**EDITORIAL**

**Reducing Risk of Adverse Cardiovascular and Renal Outcomes for Patients with Atrial Fibrillation and Type 2 Diabetes**

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When planning treatment options for people with atrial fibrillation (AF), it is important to consider co-morbidities which may have common underlying risk factors. Type 2 diabetes mellitus and chronic kidney disease (CKD) often co-exist because of associations with other risk factors, and these conditions are both individually and in combination associated with incident AF and stroke, and other AF-related complications.1, 2 Limited data exist examining the prevalence of all three conditions concurrently, but it has been estimated that over 20% of patients with AF have type 2 diabetes, and over 25% of patients with AF have Stage III or higher CKD; further the frequency of diabetes as a co-morbidity increases markedly with increasing stages of CKD.3 Therefore, studies which recognise the growing importance of examining type 2 diabetes, renal impairment and AF concomitantly are important to decision-making for patients with AF.

AF is the most prevalent arrhythmia worldwide and with the ageing population and increasing incidence of AF, there will be an estimated 14-17 million people with AF in Europe by 2030. AF is associated with significant cardiovascular morbidity including higher risk of stroke, hospitalisations, impaired quality of life, left ventricular dysfunction and HF, vascular dementia and mortality. It is estimated that 20-30% of all ischaemic strokes are in patients with AF, but stroke risk can be vastly improved by appropriate use of oral anticoagulants; therefore, early detection and treatment are critical.4

Having concurrent type 2 diabetes further increases risk of ischaemic stroke for patients with AF.4 In patients with AF and type 2 diabetes, a longer duration of diabetes has been associated with a higher risk of thromboembolism, but not a higher risk of anticoagulant-related bleeding; which highlights the importance of a detailed patient-centred approach to care, considering all co-morbidities including duration and severity.5 For patients with AF, the assessment of kidney function by serum creatinine or creatinine clearance (CrCl) is recommended to both detect CKD and monitor renal function, and subsequently decipher appropriate treatment options. An individualised, person-centred approach should be taken for treatment of all patients with AF, and all co-morbidities including type 2 diabetes and CKD should be considered appropriately when determining management of all risk factors and treatment of AF as part of patient-care.

The EMPA-REG OUTCOME study was the first randomised controlled trial to suggest a glucose-lowering intervention was associated with reduced cardiovascular outcomes in patients with type 2 diabetes.6 In patients with type 2 diabetes and high-risk of cardiovascular events, the effects of empagliflozin (reversible inhibitor of sodium-glucose co-transporter 2 (SGLT)) vs. placebo were compared and lower rates of cardiovascular outcomes and mortality with empagliflozin were reported, for example, 3.7% vs. 5.9% death from cardiovascular causes for empagliflozin compared to placebo.6

In this issue of the journal, Böhm and colleagues performed a post-hoc analysis of the EMPA-REG OUTCOME study of patients with type 2 diabetes and a high-risk of cardiovascular events and suggested empagliflozin reduced heart failure (HF)-related and renal adverse outcomes in patients with and without AF.7 In patients with and without AF, compared with placebo, empagliflozin was associated with a lower risk of adverse cardiovascular outcomes (including cardiovascular and all-cause mortality and HF hospitalisation), and a lower risk of adverse renal outcomes (including new or worsening neuropathy, new loop diuretics and new oedema). The new analysis draws on the large sample size of the original trial (n=7020), but only 5.5% (n=389) of included patients had AF present at baseline and considering AF is a focus of this analysis, this is rightly noted as a limitation. Despite the smaller proportion of patients with AF, the authors found patients with AF had a higher risk of cardiovascular events at baseline and higher rates of HF hospitalisations and renal events. Therefore, empagliflozin was associated with a greater absolute reduction in adverse events in patients with AF compared to patients without AF. Although, this was not statistically different between patients with and without AF likely due to inadequate power associated with the low numbers of patients with AF. All of the patients in the study were at high-risk of adverse cardiovascular events and the relative differences between those with and without AF of empagliflozin on cardiovascular and renal adverse events were similar.

A large observational study has previously shown associations between SGLTs and lower cardiovascular disease (CVD) and mortality compared to other glucose-lowering medications in patients with type 2 diabetes.8 Overall the study by Böhm and colleagues adds to these findings by considering the relationship between type 2 diabetes, kidney disease and AF and offers a first indication that empagliflozin may be associated with lower risk of incident HF and renal outcomes in patients with and without AF.7 However, the dataset used in the study lacks important data about AF and HF. AF at baseline was based on investigator reporting of medical history. Future research focused on investigating interventions to reduce adverse events in patients with AF and type 2 diabetes are warranted. Such studies should collect rich data on AF at baseline (e.g. duration and burden of AF, antiarrhythmic medications, full electrocardiogram (ECG) results) and also collect data on changes in cardiovascular risk profiles over time. Data collected should include incident AF, HF including ejection fraction data, stroke and other important cardiovascular and non-cardiovascular outcomes for patients with AF. AF detection may include extended ECG monitoring given that prolonged monitoring may enhance the detection of undiagnosed AF.9 In the EMPA-REG OUTCOME trial, there were low rates of incident AF for those who received empagliflozin and those who received placebo, and as the authors note future studies should further examine if empagliflozin influences rates of new onset AF. Studies should consider concurrent medications people with type 2 diabetes and AF are receiving which reduce risk of adverse cardiovascular and renal adverse outcomes and deliberate the added potential benefit of additional medications vs. potential harms. Given that the patients are older and by definition (type 2 diabetes, AF and high-risk of CVD) have multiple co-morbidities they are likely to already be exposed to established polypharmacy. Therefore, the benefits of another medication for these patients have to be weighed against the potential harms considering polypharmacy.10 If AF is to be considered an important variable to stratify results, then sufficient numbers of study participants with and without AF should be recruited with consideration that patients with AF are likely to have other risk factors.

When treating all patients with AF an integrated, tailored, holistic approach is recommended using the Atrial Fibrillation Better Care (ABC) pathway (Figure). Detailed information has been published elsewhere,11 but briefly, the ABC pathway is a simple set of steps to tailor decision-making for patients with AF:

**A: Avoid stroke**. Patients with AF and type 2 diabetes would not be low-risk according to their CHA2DS2-VASc score. Therefore, stroke prevention methods should be considered either as vitamin K antagonist (VKA) with good-quality anticoagulation control (international normalised ratio (INR) of 2.0‐3.0 and time in therapeutic range >70%) or non-VKA oral anticoagulants (NOACs). Bleeding risk should be assessed with a risk score such as the HAS-BLED,12 to identify precautions to minimise bleeding risk such as by addressing modifiable risk factors and offering frequent follow-ups.

**B: Better symptom management**. The decision whether to initiate rhythm- or rate control should be individualised, based on symptoms and should consider the type of atrial fibrillation (paroxysmal, persistent, or long-standing persistent), co-morbidities and current medications.

**C: Cardiovascular risk and comorbidity management.**

Underlying risk factors contributing to stroke risk and co-morbidities such as type 2 diabetes should be prioritised including managing lifestyle risk factors, for instance discussion of weight management and a tailored programme of diet changes and exercise for patients with obesity.13 Dose-reduced regimens of anticoagulants may be considered depending on the age of the patient and presence of other risk factors such as impaired renal function.14 If baseline CrCl is ≤60mL/min the number of months when the next check of renal function should be completed can be calculated by dividing the CrCl by 10, and for all other patients renal function should be reviewed at least annually.14 For patients with mild-to-moderate CKD (CrCl ≥30mL/min), NOACs present with a more favourable safety and efficacy profile compared to warfarin.15 For patients with severe CKD (CrCL 15-29mL/min), further research is needed, but rivaroxaban, apixaban, and edoxaban are approved for use in these patients in Europe with reduced dosage but should only be used with caution.14 There is a lack of high-quality data for treatment of AF for patients with end-stage CKD on dialysis, but NOACs should not be used and the use of a VKA should be carefully considered in discussion with the patient.14,15

When treating patients with AF it is always important to consider concomitant conditions, how these are being managed and individualise treatment plans based on these co-morbidities and cardiovascular risk factors, in discussion with the patient and their family/caregiver. Further research should investigate how empagliflozin and other treatments for diabetes should be best approached as part of the “C” in the ABC pathway for patients with AF and type 2 diabetes.

**Figure legend**

CKD: Chronic Kidney Disease; CrCl: Creatinine clearance. Low-risk defined as CHA2DS2-VASc score of 0 in men or 1 in women, with event rates of <1% per year. For patients with CrCL ≤60mL/min, the number of months when the next check of renal function should be completed is CrCl/10.

**References**

1. Allan V, Honarbakhsh S, Casas JP, Wallace J, Hunter R, Schilling R, Perel P, Morley K, Banerjee A, Hemingway H. Are cardiovascular risk factors also associated with the incidence of atrial fibrillation? A systematic review and field synopsis of 23 factors in 32 population-based cohorts of 20 million participants. *Thromb Haemost*. 2017;**117**(5):837-850.

2. Lip GYH, Freedman B, De Caterina R, Potpara TS. Stroke prevention in atrial fibrillation: Past, present and future. Comparing the guidelines and practical decision-making. *Thromb Haemost*. 2017;**117**(7):1230-1239.

3. Reinecke H, Nabauer M, Gerth A, Limbourg T, Treszl A, Engelbertz C, Eckardt L, Kirchhof P, Wegscheider K, Ravens U, Meinertz T, Steinbeck G, Breithardt G. Morbidity and treatment in patients with atrial fibrillation and chronic kidney disease. *Kidney Int*. 2015;**87**(1):200-209.

4. Lip GYH, Banerjee A, Boriani G, Chiang CE, Fargo R, Freedman B, Lane DA, Ruff CT, Turakhia M, Werring D, Patel S, Moores L. Antithrombotic Therapy for Atrial Fibrillation: CHEST Guideline and Expert Panel Report. *Chest*. 2018;**154**(5):1121-1201.

5. Overvad TF, Skjoth F, Lip GY, Lane DA, Albertsen IE, Rasmussen LH, Larsen TB. Duration of Diabetes Mellitus and Risk of Thromboembolism and Bleeding in Atrial Fibrillation: Nationwide Cohort Study. *Stroke*. 2015;**46**(8):2168-2174.

6. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, Mattheus M, Devins T, Johansen OE, Woerle HJ, Broedl UC, Inzucchi SE. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. *N Engl J Med*. 2015;**373**(22):2117-2128.

7. Böhm M, Slawik J, Brueckmann M, Mattheus M, George J, Ofstad AP, Inzucchi SE, Fitchett D, Anker SD, Marx N, Wanner C, Zinman B, Verma S. Efficacy of empagliflozin on heart failure and renal outcomes in patients with atrial fibrillation: Data from the EMPA-REG OUTCOME trial *Eur J Heart Fail*. 2019.

8. Birkeland KI, Jorgensen ME, Carstensen B, Persson F, Gulseth HL, Thuresson M, Fenici P, Nathanson D, Nystrom T, Eriksson JW, Bodegard J, Norhammar A. Cardiovascular mortality and morbidity in patients with type 2 diabetes following initiation of sodium-glucose co-transporter-2 inhibitors versus other glucose-lowering drugs (CVD-REAL Nordic): a multinational observational analysis. *Lancet Diabetes Endocrinol*. 2017;**5**(9):709-717.

9. Mairesse GH, Moran P, Van Gelder IC, Elsner C, Rosenqvist M, Mant J, Banerjee A, Gorenek B, Brachmann J, Varma N, Glotz de Lima G, Kalman J, Claes N, Lobban T, Lane D, Lip GYH, Boriani G, Group ESCSD. Screening for atrial fibrillation: a European Heart Rhythm Association (EHRA) consensus document endorsed by the Heart Rhythm Society (HRS), Asia Pacific Heart Rhythm Society (APHRS), and Sociedad Latinoamericana de Estimulacion Cardiaca y Electrofisiologia (SOLAECE). *Europace*. 2017;**19**(10):1589-1623.

10. Proietti M, Raparelli V, Olshansky B, Lip GY. Polypharmacy and major adverse events in atrial fibrillation: observations from the AFFIRM trial. *Clin Res Cardiol*. 2016;**105**(5):412-420.

11. Lip GYH. The ABC pathway: an integrated approach to improve AF management. *Nat Rev Cardiol*. 2017;**14**:627.

12. Borre ED, Goode A, Raitz G, Shah B, Lowenstern A, Chatterjee R, Sharan L, Allen LaPointe NM, Yapa R, Davis JK, Lallinger K, Schmidt R, Kosinski A, Al-Khatib SM, Sanders GD. Predicting Thromboembolic and Bleeding Event Risk in Patients with Non-Valvular Atrial Fibrillation: A Systematic Review. *Thromb Haemost*. 2018;**118**(12):2171-2187.

13. Middeldorp ME, Pathak RK, Meredith M, Mehta AB, Elliott AD, Mahajan R, Twomey D, Gallagher C, Hendriks JML, Linz D, McEvoy RD, Abhayaratna WP, Kalman JM, Lau DH, Sanders P. PREVEntion and regReSsive Effect of weight-loss and risk factor modification on Atrial Fibrillation: the REVERSE-AF study. *Europace*. 2018;**20**(12):1929-1935.

14. Steffel J, Verhamme P, Potpara TS, Albaladejo P, Antz M, Desteghe L, Haeusler KG, Oldgren J, Reinecke H, Roldan-Schilling V, Rowell N, Sinnaeve P, Collins R, Camm AJ, Heidbuchel H. The 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. *Eur Heart J*. 2018;**39**(16):1330-1393.

15. Potpara TS, Ferro CJ, Lip GYH. Use of oral anticoagulants in patients with atrial fibrillation and renal dysfunction. *Nat Rev Nephrol*. 2018;**14**(5):337-351.