενης Ιατρού Καρδιολογίας

Υπεβλήθη για την εκπλήρωση μέρους των απαιτήσεων
για την απόκτηση του Διπλώματος Μεταπτυχιακών Σπουδών
«Καρδιακή Ανεπάρκεια – Καρδιο-ογκολογία – Καρδιαγγειακή Αποκατάσταση»

Λάρισα, Φεβρουάριος 2024

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"Oral anticoagulation therapy in heart failure patients with end-stage kidney disease"

Larissa, February 2024

«Βεβαιώνω ότι η παρούσα διπλωματική εργασία είναι αποτέλεσμα δικής μου δουλειάς και δεν αποτελεί προϊόν αντιγραφής. Στις δημοσιευμένες ή μη δημοσιευμένες πηγές έχω χρησιμοποιήσει εισαγωγικά και όπου απαιτείται έχω παραθέσει τις πηγές τους στο τμήμα της βιβλιογραφίας».

Υπογραφή:

ΙΩΑΝΝΟΥ ΜΑΡΙΑ

Πανεπιστήμιο Θεσσαλίας, Σχολή Επιστημών Υγείας, Τμήμα Ιατρικής,

2024

ΔΙΕΥΘΥΝΤΗΣ ΤΟΥ ΠΡΟΓΡΑΜΜΑΤΟΣ ΜΕΤΑΠΤΥΧΙΑΚΩΝ

ΣΠΟΥΔΩΝ

ΣΚΟΥΛΑΡΙΓΚΗΣ ΙΩΑΝΝΗΣ

ΚΑΘΗΓΗΤΗΣ ΚΑΡΔΙΟΛΟΓΙΑΣ

ΤΜΗΜΑΤΟΣ ΙΑΤΡΙΚΗΣ ΠΑΝΕΠΙΣΤΗΜΙΟΥ ΘΕΣΣΑΛΙΑΣ

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"Oral anticoagulation therapy in heart failure patients with end-stage kidney disease"

Ευχαριστίες

Με την ολοκλήρωση της μεταπτυχιακής διπλωματικής μου εργασίας, θα ήθελα να εκφράσω τις θερμές μου ευχαριστίες στον επιβλέπων καθηγητή μου, κύριο Ιωάννη Στεφανίδη, καθώς και στον σύμβουλο μου, κύριο Θεόδωρο Ελευθεριάδη, για την επιστημονική τους καθοδήγηση, τις εποικοδομητικές τους υποδείξεις και το αμείωτο ενδιαφέρον που έδειξαν από την αρχή μέχρι το τέλος της όλης διαδικασίας.

Επιπλέον, ιδιαιτέρες ευχαριστίες θα ήθελα να απευθύνω στον Διευθυντή κύριο Ιωάννη Σκουλαρίγκη και στους λοιπούς Καθηγητές του του ΠΜΣ «Καρδιακή Ανεπάρκεια – Καρδιοογκολογία – Καρδιαγγειακή Αποκατάσταση», για τις γνώσεις που μας προσέφεραν.

Επίσης ευχαριστώ τον κύριο Κυριακό Γιάγκου για την παρότρυνση συμμετοχής στο συγκεκριμένο ΠΜΣ, καθώς και για την υποτροφία που έχει δωρίσει σε όλους τους Κύπριους συμμετέχοντες.

Τέλος, θα ήθελα εκφράσω την ευγνωμοσύνη μου στην οικογένειά μου και στο σύντροφό μου για όλη τη στήριξη και τη συμπαράσταση τους καθ' όλη τη διάρκεια των σπουδών μου.

Ιωάννου Μαρία

«Από του στόματος αντιπηκτική αγωγή στους ασθενείς με καρδιακή ανεπάρκεια και τελικού σταδίου νεφρική ανεπάρκεια»

Περίληψη

Υπόβαθρο: Η καρδιακή ανεπάρκεια (ΚΑ) και η τελικού σταδίου νεφρική ανεπάρκεια (ΤΣΝΑ), είναι δύο διακριτές παθολογικές οντότητες που συχνά συνυπάρχουν, λόγω της αμφίδρομης σχέσης μεταξύ καρδιάς και νεφρών. Η παρούσα βιβλιογραφία αναλύει εκτενώς το ξεχωριστό θρομβωτικό κίνδυνο για την κάθε μία, επικεντρώνοντας κυρίως στην κολπική μαρμαρυγή (ΚΜ), στο σχετιζόμενο με αυτήν εγκεφαλικό επεισόδιο ή συστημική εμβολή, καθώς και στη φλεβική θρομβοεμβολική νόσο (ΦΘΕΝ). Παρόλα αυτά, υπάρχει ένδεια δεδομένων όσον αφορά τον ενδεχόμενο αθροιστικό θρομβωτικό κίνδυνο όταν οι δύο καταστάσεις συνυπάρχουν.

Στόχος: Η μελέτη έχει ως στόχο να αναδείξει τους παθοφυσιολογικούς μηχανισμούς που κρύβονται πίσω από τον εξεσημασμένο θρομβωτικό κίνδυνο όταν ΚΑ και ΤΣΝΑ συνυπάρχουν, να παρουσιάσει τα τρέχοντα δεδομένα γύρω από την από του στόματος αντιπηκτική αγωγή, τις νέες προοπτικές στην αντιπηκτική αγωγή, αλλά και να εξετάσει την εφαρμογή εναλλακτικών θεραπευτικών προσεγγίσεων για αυτήν την ομάδα ασθενών.

Μεθοδολογία: Πραγματοποιήθηκε ηλεκτρονική αναζήτηση και προσεκτική ανασκόπηση της υπάρχουσας βιβλιογραφίας μέσω των πλατφορμών PubMed, Science Direct, και Google Scholar.

Αποτελέσματα: Λαμβάνοντας υπόψιν τη χρόνια φλεγμονώδης φύση της ΤΣΝΑ, υποτίθεται ότι η καρδία δεν μπορεί να προκαλέσει περαιτέρω βλάβη στους νεφρούς, όταν ΤΣΝΑ και ΚΑ συνυπάρχουν. Επομένως οι παθοφυσιολογικοί μηχανισμοί που συμβάλλουν στον αθροιστικό θρομβωτικό κίνδυνο, περιορίζονται στη μία κατεύθυνση της αμφίδρομης αυτής σχέσης, από τους νεφρούς στην καρδιά. Οι μηχανισμοί αυτοί, συγκλίνουν κυρίως στην νευροορμονική ενεργοποίηση που οδηγεί στην αναδιαμόρφωση της καρδιάς και στην επακόλουθη ανάπτυξη ΚΜ ή σχετιζόμενου με αυτήν εγκεφαλικού

επεισοδίου ή συστημικής εμβολής. Άλλοι μηχανισμοί, επιδρούν στην τριάδα του Virchow, αυξάνοντας τον κίνδυνο ΦΘΕΝ. Οι ανταγωνιστές της βιταμίνης Κ, μέχρι προσφάτως, αποτελούσαν την προτιμώμενη αντιπηκτική αγωγή για τους ασθενείς με ΤΣΝΑ, παρά την έλλειψη δεδομένων που να αφορούν την αποτελεσματικότητα και ασφάλεια. Πρόσφατες μελέτες υποστηρίζουν τα νεότερα από του στόματος αντιπηκτικά, ενώ αναδυόμενες προοπτικές εξετάζουν τον παράγοντα XI, ως πιθανή θεραπεία-στόχο. Εναλλακτικές προσεγγίσεις, όπως η σύγκλειση του αριστερού ωτίου αποτελεί επιλογή για τους ασθενείς με ΤΣΝΑ, αν και υπάρχουν αντικρουόμενα δεδομένα για εκείνους με συνύπαρξη ΤΣΝΑ και ΚΑ.

Συμπέρασμα: Η διαχείριση των θρομβομβολικών συμβάντων σε ασθενείς με ταυτόχρονη ΚΑ και ΤΣΝΑ, απαιτεί μια διεπιστημονική προσέγγιση. Εμπεριστατωμένες μελέτες είναι αναγκαίες, δίνοντας τη δυνατότητα στους επαγγελματίες υγείας να υποψιάζονται, να αναγνωρίζουν και να διαχειρίζονται αποτελεσματικά τέτοια συμβάντα, σε αυτή την περίπλοκη ομάδα ασθενών.

Λέξεις κλειδιά: καρδιακή ανεπάρκεια, τελικού σταδίου νεφρική ανεπάρκεια, από του στόματος αντιπηκτική αγωγή, αναστολείς παράγοντα XI, σύγκλειση αριστερού ωτίου

“Oral anticoagulation therapy in heart failure patients with end-stage kidney disease”

Abstract

Background: Heart failure (HF) and end-stage kidney disease (ESKD) are distinct pathologies, commonly coexisting, due to the bidirectional relationship between heart and kidney. Current literature extensively discusses the individual thrombotic risks associated with each condition, especially focusing on atrial fibrillation (AF) or AF-related stroke and systemic embolism (SSE) and venous thromboembolism (VTE). However, there is scarcity of data concerning the potential cumulative thrombotic risk when both conditions coincide.

Purpose: Our study seeks to elucidate the fundamental pathophysiology behind the heightened thrombotic risk in the presence of both HF and ESKD. Additionally, it aims to present the current evidence regarding oral anticoagulant agents, explore new perspectives, and discuss alternative anticoagulant approaches for this special population.

Methods: An electronic search and critical review of existing literature were conducted through PubMed, Science Direct, and Google Scholar platforms.

Results: Considering the chronic inflammatory nature of ESKD, it is hypothesized that the heart cannot induce further damage to the kidneys, when HF and ESKD coexist. Therefore, the pathophysiological mechanisms contributing to this cumulative thrombotic risk are primarily unidirectional, from the kidneys to the heart. These mechanisms predominantly converge on neurohormonal activation, leading to subsequent cardiac remodelling and the development of AF or AF-related SSE, while others influence Virchow’s triad, increasing VTE risk. Vitamin K antagonists has been the preferred anticoagulant for ESKD patients, despite the limited evidence regarding its efficacy and safety. Recent trials support direct oral anticoagulation therapy, while emerging perspectives explore the factor XI as a potential target therapy. Alternative approaches,

like left atrial appendage occlusion may be a viable option for ESKD patients, though conflicting data exists for those with concurrent HF and ESKD.

Conclusion: Managing thromboembolic events in individuals with HF and ESKD demands a multidisciplinary approach. Comprehensive studies are crucial, empowering healthcare practitioners to promptly suspect, recognize and effectively manage of such events in this complex population.

Keywords: heart failure, end-stage kidney disease, oral anticoagulation therapy, factor XI inhibitors, left atrial appendage occlusion

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Introduction

Heart Failure (HF) patients present an elevated risk of stroke and systemic embolism (SSE), along with venous thromboembolic events (VTE), with more substantial evidence available in patients with HF with reduced ejection fraction (HFrEF), and to a lesser extent for those with HF with preserved ejection fraction HF (HFpEF). The primary factor contributing to the heightened risk of SSE, is the presence of atrial fibrillation (AF), whether valvular or non-valvular, concerning both HF subtypes. Less commonly, the formation of left ventricle thrombi (LVT), predominantly observed in patients with HFrEF can also serve as a risk factor. Anticoagulation therapy is crucial in managing these conditions to prevent embolic events. Even in the absence of AF or LVT, patients with HF, especially those with HFrEF and sinus rhythm has been corelated with an increased risk of stroke (1). However, current European and American guidelines do not recommend anticoagulation nor antiplatelet therapy, for this specific condition, due to insufficient evidence (2, 3).

In HF patients, the occurrence of frequent and prolonged hospitalizations due to heart failure decompensation, significantly raises the risk of VTE, including deep vein thrombosis (DVT) and pulmonary embolism (PE). This increased risk is mainly attributed to immobility and the bedridden state experienced during hospitalization (4). HF patients, overall, are particularly susceptible to thrombotic events, requiring the use of anticoagulation therapy in order to mitigate the thrombotic risk (5).

The existence of Chronic Kidney Disease (CKD) or End-stage Kidney Disease (ESKD) has been strongly linked with an increased incidence of AF (6). Reduced estimated glomerular filtration rate (eGFR) and an elevated urine albumin-to-creatinine ratio (ACR) have shown a significant association with a higher risk of developing AF and subsequent SSE (7, 8). Consequently, AF frequently coexists with CKD, necessitating the need for anticoagulation therapy (9).

Patients with CKD, particularly ESKD, face an increased risk of VTE too. Notably, as the eGFR decreases, the risk of thrombosis escalates. (10) Notably, the incidence of DVT and PE was significantly higher in patients with ESKD, compared to those without ESKD (11). In fact, among ESKD patients, there is a greater risk of PE in those receiving haemodialysis (HD) compared to those undergoing peritoneal dialysis (PD) (12). Selecting the appropriate anticoagulant agent for these patients requires careful consideration because of many of these drugs being eliminated through the kidneys. This could result in potential drug toxicity if not adjusted properly. Additionally, beyond the concern for thromboembolic events, the bleeding risk is significantly higher in CKD patients, especially those with ESKD, further complicating the delicate balance that needs to be achieved.

In clinical practice, healthcare providers often encounter patients with concurrent HF and ESKD or with the complex bidirectional etiological relationship between heart and kidney dysfunction, called as cardiorenal syndrome (CRS). As we discussed earlier, both HF and ESKD are conditions that are associated with an independently elevated risk of thrombotic events, specifically, SSE or VTE. The coexistence of these conditions can create a synergistic effect, further amplifying the thrombotic risk. Finally, the interplay between HF and ESKD, presents challenges and requires careful management. Anticoagulation therapy, when deemed necessary, should be tailored to the patient's risk profile and medical history.

In this review, our objective is to elucidate the underlying pathophysiology, contributing to the heightened thrombotic risk, in the context of coexisting HF and ESKD syndromes, as well as the corresponding anticoagulation treatment. Particularly, through subtopics we outline (i) the underlying pathophysiology of thrombotic risk in patients with HF and ESKD (ii) the advantages and disadvantages of currently available oral anticoagulation (OAC) therapy (iii) the recommendations derived from the latest international guidelines, as well as the current evidence regarding applicability of OACs for these patients (iv) new perspectives in anticoagulation therapy, examining the factor XI as a potential target therapy, and finally (v) alternative anticoagulant approaches, focusing on the left atrial appendage occlusion (LAAO).

Definitions

HF is a clinical syndrome with symptoms and/or signs caused by a structural and/or functional cardiac disorder that impairs the heart's ability to fill with or eject blood. From a hemodynamic perspective, it is a condition in which the heart is unable to pump blood to meet the body's demands adequately or can do so only by increasing filling pressures. According to the current guidelines, HF is classified into distinct groups based on the measurement of left ventricular ejection fraction (LVEF):

- HFrEF is defined as a LVEF≤40%, accompanied by current or prior symptoms and/or signs of HF.
- HF with mildly reduced ejection fraction (HFmrEF) is defined as a LVEF between 41% and 49%, accompanied by current or prior symptoms and/or signs of HF.
- HFpEF is defined as a LVEF≥50%, accompanied by current or prior symptoms and/or signs of HF. The presence of objective evidence of structural and/or functional cardiac abnormalities and/or raised natriuretic peptides (NPs) constitutes a necessary condition (13, 14).

The guidelines established by the Kidney Disease Improving Global Outcomes (KDIGO) foundation outline the definition of CKD based on kidney damage markers, with a specific focus on assessing proteinuria and eGFR. The presence of both factors (eGFR <60 mL/min and ACR >30 mg/g) along with abnormalities of kidney structure or function lasting for more than three months defines CKD. ESKD or kidney failure is defined as a eGFR of less than 15 mL/min. Diabetic nephropathy ranks as the most prevalent cause of ESKD, followed closely by hypertension. Other contributing factors encompass glomerulonephritis, cystic kidney disease, chronic obstruction, and recurrent kidney infections. The available renal replacement therapy (RRT) options for ESKD patients are HD, PD, and renal transplantation (RT). Nevertheless, for individuals with a grim prognosis, conservative treatment may be considered as an alternative approach. (15).

CRS describes a situation where abnormalities in either the heart or the kidneys exacerbate the dysfunction of the other organ, establishing a vicious cycle. Based on the

Acute Dialysis Quality Initiative (ADQI) consensus in 2008, CRS can be classified into five types based on, the primary organ which drives the disease crosstalk (cardiorenal: CRS 1 and 2, or renocardiac: CRS 3 and 4), the disease onset (acute: CRS 1 and 3, or chronic: CRS 2 and 4) and the presence of systemic disease (CRS 5) (16). There is a possibility to transition between different cardiorenal syndrome types, which magnifies the complexity of the syndrome (17). It is noteworthy to mention that the development of CRS can be influenced by both HFrEF and HFpEF, along with all stages of CKD (18, 19). Ronco et al., suggest that the association between HF and ESKD could be categorized into CRS type 4. This is because ESKD is considered a chronic inflammatory condition, where the effect of cardiac dysfunction on the kidneys does not need to be taken into consideration, unlike in non-dialysis-dependent CKD (20).

Epidemiology

Individuals dealing with HF, particularly those with HFpEF exhibit a greater number of comorbid conditions. These comorbidities are strongly associated with more frequent and prolonged hospitalizations resulting in increased healthcare expenditures. They also contribute to adverse outcomes and higher mortality rates (21). Chamberlain et al. support that, the majority of HF patients present at least two additional chronic conditions (22) with CKD, and especially ESKD being notable among them. In a large chronic HF population of 47 716 patients sourced from the Swedish Heart Failure Registry, it was observed that 51% of these patients had eGFR <60 mL/min/1.73 m^2 and 11% had eGFR <30 mL/min/1.73 m^2, of which 2% was classified as ESKD with an eGFR <15 mL/min/1.73 m^2 (23). However, in acute decompensated HF cases, data retrieved from ADHERE registry suggests that the percentage of patients with ESKD is higher (24). Damman et al., in their extensive meta-analysis comprising 57 studies and a total of 1,076,104 patients, provide evidence in both acute and chronic HF settings. Their study revealed that CKD was present in 32% of cases and was associated with twofold increase in all-cause mortality (25). It is important to highlight that the eGFR values in the studies mentioned above, were calculated using the Modification of Diet in Renal Disease

(MDRD) equation. McAlister et al. demonstrated that the use of Chronic Kidney Disease - Epidemiology Collaboration Group (CKD-EPI) equation instead of the MDRD, results in higher estimations of renal impairment in HF patients and provides a more precise classification of mortality risk (26). Although, ESKD and more generally CKD, undeniably represent common comorbidities in HF patients, it is equally important to consider the converse scenario which is also prevalent.

Cardiovascular issues account for a significant 48% of all causes of death among ESKD patients. Approximately 40% of ESKD patients, are affected by ischemic coronary disease, while a similar proportion experience chronic HF (27). The prevalence of all HF types (HFrEF, HFpEF or unspecified type) was higher in individuals with CKD compared to those without CKD. Notably, this prevalence increased as the severity of CKD stage advanced. Approximately 44% of individuals with ESKD were found to have HF, with 10% having HFpEF, 13% having HFrEF and 21% having an unspecified type (28). Numerous observational studies have conducted comparing HD and PD settings. A recent retrospective propensity score-matched study showed that among 65,899 patients, HD was linked to elevated incidence rates of HF (HR:1.45, 95% CI 1.23–1.7) compared to PD (29). In ESKD patients with established HF, a systematic review and meta-analysis showed that PD increased the LVEF, New York Heart Association (NYHA) functional class and reduced the frequency and length of stay of HF hospitalizations (30). However, there are studies revealing that PD is associated with a notably higher risk of cardiovascular and overall mortality compared to HD (31, 32). In conclusion, a study using data from the West of Scotland renal database disclosed that the cumulative incidences of de novo congestive HF were 3.8% (95% CI 2.9–5.1), 5.2% (95% CI 4.1–6.7), and 7.1% (95% CI 5.6–8.9) at 1, 3, and 5 years, respectively, following RT. Congestive HF stands as a common post-RT complication and is associated with an increased risk of death and graft loss (33).

HF and CKD-ESKD can reciprocally influence each other, while often coexisting as they share a bidirectional relationship (34). Considering the already established risks for AF and thromboembolic events such as AF-related SSE and VTE, which characterized the HF and ESKD patients separately, the cumulative thrombotic risk expected to be heightened when both conditions are present together.

Pathophysiology of thrombotic risk in HF patients with ESKD

Frequently, there is an extensive overlap between HF and ESKD. This connection is not solely attributed to their shared risk factors such as advanced age, hypertension, and diabetes. It is also stems from the increased frequency of coronary artery disease (CAD) and non-ischaemic abnormalities affecting the structure and function cardiac chambers, as CKD progresses (35). The presence of these both conditions, predisposes to an elevated risk for thrombotic events, the management of which requires anticoagulation therapy. However, given that ESKD is a chronic "permanent" condition, where the cardiac dysfunction does not induce further CKD progression (20), our attention regarding pathophysiology, will be directed to the unidirectional aspect of this relationship, specifically from kidneys to the heart. The underlying involved pathophysiologic mechanisms could be generally divided into three categories: (a) related to afterload, (b) related to preload, (c) intrinsic factors not directly related to afterload or preload (36-38).

(a) Pathophysiological mechanisms related to afterload

- Patients with advanced CKD and ESKD exhibit a disturbance in mineral and bone metabolism known as CKD–mineral and bone disorder (CKD-MBD). This disorder arises from an imbalance in the interaction among several factors, including calcium, parathyroid hormone (PTH), vitamin D, and fibroblast growth factor 23 (FGF23), triggered by an excessive phosphate load. Consequently, vascular calcification is accelerated across various cardiovascular sites (vessels and valves), leading to a significant increase in afterload. Microcalcification within the tunica intima of blood vessels could enhanced plaque instability and potentially SSE, while it could promote local stress and inflammation in aortic valve. The macrocalcification might diminish plaque vulnerability, but its presence in the tunica media can result in increased vessel stiffness. It could be associated with aortic valve stenosis too (39). The manifestation of vessel

stiffness, notably the aortic “calcification” which often observed in CKD patients (37), leads to reduced compliance. This contributes to concentric left ventricular hypertrophy (LVH), atrial enlargement and diastolic dysfunction, which, in turn, promote the development of AF. LVH is detected in up to 90% of patients with ESKD who are undergoing HD (36, 40). This condition can become more complicated in the context of hypertension, which increase systemic arterial resistance and exacerbate pressure overload (36).

(b) *Pathophysiological mechanisms related to preload.*

- In patients with ESKD undergoing maintenance dialysis, an augmented preload occurs due to intravascular volume expansion, which is a consequence of increased intake of sodium and water. Also, the reduced eGFR contributes to the renin-angiotensin-aldosterone system (RAAS) activation, resulting in sodium and water retention in these patients (38). Hypervolemia and increased preload are associated with myocardial cell stretching and lengthening, resulting in eccentric LVH (rather than the concentric LVH which characterizes pure pressure overload) (37), which can equally increase the susceptibility for AF and eventual SSE.

- The pathophysiological mechanism of increased central venous pressure (CVP) in cases of acute decompensated heart failure (ADHF) is well-established and widely recognized (27). However, it is important to note that ESKD and subsequent volume overload, even a chronic condition, may contribute to an increase in CVP and right atrial pressure (RAP) too, indicators that reflect an augmented right ventricular preload. In a post hoc analysis of the ESCAPE trial, RAP was the only hemodynamic parameter associated with baseline renal dysfunction (41). The substantial increase in both CVP and intra-abdominal pressure (IAP) in these patients also triggers a counteractive response, leading to renal venous congestion and a decrease in filtration pressure, further exacerbating renal function (42). Consequently, this condition triggers an excessive activation of RAAS and subsequent cardiac remodeling, as mentioned above, with the risk of developing AF.

- Anaemia assumes a critical role in the pathophysiological processes of both CKD and HF. The prevalence of anaemia escalates as CKD and HF deteriorate. Silverberg et al. coined the term “cardiorenal–anaemia syndrome” to describe the interplay between anaemia, CKD, and HF (43).

  The primary factors contributing to anaemia include: (i) insufficient production of erythropoietin (EPO), (ii) iron deficiency, and (iii) chronic conditions associated with endogenous EPO-resistance.

  (i) EPO deficiency in CKD patients is significant, especially those with ESKD. As renal function declines, the mechanism of EPO production in response to hypoxia becomes compromised. This deficiency results in inadequate oxygen supply and tissue hypoxia, leading to peripheral vasodilation, reduced systemic vascular resistance and therefore activation of SNS and RAAS. The induced salt and water retention and hypervolemia, contribute to lower levels of haemoglobin (secondary anaemia) due to haemodilution (44). The concomitant use of angiotensin converting enzyme (ACE) inhibitors by HF patients, may cause erythropoiesis suppression. However, the impact of ACE inhibition on haematocrit is complicated and existing provide contradictory information.

  (ii) Iron deficiency may stem from various sources such as blood retention during dialysis in extracorporeal circuits, occult gastrointestinal bleeding, or malignancies.

  (iii) Resistance to both endogenous and exogenous EPO could be attributed to various mechanisms. The coexistence of HF and CKD establishes a chronic low-grade inflammatory environment. In this setting, proinflammatory cytokines trigger EPO resistance both directly, by counteracting EPO through erythroid progenitor cells inhibition and indirectly, by interfering with iron metabolism, with hepcidin being a central player. Hepcidin is recognized as the principal regulator of iron metabolism. Its primary mechanism involves the control of iron

release into plasma transferrin by downregulating ferroportin, the iron efflux channel in macrophages and enterocytes. Additionally, hepcidin is thought to negatively regulate the expression of the apical divalent metal transporter 1 (DMT1) in enterocytes. Therefore, hepcidin synthesis inhibits iron absorption in the small intestine and leads to the sequestraton of iron in macrophages. The presence of an inflammatory condition leads to upregulation of hepcidin, resulting in a subsequent reduction of iron concentration in the circulation. Inflammation might also impede the interaction between EPO and its receptor, as well as the intracellular EPO signalling routes. Furthermore, neocytolysis (selective haemolysis of young circulating red blood cells) could have a role (45).

Individuals with EPO-resistant anaemia present a particularly high risk of CVD. Prolonged anaemia results in LVH and myocardial cell death due to ischemia and necrosis. This process can culminate myocardial fibrosis, triggering arrhythmic events which requiring anticoagulation therapy (46). Nevertheless, caution is emphasized because the risk of CVD can be elevated not just by anaemia alone, but also by the overtreatment using erythropoiesis-stimulating agents intended to raise haemoglobin levels to ≥13 g/dl. Additionally, studies indicate that patients who were administered darbepoetin alfa had an increased likelihood of thrombotic events (27, 47).

- HD using arteriovenous fistulas (AVF) is preferred over vascular catheters due to enhanced dialysis quality and lower infection rates. However, the creation of a shunt between a high-pressure arterial and a low-resistance venous system results in high cardiac output heart failure (HOHF) (48), attributed to the shunt itself, increased venous return (preload), activation of sympathetic nervous system (SNS), alterations in neurohormonal activity (38). Prolonged increased preload leads to LVH and subsequent cardiac remodelling of left and right ventricles. Hyperkinetic pulmonary hypertension could be also a complication because of a high-flow AVF (accompanied by increased end-diastolic right ventricular pressure but significant decreased pulmonary vascular resistance) (49). ESKD patients undergoing haemodialysis through AVF, present high blood flow, which

impacts to the vascular endothelial cells (ECs). ECs cover the inner surface of blood vessels and are constantly (27) exposed to shear stress due to the frictional force created by the blood flow. Endothelial damage caused by high blood flow, also known as shear stress-induced endothelial dysfunction, leads to exposure of underlying layers of the blood vessel, promoting platelet activation and clot formation, following Virchow's triad. As a result, this condition associated with increased risk for both arterial and venous thrombosis (50).

(c) *Intrinsic factors not directly related to afterload or preload.*

- Advanced CKD and ESKD are associated with SNS and RAAS activation, in response to fluctuations in blood flow and renal perfusion. This activation results in increased sodium and water reabsorption, vasoconstriction and heightened oxidative stress. These factors collectively, contributes to CRS type 4, which is characterized by increased left ventricular mass, LVH, diastolic dysfunction, decreased coronary perfusion, apoptosis and fibrosis and ultimately leading to a decreased cardiac function (51, 52). These features constitute cardiac remodelling, inducing structural and electrophysiological alterations in the atria. This process leads to the development of an arrhythmogenic substrate and subsequent AF and potential SSE. It is important to highlight that the ESKD patients exhibit abnormal left atrium (LA) strain. LA strain (particularly reservoir and conduit strain) emerges as a significant predictor for cardiovascular outcomes (53). In fact, RAAS activation could also be associated with the development of VTE, as evidenced by the relationship between RAS inhibitors and a potential reduction in VTE risk (54). Hence, these patients frequently require anticoagulation therapy, in order to eliminate the thrombotic risk.

- Patients with ESKD are usually in a state of chronic inflammation, a condition driven by the upregulation of proinflammatory cytokines. This inflammatory state may be stimulated by RAAS activation, especially by angiotensin II (ATII) action. ATII enhances the production of endothelin-1 (ET-1), which is a powerful vasoconstrictor, proinflammatory, and profibrotic peptide. ET-1 induces the activation of transforming growth factor-β (TGF-β) and transcription nuclear factor-κB (NF-κB), sustaining the inflammatory response (44). The release of ET-

1 and TGF-β from the cardiac fibroblasts results in LVH (46), while elevated plasma levels of interleukin-6 (IL-6) and C-reactive protein (CRP) correlate with LVH and cardiac remodelling in CKD patients (55). IL-6 found to be elevated in patients with VTE too (56). The persistent inflammation leads to malnutrition and hypalbuminaemia, which, in turn, results in vascular endothelial dysfunction and calcification, along with acceleration of atherogenesis. The cluster of these pathophysiological conditions is referred to as malnutrition-inflammation-atherosclerosis (MIA) syndrome and represents a significant risk factor for CVD (57, 58).

- Uremic toxins, which accumulated due to impaired renal excretion in ESKD patients, have been identified as significant contributors to the development of cardiac remodelling (44). Protein-bound uremic toxins (PBUTs) increase oxidative stress in kidneys and heart, resulting in cardiorenal fibrosis. The development of myocardial interstitial fibrosis presents even in the early stages of CKD, prompting the term CKD-associated cardiomyopathy instead of uremic cardiomyopathy (59). Myocardial fibrosis, also provides a structural basis promoting atrial re-entrant excitation and subsequent atrial arrhythmias, necessitates the use of anticoagulant therapy (60).

The aforementioned pathophysiological mechanisms provide a detailed insight into the interaction between the heart and the kidneys. Most of them converge to neurohormonal activation, involving the SNS and RAAS. This activation contributes to cardiac remodelling, potentially leading to the development of AF or even AF-related SSE. While others, can affect the Virchow's triad, with subsequent development of VTE. In conclusion, HF and ESKD are distinct entities, each associated with an augmented individual thrombotic risk. When these two conditions occur together, they can mutually exacerbate each other, leading to a cascade of physiological changes that further increase the probability of experiencing SSE or VTE. Consequently, the need for anticoagulation therapy becomes necessary.

Advantages and Disadvantages of OAC Therapy

Both HF and ESKD pose significant challenges in their management. The intersection of these two syndromes creates a complex clinical scenario, that demands comprehensive assessment and careful consideration regarding the initiation of anticoagulant therapy, when it is indicated, as well as the selection of the appropriate agent. The currently available OAC therapy encompasses Vitamin K Antagonists (VKAs) and non-vitamin K direct oral anticoagulants (DOACs). Understanding advantages and disadvantages linked with these two categories is essential, as it plays a vital role in selecting the suitable anticoagulant agent for this complex group of patients.

VKAs

VKAs compose a class of medication that have been conventionally employed as OACs since the 1950s, with warfarin being the foremost representative. In the past, warfarin has been the anticoagulant of choice for individuals with CKD, particularly those with ESKD (CrCl < 15 mL/min), due to its distinctive pharmacokinetic and pharmacodynamic profile. The mechanism of action involves inhibiting vitamin K epoxide reductase, a crucial enzyme in reactivating vitamin K1 and its primarily eliminated through the liver, with negligible renal clearance (61). It is highly bound to proteins, remaining insusceptible to filtration, which further contributes to its effectiveness in HD settings. Consequently, warfarin could be a suitable option for patients with ESKD (60).

Controversially, VKAs present certain limitations that impact both their efficacy and safety. Primarily, close monitoring with the international normalized ratio (INR) is required due to their narrow therapeutic window. Determining the appropriate VKA dosage and maintaining the time in therapeutic range (TTR) becomes challenging in patients with advanced CKD and ESKD, leading to unpredictable response. Inadequate anticoagulation levels result in suboptimal anticoagulation, raising the risk for both thromboembolic and bleeding complications (62). Moreover, there is a potential risk of developing vascular calcification, culminating in calciphylaxis and microcirculatory

injuries, due to the effects of warfarin. This is attributed to the inhibition of matrix Gla protein, a calcification inhibitor dependent on vitamin K. Notably, warfarin can also induce tubular necrosis, hastening the progression of CKD. This process occurs as a consequence of glomerular filtration barrier disruption, resulting in bleeding within Bowman's space. The subsequent accumulation of erythrocytes forms casts in the tubules, ultimately leading to their obstruction, ischemia, and necrosis (63, 64) Lastly, warfarin administration presents several drug-drug (e.g. NSAIDs) and drug-food (e.g. leafy greens) interactions. Collectively, these factors render the management of warfarin usage difficult.

DOACs

A new chapter in OACs commenced in 2008 with the introduction of DOACs, that have gained approval by both European and American medical agencies. Since then, DOACs have constituted an appealing alternative therapeutic option to conventional VKAs, for the management of thrombotic events. DOACs offer several advantages compared to VKAs, including more immediate onset, and offset effects, reduced need for frequent monitoring due to a wider therapeutic window, resulting in a more predictable dose-response. Additionally, they present fewer interactions with other drugs and no dietary precautions (65). It is noteworthy to highlight that DOACs have been associated with anti-inflammatory effects, demonstrated by a reduction in concentration of pro-inflammatory markers in plasma (including adhesion molecules, cytokines, chemokines, tissue factor and free radicals). This aspect should be taken into consideration, particularly in instances where HF and ESKD coexist. Furthermore, DOACs provide vascular protection, primarily through the attenuation of inflammation and secondly by promoting vasorelaxation. The latter one, is facilitated by DOACs-induced augmented endothelial nitric oxide synthase (eNOS) activity. The heightened release of NO reduces platelet activation and aggregation, that could also play a role in the effectiveness of DOACs in addressing thrombotic events (62).

Despite the evident therapeutic benefits of DOACs, it's important to note that each of them presents differing levels of clearance through the kidneys and liver. Dabigatran exhibits the highest level of renal elimination, constituting 80% of its clearance, whereas edoxaban, rivaroxaban, and apixaban follow with 50%, 36%, and 27% respective reliance on renal excretion. (66, 67). In terms of hepatic metabolism, apixaban demonstrates the highest dependency, with approximately 75% of its elimination process taking place in the liver. Following this, rivaroxaban, edoxaban, and dabigatran present hepatic clearance percentages of 65%, 50%, and 20% respectively (68). Considering their distinct pharmacokinetics, determining the appropriate DOAC could be intricate, in cases involving renal or/and hepatic impairment. In addition, extreme body weight could complicate the decision-making process for selecting the suitable agent, as fixed drug doses might result in reduced drug exposures in obese patients and increased drug exposures in underweight patients due to alterations in drug pharmacokinetics (69, 70). Another limitation concerning DOACs utilization is the availability of licensed reversal agents, which is lacking in several countries (71). Lastly, the hight cost of DOACs in contrast with VKAs, could potentially limiting their accessibility (60).

Table 1: Prons and Cons of currently available OACs (VKAs and DOACs)

	Prons	**Cons**
VKAs	-Wide clinical experience -Hepatic metabolism with minimal renal clearance -Highly bound to proteins – insusceptible to HD	-Slow onset and offset -Narrow therapeutic window -Unpredictable dose-response -Frequent monitoring -Multiple drug-drug and drug-food interactions -Vascular calcification - calciphylaxis -Tubular necrosis
DOACs	-Rapid onset and offset -Wide therapeutic window -Predictable dose-response -No dietary precautions -Anti-inflammatory effect -Vascular protection	-Variable degree of renal and hepatic metabolism of each DOAC -Extreme body weight caution -Limited availability of licensed reversal agents -High cost

International Guidelines and Current Evidence regarding OAC Therapy

Individuals with HF and ESKD are particularly vulnerable to thrombotic complications, including AF-related SSE and VTE, due to a multitude of intertwined factors. The management of these conditions, as it is known, need anticoagulation therapy. DOACs have emerged as the primary therapeutic option for AF-related SSE prevention and for VTE treatment and prevention, displacing the traditional anticoagulation therapies like VKAs, in patients with normal renal function or renal impairment up to CrCl > 15 ml/min

(64). As previously mentioned, warfarin has conventionally been the anticoagulant of choice for ESKD patients, whether undergoing RRT or not, despite the limited supporting evidence regarding its effectiveness and safety. Considering the prevailing concern of "warfarin-related nephropathy", which was firstly introduced by Brodsky et al. in 2009 (72), the pursuit of more suitable alternatives was initiated.

DOACs could represent a feasible therapeutic option, even in patients with ESKD. However, it is crucial to consider their pharmacokinetic properties, particularly within this distinctive subset of patients, in order to make the right decision regarding the selection of the most suitable agent and its optimal dosage (73). For example, dabigatran at a dosage of 110 or 150 mg twice daily, demonstrated a 1.5 to 3.3 times higher exposure, as opposed to the dosage of 75mg or 110mg once daily, which exhibited similar exposure levels to those measured in patients who participated in the RE-LY study (74). Although, these findings imply that the reduced-dose regimen could be more appropriate for dialysis-patients, further data needed to support this perspective. Additionally, a reduced-dose of 10 mg once daily of rivaroxaban in dialysis-patients, was linked with drug exposure similar to that of 20 mg once daily in patients with normal renal function (75). In a study conducted by Wang et al., apixaban presented pharmacokinetic properties that render the standard-dose of 5 mg twice daily tolerable for patients undergoing HD. Also, the study's findings revealed that its cumulative exposure in ESKD patients, approximates that observed that of healthy controls after a 4-hour HD session and the study's patients did not address serial dosing or drug accumulation (76). On the other hand, Mavrakanas et al. demonstrated that a standard-dose of apixaban, led to an unacceptable supratherapeutic drug levels over an 8-days period, resulting to the strong recommendation against using the standard-dose of apixaban in dialysis-patients (77).

It is should be noted that individuals with CrCl < 30 mL/min (78-83) (< 25 mL/min for apixaban) (84, 85) were not included in the pivotal trials, concerning anticoagulant management in AF-related SSE and VTE. Nevertheless, based on the above pharmacokinetic data, the Food and Drug Administration (FDA) granted approval for the standard-dosage of apixaban as a potential anticoagulation regimen for ESKD patients, or the reduced one for patients with body weight <60kg or age >80. The FDA has also approved for the reduced-dosage of rivaroxaban in this population. The European

Medicines Agency (EMA) however, did not approve any DOAC in ESKD patients due to the absence of evidence concerning efficacy and safety (86).

International Guidelines on OACs for HF-ESKD patients

Due to the absence of evidence concerning OAC therapy in ESKD patients with AF, the guidelines issued by prominent international societies do not provide recommendations supported by a strong level of evidence for this special population. The 2019 American College of Cardiology, the American Heart Association Task Force, and the Heart Rhythm Society (ACC/AHA/HRS), state that either warfarin (target INR of 2-3) or apixaban without dose restrictions may be used, noting the necessity for further research in order to establish a more robust level of evidence. Dabigatran, rivaroxaban, and edoxaban are not endorsed for dialysis-patients, based on these guidelines (87). The 2018 American College of Chest Physicians (CHEST) guidelines for AF management in ESKD patients, indicate a general avoidance of DOACs. Instead, a well-controlled VKA regimen with a TTR>65-70%, along with an individualized decision-making are recommended (88). Similar views are also reflected by the 2020 European Society of Cardiology (ESC) guidelines for AF management, since none of the DOACs have been approved in Europe. However, the more recent 2021 European Heart Rhythm Association (EHRA), assesses the potential off-label DOACs usage in this subgroup of patients, after highlighting the uncertain benefits and obtaining an informed consent from patients (89). The 2018 KDIGO Guidelines, examine the possibility of either reduced-dosage of apixaban (2.5 mg twice daily) or either rivaroxaban (at a dosage of 15mg once daily) in ESKD patients, awaiting further clinical safety data (90). Conversely, according to the 2020 Canadian Cardiovascular Society/Canadian Heart Rhythm Society (CCS/CHRS) guidelines, there are insufficient data to either support or reject the usage of any OAC in dialysis-patients with concurrent AF (91). Lastly, the guidelines, on a global scale, do not provide specific recommendations for VTE management in ESKD patients, with the most of data predominantly discourages the use of DOACs in this population.

Current Evidence on OACs for HF-ESKD patients with VTE

There are limited available data, concerning VTE management in patients with ESKD. Cheung et al. conducted a systematic review, comparing DOACs and warfarin for VTE treatment in dialysis-patients. The findings indicated that apixaban could be considered as a viable option, with a reduced maintenance dose, omitting the initial loading dose (92). Nevertheless, this review included studies involving patients with anticoagulation indications, extending beyond VTE (including AF), failing to report VTE risk factors (93-98). Moreover, a more contemporary observational study by Wetmore et al. revealed similar findings regarding apixaban. However, in this study, the majority of patients received the FDA-approved VTE treatment (10 mg twice daily for a week, followed by 5 mg twice daily), in contrast to the dosage proposed by Cheung et al (99) A multicenter retrospective cohort study, including 203 patients with CrCl < 25 ml/min, demonstrated that the reduced-dose of apixaban could be considered for VTE treatment, while the group administered the standard-dose of apixaban exhibited a notably elevated incidence of clinically relevant bleeding (100). The VERDICT trial, which was terminated early due to recruitment difficulties, aimed to further investigate the use of DOACs for VTE in CKD patients. However, this trial, specifically focused on patients with advanced nondialysis-dependent CKD (101). Currently, there is still limited information about the usage of DOACs for treating VTE in patients with a CrCl < 15 ml/min. Apixaban might be considered a potential option for those on dialysis, although the optimal dosing regimen remains uncertain.

Current Evidence on OACs for HF-ESKD patients with AF

After the FDA's approval of DOACs for preventing SSE in individuals with NVAF, a notable increase in the off-label prescription of both dabigatran and rivaroxaban was observed among dialysis-patients, despite the lack of data. Chan et al. found a higher

incidence of hospitalization or fatal outcomes attributed to bleeding with dabigatran and rivaroxaban compared to warfarin. This suggests that these two medications might not be entirely safe for individuals undergoing HD (102). In a retrospective cohort study, the comparison between apixaban and warfarin revealed the superiority of apixaban in ESKD patients regarding both efficacy and safety. A standard-dose of apixaban (5 mg twice daily), was associated with lower incidence of SSE and mortality risk, while both standard and reduced-dose (2.5 mg twice daily) demonstrated reduced risk of major bleeding (103). A more recent study did not find any difference in primary endpoints, between apixaban and rivaroxaban in ESKD patients with AF. In fact, rivaroxaban exhibited a superior safety profile, with a more substantial decrease in bleeding events compared to warfarin (104). In addition, a meta-analysis involving 71.877 ESKD patients on long-term dialysis and concurrent AF, indicated that the use of OACs (including warfarin, apixaban, rivaroxaban and dabigatran) did not exhibit a significant reduction in SSE, compared to no anticoagulation. Also, the standard-dose of apixaban was associated with a notably decreased mortality risk, in contrast to the reduced-dose of apixaban, warfarin or no anticoagulation, as well as with a lower bleeding risk as compared to warfarin, rivaroxaban, or dabigatran. Generally, the overall findings of this study, support the hypothesis that employing DOACs in ESKD patients on long-term dialysis with AF, necessitates validation through randomized control trials (RCTs) (105).

Encouraging information has emerged through recent RCTs, regarding the effectiveness and safety of DOACs in ESKD. In the recent the “Valkyrie study”, a total of 132 patients were allocated to three groups: (i) VKA with a target INR of 2-3, (ii) reduced-dose of rivaroxaban (10 mg once daily) and (iii) reduced-dose of rivaroxaban and VitK2 group. The study’s findings indicated that a reduced-dose of rivaroxaban was associated with a decreased occurrence of cardiovascular events and major bleeding complications, together with a clear increase in 5-year survival, compared with those received VKA in ESKD patients undergoing HD and concurrent AF (106, 107).

Another two RCTs, RENAL-AF (108) and AXADIA-AFNET 8 (109) compared apixaban versus VKA in individuals with AF and ESKD on HD. The first one was prematurely terminated due to funding constraints and enrolment difficulties. Consequently, the available statistical power was inadequate for establishing any definitive conclusions regarding the bleeding rates between the two groups. It is worth

mentioning that TTR achieved only in 44% of warfarin-treated patients, with a considerable proportion in the subtherapeutic range, leading to a potential bias favoring warfarin. Additionally, the occurrence of major or clinically relevant nonmajor bleeding among trial participants ranged from 22% to 26% over a median follow-up period of less than 12 months. This demonstrated the exceedingly elevated bleeding risk for ESKD patients undergoing HD and contrasts markedly with the relatively lower incidence of ischemic stroke, falling within the range of 1% to 3%. The attribution of bleeding events directly to anticoagulation remains uncertain due to the absence of an untreated control group in the trial (110). In the second trial, which was smaller in size but with an extended follow-up period of 24 months, no discernible variations in safety or efficacy outcomes were noted. (64, 111).

The ongoing SAFE-D and SACK trials may provide insights into the assessment of DOACs, particularly apixaban, as a suitable treatment option for individuals with both ESKD and AF. The SAFE-D trial focuses on patients with ESKD undergoing dialysis (HD or PD) who experiencing AF, comparing three arms: (i) apixaban (both 5 mg and 2.5 mg twice daily), (ii) warfarin, and (iii) without anticoagulant therapy, over a 26-week duration (112). The Swedish SACK trial involves the comparison of two arms: (i) apixaban 2.5 mg twice daily and (ii) no anticoagulation, in patients with AF and ESKD, who undergoing RRT, or those with eGFR<15 mL/min not on RRT (113). Lastly, two others ongoing RCTs, AVKDIAL (114), DANWARD (115) trials, examine the incidence of stroke and bleeding events in individuals with ESKD undergoing dialysis and concomitant AF, based on a two-arm comparison: (i) VKAs against (ii) no anticoagulation therapy (116).

The presence of ESKD in HF patients, complicates the selection of appropriate anticoagulation therapy, when deemed necessary, due to insufficient evidence for these patients. The currently available data suggests that apixaban and rivaroxaban could be considered with caution in ESKD patients with concomitant AF to prevent AF-related SSE. However, it seems that only apixaban is a viable option for treating VTE in this patient population. The upcoming trials anticipated to offer further insights into the role of OACs in AF management and establish the most effective drug therapy for ESKD patients. The medical community should also conduct a clinical trial to assess the

effectiveness and safety of DOACs in comparison to VKAs for treating and preventing VTE for this specific population.

Table 2: DOACs usage for VTE and AF-related SSE management in patients with ESKD disease, according to currently available data

	Apixaban	Rivaroxaban	Dabigatran	Edoxaban
VTE management				
AF-related SSE management				

New Perspectives in Anticoagulation Therapy for HF patients with ESKD

Most of the available evidence concerning prolonged anticoagulation in patients with both HF and ESKD has mainly concentrated on VKAs or DOACs usage. However, due to the challenge of maintaining a balance between thrombotic and bleeding risk, a recent surge of interest has emerged in investigating alternative targets within coagulation cascade as possible target for intervention. Factor XI (FXI) inhibition represents a potential approach for anticoagulation therapy, particularly attractive for patients presenting an augmented thrombotic risk, as well as an intrinsic predisposition to bleeding, like those with HF and ESKD.

FXI holds a crucial role in the process of thrombus growth and stabilization within the coagulation cascade but is dispensable for haemostasis. This intriguing phenomenon can be explained through two distinct mechanisms: (a) augmentation of clot formation and (b) inhibition of clot degradation. The first mechanisms involve FXI activation, which can be triggered either by FXIIa or by thrombin, via positive feedback amplification loop. Furthermore, FXI as an integral component of the intrinsic coagulation pathway, it

promotes thrombin generation via intrinsic tenase and prothrombinase. Consequently, thrombin induces an increased activation of thrombin activatable fibrinolysis inhibitor (TAFI), which effectively attenuating the degradation of fibrin clots (117).

According to a historical cohort study, FXI deficiency was linked with a reduced occurrence of SSE and VTE (118). Furthermore, a study on human genetic data indicated that individuals with a genetic predisposition, resulting in lower XI levels, experienced a reduced risk of SSE and VTE (119). Notably, FXI deficiency seems to be linked with a relatively mild tendency towards bleeding, setting it apart from FVIII (Haemophilia A) or FIX (Haemophilia B) deficiencies, which are often characterized by spontaneous bleeding in the muscles, joints and brain (120). Individuals with FXI deficiency, typically do not exhibit spontaneous bleeding, however, they might encounter bleeding incidents following trauma or surgical procedures, especially in tissues with heightened fibrinolysis activity (possibly due to TAFI suppression). These tissues encompass areas like the nasopharyngeal, gastrointestinal, or genitourinary tracts (117). Therefore, FXI inhibition is hypothesized to be essential in reducing the risk of thrombosis, with a little impact on haemostasis.

The anticoagulant strategies currently under investigation for inhibiting FXI include: (a) Antisense oligonucleotides (ASOs) that diminish the hepatic synthesis of FXI (e.g. BAY 2976217/IONIS-416858), (b) monoclonal antibodies that suppress FXIa generation and its activity (e.g. BAY- 1213790/Osocimab, MAA-868/Abelacimab), (c) small-molecule inhibitors that bind to FXIa catalytic domain and inhibit its activity (e.g. BAY 2433334/Asundexian and BMS-986177/Milvexian) (120). Small-molecule inhibitors have the potential for oral or parenteral administration and demonstrate renal clearance rates between 8-20%, Conversely, ASOs and monoclonal antibodies require parenteral administration, but they are not eliminated through the kidneys, potentially offering an extra advantage for ESKD patients undergoing haemodialysis (121).

Published clinical trials have focused on novel FXI-targeting anticoagulants for primary VTE prevention in patients undergoing elective knee arthroplasty, comparing them with both low-molecular-weight heparin (LMWH) (122-124) and DOACs (specifically apixaban (124). In addition, ongoing trials (Phase 2) are currently examining FXI inhibitors in ESKD patients. These prospective RCTs of FXI inhibitors, are centered

around ASOs (EMERALD trial (125) / RE-THINc ESKD trial (126)) and monoclonal antibodies (CONVERT trial (127)) aiming to establish their efficacy and safety in the prevention of thrombosis. However, it is worth mentioning that there is ambiguity regarding the inclusion or exclusion of AF-related SSE or VTE in these trials.

FXI inhibitors have the capacity to enhance safety outcomes in comparison to other oral anticoagulant agents. Therefore, there is a prospect to evaluate these innovative agents in patients with kidney failure undergoing dialysis. This evaluation extends beyond the prevention of AF-related SSE to a broader scope, encompassing the prevention of adverse cardiovascular events in a high-risk population.

Alternative Anticoagulant Approaches for HF patients with ESKD

Anticoagulant therapy becomes imperative, particularly when addressing situations with heightened thrombotic risk (such as AF) arising from the coexistence of HF and ESKD. However, CKD is characterized by a delicate equilibrium between thromboembolic and bleeding risk, which is increasingly disrupted as renal function declines. In this context, the selection of suitable anticoagulation therapy becomes intricate. Even the clinical guidelines of the main international scientific societies present conflicting recommendations on this topic. Consequently, managing these patients, especially those with ESKD, poses a challenging task for healthcare providers. In this treatment conundrum, there are three potential solutions, as for every complex problem: “accept it, leave it or change it”. So, there is the possibility to either embrace the bleeding risk and continue anticoagulation treatment (“accept it”) or discontinue it (“leave it”), while there exists also the alternative option of LAAO (“change it”). (128).

LAAO is primarily indicated for patients presenting AF, with an elevated risk of both thromboembolic and bleeding events, who cannot be considered for prolonged OACs usage or those for whom OACs are contraindicated at all, representing a potentially alternative to lifelong anticoagulation for these patients. Current ESC Guidelines, state

that percutaneous LAAO “may be considered” in these patients, with a Class IIb recommendation (129). According to the German multicenter study, based on the “LAARGE” registry, the implantation of LAAO device proved to be safe with minimal complications in patients with CKD. Notably, LAAO exhibited significant efficacy in preventing stroke across all stages of CKD (130). Current data regarding efficacy and safety of LAAO in ESKD patients on RRT is confined to only five small studies (131-135). All of them, demonstrated that LAAO, could be a non-pharmacological option for thromboembolic protection in dialysis-patients and concurrent AF, with minimal complications.

The primary drawback associated with LAAO is the potential formation of thrombi on the occlusion device. Notably, the risk of device related thrombi (DRT) appears to be higher in female patients and patients with advanced renal dysfunction (with CrCl <30 ml/min), Consequently, a more frequent post-interventional transoesophageal echocardiography (TOE) could be justified for early detection of DRT (136, 137). In clinical practice, various antithrombotic strategies have been implemented empirically to mitigate the occurrence of this concerning complication. The most common approach involves the aspirin usage, initially accompanied by clopidogrel and then as a standalone therapy (132, 136, 138).

It is noteworthy to mention that unexpected admissions for HF have been observed following a successful LAAO procedure. This could be potentially due to negative impact on left atrial reservoir function and LA compliance, leading to subsequent aggravation of pre-existing HF or the emergence of new-onset HF (139). Based on Nationwide Readmissions Database from 2016 to 2018, a recent study revealed that among 29.367 patients, the overall rate of 30-day readmission after LAAO was 9.2% with most common causes: gastrointestinal bleeding (18.5%) and heart failure (13.1%) (140). Therefore, a successful LAAO procedure, could potentially result in unexpected deterioration of HF and increased HF-related readmissions.

LAAO emerges as a promising interventional treatment option, for patients with ESKD experiencing AF. This approach effectively prevents thromboembolic events, without heightening the occurrence of severe bleeding events. Nevertheless, its implementation in individuals with concurrent HF and ESKD remains uncertain due to the possible

adverse effects on cardiac structure and function. RCTs are needed to assess the effectiveness of LAAO in high-risk population, where the safety margin between stroke prevention and bleeding risk is narrowed. Additionally, these trials are crucial for determining the appropriate antithrombotic therapy required to prevent DRT.

Conclusion

HF and ESKD constitute two frequent pathologies, which often coexist. The existing literature extensively refers to the distinct thromboembolic risks related to each of these prevalent conditions, specifically centered on the presence of AF or AF-related SSE and VTE. Nevertheless, there is lack of evidence regarding the cumulative risk, when HF and ESKD coexist, which is absent also under the term of "cardiorenal syndrome". Given that the ESKD represents a chronic inflammatory condition, it is speculated that HF cannot induce further damage to the kidneys. This relationship between HF and ESKD, could potentially be classified as CRS type 4. So, the pathophysiological mechanisms explaining the cumulative thrombotic risk, primarily limited to the unilateral aspect of this relationship, particularly from the kidneys to the heart. These mechanisms could be categorized into those related to afterload, preload, as well as intrinsic mechanisms that not associated with either afterload or preload. It is important to highlight that the majority of the pathophysiological mechanisms converge on neurohormonal activation (involving the SNS and RAAS). This activation contributes to cardiac remodelling, including structural and electrophysiological changes in the atria, potentially leading to the development of AF or AF-related SSE. Other mechanisms may influence Virchow's triad with subsequent development of VTE. Anticoagulation therapy is deemed necessary, in any of these cases.

The available OACs currently used in clinical practice include VKAs, with warfarin being the representative, and DOACs. Each healthcare provider should be aware of the advantages and disadvantages linked to these two categories, to effectively select the suitable anticoagulant for intricate cases, such as the scenario of concurrent HF and

ESKD. Traditionally, warfarin has been the favored choice of anticoagulant for patients with CKD, particularly in cases of ESKD, despite the limited supporting evidence regarding its effectiveness and safety. Taking into account the concern of "warfarin-related nephropathy" attention shifted to investigating the impact of DOACs in this population. However, even the guidelines issued by prominent international societies do not provide recommendations supported by a strong level of evidence and appear to be in disagreement with each other. According to recent and upcoming RCTs, the current evidence supports that apixaban and rivaroxaban could be considered with caution in ESKD patients for preventing AF-related SSE, while only apixaban seems to be a viable option for treating VTE.

Navigating the challenge of balancing thrombotic and bleeding risk within this specific patient subgroup, has led to a recent surge of interest in exploring alternative targets within the coagulation cascade for potential intervention. Inhibiting FXI stands as an attractive approach for anticoagulation therapy, potentially linked to improved safety outcomes compared with other OACs. Other anticoagulant approaches such as LAAO, offer a promising interventional option for ESKD patient with AF. This method effectively prevents thromboembolic events without elevating the risk of bleeding. Nevertheless, uncertainty surrounds its implementation in individuals with HF and ESKD, due to potential adverse effects on cardiac structure and function.

In conclusion, the presence of thromboembolic events in individuals with concurrent HF and ESKD, presents a multifaceted challenge that involves various medical specialties and necessitates a multidisciplinary approach. Therefore, an urgent need exists for dedicated research studies, focusing on the pathophysiological mechanisms contributing to the cumulative thrombotic risk, as well as the suitable anticoagulant therapies for these patients. Such studies could provide valuable insights, empowering healthcare practitioners to promptly suspect, identify and effectively manage thromboembolic events in this specific population.

Medical Abbreviations

ACC: American College of Cardiology

ACE: Angiotensin Converting Enzyme

ACR: Albumin-to-Creatinine Ratio

ADHF: Acute Decompensated Heart Failure

AF: Atrial Fibrillation

AHA: American Heart Association

ASOs: Antisense Oligonucleotides

ATII: Angiotensin II

AVF: Arteriovenous Fistula

CAD: Coronary Artery Disease

CCS: Canadian Cardiovascular Society

CHEST: American College of Chest Physicians

CHRS: Canadian Heart Rhythm Society

CI: Confidence Interval

CKD: Chronic Kidney Disease

CKD-EPI: Chronic Kidney Disease – Epidemiology Collaboration Group

CKD-MBD: Chronic Kidney Disease – Mineral and Bone Disorder

CRP: C-Reactive Protein

CRS: Cardiorenal Syndrome

CVP: Central Venous Pressure

DMT1: Divalent Metal Trransporter 1

DOACs: Direct Oral Anticoagulants

DRT: Device Related Thrombi

DVT: Deep Vein Thrombosis

eGFR: estimated Glomerular Filtration Rate

ECs: Endothelial Cells

EHRA: European Heart Rhythm Association

EMA: European Medicines Agency

eNOS: endothelial Nitric Oxide Synthase

EPO: Erythropoietin

ESC: European Society of Cardiology

ESKD: End-Stage Kidney Disease

ET-1: Endothelin-1

FDA: Food and Drug Administration

FGF23: Fibroblast Growth Factor 23

FXI: Factor XI

HD: Haemodialysis

HF: Heart Failure

HFmrEF: Heart Failure with mildly reduced Ejection Fraction

HFpEF: Heart Failure with preserved Ejection Fraction

HFrEF: Heart Failure with reduced Ejection Fraction

HOHF: High Cardiac Output Heart Failure

HRS: Heart Rhythm Society

IAP: Intra-Abdominal Pressure

IL-6: Interleukin-6

KDIGO: Kidney Disease Improving Global Outcomes

LA: Left Atrium

LAAO: Left Atrial Appendage Occlusion

LMWH: Low-Molecular-Weight Heparin

LVEF: Left Ventricular Ejection Fraction

LVH: Left Ventricular Hypertrophy

LVT: Left Ventricle Thrombi

MDRD: Modification of Diet in Renal Disease

MIA: Malnutrition-Inflammation-Atherosclerosis

NF-κB: Nuclear Factor-κB

NYHA: New York Heart Association

OAC: Oral Anticoagulation

PBUTs: Protein-Bound Uremic Toxins

PD: Peritoneal Dialysis

PE: Pulmonary Embolism

PTH: Parathyroid Hormone

RAAS: Renin-Angiotensin-Aldosterone System

RAP: Right Atrial Pressure

RCTs: Randomized Control Trials

SNS: Sympathetic Nervous System

SSE: Stroke and Systemic Embolism

TAFI: Thrombin Activatable Fibrinolysis Inhibitor

TGF-β: Transforming Growth Factor-β

TOE: Transoesophageal Echocardiography

TTR: Time in Therapeutic Range

VKAs: Vitamin K Antagonists

VTE: Venous Thromboembolic Events

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ΠΑΝΕΠΙΣΤΗΜΙΟ ΘΕΣΣΑΛΙΑΣ

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