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Diabetes and thromboembolic risk

Report and case study

Professor Peter Rossing
Diabetologist
Copenhagen
Denmark

Professor Manesh Patel
Cardiologist
Duke University
North Carolina
USA

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Introduction

Today most practising clinicians are aware of the rampant spread of diabetes throughout the world. Most estimates suggest that diabetes affects between 30% and 35% of the population. This report considers the interface between diabetes and cardiovascular disease, which manifests as coronary artery disease, stroke and/or peripheral arterial disease, chronic kidney disease (CKD), atrial fibrillation (AF) and their individual and combined impacts on prognosis. Professor Peter Rossing discusses the links between diabetes and kidney disease and Professor Manesh Patel considers the interrelationships between diabetes, AF, chronic kidney injury and peripheral arterial disease, pointing out recent observations on the effect of NOACs in these settings.

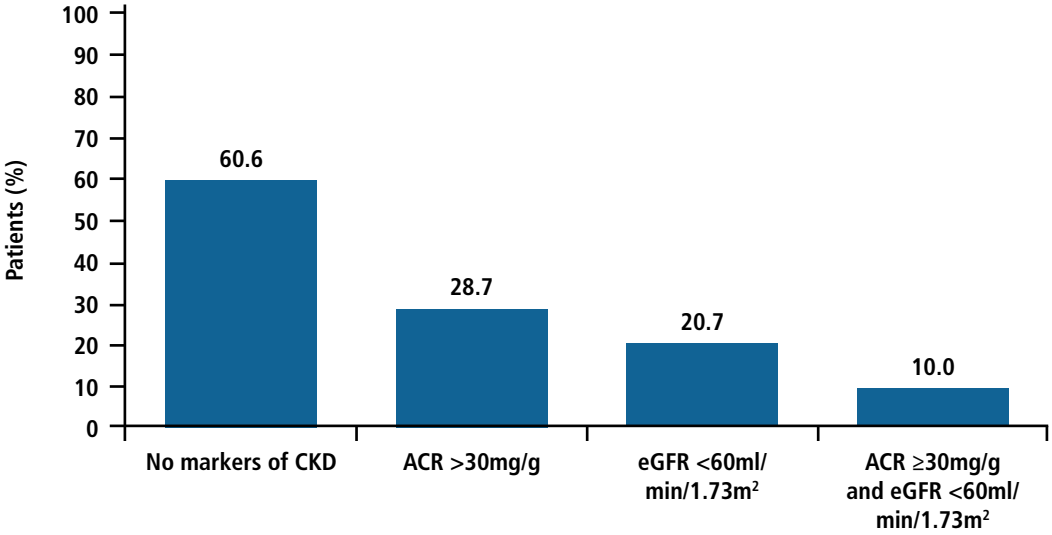
A significant percentage of patients with diabetes also have CKD; 28% will have albuminuria, 20% will have impaired renal function and 10% will have the combination of both of these. Approximately 60% of diabetics have normal kidney function (Figure 1). Glycaemic control is important, as glycaemia is related not only to the occurrence of micro- and macrovascular complications in the kidneys, but also in the eyes, vascular system and heart.

Type 2 diabetes mellitus (T2DM), often associated with obesity, can lead to kidney disease either via the metabolic pathway of hyperglycaemia or through a dynamic pathway caused by hypertension that leads to intense pressure in the kidney, glomerulosclerosis, fibrosis and the further increase of blood pressure. Resultant progressive kidney disease can lead to end-stage kidney disease (Figure 2).[1-3]

LEARNING OBJECTIVES

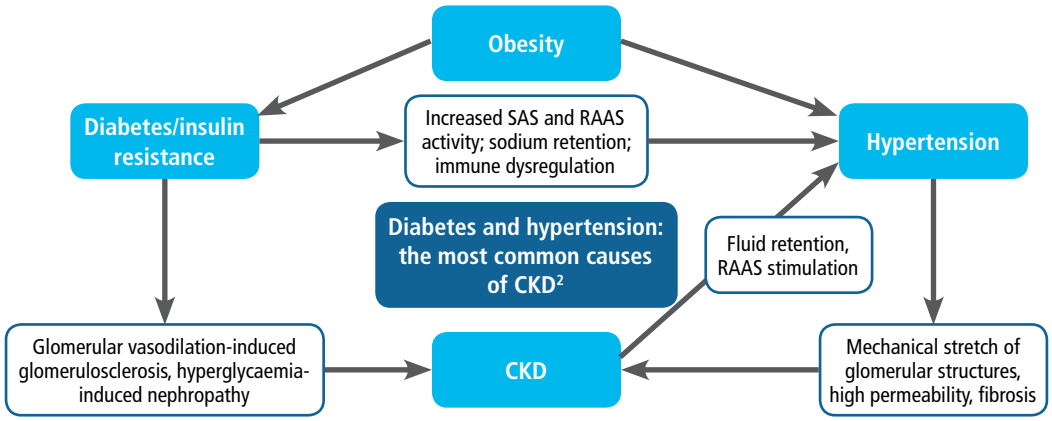
You will learn:

- The patient with diabetes is at increased risk of progressive kidney disease
- Diabetes increases the risk of developing atrial fibrillation; comorbidity is associated with increased risk of death and cerebrovascular events
- Diabetic patients with atrial fibrillation show a trend toward slower progression of acute kidney injury and reduced risk for end-stage renal disease when using non-vitamin K antagonist oral anticoagulant therapy in randomised controlled trials and real-world practice
- Diabetes patients with renal impairment have increased cardiovascular risk; randomised controlled trial and real-world data show benefit of rivaroxaban over warfarin for stroke/systemic embolism, major bleeding and intracranial haemorrhage.



CKD: chronic kidney disease; ACR: albumin-to-creatinine; eGFR: estimated glomerular filtration rate

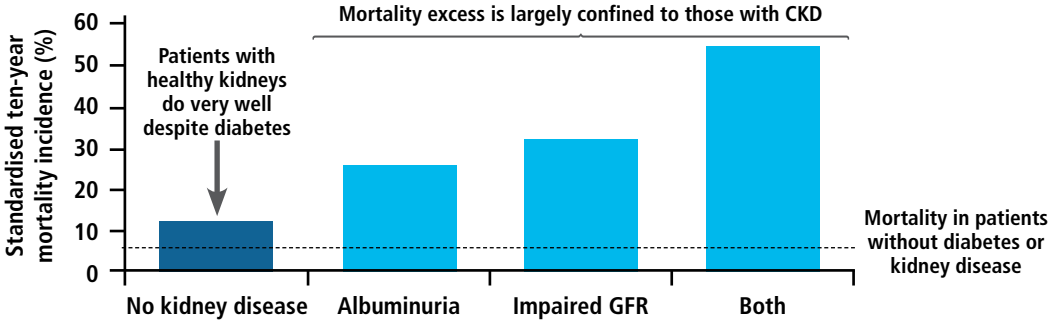
Figure 1. Kidney disease in diabetes patients – distribution of markers for CKD in NHANES participants with diabetes, 2011-2014



RAAS: renin-angiotensin-aldosterone system; CKD: chronic kidney disease

Figure 2. Diabetes increases the risk of kidney disease[1-3]

The impact of kidney disease affects the prognosis of the diabetic patient. The risk of mortality is relatively low when there is no kidney disease, but the presence of either albuminuria or impaired renal function significantly increases that risk. A combination of both proteinuria and impaired renal function significantly increases 10-year mortality in diabetes patients (Figure 3).[4]



CKD: chronic kidney disease; GFR: glomerular filtration rate

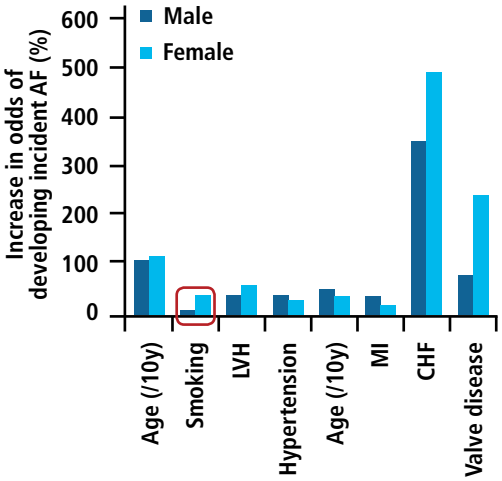
Figure 3. Mortality risk – impact of kidney disease in T2DM[4]

Diabetes predisposes patients to atrial fibrillation

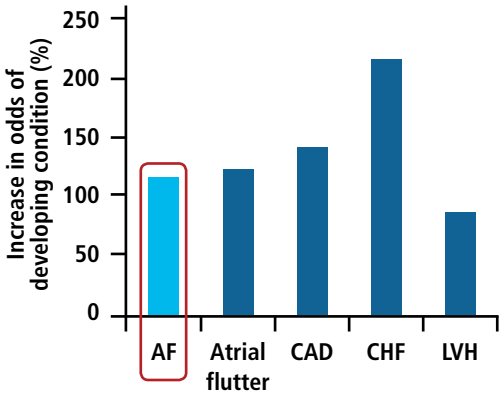
Diabetes also increases the risk for the development of AF. Two cohort studies, the first based on Framingham data and the second on a large American register from the Veterans' Health Administration Hospitals, have associated diabetes with increased AF risk. The Framingham data reflected a 40% increased risk of AF and there was a doubling of risk in the American study (Figure 4).[5,6]

In T2DM patients with AF, there is a substantially increased risk of death and cardiovascular events. This was shown in the ADVANCE trial of 11 140 T2DM patients, including 7% with AF. In this study, AF impacted on the outcome of both all-cause mortality and major cerebrovascular events over five years (Figure 5).[7]

Framingham Heart Study: diabetes increased the odds of developing AF by 40% for men and 60% for women[5]

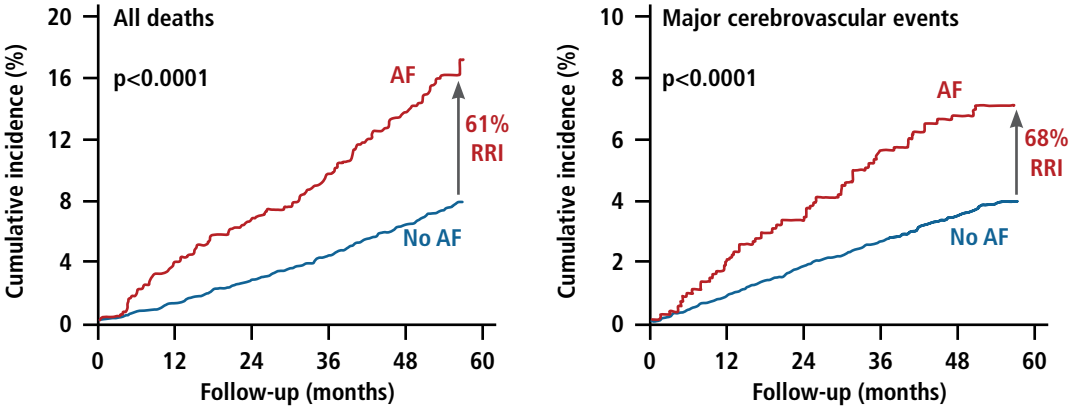


Diabetes was identified as a strong independent risk factor for AF in a large database analysis (n=293 124)[6]



AF: atrial fibrillation; LVH: left ventricular hypertrophy; MI: myocardial infarction; CHF: congestive heart failure; CAD: coronary artery disease

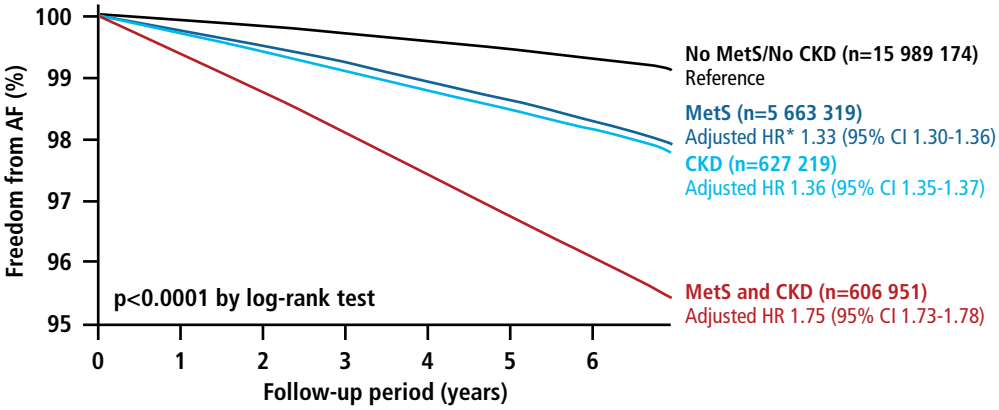
Figure 4. Diabetes predisposes patients to AF[5,6]



T2DM: type 2 diabetes mellitus; AF: atrial fibrillation; RRI: relative risk increase

Figure 5. AF and T2DM frequently co-exist and are associated with subsequent increased risk of death and cerebrovascular events[7]

The risk for development of AF is further increased in the patient with CKD and the metabolic syndrome, which is characterised by dysglycaemic traits other than diabetes (Figure 6).[8] This stresses the need for clinicians to screen not only their T2DM patients' glucose levels, but for all relevant risk factors, and to consider appropriate interventions, including non-vitamin K antagonist oral anticoagulants (NOACs) for the management of AF.



CI: confidence interval; CKD: chronic kidney disease; HR: hazard ration; MetS: metabolic syndrome

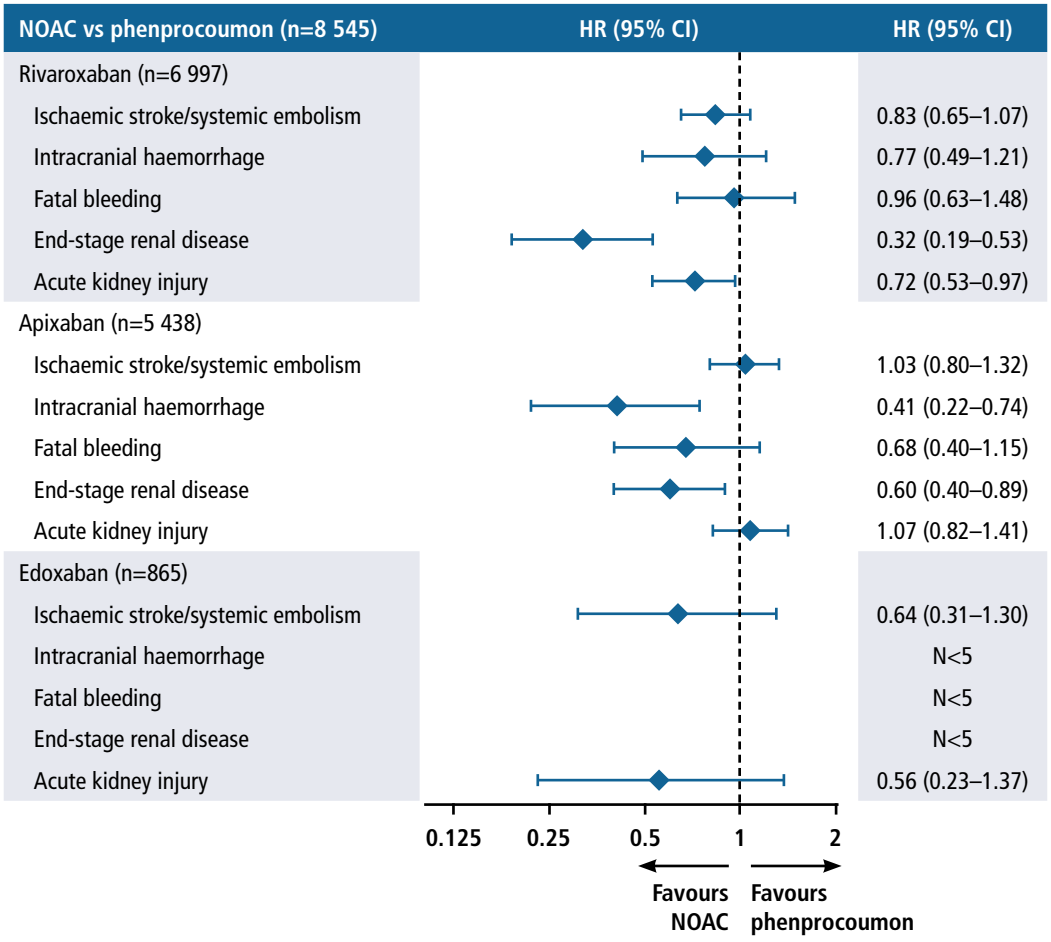
Figure 6. The metabolic syndrome and CKD increase risk of AF[8]

Kaplan-Meier curves showing the cumulative event-free survival for AF in patients classified into four groups based on the presence/absence of metabolic syndrome and CKD. *The associations were tested using a Cox proportional hazards model adjusted for age, sex, alcohol consumption, smoking status and physical activity.

These results stress the need for clinicians to screen not only their T2DM patients' glucose levels, but for all relevant risk factors, and to consider appropriate interventions including NOACs for the management of AF

Risk reduction in T2DM patients with AF using NOACs

The RELOADED study of diabetic patients with non-valvular AF (NVAF) using rivaroxaban showed a trend towards risk reduction for end-stage renal disease and a slower progression to acute kidney injury (AKI). There was no increase in ischaemic/systemic embolism, intracranial haemorrhage and fatal bleeding with the use of rivaroxaban (Figure 7).[9]



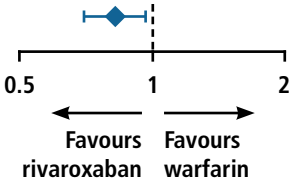
CI: confidence interval; HR: hazard ratio; NOAC: non-vitamin K antagonist oral anticoagulant; NVAF: non-valvular atrial fibrillation

Figure 7. RELOADED: Trend towards risk reductions observed in T2DM patients with NVAF using NOACs[9]

Follow-up of patients, using ICD10 diagnostic codes for diabetes and AF and prescription information from MarketScan and other real-world data sets, evaluated progression to renal dysfunction (AKI, stage 5 CKD or haemodialysis) of those patients newly initiated on either rivaroxaban or warfarin. Diabetic patients likely to be at higher risk showed renal protection using rivaroxaban treatment compared to warfarin (Figure 8).[10]

It is important to recognise that the microvascular complications (nephropathy, neuropathy, retinopathy) and the macrovascular complications (coronary disease, peripheral disease, stroke) are all manifestations of the same pathobiology of vascular dysfunction, atherothrombosis and atherosclerosis in the patient with diabetes.

	Rate per 100 PYs			
	Rivaroxaban	Warfarin	HR (95% CI)	HR (95% CI)
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)



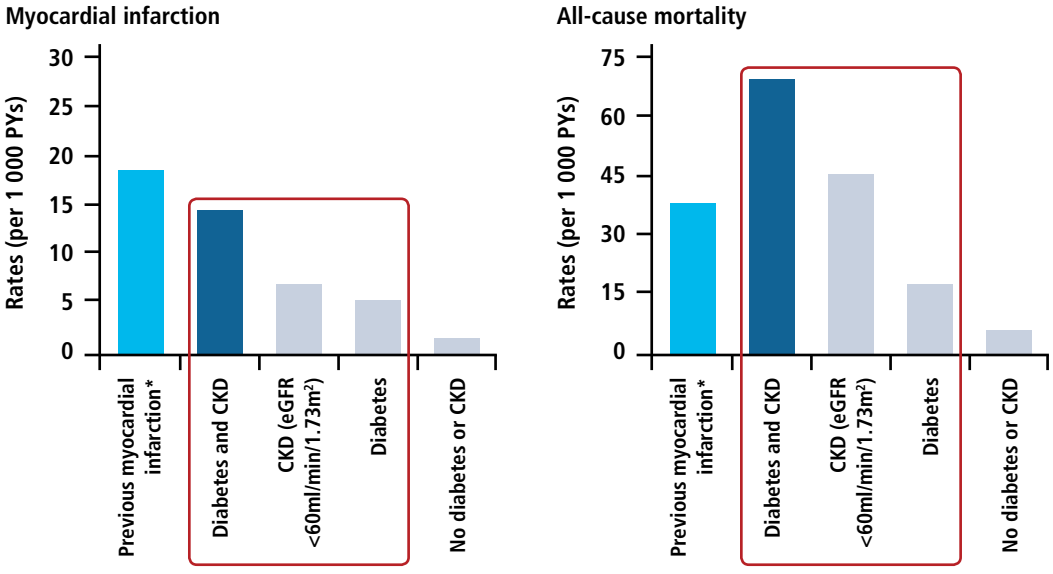
AKI: acute kidney injury; CI: confidence interval; CKD: chronic kidney disease; NVAF: non-valvular atrial fibrillation; PY: patient-years

Figure 8. Risk of major adverse renal outcomes in diabetic patients with AF receiving rivaroxaban vs warfarin[10]

Retrospective analysis of US MarketScan claims data for patients with NVAF and diabetes, newly initiating therapy with rivaroxaban (n=10 017) or warfarin (n=11 665). Patients with CKD stage 5 or on haemodialysis were excluded.

Patients with diabetes and renal impairment have increased cardiovascular risk

Meta-analysis of 1.2 million people from the Alberta Kidney Disease Network (AKDN) database and the National Health and Nutrition Examination Survey (NHANES) 2003-2006 showed, over a 48-month follow-up, a stepwise increase of cardiovascular risk in patients with diabetes and CKD as opposed to the presence of kidney dysfunction only or diabetes only (Figure 9).[11]



*Includes participants with or without diabetes and CKD. This study did not investigate patients with AF.
PYs: patient-years; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate

Figure 9. Patients with diabetes and renal impairment have increased cardiovascular risk[11]

What is the prevalence of diabetes in randomised controlled trials of NOAC use in patients with NVAF?

When interpreting the cardiovascular outcomes of randomised controlled trials (RCTs), it is important to consider the numbers of diabetic patients participating in these studies. ROCKET AF, in which almost 40% of patients had T2DM, is very representative of today's medical practice (Figure 10).[12]

Study	RE-LY	ROCKET AF	ARISTOTLE	ENGAGE-AF
Drug	**Dabigatran**	**Rivaroxaban**	**Apixaban**	**Edoxaban**
Age >75 years	40.1%	43.7%	31.2%	40.5%
$CHADS_2$ mean	2.2	3.48	2.1	2.8
Previous TIA/stroke	20.3%	54.9%	19.2%	28.1%
Hypertension	78.9%	90.3%	87.3%	93.7%
Diabetes	23.3%	39.9%	25.0%	36.4%
Heart failure	31.8%	62.6%	35.5%	58.2%

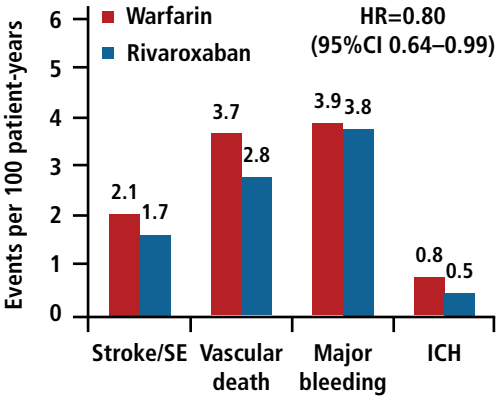
AF: atrial fibrillation; NOAC: non-vitamin K antagonist oral anticoagulant; RCT: randomised controlled trial; TIA: transient ischaemic attack

Figure 10. Clinical features and prevalence of diabetes in NOAC RCTs of patients with NVAF[12]

Effectiveness of rivaroxaban in patients with NVAF and diabetes has been evaluated in RCT and real-world settings

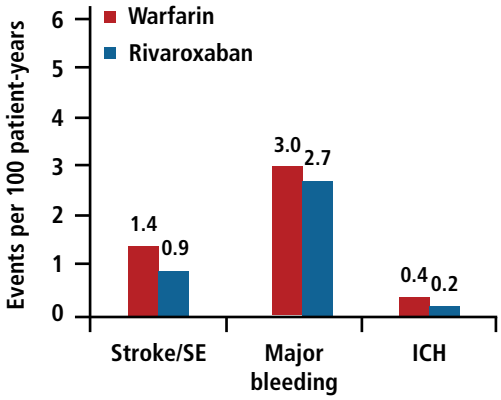
It is important to be aware that real-world data are consistent with the results of ROCKET AF. Rivaroxaban, as compared to warfarin, shows benefit for stroke/systemic embolism, major bleeding and intracranial haemorrhage in the diabetic patient with NVAF (Figure 11).

ROCKET AF – pre-specified analysis of patients with NVAF and diabetes*; n=5 695; mean $CHADS_2$ 3.7



Overall ROCKET AF population: no significant difference in the principal safety endpoint (major or non-major bleeding) versus warfarin or vascular death versus warfarin

Administrative claims database analysis patients with NVAF and diabetes; N=11 034; median $CHADS_2$ 2



Results for the all-doses analysis: rivaroxaban 15mg od was associated with a non-significant decrease in the risk of stroke/SE and ischaemic stroke versus warfarin, without an increase in major bleeding. Vascular death cannot be identified in claims databases. Rates of gastrointestinal bleeding (events/100 patients-years) were 2.1 for rivaroxaban and 2.2 for warfarin

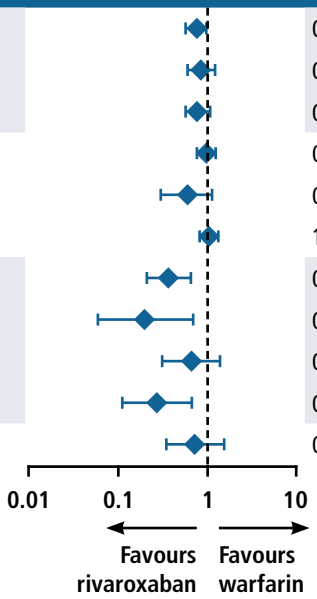
CI: confidence interval; HR: hazard ratio; ICH: intracranial haemorrhage; ITT: intention-to-treat; od: once daily; SE: systemic embolism

Figure 11. Rivaroxaban vs warfarin in the diabetic patient with NVAF - RCT and real-world data

Furthermore, rivaroxaban has been associated with lower risks of major adverse cardiovascular events (MACE) and major adverse limb events (MALE) compared to warfarin in patients with NVAF and T2DM (Figure 12).[13] MarketScan data also show that in the real-world setting, NVAF patients with T2DM were treated with warfarin or rivaroxaban at reduced doses, as suggested for the level of renal dysfunction in the patient with comorbid kidney disease - 24% of patients received a rivaroxaban dose of 15mg. Consistent with RCT data, there were no changes in bleeding rates. Observational reports suggest a reduction in MALE, another signal implying benefit of rivaroxaban beyond simply the heart, but also for the kidneys and limbs in T2DM patients with AF.

Observational reports suggest a reduction in MALE, another signal implying benefit of rivaroxaban beyond simply the heart, but also for the kidneys and limbs in T2DM patients with AF

	Event rate (per 100 PY)			
	Rivaroxaban	Warfarin	HR (95% CI)	HR (95% CI)
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)
Major 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; MI: myocardial infarction; NVAF: non-valvular atrial fibrillation; PY: patient-years; T2DM: type 2 diabetes mellitus

Figure 12. Rivaroxaban was associated with a lower risk of MACE and MALE than warfarin in patients with NVAF and T2DM[13]

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

KEY LEARNINGS

- Kidney disease in the T2DM patient may arise from both hyperglycaemia and hypertension, and significantly increases mortality and cardiovascular risk
- Diabetes predisposes toward the development of AF, with comorbidity substantially increasing all-cause mortality and major cardiovascular events
- Risk for development of AF is further increased in the diabetic patient with CKD
- Use of NOACs in diabetic patients with AF is associated with risk reduction for end-stage renal disease and slower progression to AKI.

Dr Anthony Dalby
Cardiologist, Life Fourways Hospital Johannesburg

Anticoagulation case study – special considerations in diabetes and CKD

Patient and complaint:
68-year-old female, complains of leg pain and unsteadiness when walking

Current treatment:
Metformin, amlodipine, atorvastatin

Medical history:
NVAF, diabetes, hypertension, kidney injury: eGFR = 43

Considerations:
It is unclear whether she has peripheral neuropathy or peripheral arterial disease. Clinical examination confirms the presence of AF with a heart rate around 70 beats per minute. She and her family are concerned about her unsteadiness and have heard that she may need oral anticoagulation.

13. Should she be anticoagulated?

A. Yes

B. No

Expert comment

She has confirmed NVAF so we should be guided by the CHA_2DS_2-VASc score. When her age, sex, hypertension and diabetes are taken into account, there appears to be a strong indication for anticoagulation to prevent her having a stroke. However, her impaired kidney function needs to be carefully weighed up against the need for anticoagulants. Many clinicians are guilty of preferring an act of omission rather than an act of commission, meaning they would rather avoid anticoagulation and its attendant bleeding risk than reduce the patient's risk of stroke.

CHA_2DS_2-VASc score

Only males <65 years can achieve a CHA_2DS_2-VASc score <1

Risk factor	Score
Congestive heart failure/LV dysfunction	1
Hypertension	1
Age >75	2
Diabetes mellitus	1
Stroke/TIA/thromboembolism	2
Vascular disease	1
Age 65–74	1
Sex category (i.e. female sex)	1
Maximum score	**9**

HAS-BLED score

The HAS-BLED score estimates bleeding risk, but except in patients who have a marginal indication for anticoagulation, the bleeding risk never outweighs the need to anticoagulate.

Letter	Clinical characteristic	Points awarded
H	Hypertension	1
A	Abnormal renal and liver function (1 point each)	1 or 2
S	Stroke	1
B	Bleeding	1
L	Labile INRs	1
E	Elderly (e.g. age >65 years)	1
D	Drugs or alcohol (1 point each)	1 or 2
		Maximum 9 points

14. Having decided to anticoagulate, what should be the choice of anticoagulant?

- **A.** Vitamin K antagonist - warfarin
- **B.** Aspirin
- **C.** NOAC

Expert comment

In this setting it is inappropriate to consider aspirin at all. Aspirin has little or no effect on stroke risk and carries as great a risk of bleeding as warfarin. So, our first decision is whether to use the vitamin K antagonist (warfarin) or a NOAC. Leaving aside the issues of inconvenience, drug interactions, monitoring and dose variations with warfarin, we must be aware that NOACs are equal if not better at preventing strokes in patients with NVAF and also carry a lower risk of brain bleeds. Though cost is frequently an issue that favours warfarin, we need to be aware that the best clinical advice is to use a NOAC.

Which NOAC?

Rivaroxaban **Apixaban**	**Anti-Factor Xa**
Dabigatran	**Antithrombin**

Among the NOACs we have the choice between one of two anti-factor Xa inhibitors (rivaroxaban and apixaban) and a thrombin antagonist (dabigatran). Although there were slight variations in the inclusion criteria and the results of the trials of these agents, we can conclude that as a group they are as effective as or more effective than warfarin at preventing stroke, and all have a lower risk of brain bleeding. Because there is little difference in their respective costs, personal preference, tolerability and ease of dosing play a role when deciding which NOAC to prescribe.

15. Is there a treatment that could offer benefits beyond stroke prevention in this case?

A. Yes

B. No

Expert comment

In his presentation, Professor Patel included observational data on the effects of NOACs in preventing acute kidney injury and progression to end-stage kidney failure, as well as the reduction of revascularisation and amputations in peripheral arterial disease. Observational data do not carry the same weight as the results of a randomised clinical trial; these results strongly suggest that when dealing with patients who have diabetes and NVAF, specific NOACs should be the drug of choice for those with cardiovascular disease, impaired kidney function and/or evidence of peripheral arterial disease.

In diabetes and NVAF, a NOAC should be preferred in the following settings:

- Established cardiovascular disease
- Chronic kidney injury
- Peripheral arterial disease

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70 Arlington Street, Everglen, Cape Town, 7550

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