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A new decade for patients with atrial fibrillation

Protect the irreplaceable

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Learning objectives

You will learn:

- Lessons from more than a decade of using non-vitamin K oral anticoagulants (NOACs) for stroke prevention in the patient with atrial fibrillation (AF)
- Assessment of stroke risk and key factors to consider in the patient with AF
- Real-world and clinical trial evidence for the reduction of risk in AF patients with diabetes who are using rivaroxaban
- Post-COVID-19 cardiac work-up in patients with AF.

Introduction

Even in the context of the COVID-19 pandemic, cardiovascular disease remains a leading cause of death and morbidity. Atrial fibrillation (AF) is the most common cardiovascular disorder; as of 2016, 43.6 million people have AF/atrial flutter globally and the prevalence is expected to increase as the population ages.[1]

It is over a decade since non-vitamin K oral anticoagulants (NOACs) were formulated. GARFIELD, an international registry of AF patients, shows increasing use of a NOAC for stroke prevention over this period, with 2020 being the first year that NOACs were used by more than half of the registry for antithrombotic protection. The practical benefits of NOACs are fixed dosing, no need for regular monitoring and reduced drug-drug interactions compared to warfarin.

With all that has been learned about NOACs over the last decade, Dr Manesh Patel ponders what it is that we will learn in the coming decade that we have not learned already. Dr Patel shares his own experience of treating AF and presents the real-world and clinical trial evidence that underpins current approaches to optimal use of NOACs in the AF patient.

This report was made possible by an unrestricted educational grant from **Bayer**. The content of the report is independent of the sponsor.

Case study – 'An extremely common patient'

Patient information:

Mrs ZM, 71-years-old

- AF
- Hypertension
- Diabetes.

This is the first time Mrs ZM has been referred to the cardiovascular practice; she and her family have concerns about her unsteadiness and some pain in her legs when she walks. Findings from history and examination are:

- Peripheral neuropathy
- Chronic AF with a heart rate of 73 beats per minute (bpm), but no chronic heart flutter symptoms
- eGFR 41ml/min/1.73m^2
- Possibility of peripheral artery disease (PAD).

Current medications:

- Metformin
- Amlodipine
- Atorvastatin
- Multivitamin.

Expert comment

Dr Patel is immediately alerted to the use of metformin as a glucose-lowering agent for the management of Mrs ZM's diabetes. The new antidiabetic agents, the sodium-glucose co-transporter-2 (SGLT-2) inhibitors and the glucagon-like peptide-1 receptor agonists (GLP-1 RAs), are not only efficacious for glycaemic control but also provide cardiovascular benefits.

Key questions when considering Mrs ZM's care include: "Should she be treated? What should she be treated for? How should she be treated and with what should she be treated?"

Preventing stroke is a primary goal in the management of the AF patient; other key goals are preventing cardiovascular death and vascular events, mitigating bleeding, preserving renal function and optimising medication dose

What does protection mean?

Considering that Mrs ZM has diabetes, high blood pressure and marginal renal insufficiency, which outcomes is she most at risk of? Preventing stroke is a primary goal in the management of the AF patient; other key goals are preventing cardiovascular death and vascular events, mitigating bleeding, preserving renal function and optimising medication dose.

How should the AF patient be assessed?

When assessing the risk of stroke in the AF patient, which scoring measure is currently preferred? $CHADS_2$, CHA_2DS_2-VASc, HAS-BLED, haemoglobin, creatinine? Dr Patel prefers the CHA_2DS_2-VASc score for AF stroke risk assessment because it is a good measure of the risk factors of vascular function, heart failure, hypertension and diabetes, together with others; CHA_2DS_2-VASc, compared to the other risk assessment measures mentioned above, gives him a clearer understanding of how to dose his patient.

CHA_2DS_2-VASc calculation

$$\text{eCrCl} = \frac{(140 - \text{Age}) \times \text{Weight (kg)}}{72 \times \text{Creatinine}_{\text{serum (mg/dL)}}} \times 0.85 \text{ if female}$$

Dr Patel points out that no randomised controlled trials (RCTs) of NOACs used CHA_2DS_2-VASc; the $CHADS_2$ score was used because that is what was available at the time of the original NOAC trials and also because this was the measure that warfarin was used against. In this context, a $CHADS_2$ score of ≥2 was an indication for the initiation of warfarin, but as it was increasingly understood over time that warfarin was effective for stroke prevention, it was used in patients who were scored as lower risk.

The European Society of Cardiology (ESC) 2020 guidelines for the management and diagnosis of AF[1] base the assessment of stroke risk and subsequent treatment recommendations on CHA_2DS_2-VASc. If the patient has a mechanical heart valve or moderate/severe mitral stenosis they must use warfarin as the anticoagulant for stroke prevention; if not, the CHA_2DS_2-VASc score determines whether oral anticoagulation should be considered (a score of 1) or whether it is indicated (a score ≥2). A CHA_2DS_2-VASc of 1 is a much lower risk than a $CHADS_2$ score of 2 or 1, as used in initial trials, but even so an oral anticoagulant should be considered. When oral anticoagulation is clearly indicated (CHA_2DS_2-VASc ≥2), a NOAC is preferred over a vitamin K antagonist (VKA) if the patient has no contraindications or irreversible bleeding factors. No antiplatelet or anticoagulant treatment is required with a CHA_2DS_2-VASc score of 0 (Figure 1).

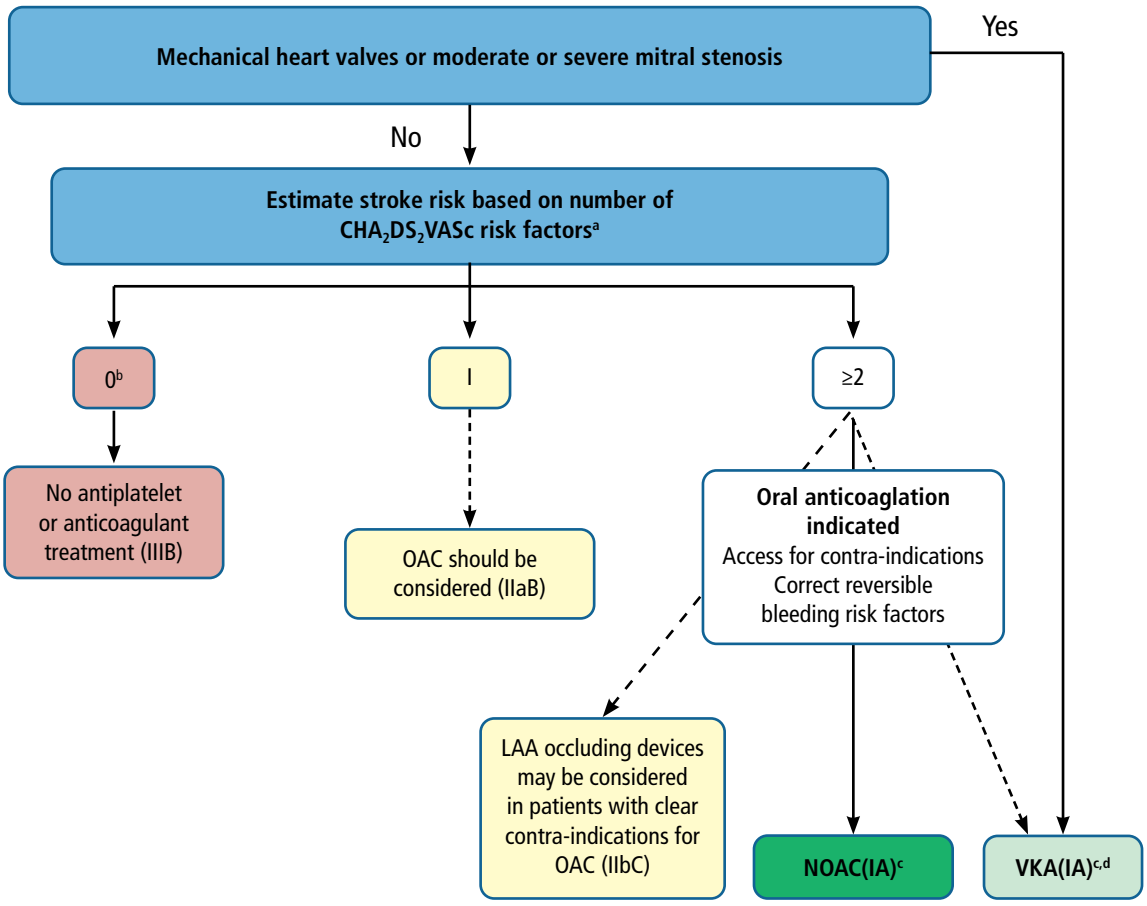


Figure 1. ESC algorithm for stroke prevention in the AF patient[1]

Diabetes has been identified as a strong and consistent independent risk factor for stroke in patients with AF

Key factors to consider in the patient with AF

Dr Patel maintains that the three features that contribute most to AF are age or coronary artery disease (CAD), renal impairment and diabetes. These factors are often associated with heart failure, hypertension and other comorbidities, and must be effectively managed to prevent adverse outcomes.

Diabetes has been identified as a strong and consistent independent risk factor for stroke in patients with AF and is a significant cardiovascular risk factor in patients with PAD or CAD. Diabetes is also independently associated with an increased risk of developing AF. Hyperglycaemia has several macrovascular and microvascular implications (Figure 2).[2] Key microvascular complications are prevented by improved glucose control over the long term and in respect of macrovascular complications such as PAD, CAD and stroke, the newer SGLT-2 inhibitors and GLP-1 RAs have demonstrated some benefit.

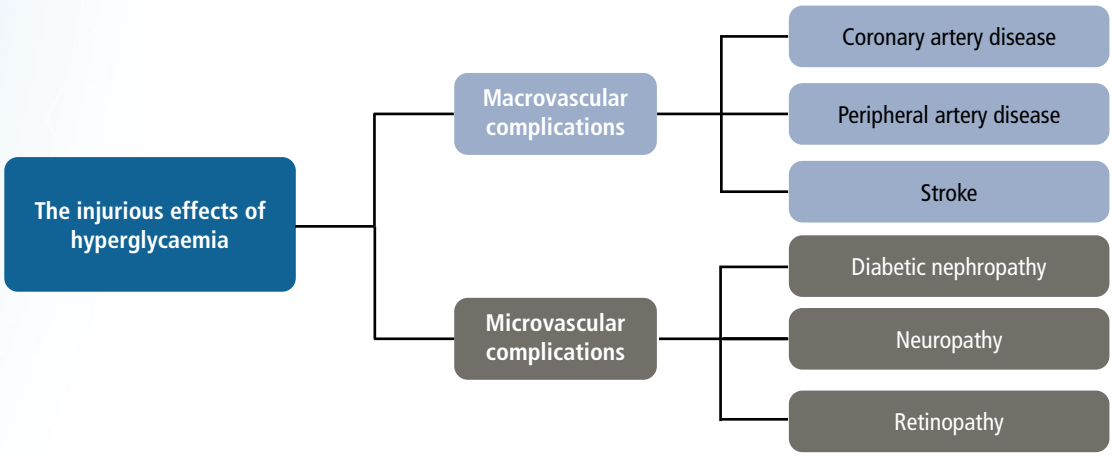


Figure 2. Macrovascular and microvascular complications of hyperglycaemia[1]

What is the evidence of risk reductions when using NOACs in AF patients with diabetes?

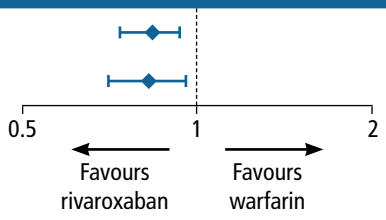
Real-world evidence can provide additional helpful information on the effectiveness and safety profiles of treatments as they are actually used

The advantages of considering real-world evidence as complementary to RCT data are that this gives further information on different patients of different ethnicities in different settings, providing valuable insights and knowledge to support patient care. Real-world evidence can provide additional helpful information on the effectiveness and safety profiles of treatments as they are actually used (including treatment errors, missed intake and inappropriate patient selection), helping to clarify whether the results reported in the RCTs are also observed in everyday use of the medication.

Real-world data from the RELOADED study[3] indicate benefit when using NOACs compared to VKAs in patients with AF and diabetes for the prevention of ischaemic stroke and systemic embolism, with less intracranial haemorrhage. There were similar rates of fatal bleeding with both VKAs and NOACs, although there were numerically fewer fatal bleeds with NOACs.

RELOADED also indicates a potentially protective effect of NOACs on end-stage renal disease and worsening renal function. US MarketScan data presented at the International Society on Thrombosis and Haemostasis 2019 Congress indicated a lower risk for acute kidney injury (AKI) in patients with AF and diabetes receiving rivaroxaban versus warfarin (Figure 3). While Dr Patel warns that observational data should be used with caution, this real-world evidence does inspire confidence that rivaroxaban may at the very least be safer, if not better, than warfarin in patients with renal dysfunction. It is important to note that patients with both diabetes and renal disease are at significantly increased risk of MI and all-cause mortality.[4]

	Rate per 100 PYs		HR (95% CI)	p-value
	Rivaroxaban	Warfarin		
AKI	7.70	13.45		0.83 (0.74–0.92)
Stage 5 CKD or haemodialysis	3.74	6.03		0.82 (0.70–0.96



Sensitivity analysis using an intention-to-treat approach, excluding patients with AKI at baseline and limited to patients with >365 days of follow-up, yielded consistent results AKI, acute kidney injury; CI, confidence interval; CKD, chronic kidney disease; NVAF, non-valvular fibrillation; PY, patient years

Figure 3. Risk of major adverse renal outcomes with rivaroxaban vs warfarin

Of the NOAC RCTs,[5-12] ROCKET AF had the highest proportion of patients (40%) with diabetes (Figure 4). The mean $CHADS_2$ score was 3.7 and 21% of subjects had moderate renal impairment, with rivaroxaban dose adjusted to 20mg if eGFR >50ml/min/1.72m^2

or 15mg if <50ml/min/1.72m^2 at the start of the trial. Sub-group analysis of these diabetic patients indicated that when treated with rivaroxaban compared to warfarin, this high-risk population certainly had a lower rate of stroke and systemic embolism, and cardiovascular death. Both RCT and observational data indicate less cardiovascular disease, major adverse cardiovascular events (MACE) and major adverse limb events (MALE) in patients using rivaroxaban versus warfarin. US MarketScan data showed that rivaroxaban was associated with lower risks of MACE and MALE versus warfarin in patients with AF and type 2 diabetes (Figure 5) in regular clinical practice.[5,13,14]

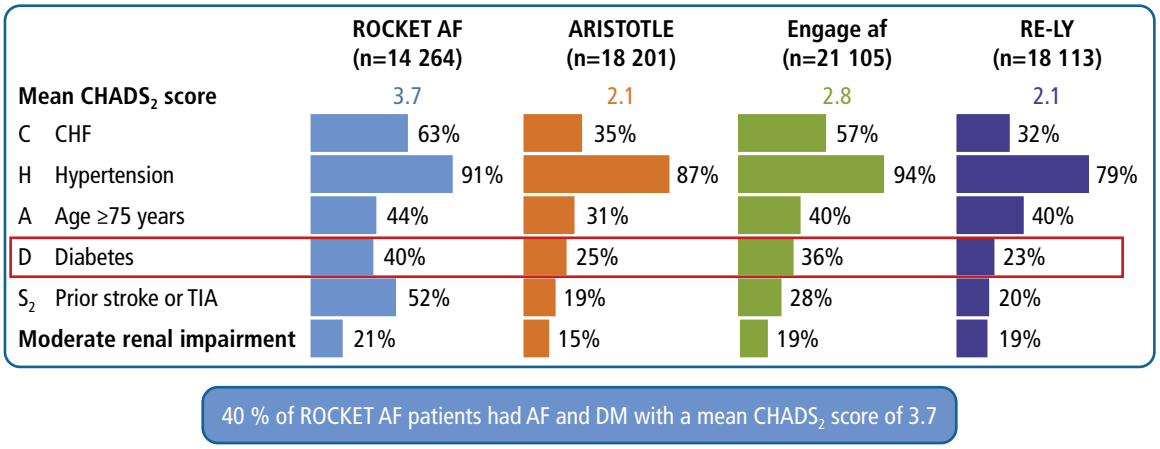
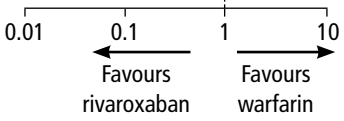


Figure 4. Baseline characteristics of study participants enrolled onto each NOAC RCT[5-12]

Both RCT and observational data indicate less cardiovascular disease, MACE and MALE in patients using rivaroxaban versus warfarin

Analysis of US MarketScan claims data for patients with NVAF and comorbid T2DM initiating therapy with warfarin (n=13 946) or rivaroxaban (n=10 700; 24.1% of these received a reduced dose)

	Event rate (per 100 PY)		HR (95% CI)	p-value
	Rivaroxaban	Warfarin		
MACE	1.26	2.07		0.75 (0.59–0.96)
Ischaemic stroke	0.66	1.01		0.83 (0.59–1.17)
MI	0.77	1.20		0.77 (0.56–1.06)
Major bleeding	2.38	3.37		0.95 (0.79–1.15)
Intracranial	0.17	0.36		0.59 (0.30–1.13)
Gastrointestinal	1.85	2.44		1.04 (0.84–1.30)
MALE	0.19	0.75		0.37 (0.21–0.65)
Major limb amputation	0.03	0.18		0.20 (0.06–0.69)
Surgical revascularisation	0.12	0.27		0.66 (0.31–1.39)
Endovascular revascularisation	0.07	0.39		0.27 (0.11–0.67)
Minor limb amputation	0.14	0.27		0.72 (0.34–1.53)



CI, confidence interval; HR, hazard ratio; MACE, major adverse cardiovascular events; MALE, major adverse limb events; NVAF, non-valvular atrial fibrillation; T2DM, type 2 diabetes mellitus

Figure 5. Real-world evidence: MACE and MALE in AF patients with type 2 diabetes using rivaroxaban vs warfarin

Meta-analysis of pooled data from the NOAC RCTs favours NOACs over warfarin for significant reduction in haemorrhagic stroke and all-cause mortality, and potential benefit for ischaemic stroke and MI (Figure 6). REVISIT-US studied the association between NOAC use (rivaroxaban, apixaban, dabigatran) and ischaemic stroke, compared to warfarin, and these data are consistent with RCT findings (Figure 7). The XANTUS registry of patients using rivaroxaban shows bleeding and stroke rates that are lower than those observed in ROCKET AF.[15-17]

	Pooled NOAC (events)	Pooled warfarin (events)	RR (95% CI)	p=value
Ischaemic stroke	665/29 292	724/29 221	0.92 (0.83–1.02)	0.10
Haemorrhagic stroke	130/29 292	283/29 221	0.49 (0.38–0.64)	<0.0001
Myocardial infarction	413/29 292	432/29 221	0.97 (0.78–1.20)	0.77
All-cause mortality	2 022/29 292	2 245/29 221	0.90 (0.85–0.95)	0.0003

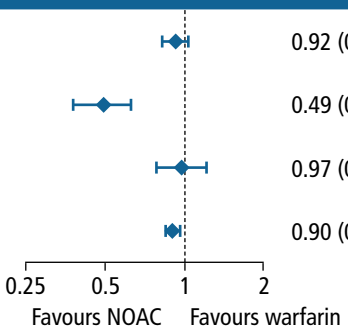
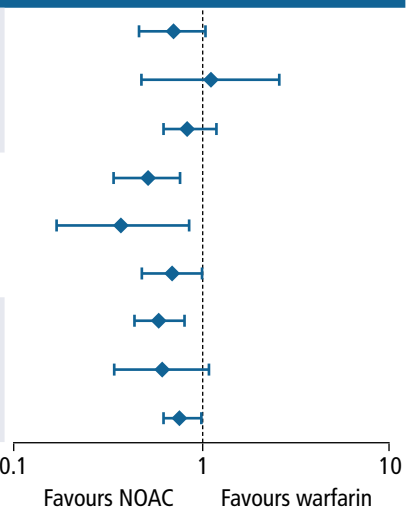


Figure 6. NOACs significantly reduce haemorrhagic stroke and all-cause mortality versus warfarin[15]

		HR (95% CI)
Ischaemic stroke	Rivaroxaban vs warfarin	0.71 (0.47–1.07)
	Apixaban vs warfarin	1.13 (0.49–2.63)
	Dabigatran vs warfarin	0.87 (0.63–1.22)
ICH	Rivaroxaban vs warfarin*	0.53 (0.35–0.79)
	Apixaban vs warfarin*	0.38 (0.17–0.88)
	Dabigatran vs warfarin	0.71 (0.49–1.02)
Ischaemic stroke and ICH	Rivaroxaban vs warfarin	0.61 (0.45–0.82)
	Apixaban vs warfarin	0.63 (0.35–1.12)
	Dabigatran vs warfarin	0.79 (0.62–1.02)



*p<0.05 vs warfarin

Figure 7. REVISIT-US: Association between NOAC use vs warfarin and ischaemic stroke or intracranial haemorrhage

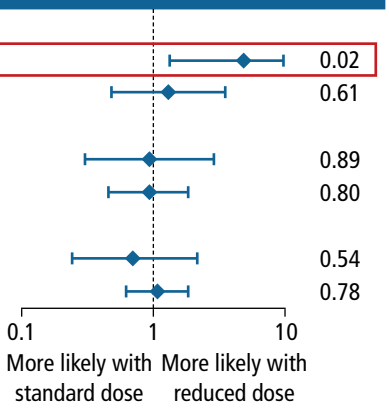
Not only is there an increased risk of stroke, but reduced NOAC doses are also associated with a higher rate of bleeds (6%) compared to standard doses (4.6%)

Getting the dose right

In terms of bleeding outcomes in patients with AF and diabetes, the ESC guidelines state: 'Bleeding risk reduction with NOACs was similar in diabetic and non-diabetic patients except for apixaban.' Dr Patel considers that the issue with apixaban may arise from dose confusion in patients with renal impairment, and with inappropriate dose lowering or use of a different dose that does not give rise to the same benefit.[1,5,18,19]

In clinical practice, as many as 44% of patients are prescribed the low dose of apixaban (2.5mg); patients and doctors both want to use a lower dose as they think it will reduce the risk of bleeds. US insurance claims data on the use of NOACs without a renal indication for dose adjustment indicates a stroke rate of 2.5% with the 2.5mg dose versus a 0.54% risk in patients using the standard 5mg dose. Not only is there an increased risk of stroke, but reduced NOAC doses are also associated with a higher rate of bleeds (6%) compared to standard doses (4.6%) (Figure 8). These data highlight the importance of getting the dose right.[8,20]

	Reduced dose %/year	Standard dose %/year	HR	95% CI	p-value
Apixaban (n=550 per group)*					
Stroke/SE	2.57	0.54	4.87	1.30–18.26	0.02
Major bleeding	6.01	4.64	1.29	0.48–3.42	0.61
Dabigatran (n=412 per group)*					
Stroke/SE	1.64	1.75	0.92	0.30–2.87	0.89
Major bleeding	4.99	5.54	0.91	0.45–1.85	0.80
Rivaroxaban (n=815 per group)*					
Stroke/SE	1.23	1.65	0.71	0.24–2.09	0.54
Major bleeding	5.42	4.90	1.09	0.63–1.87	0.78



*Propensity-score matched based on 50 socio-demographic characteristics, co-morbidities and baseline medication used.

Figure 8. Patient outcomes when initiating NOACs are reduced versus standard dose

Post-COVID-19 cardiac work-up

Suboptimal adherence gives rise to a 0% increase in risk of ischaemic stroke, irrespective of dosing regimen

Six weeks ago, Mrs ZM was infected with COVID-19; although she did not have to be hospitalised, she remains quite fatigued and has lost her sense of taste and smell. She consults with you for advice on whether she should continue taking her medication and if she can return to the activities of her normal lifestyle.

Throughout this period she has adhered to the 15mg rivaroxaban once-daily regimen that you prescribed at her initial consultation. People are more likely to be adherent to a once-daily regimen, with 81% of patients preferring once-daily anticoagulation; self-reported adherence data indicate that of those prescribed a twice-daily regimen, as many as one-third were actually only taking their dose once daily. Suboptimal adherence gives rise to a 50% increase in risk of ischaemic stroke, irrespective of dosing regimen.[21-23]

Which, if any, tests should be performed to see if Mrs ZM has any COVID-19-related myocardial involvement? A post-COVID-19 pro-athlete screening study using ECG, troponin and a Doppler echo found that 3% of the athletes had more than one abnormal test result, indicating the potential degree of COVID-19 myocardial involvement in the healthy heart, with few cases of inflammatory heart disease being detected.[24,25] Because Mrs ZM has AF, there is the likelihood that there may be an effusion or change in wall motion, or some other functional decline, and it is therefore advisable that she have an ECG and, if possible, a cardiac MRI scan to see whether COVID-19 myocarditis is present.

There is a thrombosis risk associated with COVID-19, with best available current review data indicating that among COVID-19 patients, venous thromboembolism was present in 20% and stroke was present in 3%; this indicates a significant increase in the risk of thrombosis in the AF patient infected with COVID-19, highlighting the importance of adherence to NOAC therapy.

Key learnings

- The practical benefits of NOACs include fixed dosing, no need for regular monitoring and reduced drug-drug interactions compared to warfarin
- Although stroke prevention is the primary goal in managing AF, other key goals must be taken into consideration, including management of renal impairment and diabetes
- CHA_2DS_2-VASc is best for assessing stroke risk
- Real-world and RCT evidence indicate benefit when using NOACs compared to VKAs in patients with AF and diabetes for the prevention of ischaemic stroke and systemic embolism, with less intracranial haemorrhage
- Rivaroxaban is associated with lower risks of MACE and MALE versus warfarin in patients with AF and type 2 diabetes
- Post-COVID-19 investigations of the AF patient should include an ECG and cardiac MRI scan to determine the presence of COVID-19 myocarditis.

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This CPD accredited programme was written for *deNovo Medica* by
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