Managing anticoagulation in eligible non-valvular atrial fibrillation (AF)

Introduction

This review explores some of the latest evidence on managing anticoagulation for the high-risk atrial fibrillation (AF) patient group with diabetes and chronic kidney disease (CKD); it focuses particularly on CKD and renal impairment - very common in both AF and diabetic patients.

KEY MESSAGES

- Patients with AF frequently have renal impairment and diabetes
- AF, renal failure and diabetes are all independent risk factors for stroke
- It is important to protect against renal function decline in high-risk non-valvular atrial fibrillation (NVAF) patients with diabetes and renal impairment
- Renal function decline is significantly greater with long-term warfarin use as compared to some novel oral anticoagulants (NOACs) (dabigatran, rivaroxaban)
- Vitamin K antagonist (VKA)-induced vascular calcification may be causally linked to renal function decline.

AF patients with concomitant diabetes and/or moderate renal impairment

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Patients with AF frequently have renal impairment. Renal impairment is a very important component of AF (Figure 1).\textsuperscript{1,2} This is because as people age, the prevalence of both AF and chronic renal failure increases exponentially. It is important to realise that one out of three AF patients will have a significant reduction of estimated glomerular filtration rate (eGFR) to <50-60ml/min.

Figure 1. Patients with AF frequently have renal impairment

- Prevalence of both AF and CKD\textsuperscript{*} increases with age\textsuperscript{1,2}
- One in 3 patients with AF has CKD\textsuperscript{2}

\textsuperscript{*}Each circle represents a study prevalence estimate with the size denoting the precision of the estimate
AF: atrial fibrillation, CKD: chronic kidney disease, eGFR: estimated glomerular filtration rate

The green, blue and red lines represent Developed, Global and Developing countries, respectively.

This report was made possible by an unrestricted educational grant from Bayer. The content of the report is independent of the sponsor. The expert participated voluntarily.
Diabetes and AF frequently occur together

Patients with diabetes frequently have renal failure, while renal failure patients also frequently develop AF like their diabetic counterparts. In fact, 30% of patients with AF will have diabetes as a comorbidity and 15% of patients with diabetes will also have AF (Figure 2).

AF, renal failure and diabetes are all independent risk factors for stroke. AF increases the risk of stroke five-fold. In non-anticoagulated patients, diabetes is associated with a two-fold increase in the risk of stroke and is also a major risk factor for myocardial infarction (MI) and peripheral atherosclerotic disease. In addition, patients with chronic renal failure experience an increased prevalence of stroke events and are also at greater risk of developing MI and vascular disease.

Exploring the latest evidence: High-risk patients with diabetes and CKD

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Almost two-thirds of patients with NVAF have some degree of renal dysfunction, and renal impairment increases with age. This is clinically important because in patients with AF, the presence of CKD is associated with thromboembolic events, an increased risk of bleeding events and an overall increased mortality. These are clearly a high-risk group of patients.

CKD prevalence in patients with diabetes is high

United States data on diabetic patients show that 19% have some degree of moderate renal impairment (<60ml/min). In Europe, 24% of dialysis patients requiring renal replacement therapy (RRT) have diabetes, the most prevalent single cause of end-stage renal disease (ESRD) in Europe, increasing particularly in the ageing population (Figure 3).
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Diabetes and renal function are closely interlinked and increase cardiovascular (CV) risk. The US population-based NHANES survey highlights the impact on CV risk of both diabetes and kidney disease separately and if they occur comorbidly, as compared to patients that are not affected by these two conditions (Figure 4). There is an enormous increase in CV risk in patients affected by both diabetes and CKD.

Preserving renal function

A post-hoc analysis of the RE-LY trial showed differential effects of treatment with warfarin or dabigatran on renal function decline in AF patients over the course of 30 months. Renal function decline was significantly greater in patients treated with warfarin. A similar finding from a post-hoc analysis of the ROCKET AF trial (rivaroxaban compared to warfarin over 21 months) showed that creatinine clearance (CrCl) decline, as a measure of renal function decline, was significantly greater in patients on warfarin compared to those treated with rivaroxaban (Figure 5).
Rivaroxaban versus warfarin in patients with worsening renal function

Post-hoc analysis of the development of worsening renal function (>20% decline in CrCl) during the course of the ROCKET AF trial showed differential outcomes in relation to treatment (Figure 6). In patients who developed worsening renal function, there was no difference in the number of non-major, clinically relevant bleeding events or major bleeding events. However, with regard to thromboembolic events, stroke and systemic embolism, patients who developed worsening renal function had a better outcome when they were treated with rivaroxaban rather than warfarin. This is a very important finding that has clinical relevance.

<table>
<thead>
<tr>
<th>Outcomes by renal function status</th>
<th>HR</th>
<th>95% CI</th>
<th>Interaction p-value</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major/NMCR bleeding</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Worsening (n=3 320)</td>
<td>1.06</td>
<td>0.80-1.39</td>
<td>0.61</td>
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<tr>
<td>Stable (n=9 292)</td>
<td>0.98</td>
<td>0.89-1.08</td>
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<tr>
<td>Major bleeding</td>
<td></td>
<td></td>
<td>0.13</td>
<td></td>
</tr>
<tr>
<td>Worsening (n=3 320)</td>
<td>1.45</td>
<td>0.90-2.35</td>
<td></td>
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<tr>
<td>Stable (n=9 292)</td>
<td>0.98</td>
<td>0.82-1.18</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke/SE</td>
<td></td>
<td></td>
<td>0.05</td>
<td></td>
</tr>
<tr>
<td>Worsening (n=3 320)</td>
<td>0.50</td>
<td>0.27-0.93</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stable (n=9 292)</td>
<td>0.97</td>
<td>0.76-1.24</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Worsening renal function defined as a decrease in CrCl of >20% from screening

Patients were included in the subanalysis if they had ≥1 post randomisation creatinine measurement during the on-treatment period. The LEADER trial (n=9 340) demonstrated an absolute risk reduction of 1.9% for MACE compared with placebo over 3.8 years.

What is the potential mechanism of VKA-induced renal damage?

Patients with CKD develop some severe forms of atrial calcification - ‘intimal calcification’ occurring often in atherosclerotic patients, and a form of ‘medial calcification’ with micro-calcifications in the vascular smooth muscle layer. This leads to stiffening of the artery, vascular injury and vascular dysfunction (Figure 7).

MGP: matrix Gla protein; VKA: vitamin K antagonist

The influence of VKA treatment is potentially related to a pathomechanism pathway as shown in Figure 8. Matrix Gla protein (MGP) is considered to be the major inhibitor of vascular calcification in this context. The important concept is that MGP requires gamma-carboxylation by vitamin K in order to be fully active and protect against vascular calcification. VKA treatment inhibits the activation of MGP, which is then associated with a progressive or accelerated vascular calcification and injury process that might be causally related to a decline in renal function.
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It is interesting to note that post-hoc analysis of the ARISTOTLE study showed that apixaban use was not associated with a protective effect for renal function decline, but rather associated with a greater decline in renal function over time compared to warfarin (Figure 9).18

Peripheral artery calcification and warfarin treatment

It is known, from experimental studies in animal models and predominantly observational pathophysiological studies in humans, that VKA treatment over a long period is associated with vascular calcification.

A well-conducted small study with a matched control design (age, sex, diabetes and long-term warfarin treatment) analysed the calcification of the arteries below the knee using simple X-ray analysis (Figure 10).19 Results show that patients treated over five years with warfarin had a significantly two-fold higher presence of arterial calcification. This is one of several studies supporting the concept that VKA treatment leads to calcification of arteries and vascular injury.
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VKA exposure may potentially accelerate progression of kidney disease in patients with NVAF and CKD

“This was recently confirmed by our research in a real-life setting, evaluating data from more than 14,000 patients and analysing almost 100,000 creatinine measurements and eGFR levels over the course of five years,” Professor Kreutz noted. The question addressed was whether VKA exposure was associated with renal function decline compared to patients that were not treated with a VKA, against the background of AF (Figure 11). Of importance, the mean eGFR in this population was 50 ml/min, so half of the study group already had moderate to severe renal impairment. Also, VKA exposure was associated with a significantly enhanced decline in renal function over time. Figure 10 illustrates a similar result, but as a percentage and not as an absolute decline. There was approximately a 50% larger decline in renal function observed in this dataset.

![Figure 10. Peripheral artery calcification and warfarin treatment](image1)

![Figure 11. VKA exposure may potentially accelerate progression of kidney disease in patients with NVAF and CKD](image2)
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Real-world evidence supports preservation of renal function with rivaroxaban versus warfarin

Another important retrospective analysis of a real-life dataset from the United States illustrates important additional results, emphasising a potential renal protective effect of rivaroxaban (Figure 12). There was a significant risk reduction not only in renal function decline, but also other categories of renal endpoints - decline in eGFR (30%), doubling of creatinine (27%), reduction in overall risk (54%) and significant reduction with regard to acute kidney injury (31%). Because of the confidence interval, a reduction of kidney failure could not be shown.

All the above data support the idea that NOAC treatment, rivaroxaban in particular, might be beneficial and protective in patients with AF and particularly in persons with impaired renal function.

![Figure 12. Real world evidence supports preservation of renal function with rivaroxaban versus warfarin](image)

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Weighted event rate (per 100 Person-Years)</th>
<th>HR (95% CI)</th>
<th>RRR (p-value)</th>
<th>ARR</th>
</tr>
</thead>
<tbody>
<tr>
<td>30% decline in eGFR</td>
<td>15.10</td>
<td>20.64</td>
<td>0.73 (0.62-0.87)</td>
<td>27% (p&lt;0.001)</td>
</tr>
<tr>
<td>Doubling of creatinine</td>
<td>1.47</td>
<td>3.26</td>
<td>0.46 (0.28-0.75)</td>
<td>54% (p&lt;0.001)</td>
</tr>
<tr>
<td>Acute kidney injury</td>
<td>7.63</td>
<td>11.15</td>
<td>0.69 (0.57-0.84)</td>
<td>31% (p&lt;0.001)</td>
</tr>
<tr>
<td>Kidney failure</td>
<td>0.80</td>
<td>1.28</td>
<td>0.63 (0.35-1.15)</td>
<td>37% (p&lt;0.13)</td>
</tr>
</tbody>
</table>

ARR: absolute risk reduction; RRR: relative risk reduction; RWE: real-world evidence

Conclusion

Diabetes is clearly a risk factor for both renal impairment and stroke. Renal function is an important consideration when selecting an anticoagulant in patients with NVAF. Because of the differential effects on renal function decline observed with some NOACs, notably rivaroxaban and dabigatran, these have been associated with better preservation of renal function than warfarin based on both post-hoc analysis of phase III pivotal trials and, more recently, on real-world observational study.

Disclosures

Dr Marcelo Sanmartin
Conferences and advisory board: Amgen, Bayer, Boehringer-Ingelheim, Sanofi, BMS
Research grants: Bayer

Professor Reinhold Kreutz
Honoraria for consultancy, lectures and support for research during the last three years from: Bayer Pharma, Berlin-Chemie Menarini, Daiichi Sankyo, Servier
Secretary General: European Society of Hypertension
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References
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