Comments on "Nonvalvular atrial fibrillation in patients undergoing chronic haemodialysis. Should dialysis patients with atrial fibrillation receive oral anticoagulation?"

Comentarios a «Fibrilación auricular no valvular en pacientes en hemodiálisis crónica. ¿Debemos anticoagular?»

Dear Editor,

It was with interest that we read "Non-valvular atrial fibrillation in patients undergoing chronic haemodialysis. Should we anti-coagulate?",[1] and we found it engaging and up-to-date, but we want to make some observations.

Thrombotic risk assessment to indicate anti-coagulation in patients with atrial fibrillation (AFib) in the general population has been based on the CHA_2DS_2-VASc. However, data from the recent SCREAM study call the validity of this *score* into question across the spectrum of chronic kidney disease (CKD), proposing the use of the modified CHADS.[2] In dialysis patients, de Vriese et al. alternatively propose the dialysis risk score, which includes prior stroke or transient ischaemic attack, diabetes, age >75 years, and gastrointestinal bleeding,[3] which would drastically reduce the indication for anti-coagulation in these patients, although its validation is required. The authors comment on the poor predictive value of the bleeding risk of the *scores* used on the general population of hemodialysis, and mention the CHA_2DS_2-VASc.[1] This does not measure the risk of bleeding, nor is it analysed in the referenced study, which may lead to confusion.

Regarding treatment with coumarins or vitamin K antagonists (VKA), the authors mention the risk of vascular calcification and arterial stiffness,[1] which is correct, but it should be noted that they also increase the risk of peripheral vascular disease, valve calcification or calciphylaxis (already prevalent in this population), which calls into question their safety profile in dialysis.[4,5]

We agree with the authors that the time in therapeutic range (TTR) is low in patients with CKD,[1] and especially those on haemodialysis, as demonstrated by clinical trials (CT) (Renal-AF or Valkyrie), in which better control of this is assumed, as well as in numerous observational studies. A worse TTR is associated with a higher risk of stroke or death,[6] so nephrologists should be more involved and be aware of the TTR of our patients being treated with VKA so we can proactively suggest other therapeutic alternatives if this is unsatisfactory. Furthermore, an Italian group proposes that the variability of the international normalised ratio (INR) (high in this population) would be a better marker of mortality and risk of bleeding.[7] In fact, de Vriese et al. propose that anti-coagulation in patients with AFib on dialysis should be done with apixaban or rivaroxaban for this reason, among others.[3]

Regarding the CTs with VKA vs no anti-coagulation in dialysis patients with AFib, in addition to the aforementioned AVKDIAL, the *Danish Warfarin-Dialysis Study Safety and Efficacy of Warfarin in Patients with Atrial Fibrillation on Dialysis* (DANWARD) (NCT03862859) is underway. Both studies will provide valuable information on the risk-benefit of VKAs in dialysis patients, which has been questioned by observational studies and meta-analyses.[8,9]

Regarding the comments made about warfarin-related nephropathy, this has a clear definition; acute kidney injury after an INR > 3. Anticoagulant-related nephropathy has had its definition extended to include direct oral anti-coagulants (DOACs), with which it has also been described (although less frequently than with VKAs) in patients with underlying kidney disease.[10] This should be differentiated and not confused with the more rapid deterioration of kidney function associated with VKA and recognised even in clinical guidelines[11] and whose cause is probably multifactorial, according to the review by Gómez-Fernández et al.[10]

Regarding DOACs, apixaban and rivaroxaban seem to be alternatives to classical oral anti-coagulation, although some observational studies question the benefit of DOACs vs no anti-coagulation in this population, which needs to be demonstrated.[12] The Valkyrie study, mentioned in the article, has demonstrated a reduction in cardiovascular events with rivaroxaban 10 mg/day vs VKA (including fewer peripheral vascular events) with a better safety profile. Therefore, to date it is the only clinical trial that has demonstrated a bet-

DOI of original article:
https://doi.org/10.1016/j.nefro.2022.05.001.

ter risk-benefit profile in this population, pending the results of the two studies with apixaban (AXADIA and SAFE-D) mentioned by the authors.[1]

Finally, although percutaneous left atrial appendage closure (LAAC) is an attractive alternative to oral anti-coagulation to prevent thromboembolic events in dialysis patients, as demonstrated by the study by Genovesi et al.[13] mentioned in the article; a recent analysis of a LAAC registry with a much larger sample found higher mortality during hospitalisation and a trend towards increased mortality in the sub-group of dialysis patients.[14]

Therefore, anti-coagulant treatment in dialysis patients with AFib will remain a controversial issue due to the scant evidence from CT, starting with the selection of patients who may benefit from it. This requires a greater involvement of the nephrologist in the indication and follow-up of oral anticoagulation and, consideration of the alternative of DOACs (limited by approval for dialysis by the EMA), to avoid/reduce the risks associated with VKAs, and consideration of LAAC as an option, but carefully assessing the risk-benefit profile.

Funding

The authors declare that they have not received funding for this article.

Conflicts of interest

The authors have no conflicts of interest to declare.

REFERENCES

1. Sánchez-González C, Herrero Calvo JA. Fibrilación auricular no valvular en pacientes en hemodiálisis crónica. ¿Debemos anticoagular? Nefrología. 2022, http://dx.doi.org/10.1016/J.NEFRO.2022.01.005. Published online January.
2. de Jong Y, Fu EL, van Diepen M, Trevisan M, Szummer K, Dekker FW, et al. Validation of risk scores for ischaemic stroke in atrial fibrillation across the spectrum of kidney function. Eur Heart J. 2021;42:1476–85, http://dx.doi.org/10.1093/EURHEARTJ/EHAB059.
3. de Vriese AS, Heine G. Anticoagulation management in hemodialysis patients with atrial fibrillation: evidence and opinion. Nephrol Dial Transplant. 2021, http://dx.doi.org/10.1093/NDT/GFAB060. Published online February.
4. Lee KH, Li SY, Liu JS, Huang CT, Chen YY, Lin YP, et al. Association of warfarin with congestive heart failure and peripheral artery occlusive disease in hemodialysis patients with atrial fibrillation. J Chin Med Assoc. 2017;80:277–82, http://dx.doi.org/10.1016/J.JCMA.2016.10.012.
5. di Lullo L, Tripepi G, Ronco C, D'Arrigo G, Barbera V, Russo D, et al. Cardiac valve calcification and use of anticoagulants: preliminary observation of a potentially modifiable risk factor. Int J Cardiol. 2019;278:243–9, http://dx.doi.org/10.1016/J.IJCARD.2018.11.119.
6. Morgan CL, McEwan P, Tukiendorf A, Robinson PA, Clemens A, Plumb JM. Warfarin treatment in patients with atrial fibrillation: observing outcomes associated with varying levels of INR control. Thromb Res. 2009;124:37–41, http://dx.doi.org/10.1016/J.THROMRES.2008.09.016.
7. Rebora P, Moia M, Carpenedo M, Valsecchi MG, Genovesi S. Best quality indicator of vitamin K antagonist therapy to predict mortality and bleeding in haemodialysis patients with atrial fibrillation. Blood Transfus. 2021;19:487–94, http://dx.doi.org/10.2450/2020.0217-20.
8. Kuno T, Takagi H, Ando T, Sugiyama T, Miyashita S, Valentin N, et al. Oral anticoagulation for patients with atrial fibrillation on long-term hemodialysis. J Am Coll Cardiol. 2020;75:273–85, http://dx.doi.org/10.1016/J.JACC.2019.10.059.
9. Randhawa MS, Vishwanath R, Rai MP, Wang L, Randhawa AK, Abela G, et al. Association between use of warfarin for atrial fibrillation and outcomes among patients with end-stage renal disease: a systematic review and meta-analysis. JAMA Netw Open. 2020;3:e202175, http://dx.doi.org/10.1001/JAMANETWORKOPEN.2020.2175.
10. Gómez-Fernández P, Martín Santana A, Arjona Barrionuevo JD. Oral anticoagulation in chronic kidney disease with atrial fibrillation. Nefrologia. 2021;41:137–53, http://dx.doi.org/10.1016/J.NEFRO.2020.08.007.
11. January CT, Wann LS, Calkins H, Chen LY, Cigarroa JE, Cleveland JC Jr, et al. 2019 AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol. 2019;74:104–32, http://dx.doi.org/10.1016/J.JACC.2019.01.011.
12. See LC, Lee HF, Chao TF, Li PR, Liu JR, Wu LS, et al. Effectiveness and safety of direct oral anticoagulants in an Asian population with atrial fibrillation undergoing dialysis: a population-based cohort study and meta-analysis. Cardiovasc Drugs Ther. 2021;35:975–86, http://dx.doi.org/10.1007/S10557-020-07108-4.
13. Genovesi S, Vincenti A, Rossi E, Pogliani D, Acquistapace I, Stella A, et al. Atrial fibrillation and morbidity and mortality in a cohort of long-term hemodialysis patients. Am J Kidney Dis. 2008;51:255–62, http://dx.doi.org/10.1053/j.ajkd.2007.10.034.
14. Ahuja KR, Ariss RW, Nazir S, Vyas R, Saad AM, Macciocca M, et al. The association of chronic kidney disease with outcomes following percutaneous left atrial appendage closure. JACC Cardiovasc Interv. 2021;14:1830–9, http://dx.doi.org/10.1016/J.JCIN.2021.06.008.

Aleix Cases[a,b,c], José Jesús Broseta[c,*], Diana Rodriguez-Espinosa[c], José Luis Górriz[d,e,f]

[a] *Universitat de Barcelona, Barcelona, Spain*
[b] *Institut d'Investigaciones Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain*
[c] *Servicio de Nefrología y Trasplante Renal, Hospital Clínic de Barcelona, Barcelona, Spain*
[d] *Servicio de Nefrología, Hospital Clínico Universitario, Valencia, Spain*

[e] INCLIVA, Valencia, Spain
[f] Universitat de València, Valencia, Spain

* Corresponding author.
E-mail address: jjbroseta@clinic.cat (J.J. Broseta).

https://doi.org/10.1016/j.nefroe.2023.03.013

Reply to the letter to the editor regarding "Nonvalvular atrial fibrillation in patients undergoing chronic haemodialysis, should we anticoagulate?"

Respuesta a la carta al director referida a «Fibrilación auricular no valvular en pacientes en hemodiálisis crónica. ¿Debemos anticoagular?»

Dear Editor,

We would like to thank our colleagues Aleix Cases et al. for the observations described in the letter to the editor sent on the occasion of the publication of the article N̈onvalvular atrial fibrillation in patients undergoing chronic haemodialysis, should we anticoagulate?;[1] fundamentally, because we are in total agreement with them and because they have helped to emphasise the conclusions referred to in our original review.[1]

Thus, we agree that tools other than the CHA_2DS_2-VASc have recently been proposed to assess bleeding risk in the haemodialysis (HD) population, given the fact that this *score* has not been shown to be useful in these patients, we did not reference it in our original article. The article referenced in the original review (Ocak et al., reference 40 of the original article) alludes to other *scores* that could not be validated in chronic kidney disease (CKD) to assess the indication for anticoagulation in these patients either.[2] Others like the modified CHADS[3] and the *dialysis risk score*,[4] proposed by Vriese et al., also need to be validated in the HD population. Therefore, we emphasise the low predictive value of these scales used in the general population to assess bleeding risk in HD patients, including the classic HAS-BLED scoring system developed to assess the one-year risk of major bleeding in patients with atrial fibrillation and which was developed in 2010 with data from 3978 patients in the *Euro Heart Survey*.[5]

The authors of the letter to the editor also agree with us regarding the increased risk of calciphylaxis and peripheral vascular disease that the use of vitamin K antagonists (VKA) produces in HD patients, as demonstrated in the articles that we referenced in the original review. We chose to use the term 'vascular health' to include these and other vascular diseases, but perhaps we should have been more explicit. We appreciate the clarification.

Likewise, we agree on the difficulty of achieving adequate coagulation control in HD patients, as described in the headings Ḧigh bleeding risk and lack of efficacyänd Öbjective anticoagulation level difficult to control;̈ on discussing the use of VKAs in the HD population. Additionally, the time in the therapeutic range is low in CKD patients, especially in HD patients, a fact that we should be aware of in this population treated with VKA in order to consider all treatment strategies.

We appreciate the mention of another ongoing clinical trial, such as the *Danish Warfarin-Dialysis Study Safety and Efficacy of Warfarin in Patients with Atrial Fibrillation on Dialysis* (DANWARD) (NCT03862859), which, along with the study mentioned in the original publication (AVK [VKA]-Dial), will provide greater knowledge about the risk-benefit of the use of VKAs in the dialysis population. We would add two further randomised studies with apixaban vs no anticoagulation (EDTA PARIS 2022):

- SACK (Sweden, Norway, Finland, Iceland and Poland), comparing 2.5 mg × 2 tablets apixaban vs no anticoagulation.
- ApiDP (France), nonrandomised, apixaban 5 mg × 2 vs normal kidney function.

Fortunately, the initiation of new clinical trials highlights the concern of this issue in the nephrology and medical community in general.

In the letter to the editor, reference is also made to the warfarin-related nephropathy mentioned in the original review, both acute and possible progression of CKD, included in the recent review of Gómez-Fernández et al.[6] As we pointed out in reference 103 of the original article (Brodsky et al.[7]), oral anticoagulant nephropathy has also been reported with direct-acting oral anticoagulants,[7] as well as the possibility of undiagnosed IgA nephropathy (references 104 and 105 of the original article).[8,9]

We also agree that percutaneous appendage closure is a therapeutic alternative without risk, as inferred from a recent publication[10] already referenced in the letter.

In summary and to conclude, we would like to express our satisfaction, given that, in the points referred to in the letter to the editor and which, again, we are grateful for, the authors

DOI of original article:
https://doi.org/10.1016/j.nefro.2022.05.007.