Preserving the Balance in Stroke Prevention: Brain, Heart and Kidneys (symposium summary sponsored by Bayer)

PRESENTERS: GRAEME J. HANKEY[1], HENDRIK BONNEMEIER[2], MIKE SHARMA[3]

[1]Medical School, The University of Western Australia, Perth, Australia.
[2]University Clinic Schleswig-Holstein, Department für Rhythmology and Electrophysiology, Arnold-Heller-Str. 3, 24105 Kiel, Germany.
[3]McMaster University / Population Health Research Institute, 237 Barton Street East, HGH-DBCVSRI C4-120, Hamilton, Ontario, L8L 2X2, Canada.

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Abstract

Stroke is the second leading cause of death after ischaemic heart disease, and the second leading cause of Disability Adjusted Life Years (DALYs) lost globally. A holistic approach to the prevention and management of stroke can reduce stroke-related mortality and morbidity. The association between diabetes, atrial fibrillation, and renal disease as risk factors for stroke are discussed in this meeting summary. The results of phase 3 trials for anticoagulation therapy are reviewed and presented in the context of defining high-risk patients for stroke and cardiovascular disease.

KEYWORDS: ATRIAL FIBRILLATION, CARDIOVASCULAR DISEASE, CHRONIC KIDNEY DISEASE, DIABETES, ISCHAEMIC HEART DISEASE, STROKE.

Corresponding author: Allison Kirsop – a.kirsop@scientific-writers.com

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Introduction

The global burden of stroke is substantial and increasing.[1] The Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) 2016 estimated that in 2016, there were 13.7 million (95% uncertainty interval [UI]: 12.7 to 14.7) incident cases of stroke, which added to a pool of 80.1 million (74.1–86.3), prevalent stroke survivors worldwide. There were 5·5 million (5.3 to 5.7) deaths and 116.4 million (111.4–121.4) Disability-Adjusted Life Years (DALYs) lost due to stroke, making stroke the second leading cause of death after ischaemic heart disease and second leading cause of DALYs lost globally.[2] However, the incidence and outcome of stroke, in terms of stroke-related mortality and morbidity, can be reduced by a balanced, integrated, holistic approach to the prevention and management of stroke. Although the primary interest of clinicians who manage stroke patients may be the brain, and how vascular lesions of the brain manifest clinically, stroke clinicians also recognise that stroke is often a manifestation

of an underlying general medical condition, and has many systemic and metabolic causes and consequences. These comorbidities are significant, not only in establishing the aetiology of the stroke and defining treatments but also in determining prognosis and response to therapies. A study across 32 countries investigated 13,447 cases of acute first stroke with 13,472 healthy controls matched for age and sex and found there were ten independent significant risk factors for stroke that accounted for 90% of the population's attributable risk of stroke. The implications of these findings are that better control of these risk factors in the population could, in theory, reduce the incidence of first stroke by up to 90%.

The GBD 2016 study also found that several of the lifestyle factors that predict the risk of incident stroke are also important in predicting the outcome of stroke, as defined by stroke-related DALYs. These factors included high blood sugar or diabetes, and renal impairment. Hence, the implications from this study were that better control of these risk factors in the population could, in theory, improve the outcome of stroke by reducing stroke-related DALYs (TABLE 1).

The focus of this meeting summary will be on the association between diabetes, renal impairment, and atrial fibrillation (AF), and how better recognition and management of these disorders may reduce the global burden of first stroke.

Risk factors for stroke: diabetes

The prevalence of cardiovascular (CV) risk factors reported in the REACH registry of 45,227 patients ≥45 years of age with ≥1 of symptomatic coronary artery disease (CAD), coronary vascular disease (CVD) or peripheral artery disease (PAD), or ≥3 atherothrombotic risk factors revealed that around two-fifths of patients had diabetes.[3] The presence of diabetes at baseline was associated with increased atherothrombotic ischaemic events and all-cause mortality during 4-years of follow up. Other studies report similar results.[4,5] The major mechanisms by which diabetes increases cardiovascular events and mortality is by means of accelerating atherosclerosis.[6] For example, diabetes is a risk factor for the occurrence and progression of carotid stenosis.[7-9] However, diabetes also increases the incidence likelihood of AF.[10-12] This is probably because diabetes predisposes to ischaemic heart disease (IHD), and thereby microvascular and macrovascular disease, and ischaemia to the left atrium and sinoatrial node. Diabetes not only causes AF, but it also increases the risk of stroke among individuals with AF, as shown by the independent, significant role of diabetes **(D)** in the CHA**D**S^2 with CHA$_2$**D**S$_2$-VASc scores of risk of future stroke in patients with AF.[10,13,14]

Table 1. Risk Factors Associated With Stroke-Related Disability-Adjusted Life Years (DALY)

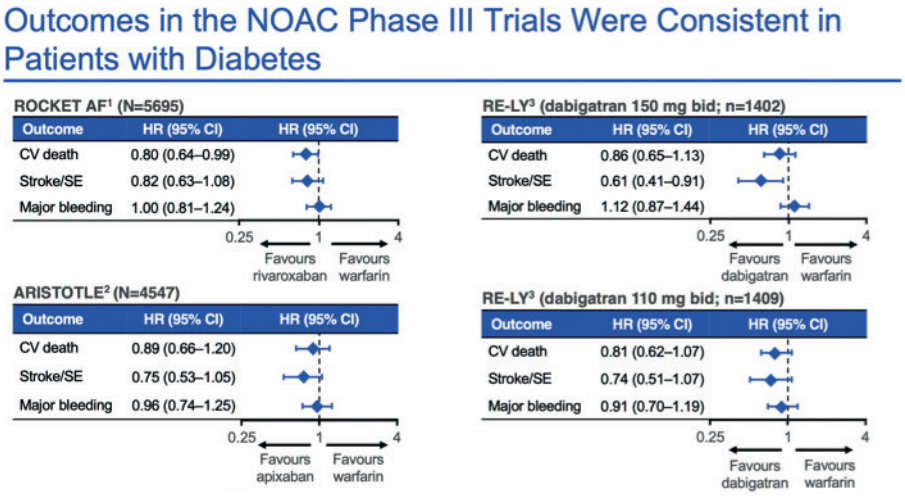
90.5% (95% UI 88.5-92.2) of Population Attributable Fraction of Stroke-Related Disability-Adjusted Life Years due to Modifiable Risk Factors	
Risk factors	**Percentage DALYs (95% uncertainty intervals)**
Air pollution and environmental risks	
Ambient PM$^{2-5}$ pollution	16.9 (16.6–17)
Household air pollution from solid fuels	15.7 (14.5–16.4)
Lead exposure	6.6 (4.8–8.4)
Dietary risks	
Diet high in sodium	22.6 (12.5–33.0)
Diet high in sugar-sweetened beverages	0.3 (0.2–0.4)
Diet low in fruits	35.6 (26.5–42.0)
Diet low in vegetables	20.0 (17.0–22.4)
Diet low in whole grains	15.0 (12.5–16.9)
Alcohol use	7.0 (5.6–8)
Physical activity	
Low physical activity	7.7 (5.6–9.2)
Tobacco smoke	
Smoking	20.7 (18.2–22.7)
Second-hand smoke	2.2 (2.1–2.2)
Physiological factors	
High BMI	23.5 (20.7–26.1)
High fasting plasma glucose	11.7 (7.6–15.7)
High systolic blood pressure	64.1 (61.3–65.8)
High total cholesterol	4.5 (3.0–6.6)
Low glomerular filtration rate	7.1 (6.4–7.8)

Abbrev: BMI, body mass index; PM, particulate matter pollution of aerodynamic diameter <2.5 μm[63]

Defining high risk in patients with diabetes

Diabetes is also associated with a poor outcome after stroke because it is linked to increased stroke severity, recurrence, and mortality after stroke, and thus clinicians need to identify patients with diabetes as a population at high risk. In patients with diabetes the risk of recurrent stroke is increased 1.5-fold,[15] with prolonged hospital stay, and worse functional outcomes after stroke.[5]

Phase 3 trials of novel oral anticoagulants (NOACs) vs warfarin for stroke prevention in patients with AF enrolled patients at high-risk of stroke, such as those with diabetes. Patients with diabetes accounted for 23% of participants in the RE-LY trial,[16] 25% in ARISTOTLE trial,[17] 36% in the ENGAGE-AF-TIMI study,[18] and 40% in the ROCKET-AF trial.[19] Outcomes within the ROCKET-AF trial of rivaroxaban compared with warfarin showed a reduction in stroke/systemic embolism events and in ICH which is substantially reduced with all of the NOACs evaluated compared with warfarin, but no significant difference in the primary safety endpoints of major or non-major bleeding. Rivaroxaban also presented a reduction in cardiovascular death compared with warfarin in this diabetic subgroup.[19,20] The relative benefits and safety of NOACs vs warfarin were consistent among patients with and without diabetes, but the absolute benefits of NOACs vs warfarin in preventing stroke and systemic embolism were higher in patients with diabetes than without, because diabetics were at higher absolute risk of stroke (Figure 1).[20-22]



Abbrev: AF, atrial fibrillation; bid, twice daily; CI, confidence interval; CV, cardiovascular; HR, hazard ratio; NOAC, non-vitamin K antagonist oral anticoagulant; SE, systemic embolism

Figure 1. Outcomes from NOAC Phase 3 Trials ROCKET-AF, RE-LY, ARISTOTLE and the effect of NOAC medication in patients with diabetes.[20-22]

The benefits of rivaroxaban vs warfarin in patients with AF and diabetes reported in clinical trials have also been observed in phase 4 studies of larger populations outside the clinical trials. Results from an administrative claims database analysis of patients with non-valvular AF and diabetes (n=11,034) showed consistency of results with the phase 3 trials. In this analysis rivaroxaban was associated with nonsignificant reductions in stroke or systemic embolism and ischaemic stroke compared with warfarin without any differences in major bleeding events. Furthermore, rivaroxaban 15 mg od was associated with a significant decrease in the risk of stroke/systemic embolism and ischaemic stroke vs warfarin (0.9 vs 1.4 events per 100 patient-years, respectively), with no increase in major bleeding.[23]

Diabetes is also a risk factor for the occurrence and progression of carotid stenosis,[7] a marker of atherosclerotic disease. Individuals with carotid stenosis have an increased risk of ipsilateral and contralateral stroke but also an increased risk of MI.[8,9]

The COMPASS trial

A new approach to treating individuals with atherosclerotic, large vessel disease was investigated in the double blind COMPASS trial which evaluated 27,395 participants with stable atherosclerotic disease.[24,25] The objective was to determine the efficacy and safety of rivaroxaban alone, vascular dose of rivaroxaban plus aspirin, or aspirin alone in reducing the risk of MI, stroke and CV death in patients with chronic CAD, PAD, or carotid stenosis. The comparator was aspirin 100 mg od as compared with rivaroxaban 5 mg bid and a combination of rivaroxaban 2.5 mg bid plus aspirin 100 mg od. Antithrombotic investigations were stopped one year ahead of expectations in February 2017 due to overwhelming efficacy in the rivaroxaban 2.5 mg bid plus aspirin 100 mg od arm. Of the total trial participants, 38% had diabetes (n=10,341),[24] 37% had CAD and diabetes (n=9098) and 44% of patients with PAD also had diabetes at baseline,[26] providing a large dataset of patients with diabetes and chronic vascular disease. Results showed that

stroke was reduced by 42% with the combination of rivaroxaban 2.5 mg bid plus aspirin over aspirin alone – a very significant benefit. Of note, the definition of PAD in the trial design included carotid stenosis. The dose of rivaroxaban was developed initially in the ATLAS series of trials to work with antiplatelets,[27] and in hindsight a combination approach may have provided a different outcome in the NAVIGATE trial.[28] Bleeding rates increased but were low with rivaroxaban vascular dose 2.5 mg bid plus aspirin compared with aspirin alone. Modified major ISTH haemorrhage was increased by approximately 1%, although the data included patients who sought any medical care for bleeding. Fatal haemorrhage, non-fatal ICH, and non-fatal critical organ bleeding were not increased. Bleeding events were minor and reflected in the fact that mortality was decreased with the combination of rivaroxaban and aspirin compared with aspirin alone. Had bleeding events been severe it would have been seen in the fatal bleeding, ICH, critical organ bleeding and also in the mortality endpoints – none of which were affected.[24]

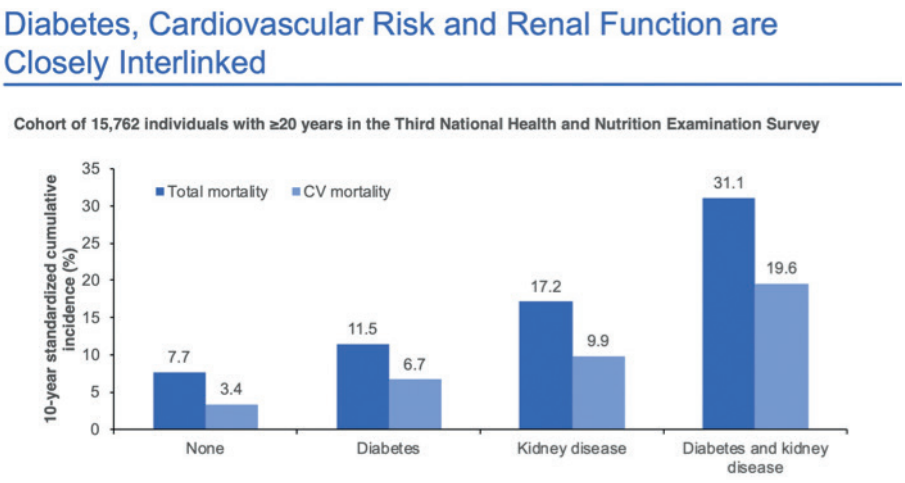
A significant benefit of rivaroxaban 2.5 mg bid plus aspirin was further demonstrated in patients with previous stroke.[29] In the COMPASS trial, patients who had been stable post stroke for more than 4 years prior to trial entry who were given aspirin had a recurrence risk of 3.4% per year, meaning that in 4 years' time these patients have a >12% cumulative risk, and are, therefore, a very high-risk population. The risk of stroke in this group was significantly reduced from 3.4% to 0.7% with 2.5 mg bid rivaroxaban plus aspirin and this is more effective than medical treatments used to prevent stroke in a secondary population. For patients with no history of stroke, independent risk factors were identified in the trial. These included age ≥75 years, high blood pressure, history of hypertension or diabetes, and whether patients had Asian ethnicity.[29] A reduction in major adverse cardiovascular events (MACE) or major adverse limb events (MALE - including major amputation) with low dose rivaroxaban plus aspirin was consistent across subgroups – approximately 2000 individuals with carotid disease in this trial had the same benefit as the overall COMPASS population with fewer deaths, fewer MI, and fewer lower extremity complications using the combination therapy.

Diabetes, CV, and renal function

Around one-quarter of patients with chronic kidney disease (CKD) have diabetes, as does almost one in every two patients in end-stage renal disease, e.g. patients on dialysis.[30] CKD prevalence is high in individuals with diabetes, and there is a strong causality with an associated increase in risk,[31,32] indicating that diabetes is a significant factor, not only to treat but to examine the prognosis of those patients. An epidemiology study, the Third National Health and Nutrition Examination Survey (NHANES III) revealed how diabetes, CV risk, and renal function are closely interlinked.[33] A total of 15,762 individuals aged ≥20 years were studied; 74% (n=11,742) had no diabetes or kidney disease, and total mortality and CV mortality were 7.7% and 3.4%, respectively. A total of 5% of the population had diabetes with a significantly higher total mortality of 11.5% (around 3.9% absolute increase, CI: 0.1-4.6) and also of CV mortality (6.7%). Of the 12% of the population who had kidney disease, total and CV mortality were even higher (17.2% and 9.9%, respectively) and of the 4% who had both diabetes and CKD there was a 23% excess mortality in absolute terms in this Registry compared with the general population with no diabetes or CKD. Therefore, these results showed that total mortality and CV mortality were both increased when individuals had diabetes or isolated CKD, but an exponential increase is seen in total mortality and also in atherosclerosis-associated mortality in individuals with both diabetes and CKD. (Figure 2)

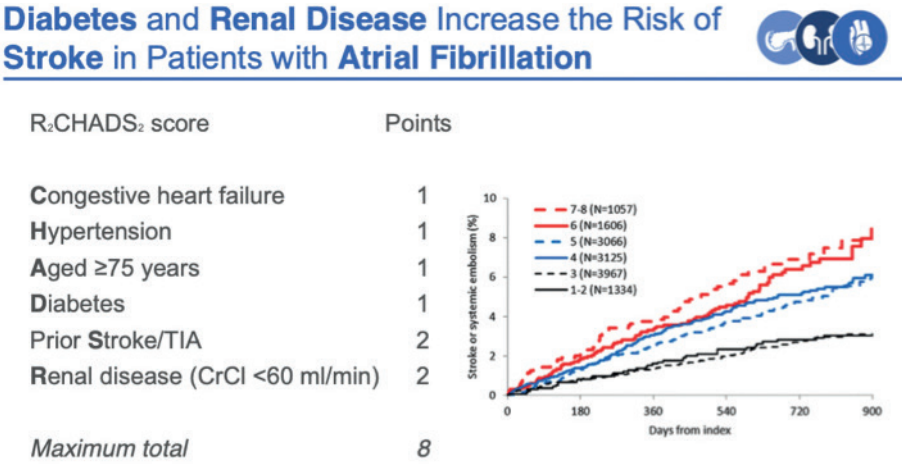
Risk factors in patients with AF: diabetes and renal disease

Renal disease and diabetes also increase the risk of stroke in patients with AF. The ROCKET-AF clinical trial studied 14,000 patients with AF, who were randomised to rivaroxaban or warfarin with follow-up at 1, 2, and 4 weeks and monthly thereafter for the duration of the study. Independent predictors of stroke were evaluated in both groups and, in addition to disorders that provided the $CHADS^2$ scores, renal disease was the second highest risk factor after prior stroke; almost as strong as a prior stroke in predicting future stroke. In the R_2CHADS_2 scores, people with renal disease are assigned two points similar to those with prior stroke, and one point assigned to the remaining CHAD. The higher the R_2CHADS_2 score, the higher the risk of stroke in this cohort of 14,000 people in the ROCKET-AF trial (Figure 3).[35] Renal disease in AF also increased the risk of cardiovascular events, as shown in a Danish Registry of 132,372 patients with non-valvular AF with follow-up over at least ten years.[36-38] Those without renal disease (n=127,884) had a 3.61% per year risk of stroke or systemic embolism and a 3.54% risk of bleeding, whereas those with non-end-stage



Abbrev: AF, atrial fibrillation; CKD, chronic kidney disease; CV, cardiovascular

Figure 2. The association between diabetes, CV risk, and renal function: an exponential increase is seen in total mortality in individuals with both diabetes and CKD.[33]



Abbrev: CrCl, creatinine clearance; TIA, transient ischaemic attack

Figure 3. Relationship of R2CHADS2 score and the increased risk of stroke in patients with atrial fibrillation.[35]

CKD (n=3587) had a doubling in the rate of stroke and systemic embolism and a doubling in the rate of bleeding. Therefore, AF patients with kidney disease are at high risk of embolic events and also of bleeding events.

In the pathophysiology, diabetes is associated with a two-fold increase in stroke;[39] it accelerates atheroma of large and small arteries and predisposes to AF through IHD. If not treated, AF increases the risk of stroke at least 5-fold,[40] and diabetes – perhaps through microvascular and macrovascular disease – causes CKD, which leads to hypertension and AF, which causes stroke.[41]

Why do the kidneys matter in AF?

As anticoagulation therapy can have adverse effects on renal function, it is critical to determine if a patient's AF is associated with CKD and *vice versa* and whether renal function has deteriorated with age as AF is more frequent in the elderly. CKD is associated with an increased risk of subsequently developing AF,[42] and AF has been shown to accelerate CKD progression.[43] This association is likely due to the underlying comorbidities, e.g. hypertension and CAD, and each is an underlying factor for the development of diabetes, stroke, AF, and CKD, thus a surrogate marker for comorbidity.[15,30,44-47]

Renal function in patients with AF

The importance of maintaining adequate renal function in patients with AF is critical as renal function decline is widespread in these patients.[56] Preserving renal function is particularly important in anticoagulated patients with AF as worsening renal function has been shown to increase the risks of stroke and bleeding,[57,58] and dose adjustment is essential.[56] Additionally, patients receiving warfarin over time have a significantly higher risk for calcification of the arteries,[59] suggesting that vitamin K antagonists may induce vascular calcification. In the 21-month follow up of the ROCKET-AF trial, there was a much steeper deterioration of renal function in patients who received warfarin compared with rivaroxaban.[60] This observation was confirmed with real-world evidence supporting the preservation of renal function with rivaroxaban vs warfarin, and those patients who received warfarin showed significantly higher rates of more than 30% decline in eGFR.[56] There was a significantly higher rate of patients on vitamin K antagonist with a doubling of serum creatinine,

occurrence of acute kidney injury, and a trend towards a higher rate of kidney disease. Analyses performed in a diabetes subgroup showed consistent results.

These observations led to the retrospective RELOADED study of factor Xa inhibitors versus phenprocoumon,[61] in patients with non-valvular AF and renal disease – a new user cohort study utilising German claims data between 1 January 2013 and 30 June 2017, (n=23,552). Effectiveness and safety of rivaroxaban vs phenprocoumon was confirmed in this cohort for ischaemic stroke/systemic embolism and intracranial haemorrhage (ICH), in patients with and without renal disease, and a lower risk of stroke for rivaroxaban vs phenprocoumon with significant decrease in ICH and fatal bleeding in those patients with renal dysfunction. The results of the rivaroxaban vs phenprocoumon study showed a trend towards a lower risk for stroke. However, there was a significant decrease in intracranial haemorrhage (ICH) and fatal bleeding in those patients with renal dysfunction. After follow-up, in patients with end-stage renal disease (ESRD), there was a significant lower incidence of ESRD and dialysis in those patients receiving rivaroxaban compared to those patients receiving phenprocoumon. Also, acute kidney disease was more frequently observed in patients who were on phenprocoumon. The latest update of the ACC/AHA/HRS guidelines reflect the benefit of rivaroxaban and dabigatran for the preservation of renal function in patients with AF.[62]

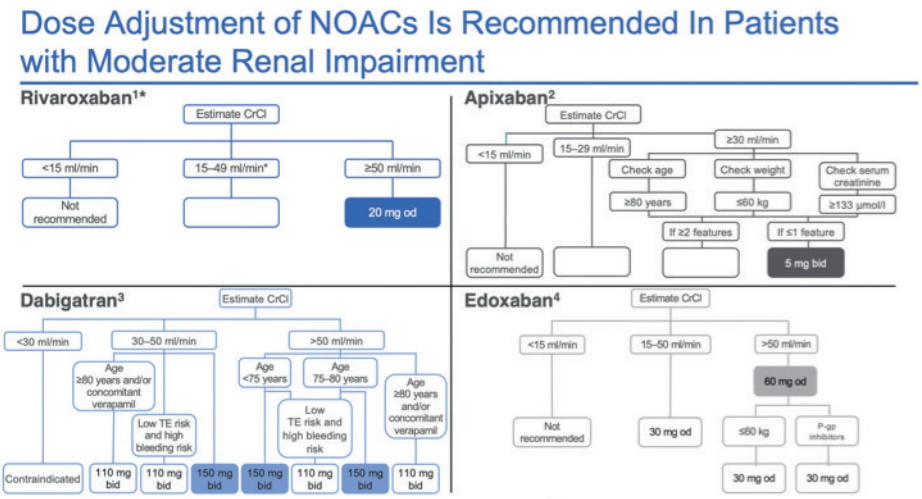
In AF there are several different patient groups to treat in clinical practice, and cardiologists work closely with neurologists where patients have comorbid diseases which impact the left and right atrium. Hypertension, hypertensive heart disease, coronary heart disease, myocardial infarction, heart failure, chronic renal dysfunction, chronic obstructive pulmonary disease, and diabetes are all interrelated. Analyses of the RELOADED study data indicated that NOACs may be associated with a lower risk of worsening renal function compared with phenprocoumon in patients with AF, with or without diabetes. In the subgroup of patients with diabetes, the risk of acute kidney injury was significantly lower only in patients receiving rivaroxaban.[61] AF is not the only factor of induced stroke, but also obesity, sedentary, arterial hypertension, obstructive sleep apnoea, HFpEF, HFrEF, coronary artery disease and chronic kidney disease may amplify those risks for patients with AF regarding stroke risk.

Patients with chronic renal disease have an independent risk for stroke if they have non-valvular AF, and studies suggest that anticoagulants, especially vitamin-K antagonists, may induce vascular calcification and vascular nephropathy with a deterioration of renal function during anticoagulation.[48] Cardiologists and neurologists tend to favour factor Xa inhibitor and direct thrombin antagonists in preference to vitamin K antagonists for stroke prevention in patients with AF, and this meeting summary discusses the data that drive the guidelines to anticoagulate patients with non-valvular AF.

Phase 3 trials for NOACs

Phase 3 trials that evaluated the safety and efficacy of NOACs in patients with moderate renal impairment have driven the clinical guidelines. In these trials, there were significant differences among the number of patients studied with the low dose NOAC intervention. In the ROCKET-AF trial, (n=14,264),[49] low dose rivaroxaban (15 mg od) was prescribed for patients with a creatine clearance (CrCl) lower than 50 mL/min (n=1474), an exclusive dose reduction criterion. In the ENGAGE AF trial, (n=21,105),[18,50] approximately 1700 patients were treated with the lower dose edoxaban (30 mg od), mostly due to renal dysfunction, P-glycoprotein inhibitor use, or because the patient had a lower weight. In the RE-LY trial, (n=18,113)[16,51] where there was no dose reduction criterion, 6015 patients had the low dose of dabigatran (110 mg bid) – only in the ROCKET-AF trial were all low dose patients diagnosed with moderate renal dysfunction (n=1474, 20.7%), although this was also true for a similarly large percentage in the ENGAGE TRIAL (n=1379, 19.6%). Even in the RE-LY dabigatran trial, the first NOAC trial, there were around 1200 patients with moderate renal impairment (9.9%), but data relating to patients with renal dysfunction on the reduced dose of apixaban on the ARISTOTLE AF trial, (n=18,201),[17,52,53] came from only 149 patients (1.6%). Accordingly, dose adjustment of NOACs is recommended in patients with moderate renal impairment, (Figure 4) and these results formed the basis of the data used in the clinical world which subsequently led to the current guidelines.[54]

Sub-studies of the ROCKET-AF trial demonstrated that patients with moderate renal impairment show consistent data compared with patients with no renal impairment, with a trend towards lower stroke and systemic embolism in patients receiving rivaroxaban compared with warfarin.[49]



Abbrev: bid, twice daily; CrCl, creatinine clearance; NOAC, non-vitamin K antagonist oral anticoagulant; od, once daily; TE, thromboembolic
**Rivaroxaban is to be used with caution in patients with CrCl 15–29 mL/min*
1. Rivaroxaban SmPC; 2. Apixaban SmPC; 3. Dabigatran SmPC; 4. Edoxaban SmPC

Figure 4. Comparison of NOAC dose adjustment criteria in patients with moderate renal impairment.

Rivaroxaban also showed consistent safety when compared with warfarin in patients with non-valvular AF and moderate renal impairment.[49]

Conclusion

Diabetes, AF, and CKD are all risk factors for stroke, and there are many facets to the cause of ischaemic and haemorrhagic stroke, the prognosis, and also the management and risks of therapies. These factors are interrelated; AF is not merely a factor to induce stroke, but significant other diagnoses – obesity, arterial hypertension, diabetes, obstructive sleep apnea, heart failure, CAD and CKD – may amplify those risks for patients with AF regarding stroke risk. Diabetes significantly increases the risk of stroke by at least 50%. People who have AF and diabetes showed the same pattern of benefit in all the NOAC trials as shown in the primary trial, so this was not a condition which led to loss of benefit, nor was it a condition where an excess of haemorrhage was observed, as might be expected. Diabetes patients benefit from the effect of rivaroxaban and dabigatran in preserving their renal function, since they are at higher risk of developing ESRD. In the COMPASS trial, individuals were identified by CAD or PAD, including carotid disease, and benefited significantly from the combination of low dose rivaroxaban 2.5 mg bid plus aspirin when compared with aspirin alone for stroke, with additional benefit for mortality and MI. Patients with a history of stroke, with carotid disease, ≥75 years, hypertensive, diabetic, and of Asian ethnicity all benefited from the intervention treatment.

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