Acta Diabetologica (2019) 56:1247–1258
https://doi.org/10.1007/s00592-019-01426-2

REVIEW ARTICLE

The continuous challenge of antithrombotic strategies in diabetes: focus on direct oral anticoagulants

Fulvio Pomero[1] · Francesco Dentali[2] · Nicola Mumoli[3] · Pietro Salomone[4] · Flavio Tangianu[2] · Giovambattista Desideri[5] · Daniela Mastroiacovo[6]

Received: 3 July 2019 / Accepted: 17 September 2019 / Published online: 24 September 2019

Abstract

Direct oral anticoagulants (DOACs) include dabigatran, which inhibits thrombin, and apixaban, edoxaban, and rivaroxaban, which inhibit factor Xa. They have been extensively studied in large trials involving patients affected by the most common cardiovascular diseases. As the presence of diabetes leads to peculiar changes in primary and secondary hemostasis, in this review we highlight the current evidence regarding DOAC use in diabetic patients included in the majority of recently conducted studies. Overall, in trials involving patients with atrial fibrillation, data seem to confirm at least a similar efficacy and safety of DOACs compared to warfarin in patients with or without diabetes. Furthermore, in diabetic patients, treatment with DOACs is associated with a significant relative reduction in vascular death compared to warfarin. In trials enrolling patients undergoing percutaneous coronary intervention, results concerning bleeding events are consistent in patients with or without diabetes. With regards to the COMPASS study, in patients with diabetes ($n = 10{,}241$), addition of rivaroxaban 2.5 mg to aspirin resulted in a significantly lower incidence of major adverse cardiovascular events (HR 0.74, 95% CI 0.61–0.90; interaction $p = 0.68$) with higher rates of major bleeding expected (HR 1.70, 95% CI 1.25–2.31). The 3287 patients with peripheral artery disease and diabetes receiving rivaroxaban plus aspirin had a twofold higher absolute reduction in the composite endpoint (cardiovascular death, myocardial infarction, and stroke) than patients without diabetes. Finally, we report the involvement of cytochromes or P-glycoprotein on the metabolism of the most commonly prescribed glucose-lowering drugs. No clinically relevant interactions are expected during the concomitant use of DOACs and anti-diabetic agents.

Keywords Direct oral anticoagulants · Diabetes mellitus · Atrial fibrillation · Coronary artery disease · Peripheral artery disease · Acute coronary syndrome · Drug–drug interactions

Managed By Massimo Porta.

✉ Fulvio Pomero
fulviopomero@yahoo.it

[1] Department of Internal Medicine, S. Lazzaro Hospital, Alba, CN, Italy

[2] Department of Clinical and Experimental Medicine, University of Insubria, Varese, Italy

[3] Department of Internal Medicine, Ospedale Fornaroli, Magenta, Italy

[4] Specialty Training in Internal Medicine, University of Turin, Turin, Italy

[5] Department of Life, Health and Environmental Science, San Salvatore Hospital, University of L'Aquila, Building Delta 6, L'Aquila, Italy

[6] Angiology Unit, "SS Filippo and Nicola" Hospital, Avezzano, AQ, Italy

Abbreviations

DM	Diabetes mellitus
CV	Cardiovascular
CAD	Coronary artery disease
ACS	Acute coronary syndrome
PAD	Peripheral arterial disease
AF	Atrial fibrillation
DOACs	Direct oral anticoagulants
VTE	Venous thromboembolism
PCI	Percutaneous coronary intervention
PK	Pharmacokinetic
DDIs	Drug–drug interactions
RR	Relative risk
CI	Confidence interval
HR	Hazard ratio
MI	Myocardial infarction
SSE	Stroke/systemic embolism
VKA	Vitamin K antagonists

MB	Major bleeding
NIDDM	Non-insulin-dependent DM
IDDM	Insulin-dependent DM
ICH	Intracranial hemorrhage
MACE	Major adverse cardiovascular events
SBP	Systolic blood pressure
MALE	Major adverse limb events
P-gp	Permeability glycoprotein
CYP	Cytochrome

Introduction

Despite the advances in technology achieved in the past decades and the improvement in diabetes care and complications following both the development of multidisciplinary approaches and a broad attention to advantages of lifestyle changes [1, 2], to date, diabetes mellitus (DM) still represents a major public concern [3, 4]. The prevalence of this worldwide epidemic disease is even expected to increase, according to the most recent estimates. Indeed, by 2060, the number of US adults with diagnosed diabetes is projected to nearly triple, increasing from 22.3 million in 2014 to 60.6 million in 2060 [5, 6].

As DM is a recognized major risk factor for cardiovascular (CV) disease, such as stable coronary artery disease (CAD), acute coronary syndrome (ACS), cerebral ischemic events, peripheral arterial disease (PAD), and atrial fibrillation (AF), an aggressive management is crucial [7, 8]. Indeed, patients with DM present peculiar changes in primary (platelet aggregation and vascular function) and secondary (coagulation and fibrinolysis) hemostasis. The resultant hypercoagulable and prothrombotic status is primarily due to a platelet dysfunction generated by the interaction of multiple factors such as hyperglycemia, insulin deficiency or resistance, associated metabolic pathologies (dyslipidemia, inflammation, and obesity), and cellular abnormalities (e.g., accelerated platelet turnover, increased generation of thrombin, decreased production of nitric oxide, up-regulation of $P2Y_{12}$ receptor) [9, 10].

In this context, contemporary antithrombotic therapies could be effective for both primary and secondary prevention of atherothrombotic and thromboembolic events, moderating the impact of thrombosis on the global diabetes burden [11].

In the last few years, direct oral anticoagulants (DOACs) have been extensively studied in large phase III and phase IV international trials. These involved a great number of patients requiring anticoagulant treatment for common CV diseases like AF, CAD, PAD, venous thromboembolism (VTE), or ACS needing percutaneous coronary intervention (PCI) [12]. The majority of these trials have included a non-negligible proportion of patients with DM. Thus, the aim of this review is to provide an overview on the current evidence regarding DOAC treatment in patients with DM. Furthermore, as DOACs have the potential for pharmacokinetic (PK) interaction with a number of anti-diabetic agents, we examine the potential drug–drug interactions (DDIs) among DOACs and these drugs.

Prevention of stroke and systemic embolism in atrial fibrillation

DM seems associated with a higher risk of development and progression of AF [13]. The impact of diabetes on AF occurrence is actually debated due to conflicting results from different studies [14–16]. The results of a meta-analysis showed that DM was associated with a 40% increase in the risk of AF [relative risk (RR) 1.39, $p < 0.001$ compared with non-DM], which remained borderline significant even after correction for publication bias [RR 1.34, 95% confidence interval (CI) 1.07–1.68, $p = 0.003$] and multiple risk factors (RR 1.24, 95% CI 1.06–1.44, and 1.70, 1.29–2.22, $p = 0.053$, most-adjusted versus least-adjusted studies, respectively). Furthermore, the analysis of the impact of cumulative exposure to DM showed that the risk of prevalent AF was approximately 64% in individuals with DM for more than 10 years, compared with non-diabetic patients. In contrast, the risk was only 7% in those with DM for less than 5 years. However, the specific pathophysiological mechanism linking DM with increased risk for developing AF is not completely explained [17]. In 10,082 diabetic patients from the Action to Control Cardiovascular Risk in Diabetes (ACCORD) cohort randomized to an intensive or a standard therapeutic glycemic strategy, the intensive glycemic control did not affect the rate of new onset AF. However, patients with DM and incident AF had an increased risk of morbidity and mortality compared to those without AF [hazard ratio (HR) 2.65 for all-cause mortality; HR of 2.1 for myocardial infarction (MI); HR of 3.80 for heart failure] [18].

In patients with coexisting DM, the risk of cardioembolic stroke resulted increased with an incidence ranging between 3.6 and 8.6% per year in different studies [19]. In the ATRIA (Anticoagulation and Risk Factors in Atrial Fibrillation) study, duration of diabetes ≥ 3 years was a greater predictor of ischemic stroke (adjusted HR 1.74, 95% CI 1.10–2.76) than poor glycemic control (HbA1c > 9.0%: adjusted HR 1.04, 95% CI 0.57–1.92) in AF patients [20]. An analysis from the PREFER in AF (Prevention of thromboembolic events—European Registry in Atrial Fibrillation) indicated that DM patients treated with insulin had a significantly increased risk of stroke/systemic embolism (SSE) at 1 year versus either no diabetes (5.2% versus 1.9% HR 2.89; 95% CI 1.67–5.02; $p = 0.0002$) or diabetes without insulin treatment (5.2% vs 1.8%; HR 2.96; 95% CI 1.49–5.87; $p = 0.0019$). Conversely, SSE rates were similar in patients

with diabetes not receiving insulin versus patients without diabetes (HR 0.97; 95% CI 0.58–1.61; $p=0.90$). Moreover, the selective predictive role of insulin-requiring diabetes was independent of potential confounders, including diabetes duration [21].

DM has been included as one of the items of the CHADS2 score and of the CHA2DS2–VASc stroke risk factor scoring systems in patients with non-valvular AF [22, 23]. The latest European Society of Cardiology [24, 25] and North American [26] guidelines on AF either recommend anticoagulating people with a CHA2DS2–VASc score of ≥ 2 with a consensus for a Class I recommendation. Conversely, guidelines differ on recommendations regarding patients with a CHA2DS2–VASc score of 1. Indeed, the European guidelines approve anticoagulation in all people with non-valvular AF and diabetes (Class IIa, Level of recommendation B) with a preference for DOACs over vitamin K antagonists (VKA) (Class I, Level of recommendation A). Conversely, the American College of Cardiology/American Heart Association/Heart Rhythm Society guidelines state that even antithrombotic therapy with aspirin may be taken into consideration (Class IIb, Level of recommendation C) in patients belonging to this risk class.

However, it has been demonstrated that not all risk factors in the CHA2DS2–VASc score carry the same weight in estimating stroke risk. In a retrospective cohort study involving 186 570 AF patients, in male patients with a CHA2DS2–VASc score of 1, the highest risk for stroke was seen in those 65–74 years of age (HR 3.085; 95% CI 2.790–3.410) or those with DM (HR 2.655; 95% CI 2.230–3161). Similar results were reported in women with a CHA2DS2–VAScscore of 2 [27]. These findings were consistent with those reported by Olesen et al. [28] in the Danish nationwide study. Therefore, it seems reasonable to consider anticoagulation when diabetes is present, even if it is the only risk factor among the CHA2DS2–VASc factors [29].

Participants with diabetes represented a considerable proportion in the phase III randomized controlled trials with DOACs, ranging from 4221 (23%) in the RE-LY and 4547 (25%) in the ARISTOTLE studies to 5695 (40%) in the ROCKET AF and 7624 (36%) in the ENGAGE AF-TIMI [30–33]. Pre-specified post hoc analyses, examining the characteristics, efficacy, and safety profiles of these subgroups, showed that diabetic patients had more comorbidities and higher risk of SSE than participants without diabetes [34–36]. This risk was decreased using DOACs, with no significant interaction to diabetic status or the specific drug used. A lower embolic rate was observed in DM patients both in the ENGAGE and in the ROCKET studies (Table 1). Notably, DM patients were not equally represented in the subgroups of patients with previous stroke in either of the above-mentioned trials [34, 37]. Conversely, in the ARISTOTLE and in the RE-LY trials, the proportion of DM subjects was similar between patients with and without a previous cerebral event [36, 38]. As previous stroke is a recognized major risk factor for subsequent stroke, accounting for 2 points in the CHAD–VASc score, we may speculate that the lower proportion of DM patients among patients with a previous stroke enrolled in the ENGAGE and in the ROCKET could explicate the lower embolic rate observed in those studies.

Overall, compared with warfarin, DOACs reduced the incidence of major bleeding (MB), although there were some differences among those trials with regard to drug safety [39] (Table 1). Specifically, the 5647 patients with DM ($\approx 40\%$) in ROCKET AF were younger, were more obese, and had more persistent AF, but fewer had previous stroke. The relative efficacy of rivaroxaban and warfarin for the prevention of SSE was similar in patients with (1.74 vs 2.14/100 patient-years, HR 0.82) and without (2.12 vs 2.32/100 patient-years, HR 0.92) DM (interaction $p=0.53$). Conversely, the efficacy of rivaroxaban versus warfarin (2.83 vs 3.65/100 patient-years, HR 0.80; 95% CI 0.64–0.99) was more evident in DM patients for the secondary outcome of vascular death (interaction $p=0.037$).

The safety of rivaroxaban versus warfarin regarding MB (HRs 1.00 and 1.12 for patients with and without DM, respectively; interaction $p=0.43$), or non-major clinically relevant bleeding (HRs 0.98 and 1.09; interaction $p=0.17$), and intracranial hemorrhage (ICH) (HRs 0.62 and 0.72; interaction $p=0.67$) was independent of DM status. As would be expected, adjusted exploratory analyses suggested 1.3-, 1.5-, and 1.9-fold higher 2-year rates of stroke, vascular mortality, and myocardial infarction in DM patients, respectively [34].

In the RE-LY trial, the 4221(23.3%) patients with DM were younger (70.9 vs 71.7 years), more likely to have hypertension (86.6% vs 76.5%), CAD (37.4% vs 24.9%), and PAD (5.6% vs 3.2%) (all $p<0.01$). Time in therapeutic range for warfarin-treated patients was 65% for diabetic versus 68% for non-diabetic patients ($p<0.001$). Regardless of assigned treatment, SSE was more common among patients with DM (1.9% per year vs 1.3% per year, $p<0.001$). DM was also associated with an increased risk of death (5.1% per year vs 3.5% per year, $p<0.001$) and MB (4.2% per year vs 3.0% per year, $p<0.001$). The absolute reduction in SSE with dabigatran compared to warfarin was greater among patients with DM than in those without DM (dabigatran 110 mg: 0.59% per year vs 0.05% per year; dabigatran 150 mg: 0.89% per year vs 0.51% per year). Therefore, compared to non-DM patients, AF patients with DM derive a greater absolute risk reduction in embolic events when treated with dabigatran [35]. In another pre-specified analysis of RE-LY, a multiple logistic regression model showed that the risk of ischemic events was inversely related to trough dabigatran concentrations ($p=0.045$), with age and previous stroke

Table 1 Efficacy and safety of non-vitamin K antagonist oral anticoagulants versus warfarin in diabetic patients with atrial fibrillation

Efficacy	Diabetes mellitus Total patients (% per year)	RR (95% CI)		No diabetes mellitus Total patients (% per year)	RR (95% CI)		Interaction *p* Value	
(A) Efficacy outcomes								
RE-LY								
Dabigatran 110 mg	1409 (1.76%)	0.74 (0.51, 1.07)		4606 (1.47%)	0.97 (0.76, 1.23)		0.24	
Warfarin	1410 (2.35%)		0.61 (0.41, 1.91)	4612 (1.52%)		0.67 (0.51, 0.86)		0.76
Dabigatran 150 mg	1402 (1.46%)			4674 (1.01%)				
ROCKET								
Rivaroxaban	2851 (1.74%)	0.82 (0.63, 1.08)		4230 (2.12%)	0.92 (0.75, 1.13)		0.53	
Warfarin	2796 (2.14%)			4294 (2.32%)				
ARISTOTLE								
Apixaban	2284 (1.39%)	0.75 (0.53, 1.05)		6836 (1.23%)	0.81 (0.65, 1.00)		0.71	
Warfarin	2263 (1.86%)			6818 (1.51%)				
ENGAGE								
Edoxaban 30 mg	2544 (1.90%)	1.25 (0.82, 1.90)		4490 (2.12%)	1.08 (0.81, 1.44)		0.35	
Warfarin	2521 (1.52%)		0.91 (0.69, 1, 19)	4515 (1.96%)		0.85 (0.71, 1.03)		0.54
Edoxaban 60 mg	2559 (1.42%)			4476 (1.65%)				
Major bleeding	Diabetes mellitus Total patients (% per year)	RR (95% CI)		No diabetes mellitus Total patients (% per year)	RR (95% CI)		Interaction *p* Value	
(B) Safety outcomes (major bleeding)								
RE-LY								
Dabigatran 110 mg	1409 (3.81%)	0.91 (0.70, 1.19)		4606 (2.59%)	0.76 (0.64, 0.90)		0.26	
Warfarin	1410 (4.19%)		1.12 (0.87, 1.44)	4612 (3.38%)		0.86 (0.73, 1.02)		0.09
Dabigatran 150 mg	1402 (4.66%)			4674 (2.92%)				
ROCKET								
Rivaroxaban	2842 (3.79%)	1.00 (0.81, 1.24)		4219 (3.47%)	1.12 (0.93, 1.35)		0.43	
Warfarin	2793 (3.90%)			4289 (3.17%)				
ARISTOTLE								
Apixaban	2284 (3.01%)	0.96 (0.74, 1.25)		6836 (1.85%)	0.60 (0.51, 0.72)		0.003	
Warfarin	2263 (3.13%)			6818 (3.08%)				
ENGAGE								
Edoxaban 30 mg	2544 (1.74%)	0.45 (0.32, 0.64)		4490 (1.54%)	0.50 (0.37, 0.66)		0.52	
Warfarin	2521 (3.94%)		0.78 (0.63, 0.95)	4515 (3.15%)		0.81 (0.69, 0.95)		0.70
Edoxaban 60 mg	2559 (3.06%)			4476 (2.58%)				
Intracranial bleeding	Diabetes mellitus Total patients (% per year)		RR (95% CI)	No diabetes mellitus Total patients (% per year)		RR (95% CI)		
(C) Safety outcomes (intracranial bleeding)								
RE-LY								
Dabigatran 150 mg	1402 (0.93%)		0.59 (0.30, 1.17)	4674 (0.53%)		0.36 (0.23, 0.57)		
Warfarin	1410 (1.56%)			4612 (1.47%)				
ROCKET								
Rivaroxaban	2878 (0.76%)		0.60 (0.35, 1.01)	4253 (0.78%)		0.70 (0.45, 1.08)		
Warfarin	2817 (1.27%)			4316 (1.11%)				
ARISTOTLE								
Apixaban	2284 (0.57%)		0.50 (0.26, 0.96)	6836 (0.57%)		0.41 (0.28, 0.59)		
Warfarin	2263 (1.15%)			6818 (1.40%)				

Test for subgroup difference: $\chi^2 = 0.53$, $p = 0.47$

(both $p < 0.0001$) as significant covariates and that MB risk increased with dabigatran exposure ($p < 0.0001$), age ($p < 0.0001$), acetylsalicylic acid use ($p < 0.0003$), and diabetes ($p = 0.018$) as significant covariates [40, 41].

The 4547 (24.9%) diabetic patients enrolled in the ARISTOTLE trial were younger (69 vs 70 years), had more CAD (39 vs 31%) and higher mean CHADS2 (2.9 vs 1.9) and HAS-BLED scores (1.9 vs 1.7) (all $p < 0.0001$) than patients without DM. Patients with diabetes receiving apixaban had lower rates of SSE (HR 0.75, 95% CI 0.53–1.05), all-cause mortality (HR 0.83, 95% CI 0.67–1.02), CV mortality (HR 0.89, 95% CI 0.66–1.20), intracranial hemorrhage (HR 0.49, 95% CI 0.25–0.95), and a similar rate of myocardial infarction (HR 1.02, 95% CI 0.62–1.67) compared with warfarin. For MB, a quantitative interaction was seen (interaction $p = 0.003$) with a greater reduction in MB in patients without diabetes even after multivariable adjustment. Other measures of bleeding showed a consistent reduction with apixaban compared with warfarin without a significant interaction based on diabetes status [36, 42]. With regard to edoxaban, the primary outcomes were consistent in the 7624 (36%) patients with DM [33]. Patients with diabetes receiving edoxaban had similar rates of SSE (risk ratio 0.91, 95% CI 0.69–1.19) compared with warfarin. Of note, the use of edoxaban 60 mg was associated with significant decrease in MB irrespective of diabetes status (risk ratio 0.78, 95% CI 0.63–0.95 in DM vs 0.81, 95% CI 0.69–0.95 in no-DM) confirming a good safety of edoxaban in this setting [39]. An additional subgroup analysis stratified 21,105 patients in ENGAGE AF-TIMI into pre-specified categories: no-DM ($n = 13{,}481$); non-insulin-dependent DM (NIDDM, $n = 6354$); and IDDM ($n = 1270$). Patients with IDDM were younger (mean age 68.8 vs 69.5 vs 71.3 yrs) and had higher BMIs (32.9 vs 31.0 vs 28.4 kg/m^2) and CHA2DS2–VASc scores (mean 4.8 vs 4.6 vs 4.2) as compared to those with NIDDM or no-DM (each $p < 0.001$). The annualized rate of the net outcome of stroke/SEE, MB, or CV death was 7.2% in no-DM versus 7.0% in NIDDM (adjusted HR 1.15) versus 11.2% in IDDM (adjusted HR 1.80), both $p < 0.001$. Secondary outcomes followed similar patterns. The efficacy and safety profiles of edoxaban as compared to warfarin were not modified by DM status (each interaction $p > 0.10$). [43].

Taken together, these studies seem to confirm at least a similar efficacy and safety trade-off compared to warfarin in patients with or without diabetes. However, single trials may be underpowered to specifically evaluate clinical results of DOACs in definite subgroups of patients, especially for endpoints at low incidence. Moreover, they differ with regard to the inclusion of participants with diabetes, since criteria for the diagnosis of diabetes were mostly based on either documentation of diabetes at baseline or the use of glucose-lowering medications. Furthermore, most trials did not report data on HbA1c or blood glucose levels. Of note, all the phase III trials excluded participants with severe chronic kidney disease, thus possibly also excluding patients with diabetic nephropathy, a subgroup with higher risk of vascular complications and marked bleeding tendency [44]. On the other hand, several studies have shown that patients in treatment with VKAs have increased coronary and renal artery calcification, which, in turn, could be responsible of a higher risk of cardiac events and of an acceleration in the decline of renal function in diabetic individuals [45]. In the RE-LY study, the decline in renal function, after an average of 30 months, was more substantial in patients taking warfarin versus dabigatran, and it was greater in people with diabetes and in previous VKA users [40]. Renal calcinosis VKAs-related may at least partially play a role in inducing an anticoagulant-related nephropathy, caused by glomerular hemorrhage, tubular injury, and obstruction due to red blood cell casts, and observed more frequently with VKA than with DOACs [46, 47]. Furthermore, since warfarin inhibits the vitamin K-dependent gamma-glutamyl carboxylation of proteins, including osteocalcin and matrix Gla protein, it may increase the risk of osteoporotic bone fracture and some authors raise concerns about its use in diabetic patients with AF [45, 48].

A study-level meta-analysis [39], including 18,134 patients with DM and 40,454 without DM, highlighted that the use of DOACs compared with warfarin similarly reduced SSE in diabetic (RR 0.80, 95% CI 0.68–0.93; $p = 0.004$) and non-diabetic patients (RR 0.83, 95% CI 0.73–0.93; $p = 0.001$) (interaction $p = 0.72$). No interaction between diabetes status and benefits of DOACs was found for the occurrence of ischemic stroke, MB, or intracranial bleeding (p for interaction > 0.05 for each comparison). Notably, reduction in vascular death rates with DOACs was significant in diabetic patients (4.97% vs 5.99% with warfarin; RR 0.83, 95% CI 0.72–0.96; $p = 0.01$), in whom the absolute reduction in this outcome measure was higher than in non-diabetics (1.02% vs 0.27%), although no interaction was present ($p = 0.23$). The number needed to treat for this outcome measure with DOACs was 98 in diabetic patients and 370 in non-diabetic ones. In light of the current evidence, a recent Consensus Statement from the Working Group on Thrombosis of the Italian Society of Cardiology recommends oral anticoagulant therapy, and preferably a DOAC, for patients affected by AF and diabetes [49].

Antithrombotic strategies for patients with atrial fibrillation undergoing percutaneous coronary intervention

According to the recent 2018 joint European consensus document [50], DOACs as part of triple antithrombotic therapy or dual antithrombotic therapy are safer than VKAs with respect to bleeding risk and are preferable to VKAs in the absence of contraindications to the use of these drugs in anticoagulated AF patients undergoing PCI. Three randomized trials on DOAC versus VKA in combination with antiplatelets for patients with AF undergoing PCI have been recently published [51–53], and at least another large trial is ongoing [55]. The design and the principal outcomes of PIONEER AF PCI [51], RE-DUAL PCI [52], AUGUSTUS [53], and ENTRUST-AF-PCI [54] are summarized in Table 2. All these trials are designed to evaluate safety and are not sufficiently powered for ischemic outcomes. With regards to diabetes status, 624 (29, 4%) patients enrolled in the PIONEER trial presented DM among comorbidities at baseline. No specific subgroup analysis is available for these patients [51]. In the RE-DUAL study, a total of 1296 (37%) DM patients were randomized to dual therapy with dabigatran or triple therapy with VKA. The results were consistent in patients with or without diabetes for both primary and secondary endpoints (all interaction p values > 0.05) [52]. The more recent AUGUSTUS trial studied apixaban as part of dual or triple therapy in patients with AF and ACS or PCI, involving 1678 (36.4%) patients with DM. In this two-by-two factorial design trial, the effects of apixaban as compared with VKA and of aspirin as compared with placebo were generally consistent across pre-specified subgroups with regard to bleeding events. Conversely, a significant interaction was found in the DM subgroup for the secondary outcome of death or ischemic events. Indeed, the cumulative incidence of death or ischemic events was higher in DM patients (8.6%) as compared with no diabetic patients (5.9%) with a trend toward advantage of treatment with VKA in the DM group (HR 1.30; 95% CI 0.94–1.81 in favor of VKA; interaction $p = 0.007$). No significant interaction was observed between the two randomization factors with regard to death or hospitalization (interaction $p = 0.053$) [53]. Lastly, the ENTRUST trial (NCT02866175) is still ongoing and a pre-specified subgroup analysis for patients with DM is planned [54].

Secondary prevention of CAD and PAD

Patients with established CV disease may suffer further CV events, despite receiving optimal medical treatment. Although platelet inhibition plays a central role in the prevention of new events and improves outcomes in patients with atherothrombotic disease, principally by the thromboxane A2 and the ADP P2Y12 platelet activation pathways, it minimally affects other pathways, while agonists such as thrombin, considered to be the most potent platelet activator, continue to stimulate platelet activation and thrombosis [55]. The recent COMPASS (Rivaroxaban for the Prevention of Major Cardiovascular Events in Coronary or Peripheral Artery Disease) study [56] investigated the effects of the inhibition of thrombin generation, evaluating 27,395 participants with stable atherosclerotic vascular disease randomized to receive rivaroxaban (2.5 mg twice daily) plus aspirin (100 mg once daily), rivaroxaban (5 mg twice daily), or aspirin (100 mg once daily). A total of 90.6% of the participants had a history of CAD, and 27.3% had a history of PAD. The mean age was 68 years, and the majority of participants (78%) were men. This study was prematurely stopped for superiority of the rivaroxaban plus aspirin versus aspirin-alone group after a mean follow-up of 23 months in terms of major adverse cardiovascular events (MACE) such as CV death, MI, or stroke and all-cause death. Indeed, the combination arm resulted in a 24% reduction in the primary endpoint of CV death, stroke, or MI, and an 18% reduction in mortality (3.4 vs 4.1%, HR 0.82, 95% CI 0.71–0.96; $p = 0.01$). When separately examining components of the primary outcome, the combination treatment produced a larger relative effect on stroke than on CV death and MI: Stroke was reduced by 42% and ischemic stroke by 49%. As reported in a recent detailed analysis on stroke outcomes, age, systolic blood pressure (SBP) at baseline, history of hypertension, diabetes, prior stroke, and Asian ethnicity all resulted as independent predictors of stroke. Prior stroke was the strongest predictor of incident stroke (HR 3.63, 95% CI 2.65–4.97, $p < 0.0001$) and was associated with a 3.4% per year rate of stroke recurrence on aspirin. Excluding patients with prior stroke, independent risk factors for stroke included age (≥ 75 vs < 65 HR 1.71, 95% CI 1.20–2.44, $p < 0.0001$), SBP at entry (≥ 140 vs ≤ 120 HR 1.66, 95% CI 1.16–2.37, $p = 0.01$), history of hypertension (HR 1.36, 95% CI 1.01–1.84, $p = 0.05$), diabetes (HR 1.46, 95% CI 1.15–1.84, $p = 0.002$), and Asian ethnicity (HR 1.69, 95% CI 1.27–2.25, $p = 0.001$). Similar effects of combination treatment were seen across all the subgroups identified, as predictors of stroke occurrence with no significant treatment interactions [57]. Interestingly, hemorrhagic stroke resulted associated with SBP, tobacco use, prior stroke, and Asian ethnicity but not with diabetes (HR 0.82; 95% CI 0.45–1.47, $p = 0.50$), age > 75 years (HR 2.10; 95% CI 0.82–5.36, $p = 0.29$) or hypertension (HR 1.20, 95% CI 0.61–2.37, $p = 0.60$), suggesting, for the latter subgroups, a greatest benefit of the combination therapy in terms of reduction in ischemic events without

Table 2 Randomized trials comparing DOAC versus VKA in atrial fibrillation patients presenting with acute coronary syndrome and/or undergoing percutaneous coronary intervention/stenting

References	Study design	Size (*n*)	Diabetic patients (*n*) (%)	Comparison	Summary of findings	Comment
Gibson et al. [51] (PIONEER)	RCT Open-label	2124	624 (29.4%)	15 mg rivaroxaban OD plus P2Y12 inhibitors for 12 months, rivaroxaban 2.5 bid plus DAPT for 1, 6, or 12 months, or standard therapy with dose-adjusted vitamin K antagonist (od) plus DAPT for 1, 6, or 12 months	Rates of clinically significant bleeding were lower in the two groups receiving rivaroxaban than in the group receiving standard therapy with VKA (16.8% vs 26.7% and 18.0% vs 26.7% $p < 0.001$ for both comparison)	Not powered for efficacy
Cannon et al. [52] (RE-DUAL)	RCT Open-label PROBE design	2725	1296 (37%)	Dual antithrombotic therapy with dabigatran etexilate (110 mg or 150 mg bid) plus clopidogrel or ticagrelor is compared with triple therapy with warfarin	ISTH major or CRNM bleeding was significantly lower in the two groups receiving dual therapy with dabigatran than in the group receiving triple therapy with warfarin (15.4% vs 26.9% and 20.2% vs 25.7%)(HR 0.52; 95% CI 0.42–0.63 and HR 0.72; 95% CI 0.58–0.88, respectively)	Not powered for efficacy
Lopes et al. [53] (AUGUSTUS)	RCT Open-label 2 × 2 factorial design	4600	1678 (36.4%)	Two randomization steps include: (1) apixaban (5 mg bid) versus VKA base triple antithrombotic therapy; (2) aspirin versus aspirin placebo	Major or CRNM bleeding was noted in 10.5% with apixaban versus 14.7% with VKA (HR 0.69; 95% CI 0.58–0.81; $p < 0.001$), and in 16.1% with aspirin versus 9.0% with placebo (HR 1.89; 95% CI 1.59–2.24; $p < 0.001$)	Not powered for efficacy
ENTRUST (ongoing)	RCT	1500	Ongoing	Edoxaban-based regimen (60 mg od) is compared with a VKA-based triple antithrombotic therapy	Primary outcomes ISTH major or CRNM bleeding during the treatment period	Estimated completion 2019

any significant increase in bleeding. Equally, consistent with the overall study results, in patients with diabetes ($n = 10{,}241$; 37, 4%), addition of rivaroxaban to aspirin resulted in significantly lower incidence of MACE (HR 0.74, 95% CI 0.61–0.90; interaction $p = 0.68$) with expected higher rates of MB (HR 1.70, 95% CI 1.25–2.31) (Table 3). The net clinical benefit of the overall population was significantly in favor of combination therapy (HR 0.80; 95% CI 0.70–0.91; $p < 0.001$), without increased rates of ICH (HR 1.16; 95% CI 0.67–2.00; $p = 0.60$) [57]. Results in participants with CAD and in those with PAD were also consistent [58, 59] and occurred regardless of diabetic status. Furthermore, in the high-risk PAD population, the HR for major adverse limb events (MALE, defined as acute limb ischemia or intervention for chronic limb ischemia) was 0.54 (95% CI 0.35–0.84); $p = 0.0054$, and the HR for major amputation was 0.30 (95% CI 0.11–0.80); $p = 0.011$, without a concerning increase in ICH. Patients with PAD and diabetes ($n = 3287$; 44% of PAD subgroup) receiving rivaroxaban plus aspirin had a twofold higher absolute reduction in the composite endpoint (CV death, MI, and stroke) than patients with PAD but without diabetes. Interestingly, the mortality benefit of the COMPASS study was unique in trials of long-term antithrombotics and it is likely to influence future treatment guidelines for patients with stable CV disease. Combination therapy is particularly promising for the PAD population, for which few effective treatments have been proven. In addition, the ongoing VOYAGER PAD trial (NCT02504216) is evaluating the efficacy and safety of the vascular dose of rivaroxaban (2.5 mg twice daily) in patients with symptomatic PAD undergoing peripheral surgical and/or endovascular revascularization [60].

Treatment of venous thromboembolism

The role of diabetes as independent predictor of VTE is uncertain. In a recent analysis of individual participant data from the Emerging Risk Factors Collaboration and the UK Biobank including 1.1 million participants, among a range of established CV risk factors, older age, smoking, and greater adiposity were consistently associated with higher VTE risk. Conversely, there were inconsistent associations of VTE with diabetes and blood pressure [61]. In general, the presence of DM does not influence standard antithrombotic treatment. Accordingly, no specific subgroup analyses have been performed on patients with diabetes in VTE trials comparing DOACs and warfarin and, to our knowledge, no data on specific subgroups are available [62].

Metabolism of direct oral anticoagulants and of non-insulin anti-diabetic drugs: potential drug–drug interactions

One of the advantages of DOACs over VKAs is their predictable pharmacokinetic (PK) and pharmacodynamic profile with fewer interactions with drugs, foods, and herbal medicines and, in turn, fewer clinically significant DDIs [63]. Knowledge regarding interactions, with effect on plasma levels and especially on clinical effects of DOAC drugs, is currently growing, so new information may modify existing recommendations in the near future [64]. Likewise, little information is available, so far, on the potential interactions between DOACs and glucose-lowering agents. However, because DOACs have multiple elimination pathways, they have no clinically relevant interactions with most commonly prescribed medications. All DOACs are substrates of the permeability glycoprotein (P-gp). This cell efflux transporter mediates the export of drugs from cells located in the small intestine, blood–brain barrier, hepatocytes, and kidney proximal tubule. Intestinal absorption, biliary excretion, and urinary excretion of P-gp substrates can be altered by either the inhibition or induction of P-gp [65]. In addition, PK of DOACs may be partially affected by the co-administration of inducers/inhibitors of cytochrome P450 (CYP) 3A4. Indeed, DOACs exposure will likely be increased by the administration of strong P-gp and CYP P450 3A4-inhibitors (e.g., ketoconazole or protease inhibitors of HIV) increasing the risk of bleeds. In general, DOAC use is not recommended in combination with drugs that are strong inhibitors of both

Table 3 The COMPASS trial: rivaroxaban for the prevention of major cardiovascular events in coronary or peripheral artery disease

	Diabetes mellitus Total patients/% per year	HR (95% CI)	No diabetes mellitus Total patients/% per year	HR (95% CI)	Interaction *p* Value
Cardiovascular death, stroke, or myocardial infarction					
Rivaroxaban 2.5 bid + Aspirin 100 mg	179/3448 (5.2%)	0.74 (0.61, 0.90)	200/5704 (3.5%)	0.77 (0.64, 0.93)	0.77
Aspirin 100 mg	239/3474 (6.9%)		257/5652 (4.5%)		
Major bleeding					
Rivaroxaban 2.5 bid + Aspirin 100 mg	110/3448 (3.2%)	1.70 (1.25, 2.31)	178/5704 (3.1%)	1.69 (1.33, 2.15)	0.97
Aspirin 100 mg	65/3474 (1.9%)		105/5652 (1.9%)		

Table 4 Involvement of P-glycoprotein and cytochrome P450 isoforms in the metabolism of non-insulin anti-diabetic drugs

	P-glycoprotein	CYP3A4	CYP450 (other isoforms)	Advices by summary of product characteristics
BIGUANIDES				
Metformin	Inhibitor	No	No	
THIAZOLIDINEDIONES				
Pioglitazone	Inhibitor	No	Yes	Should be used with caution during concomitant administration of cytochrome P450 2C8 inhibitors or inducers. Glycemic control should be monitored closely.
GLINIDES				
Repaglinide	No	Yes	Yes (predominantly CYP2C8)	Special care should be taken when inhibitors of both CYP2C8 and 3A4 are co-administered simultaneously with repaglinide
SULFONYLUREAS				
Glibenclamide	No	No	Yes (CYP2C9)	
Glimepiride	No	No	Yes (CYP2C9)	
Gliclazide	Inhibitor	No	Yes (CYP2C9)	
DIPEPTIDYL PEPTIDASE-4 (DPP-4) INHIBITORS				
Sitagliptin	Substrate (mild inhibitor)	No	No	
Vildagliptin	No	No	No	
Saxagliptin	Substrate	Yes	No	
Linagliptin	Substrate	Yes (weak inhibitor)	No	
Alogliptin	No	Yes (mild inducer)	No	Studies in vitro have shown alogliptin to be a mild inducer of CYP3A4, but alogliptin has not been shown to induce CYP3A4 in studies in vivo.
GLUCAGON-LIKE PEPTIDE-1 RECEPTOR AGONISTS				
Liraglutide	No	No	No	
Dulaglutide	No	No	No	
Exenatide	No	No	No	
ALPHA-GLUCOSIDASE INHIBITORS				
Acarbose	No	No	No	
SODIUM/GLUCOSE COTRANSPORTER 2 (SGLT2) INHIBITORS				
Dapagliflozin	No	No	No	
Canagliflozin	Yes (weak inhibitor)	No	No	The effect of concomitant administration of canagliflozin (a weak P-gp inhibitor) on dabigatran etexilate (a P-gp substrate) has not been studied. As dabigatran concentrations may be increased in the presence of canagliflozin, monitoring (looking for signs of bleeding or anemia) should be exercised when dabigatran is combined with canagliflozin.
Empagliflozin	Substrate	No	No	Empagliflozin does not inhibit P-gp at therapeutic doses. Based on in vitro studies, empagliflozin is considered unlikely to cause interactions with active substances that are P-gp substrates.

CYP3A4 and P-gp. Conversely, strong inducers of P-gp and/or CYP3A4 (such as rifampicin or carbamazepine) will markedly reduce DOAC plasma levels; such combinations should be avoided or used with great caution and surveillance [64].

The clinical importance of any DDI depends on factors that are drug-, patient-, and administration-related. DM patients are generally geriatric and multimorbid subjects receiving polytherapy to reduce their CV risk, especially lipid-lowering agents, antihypertensive drugs, and

antiplatelet medications. Thus, many DDIs may potentially contribute to harmful effects of glucose-lowering drugs. Fortunately, although CYP-mediated DDIs are numerous, most of them only moderately influence PK parameters without dramatically affecting efficacy or inducing clinically relevant adverse events. The effects of inducers or inhibitors of CYP have been tested on the metabolism and PK of oral anti-diabetics of each pharmacological class [66, 67]. A vast amount of small-sized in vitro studies and investigations, mostly including healthy volunteers and surrogate parameters of concomitant CV drug use, is available. Although current data suggest that modest PK interferences among some CV drug combinations exist, clinicians can be reassured because they do not seem to have substantial clinical consequences [68]. In Table 4, we report the involvement of CYP or P-gp on the metabolism of the most commonly prescribed glucose-lowering drugs. Because insulins are not described as inhibitors or inducers of human CYP, we do not report any information regarding them. Among non-insulin agents, no strong inducer or inhibitor of P-gp and/or CYP3A4 exists and no clinically relevant interactions are expected during the use of DOACs [69]. In addition, we highlight particular advice if reported in the summary of product characteristics of each drug [70].

Conclusions

DOACs have been extensively studied in large phase III trials. They represent an attractive option in the management of DM patients affected by CV diseases, being at least as effective and safe as in non-DM patients. Current data suggest that they may improve the prognosis of such patients and a vast amount of evidence regarding their net clinical benefit is still growing fast. Specifically, in AF diabetic patients, treatment with DOACs was associated with a significant 17% relative reduction in vascular death compared with warfarin [49]. In addition, results from the COMPASS trial are reassuring in terms of reduction in MI, stroke, vascular death, and all-cause death both in patients with CAD and PAD. Ongoing analyses and studies are promising for the diabetic PAD population [57, 61]. However, clinicians should reserve particular caution to patients with severe chronic kidney disease, as DOACs are contraindicated in this situation. Finally, yet importantly, no clinically relevant interactions are expected during the concomitant use of DOACs with most anti-diabetic drugs.

Acknowledgements We gratefully acknowledge D'Anna Stefano for the study of potential drug–drug interactions.

Compliance with ethical standards

Conflict of interest The authors have no conflict of interest to declare.

Ethical standard This article does not contain any studies with human partecipants or animals performed by any of the authors.

Informed consent For this type of study formal consent is not required.

References

1. Standards of Medical Care in Diabetes (2018) Abridged for primary care providers. American Diabetes Association. Clin Diabetes 36(1):14–37
2. Kodama S, Tanaka S, Heianza Y et al (2013) Association between physical activity and risk of all-cause mortality and cardiovascular disease in patients with diabetes: a meta-analysis. Diabetes Care 36(2):471–479
3. Vetrone LM, Zaccardi F, Webb DR et al (2019) Cardiovascular and mortality events in type 2 diabetes cardiovascular outcomes trials: a systematic review with trend analysis. Acta Diabetol 56(3):331–339
4. Rawshani A, Rawshani A, Franzén S et al (2017) Mortality and cardiovascular disease in type 1 and type 2 diabetes. N Engl J Med 376(15):1407–1418
5. Lin J, Thompson TJ, Cheng YJ et al (2018) Projection of the future diabetes burden in the United States through 2060. Popul Health Metr 16(1):9
6. http://www.cdc.gov/diabetes/statistics/prevalence_national.htm. Accessed 20 Apr 2019
7. Marzona I, Avanzini F, Lucisano G et al (2017) Are all people with diabetes and cardiovascular risk factors or microvascular complications at very high risk? Findings from the Risk and Prevention Study. Acta Diabetol 54(2):123–131
8. Ramezankhani A, Azizi F, Hadaegh F, Momenan AA (2018) Diabetes and number of years of life lost with and without cardiovascular disease: a multi-state homogeneous semi-Markov model. Acta Diabetol 55(3):253–262
9. Ferreiro JL, Angiolillo DJ (2011) Diabetes and antiplatelet therapy in acute coronary syndrome. Circulation 123(7):798–813
10. Pomero F, Di Minno MN, Fenoglio L, Gianni M, Ageno W, Dentali F (2015) Is diabetes a hypercoagulable state? A critical appraisal. Acta Diabetol 52(6):1007–1016
11. Cavender MA, Steg PG, Smith SC Jr, REACH Registry Investigators et al (2015) Impact of diabetes mellitus on hospitalization for heart failure, cardiovascular events, and death: outcomes at 4 years from the reduction of atherothrombosis for continued health (REACH) registry. Circulation 132(10):923–931
12. De Caterina R, Ageno W, Agnelli G et al (2019) The non-vitamin K antagonist oral anticoagulants in heart disease: section V-special situations. Thromb Haemost 119(1):14–38
13. Tadic M, Cuspidi C (2015) Type 2 diabetes mellitus and atrial fibrillation: from mechanisms to clinical practice. Arch Cardiovasc Dis 108(4):269–276
14. Movahed MR, Hashemzadeh M, Jamal MM (2005) Diabetes mellitus is a strong, independent risk for atrial fibrillation and flutter in addition to other cardiovascular disease. Int J Cardiol 105:315–318
15. Ruigomez A, Johansson S, Wallander MA, Rodriguez LA (2002) Incidence of chronic atrial fibrillation in general practice and its treatment pattern. J Clin Epidemiol 55:358–363

16. Johansen OE, Brustad E, Enger S, Tveit A (2008) Prevalence of abnormal glucose metabolism in atrial fibrillation: a case control study in 75-year old subjects. Cardiovasc Diabetol 7:28
17. Huxley RR, Filion KB, Konety S et al (2011) Meta-analysis of cohort and case-control studies of type 2 diabetes mellitus and risk of atrial fibrillation. Am J Cardiol 108:56–62
18. Fatemi O, Yuriditsky E, Tsioufis C et al (2014) Impact of intensive glycemic control on the incidence of atrial fibrillation and associated cardiovascular outcomes in patients with type 2 diabetes mellitus (from the Action to Control Cardiovascular Risk in Diabetes Study). Am J Cardiol 114:1217–1222
19. Stroke Risk in Atrial Fibrillation Working Group (2007) Independent predictors of stroke in patients with atrial fibrillation: a systematic review. Neurology 69:546–554
20. Ashburner JM, Go AS, Chang Y et al (2016) Effect of diabetes and glycemic control on ischemic stroke risk in AF patients: ATRIA study. J Am Coll Cardiol 67:239–247
21. Patti G, Lucerna M, Cavallari I et al (2017) Insulin-requiring versus noninsulin-requiring diabetes and thromboembolic risk in patients with atrial fibrillation: PREFER in AF. J Am Coll Cardiol 69:409–419
22. Gage BF, Waterman AD, Shannon W et al (2001) Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. JAMA 285:2864–2870
23. Lip GY, Nieuwlaat R, Pisters R et al (2010) Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. Chest 137:263–272
24. KirchhofP BS, Kotecha D et al (2016) 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Eur Heart J 37:2893–2962
25. Ryden L, Grant PJ, Anker SD, Berne C et al (2014) ESC guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD—summary. Diabetes Vasc Dis Res 11:133–173
26. January CT, Wann LS, Alpert JS et al (2014) 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol 64:e1–e76
27. Chao TF, Liu CJ, Wang KL et al (2015) Should atrial fibrillation patients with 1 additional risk factor of the CHA2DS2-VASc score (beyond sex) receive oral anticoagulation? J Am Coll Cardiol 65(7):635–642
28. Olesen JB, Lip GY, Hansen ML et al (2011) Validation of risk stratification schemes for predicting stroke and thromboembolism in patients with atrial fibrillation: nationwide cohort study. BMJ 342:d124
29. Plitt A, McGuire DK, Giugliano RP (2017) Atrial fibrillation, type 2 diabetes, and non-vitamin K antagonist oral anticoagulants: a review. JAMA Cardiol 2(4):442–448
30. Connolly SJ, Ezekowitz MD, Yusuf S et al (2009) Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 361:1139–1151
31. Granger CB, Alexander JH, McMurray JJ et al (2011) Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med 365:981–992
32. Patel MR, Mahaffey KW, Garg J, Pan G et al (2011) Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med 365:883–891
33. Giugliano RP, Ruff CT, Braunwald E et al (2013) Edoxaban versus warfarin in patients with atrial fibrillation. N Engl J Med 369:2093–2104
34. Bansilal S, Bloomgarden Z, Halperin JL et al (2015) Efficacy and safety of rivaroxaban in patients with diabetes and nonvalvular atrial fibrillation: the Rivaroxaban Once-daily, Oral, Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF Trial). Am Heart J 170(4):675.e8–682.e8
35. Brambatti M, Darius H, Oldgren J et al (2015) Comparison of dabigatran versus warfarin in diabetic patients with atrial fibrillation: results from the RE-LY trial. Int J Cardiol 196:127–131
36. Ezekowitz JA, Lewis BS, Lopes RD et al (2015) Clinical outcomes of patients with diabetes and atrial fibrillation treated with apixaban: results from the ARISTOTLE trial. Eur Heart J Cardiovasc Pharmacother 1(2):86–94
37. Rost NS, Giugliano RP, Ruff CT, ENGAGE AF-TIMI 48 Investigators et al (2016) Outcomes with edoxaban versus warfarin in patients with previous cerebrovascular events: findings from ENGAGE AF-TIMI 48 (Effective Anticoagulation With Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis in Myocardial Infarction 48). Stroke 47(8):2075–2082
38. Diener HC, Connolly SJ, Ezekowitz MD, RE-LY study group et al (2010) Dabigatran compared with warfarin in patients with atrial fibrillation and previous transient ischaemic attack or stroke: a subgroup analysis of the RE-LY trial. Lancet Neurol 9(12):1157–1163
39. Patti G, Di Gioia G, Cavallari I, Nenna A (2017) Safety and efficacy of non-vitamin K antagonist oral anticoagulants versus warfarin in diabetic patients with atrial fibrillation: a study-level meta-analysis of phase III randomized trials. Diabetes Metab Res Rev 33(3):e2876
40. Mumoli N, Mastroiacovo D, Tamborini-Permunian E et al (2017) Dabigatran in nonvalvular atrial fibrillation: from clinical trials to real-life experience. J Cardiovasc Med (Hagerstown) 18(7):467–477
41. Reilly P, Lehr T, Haertter S, RE-LY Investigators et al (2014) The effect of dabigatran plasma concentrations and patient characteristics on the frequency of ischemic stroke and major bleeding in atrial fibrillation patients: the RE-LY Trial (Randomized Evaluation of Long-Term Anticoagulation Therapy). J Am Coll Cardiol 63(4):321–328
42. Hylek EM, Held C, Alexander JH et al (2014) Major bleeding in patients with atrial fibrillation receiving apixaban or warfarin: the ARISTOTLE Trial (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation): Predictors, Characteristics, and Clinical Outcomes. J Am Coll Cardiol 63(20):2141–2147
43. Plitt A, Ruff C, Goudev A et al (2016) Abstract 16551: efficacy and safety of oral anticoagulation in 21105 patients with atrial fibrillation stratified by diabetic status in the ENGAGE AF-TIMI 48 Trial. Circulation 134(suppl_1):16551
44. Penno G, Solini A, Bonora E, Renal Insufficiency and Cardiovascular Events (RIACE) Study Group et al (2018) Defining the contribution of chronic kidney disease to all-cause mortality in patients with type 2 diabetes: the renal insufficiency and cardiovascular events (RIACE) Italian Multicenter Study. Acta Diabetol 55(6):603–612
45. Yamagishi SI (2019) Concerns about clinical efficacy and safety of warfarin in diabetic patients with atrial fibrillation. Cardiovasc Diabetol 18(1):12
46. Brodsky SV, Hebert L (2016) Anticoagulant-related nephropathy: an AKI elephant hiding in plain view? J Am Coll Cardiol 68(21):2284–2286
47. Chan Y-H, Yeh Y-H, Hsieh MY et al (2018) The risk of acute kidney injury in Asians treated with apixaban, rivaroxaban, dabigatran, or warfarin for non-valvular atrial fibrillation: a nationwide cohort study in Taiwan. Int J Cardiol 265:83–89
48. Gu ZC, Zhou LY, Shen L et al (2018) Non-vitamin K antagonist oral anticoagulants vs. warfarin at risk of fractures: a systematic

review and meta-analysis of randomized controlled trials. Front Pharmacol 9:348
49. Patti G, Cavallari I, Andreotti F, Working Group on Thrombosis of the Italian Society of Cardiology et al (2019) Prevention of atherothrombotic events in patients with diabetes mellitus: from antithrombotic therapies to new-generation glucose-lowering drugs. Nat Rev Cardiol 16(2):113–130
50. Lip GYH, Collet JP, Haude M, ESC Scientific Document Group et al (2019) Joint European consensus document on the management of antithrombotic therapy in atrial fibrillation patients presenting with acute coronary syndrome and/or undergoing percutaneous cardiovascular interventions: a joint consensus document of the European Heart Rhythm Association (EHRA), European Society of Cardiology Working Group on Thrombosis, European Association of Percutaneous Cardiovascular Interventions (EAPCI), and European Association of Acute Cardiac Care (ACCA) endorsed by the Heart Rhythm Society (HRS), Asia-Pacific Heart Rhythm Society (APHRS), Latin America Heart Rhythm Society (LAHRS), and Cardiac Arrhythmia Society of Southern Africa (CASSA). Europace 21(2):192–193
51. Gibson CM, Mehran R, Bode C et al (2016) Prevention of bleeding in patients with atrial fibrillation undergoing PCI. N Engl J Med 375:2423–2434
52. Cannon CP, Bhatt DL, Oldgren J et al (2017) Dual antithrombotic therapy with dabigatran after PCI in atrial fibrillation. N Engl J Med 377:1513–1524
53. Lopes RD, Heizer G, Aronson R et al (2019) Antithrombotic therapy after acute coronary syndrome or PCI in atrial fibrillation. N Engl J Med 380:1509–1524
54. Vranckx P, Lewalter T, Valgimigli M et al (2018) Evaluation of the safety and efficacy of an edoxaban-based antithrombotic regimen in patients with atrial fibrillation following successful percutaneous coronary intervention (PCI) with stent placement: rationale and design of the ENTRUST-AF PCI trial. Am Heart J 196:105–112
55. Angiolillo DJ, Capodanno D, Goto S (2010) Platelet thrombin receptor antagonism and atherothrombosis. Eur Heart J 31(1):17–28
56. Eikelboom JW, Connolly SJ, Bosch J et al (2017) Rivaroxaban with or without Aspirin in stable cardiovascular disease. N Engl J Med 377(14):1319–1330
57. Sharma M, Hart RG, Connolly SJ et al (2019) Stroke outcomes in the COMPASS trial. Circulation 139(9):1134–1145
58. Connolly SJ, Eikelboom JW, Bosch J, COMPASS investigators et al (2018) Rivaroxaban with or without aspirin in patients with stable coronary artery disease: an international, randomised, double-blind, placebo-controlled trial. Lancet 391(10117):205–218
59. Anand SS, Bosch J, Eikelboom JW, COMPASS Investigators et al (2018) Rivaroxaban with or without aspirin in patients with stable peripheral or carotid artery disease: an international, randomised, double-blind, placebo-controlled trial. Lancet 391(10117):219–229
60. Capell WH, Bonaca MP, Nehler MR et al (2018) Rationale and design for the Vascular Outcomes study of ASA along with rivaroxaban in endovascular or surgical limb revascularization for peripheral artery disease (VOYAGER PAD). Am Heart J 199:83–91
61. Gregson J, Kaptoge S, Bolton T et al (2019) Emerging risk factors collaboration. cardiovascular risk factors associated with venous thromboembolism. JAMA Cardiol 4(2):163–173
62. Blann AD, Lip GY (2016) Non-vitamin K antagonist oral anticoagulants (NOACs) for the management of venous thromboembolism. Heart 102(12):975–983
63. Prisco D, Ageno W, Becattini C, SIMI (Italian Society of Internal Medicine); FADOI (Federation of Associations of Hospital Doctors on Internal Medicine); SISET (Italian Society for the Study of Haemostasis and Thrombosis) et al (2017) Italian intersociety consensus on DOAC use in internal medicine. Intern Emerg Med 12(3):387–406
64. Steffel J, Verhamme P, Potpara TS, ESC Scientific Document Group et al (2018) 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 39(16):1330–1393
65. Wessler JD, Grip LT, Mendell J, Giugliano RP (2013) The P-glycoprotein transport system and cardiovascular drugs. J Am Coll Cardiol 61(25):2495–2502
66. Abbasi MM, Valizadeh H, Hamishehkar H, Zakeri-Milani P (2016) Inhibition of P-glycoprotein expression and function by anti-diabetic drugs gliclazide, metformin, and pioglitazone in vitro and in situ. Res Pharm Sci 11(3):177–186
67. Scheen AJ (2011) Cytochrome P450-mediated cardiovascular drug interactions. Expert Opin Drug Metab Toxicol 7(9):1065–1082
68. Ruscica M, Baldessin L, Boccia D, Racagni G, Mitro N (2017) Non-insulin anti-diabetic drugs: an update on pharmacological interactions. Pharmacol Res 115:14–24
69. Gelosa P, Castiglioni L, Tenconi M et al (2018) Pharmacokinetic drug interactions of the non-vitamin K antagonist oral anticoagulants (NOACs). Pharmacol Res 135:60–79
70. www.ema.europa.eu/en/documents/product-information. Accessed 13 May 2019