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Drug interactions of direct oral anticoagulants in elderly patients with cardiometabolic diseases

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ABSTRACT

In the present review we summarized current knowledge about significant interactions (DIs) of direct oral anticoagulants (DOACs) with other medications frequently prescribed to elderly patients with cardiometabolic diseases.

Literature search was performed using PubMed from 1990 to October 2020. Randomized clinical trials (RCTs), subgroup analyses from RCTs, longitudinal studies, case series and case reports were included. Only studies in humans were considered. Elderly was defined as ≥75 years.

Assessment of DIs with DOACs is often tricky because of the lack of validated tools to routinely assess magnitude of their anti-coagulation effect. Most of reports in the cardiometabolic area regarded the classes of anti-antiarrhythmic, lipid-lowering and platelet-inhibitors drugs, namely drugs that are widely used to reduce cardiovascular risk in patients with common metabolic diseases. Reports about elderly are limited in general, and it is not known whether certain types of DIs occur more frequently in elderly subjects. DIs were more frequently reported in association with dabigatran, which however has been available for a longer period of time compared with other DOACs. In most cases, no complete information about dosages of medications was available. DIs of DOACs leading to adverse events (both ischemic and bleeding ones) were generally facilitated by older age, polymedication and impaired renal function.

Further studies should be carried out to properly investigate DIs of DOACs with cardiometabolic drugs in elderly patients, with particular focus on differences between DOACs and the influence of different dosages.

1. Introduction

According to current guidelines, pharmacological treatment of atrial fibrillation (AF) includes anticoagulant agents targeted to minimize the risk of ischemic stroke and peripheral thromboembolism (Kirchhof et al., 2016). The use of direct oral anticoagulants (DOACs) is now robustly encouraged in comparison with traditional vitamin K antagonists (VKAs), because of the better benefit/risk profiles, fewer drugs and food interactions and no need for routine coagulation monitoring (Olesen et al., 2015a). In the class of DOACs are now included the thrombin-inhibitor dabigatran and the factor Xa inhibitors rivaroxaban, apixaban and edoxaban, all of which are widely used in most European countries in patients with non-valvular AF. All these compounds, when compared with the VKA warfarin in dedicated large randomized clinical trials (RCTs), have proven non-inferiority for prevention of stroke or systemic embolism and superiority for occurrence of major intracranial bleedings in patients with AF (Connolly et al., 2009; Granger et al., 2011; Patel et al., 2011; Giugliano et al., 2013). Noteworthy, all these trials included a remarkable proportion of patients over 75 years (ranging from 31 to 40%) (Table 1), thus reflecting study populations with multiple comorbidities in addition to AF and potential meaningful drug interactions (DIs). This last point is of particular value in studies with DOACs, since the major disadvantage of traditional VKAs was the high incidence of bleeding and thrombotic events in patients under VKAs due to DIs leading to significant deviations of the coagulation tests.

Even though DOACs are assumed to have lower impact on DIs than traditional VKAs, their risk of DIs, especially in elderly comorbid patients, is not negligible. Two potential mechanisms are called into question. The first mechanism is brought about by compounds affecting platelet-activity, such as nonsteroidal anti-inflammatory drugs (NSAIDs),

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Table 1
Randomized controlled trials with DOACs in atrial fibrillation.

References	Drug	Trial name	Patients (n)	≥75 years (%)	Mean age (years)	Median follow-up (months)
Connolly SJ (Connolly et al., 2009)	DAB	RE-LY	18,113	40%	71	24
Granger CB (Granger et al., 2011)	APX	ARISTOTLE	18,201	31%	70	22
Patel MR (Patel et al., 2011)	RVB	ROCKET-AF	14,264	38%	73	20
Giugliano RP (Giugliano et al., 2013)	EDX	ENGAGE AF-TIMI	21,105	40%	72	34

Abbreviations: DOACs = direct oral anticoagulants; DAB = Dabigratan; APX = Apixaban; RVB = Rivaroxaban; EDX = Edoxaban.

acetylsalicylic acid, ticlopidine, prasugrel, clopidogrel, ticagrelor and selective serotonin-reuptake inhibitors (SSRIs). Concomitant administration of these platelet-aggregation inhibiting drugs with any anticoagulant drugs, including DOACs, can substantially increase the risk of major bleedings. As summarized in Table 2, the second mechanism for DIs with DOACSs is concomitant intake of drugs affecting the activity of the cytochrome P450 isoenzymes 3A4 (CYP3A4), 2C9 (CYP2C9) and P glycoprotein (*P*-gp), a drug efflux pump involved in the metabolism of a number of xenobiotics. These latter transporters expressed on the luminal surface of the gut and the kidney exert a central role in the pathway of DOACs clearance, whereas hepatic cytochrome P450 enzymes are primarily involved in clearing apixaban and rivaroxaban. As a result, DOACs have clinically important interactions with drugs that are strong inducers or inhibitors of *P*-gp, and both apixaban and rivaroxaban also interact with drugs that are strong inducers or inhibitors of *P*-gp and CYP3A4. DOACs are also reported to potentially impact on circulating levels of several immunosuppressant, anti-depressive and analgesic drugs. Finally, it is worth reminding that DOACs bioavailability can be also influenced by changes of the gastric pH induced by proton pump inhibitors (PPIs). The assumption that DOACs have fewer DIs than traditional anticoagulants is largely driven by data obtained in healthy volunteers, in whom the interaction of a single drug with a DOAC has been inquired (Mueck et al., 2013; Vakkalagadda et al., 2016; Parasrampuria et al., 2016; Mendell et al., 2013; Frost et al., 2015a; Stangier et al., 2009a; Matsushima et al., 2013; Härtter et al., 2013). Elderly subjects with AF, however, are frequently on multiple medications because of several metabolic comorbidities. In the ROCKET AF trial with rivaroxaban (Piccini et al., 2016), more than 60% of the included patients were on ≥5 and 13% were on ≥10 daily administrated medications. In the ARISTOTLE trial with apixaban, the rate of polymedication (≥5) was even higher, up to 77% (Jaspers Focks et al., 2016). In both trials, polymedication was remarkably more frequent in older than in younger patients, reflecting the age-dependent prevalence of AF which significantly increases among individuals older than 75 years (Chugh et al., 2014). Even though individuals over 75 years constituted only up to 40% of the population of the DOACs-investigating trials (Table 1), a steep increase in the prescription rate of DOACs in older patients has been reported in several countries worldwide (Xu et al., 2013; Olesen et al., 2015b; Schuh et al., 2016; Olimpieri et al., 2020). A time-series analysis of prescription trends between 2010 and 2012 in Ontario, Canada, for all orally administered anticoagulants (warfarin, dabigatran and rivaroxaban) found prescription rates of dabigatran significantly increased among individuals aged 85 years or older (Xu et al., 2013). In the Danish nationwide administrative register, all oral anticoagulation-naïve AF patients starting oral anticoagulation from 2011 to 2013 were identified. Older age resulted one of the most relevant factor driving prescriptions toward DOACs instead of warfarin (Olesen et al., 2015b). A further study using the administrative prescription register for DOACs of the Italian Medicine Agency, in which 683,172 patients were included from June 2013 to December 2017, the median age was 78 years (range 18–109 years) with 9.5% of patients aged 85 and older (Olimpieri et al., 2020). Finally, a study from Austria reporting the accounting data of insurance funds from 2011 to 2014, covering more than 90% of the population, found that in 2011 the mean age of patients receiving VKAs was higher than DOACs (72 vs. 68 years), whereas in 2014 the figure was opposite and the proportion of patients ≥80 years receiving VKAs declined from 26 to 21% of all oral anti-coagulants prescriptions (Schuh et al., 2016). Moreover, among nonagenarians, the percentage of subjects receiving VKAs was substantially unchanged (around 2%), whereas a 40-fold increase in the proportion of patients receiving DOACs was observed (Schuh et al., 2016).

Table 2
Pharmacological properties of DOACs.

	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
Target	Thrombin	Factor Xa	Factor Xa	Factor Xa
Protein binding (%)	35%	87%	40–60%	92–95%
Bioavailability (%)	6–7%	50%	62%	66%*
Time to maximum concentration (h)	2	1–3	1–2	2–4
Half-life (h)	12–14	8–15	9–14	9–13
Renal clearance (%)	>80%	25%	50%	33%
Metabolism via cytochrome P450 enzymes (%)	<2%	<32%	<5%	57%
Drug interactions	Inhibitors and inducers of *P*-gp	Dual inhibitors and inducers of CYP3A4 and *P*-gp	Inhibitors and inducers of *P*-gp	Dual inhibitors and inducers of CYP3A4 and *P*-gp

Abbreviations as described in the text.

According to this background, the use of DOACs in elderly patients with relevant comorbidities still represent an area of clinical uncertainty. This is particularly true for patients on polymedication with drugs that differently affect the metabolism of DOACs, so that it is tricky to assess the impact of a single drug on a certain adverse event in most cases. Accordingly, an analysis of the reports about drug-induced liver injury associated with dabigatran and rivaroxaban of the FDA Adverse Event Reporting System found a significant accumulation of polymedication. In that analysis, 56% of patients were ≥75 years (Raschi et al., 2015). Therefore, aim of the present review is to summarize the current state of knowledge about DIs of DOACs with potentially interacting medications frequently used by elderly patients with cardiometabolic diseases.

2. Methods

2.1. Literature search

Literature search was performed using PubMed from 1990 to October 2020 with the search terms: “CYP3A4”, “CYP2C9”, “*P*-glycoprotein”, “*P*-gp”, “acetylsalicylic acid”, “aspirin”, “clopidogrel”, “prasugrel”, “ticaglelor”, “aliskiren”, “amiodarone”, “dronedarone”, “quinidine”, “thyroid diseases”, “hyperthyroidism”, “thyrotoxicosis, “statins”, “simvastatin”, “atorvastatin”, “pravastatin”, “lovastatin”, “rosuvastatin”, “ezetimibe”, “fenofibrate” “dyslipidemia”, “cholesterol”, “hypercholesterolemia”, “beta-blockers”, “propranolol”, “bisoprolol”, “carvedilol”, “calcium-channel blockers”, “diltiazem”, “verapamil” and “dabigatran”, “rivaroxaban”, “edoxaban”, or “apixaban”. RCTs, subgroup analyses from RCTs, longitudinal studies, case series and case reports have been included.

Only human data were considered while non-human experimental data were excluded from the review, as regards the clinical effects DIs of DOACs in elderly patients with cardiometabolic diseases. We particularly focused on: 1) age of patients; 2) potential differences among DOACs regarding their DIs; 3) potential differences in DIs according to age; 4) potential dose-dependency in DIs and metabolic effects with DOACs. Citations retrieved from the electronic search were reviewed in order to identify potentially relevant articles for the present review and determine their eligibility. Quality assessment of each article was performed evaluating the study's aim, case and control definitions, inclusion and exclusion criteria, sample selection and analysis, and statistical definition of significant differential expression. Bibliographies of all identified studies and review articles were reviewed looking for additional papers of interest; only publications in English were retrieved. We referred to the Anatomical Therapeutic Chemical (ATC) classification system to identify potentially interacting medications in the cardiometabolic area (World Health Organization, 2015).

2.2. Definition of "elderly "

The global population is ageing and, according to the World Health Organization (WHO), in 2050, the population aged 60 years or older will double, whilst those aged 80 years or older will number 400 million people (World Health Organisation, 2012). Unfortunately, there is no uniformly accepted definition of 'elderly' persons (Singh and Bajorek, 2014). According to the prevalence of AF, which is significantly increasing in patients older than 75 years, in the current review we have considered "elderly" as being ≥75 years (Chugh et al., 2014).

3. Results

3.1. Subgroup analyses of RCTs

Subgroup analyses of elderly individuals, included in large RCTs with DOACs in patients with AF, were performed for rivaroxaban, apixaban, edoxaban and dabigatran (Halperin et al., 2014; Halvorsen et al., 2014; Lauw et al., 2017; Kato et al., 2016). In all these subgroup analyses, elderly subjects experienced higher rates of ischemic strokes and bleedings than younger patients, but unfortunately no information is reported about potential influence of comedication and DIs on these events. Effects of concomitant medications on efficacy and safety outcomes were investigated in two post-hoc analyses of these trials (Piccini et al., 2016; Jaspers Focks et al., 2016). In both these analyses, however, authors did not consider difference in dosages of the selected DOAC (rivaroxaban or apixaban) regarding potential effects of comedications on the incidence of stroke and bleeding events. In ROCKET-AF with rivaroxaban, an increased number of concomitant drugs were associated with higher absolute risk of bleedings, but not of ischemic stroke. Unexpectedly, concomitant administration of ≥2 combined inhibitors seemed to be associated with higher incidence of bleedings with rivaroxaban than with warfarin, but the sample size was quite limited to drawn firm conclusions (Piccini et al., 2016). In the ARISTOTLE trial with apixaban, the use of concomitant medications in older patients was more frequent than in other trials. Consistently, the number of comorbidities increased across groups of increasing numbers of taken drugs (0–5, 6–8, ≥9 drugs daily). Overall mortality was also significantly associated with the number of drugs administered daily, as did incidence rates of stroke or systemic embolism and major (especially intracranial) bleeding. However, outcomes incidence did not significantly differ between patients with or without combined CYP3A4 and *P*-gp inhibitors (Jaspers Focks et al., 2016), raising the question of complexity and frailty of these comorbid patients, rather than occurrence of DIs, as major drivers of the increased number of events.

3.2. Influence of age on DOACs plasma levels

Whereas circulating levels of VKAs are easy to indirectly assess by measurement of the international normalized ratio (INR), the anticoagulant effect of NOACs cannot be routinely measured by common laboratory tests. As a matter of fact, assessment of DOACs plasma levels requires sophisticated technologies that are not routinely available in clinical practice. This drawback determines some difficulties in evaluating the influence of age on plasma concentrations of DOACs, which can be additionally confounded by the influence of age itself on renal function. Since all DOACs are excreted to some extent by the kidneys, reduced dosages of DOACs are usually recommended for elderly, even with just mild impaired renal function. Pharmacokinetic properties of DOACs have been studied in different populations with different age groups, however just few studies were carried out independently of the drug manufacturer. In these studies, absorption of dabigatran appeared to be highly variable in healthy subjects (Delavenne et al., 2013; Ollier et al., 2015). On the other side, plasma levels of dabigratan were found to be closely related with renal function in elderly (Tomita et al., 2016). Similar results, in terms of dependence of plasma levels on age and renal function, were observed with rivaroxaban and edoxaban in ROCKET-AF and ENGAGE AF-TIMI 48-trials, respectively (Girgis et al., 2014; Yin et al., 2014). By contrast, the influence of age on plasma levels of apixabans has only been investigated in healthy volunteers (Frost et al., 2015b). In the end, multiple factors contribute to the age-dependency of plasma-DOACs levels, including renal impairment, comedications, and age-related changes in intestinal absorption and metabolism of DOACs. The clinical relevance of increasing age on occurrence of bleedings with DOACs-anticoagulation is further highlighted by a surveillance study which analyzed gastrointestinal and intracranial bleeding events recorded in the FDA Adverse Event Reporting System database between 2004 and 2014 (Abe et al., 2015). The Authors observed that the reporting of dabigatran-associated gastrointestinal hemorrhages was significantly increased in patients older than 80 years of age, whereas aging unexpectedly turned out to have little effect on gastrointestinal hemorrhages in people treated with VKAs. On the other hand, reporting of anticoagulant-associated intracranial bleedings was not affected by aging, in both dabigatran and VKAs users. These data confirm that pharmacokinetic of dabigatran may be actually affected by aging, as compared to VKA. However, what contributed the most to this issue in elderly patients, whether renal function decline, metabolic comorbidities or comedications, was not investigated in this analysis (Abe et al., 2015).

3.3. Concomitant medications and DOACs-related adverse events

As said before, DIs of DOACs are quite difficult to detect, because of the lack of unexpected deviations of routinely used hemostasis parameters. Since measurements of DOACs plasma concentrations are not available in routine care of patients, potential DIs will be detected only if a complication – either bleeding or thromboembolism - occurs. In an observational analysis of 16,160 spontaneous reports from Australia, Canada and USA, gastrointestinal adverse events were the most frequently reported in patients taking dabigatran, ranging from 29% for Australia to 41% for USA. According to that study, concomitant use of drugs with the potential for increasing risk of bleedings ranged from 34% for Australia to 51% for the USA (McDonald et al., 2015). Among these concomitant medications, the most frequently used were acetylsalicylic acid, NSAIDs, SSRIs, amiodarone and dronedarone (McDonald et al., 2015). Interestingly, mean age of subjects included in the analysis was 76 years, namely a population likely to be burdened by a number of chronic comorbidities. However, Authors did not provide details about potential age-associated severity of the adverse events and no information was given about the dabigatran dose as well.

3.4. DIs of DOACs with drugs for cardiometabolic diseases

Aliskiren is a direct renin inhibitor approved by FDA to treat hypertension in adults. Patients taking aliskiren have increased risk of hyperkalemia and impaired renal function, therefore the most appropriate use of this drug remains as an add-on therapy in patients with still uncontrolled hypertension and high cardiovascular risk. Aliskiren is also a *P*-gp-inhibitor, and bleeding events in patients treated with aliskiren and either rivaroxaban (20 mg) or dabigatran (300 mg) were described in two case reports (Stöllberger et al., 2013; Raschi et al., 2015). In both cases, patients were >75 years and on polypharmacy.

Amiodarone is a widely used antiarrhythmic drug and also an inhibitor of CYP2C9 as well as CYP3A4 and *P*-gp. A retrospective analysis of patients admitted to an emergency unit reported that 44% of those who experienced bleeding events under dabigatran or rivaroxaban were taking amiodarone concomitantly. Mean age of patients was 76 years (Moustafa et al., 2015). In a retrospective cohort study using data from the Taiwan National Health Insurance database and including 91,330 patients with nonvalvular AF who received at least one DOAC prescription (mean age 74.7 years), concurrent use of amiodarone significantly increased adjusted incidence rate of major bleedings than DOAC alone (52 vs 38 events per 1 000 person-years) (Chang et al., 2017). The effects of comedication with amiodarone have been reported in subgroup-analyses of the dabigatran-, apixaban- and edoxaban-investigating RCTs. In the RE-LY trial, concomitant medication with amiodarone significantly affected the bioavailability of dabigatran that, according to the authors, "showed only small to moderate effects" (<26% change in exposure at steady state) (Liesenfeld et al., 2011). By contrast, a subgroup-analysis of the ARISTOTLE trial (in which approximately 10% of patients received amiodarone at randomization), found that interaction values for amiodarone use by apixaban treatment effects were not significant (Flaker et al., 2014). Similar findings were reported from a subgroup-analysis of the edoxaban-investigating trial (Steffel et al., 2015). On the other hand, amiodarone can also affect thyroid function, resulting in hyperthyroidism potentially influencing the anticoagulant effects of DOACs. In this context, the above-mentioned lack of a validated test for assessing DOACs activity can be extremely dangerous, especially in elderly. As a matter of fact, excess thyroid hormone affects several coagulation and fibrinolytic parameters, with a shift of haemostasis towards a hypercoagulable and hypofibrinolytic state, attributable to a rise in factors VIII and IX, fibrinogen, von Willibrand factor, and plasminogen activator inhibitor-1 (Stuijver et al., 2012). Additionally, amiodarone-induced thyrotoxicosis can impair gastrointestinal mobility leading to diarrhea and malabsorption of DOACs (Sbrana et al., 2016). Research has demonstrated age as an independent predictor of cerebral ischaemic events in thyrotoxic AF (Daniels, 2001) and, therefore, presence of hyperthyroidism associated with amiodarone use should be integrated into the decision-making on anticoagulation with DOACs in elderly.

Dronedarone is another antiarrhythmic drug with therapeutic indication for paroxysmal AF as second-line treatment when amiodarone is not tolerated, for example in patients who had developed thyrotoxicosis. As amiodarone, dronedarone is an inhibitor of CYP3A4 as well as *P*-gp. However, experience with dronedarone in elderly patients with comorbidities is limited, mostly because of the not completely favorable safety profile (Nantsupawat et al., 2013). Bleeding events in patients taking dronedarone and rivaroxaban (20 mg, n = 1) or dabigatran (300 mg, n = 1) have been reported, and in one case the patient was ≥75 years (Raschi et al., 2015; Menendez and Michel, 2016). An increased serum dabigatran level was measured in a patient with concomitant administration of dronedarone and dabigatran 300 mg (Lock et al., 2016). Concomitant use of dronedarone with dabigatran was prospectively investigated in a small cohort of 33 patients with AF and mean age of 64 years (Mochalina et al., 2015). This is the only study exploring this clinical issue. In these patients, plasma concentrations of dabigatran were not dissimilar to those detected in patients not taking dronedarone and reported in earlier studies. Median follow-up and duration of treatment was 13 months. One major bleeding event was reported (3% per patient-year), with no thrombotic events during a total of 35.5 patient-years (Mochalina et al., 2015). However, findings of this study should be cautiously interpreted since patients included were relatively young and reported less comedications than those enrolled in the RE-LY study. Therefore, it is unknown if these results can also be applied to patients ≥75 years. Among DOACs other than dabigatran, DIs of dronedarone with edoxaban have been studied in healthy subjects, and coadministration of dronedarone increased edoxaban exposure (Mendell et al., 2013). Whether this latter interaction can translate into clinical relevance is not known.

Quinidine is another antiarrhythmic drug with *P*-gp-inhibition properties. Comedication with quinidine has been shown to increase edoxaban bioavailability and decrease volume of distribution of edoxaban, as reported in a pooled analysis on 1 134 subjects treated with edoxaban from 11 clinical trials (Yin et al., 2014). DIs of quinidine with edoxaban have been additionally investigated in healthy subjects, with evidence of increased total edoxaban exposure by 35% and decreased total clearance by 25% when quinidine is co-administered (Mendell et al., 2013; Matsushima et al., 2013).

Some calcium channel blockers are CYP3A4-and *P*-gp-inhibitor. A retrospective cohort analysis using US population data on 48,442 patients with AF and normal kidney function who had received a prescription of DOACs, found increased bleeding risk associated with dabigatran when used concomitantly with the *P*-gp inhibitors verapamil and diltiazem (Pham et al., 2020). Gastrointestinal bleeding and severe multi-organ failure have been reported in an 84-year-old female treated with diltiazem and dabigatran 300 mg daily (Raschi et al., 2015). DIs of diltiazem with apixaban have been also studied in healthy subjects and a 1.4-fold increase in apixaban exposure was observed with co-administration of diltiazem (Frost et al., 2015a). A study in 137 patients taking dabigatran for AF reported that verapamil concomitant use was independently associated with elevation of dabigatran plasma levels (Okubo et al., 2015). A bleeding event has been reported in a 72-year-old patient taking a number of medications, including verapamil and dabigatran 300 mg (Raschi et al., 2015). A subgroup-analysis of the RELY trial revealed that concomitant administration of verapamil significantly affected bioavailability of dabigatran, resulting in increased exposure at steady state by 23% (Liesenfeld et al., 2011). DIs of verapamil with edoxaban and dabigatran have been finally investigated in healthy subjects, with increased exposure of both DOACs when verapamil is co-administered (Mendell et al., 2013; Härtter et al., 2013).

Some beta-blocking agents have also *P*-gp-inhibiting properties. Bleeding events in patients with polymedication, including bisoprolol and either rivaroxaban (20 mg, n = 1; 15 mg, n = 2) or dabigatran (300 mg, n = 1; 220 mg, n = 3), have been described in several case reports, with six of these patients being ≥75 years (Stöllberger et al., 2013, 2017; Raschi et al., 2015). Bleeding events were also reported in patients taking carvedilol in association with either rivaroxaban or dabigatran (300 mg, n = 3), and three of the patients were ≥75 years (Raschi et al., 2015). As well, bleeding event has been reported in an 80-year-old patient treated with propranolol and dabigatran (220 mg daily) (Raschi et al., 2015).

Atorvastatin is a first-line widely used lipid modifying agent. Additionally, it is metabolized by CYP3A4 and is also a *P*-gp-inhibitor. The use of atorvastatin, as for the class of statins as a whole, is a cornerstone of cardiovascular risk-modifying interventions, and for this purpose it is highly recommended even in older patients in both primary and secondary prevention, to reduce all-cause mortality and incidence rates of major cardiovascular events (Lavie et al., 2020; Afilalo et al., 2008). Potential DIs of atorvastatin with rivaroxaban, edoxaban and dabigatran have been studied in healthy subjects, with reassuring results. Basing on these studies, atorvastatin seemed not to affect the pharmacokinetic/-pharmacodynamics profile of either rivaroxaban or dabigatran (Afilalo et al., 2008; Bolek et al., 2020), whereas only minor effects on the pharmacokinetics of edoxaban have been observed (Mendell et al., 2013). No clear information is available on potential interaction between atorvastatin and apixaban. Isolate bleeding events in patients treated

with atorvastatin and either rivaroxaban (20 mg, n = 1) or dabigatran (300 mg, n = 2; 150 mg, n = 2) for AF have been described in several case reports, with five of these patients being over 75 years (Raschi et al., 2015; Stöllberger et al., 2017; Kubitza et al., 2012). However, in a prospective observational study on 65 consecutive dabigatran-treated patients with AF, there was no significant difference in dabigatran plasma levels between those concomitantly treated with atorvastatin 40 mg daily and matched controls without statin therapy (Antoniou et al., 2017), irrespectively of dosage of dabigatran (150 or 110 mg twice daily) and age.

Simvastatin is another frequently used lipid-lowering drug with proved efficacy on cardiovascular risk reduction in various subgroups, including elderly patients (Lavie et al., 2020). Simvastatin is also a *P*-gp-inhibitor. In a population-based, nested case–control study involving 45,991 Ontario residents ≥66 years who started dabigatran between 2012 and 2014, use of simvastatin or lovastatin was associated with a higher risk of major bleeding relative to other statins (Ing Lorenzini et al., 2016), whereas the risk of ischemic stroke was unchanged. Bleeding events in patients receiving simvastatin concomitantly with rivaroxaban (20 mg, n = 1; 15 mg, n = 1) as well as dabigatran (300 mg, n = 5; 220 mg, n = 1) have been also reported, with eight of these patients being older than 75 years (Raschi et al., 2015; Shah et al., 2016).

As said above, concomitant use of lovastatin was associated with increased risk of bleedings in patients taking dabigatran (Ing Lorenzini et al., 2016). This cohort generally included patients ≥65 years who started dabigatran after having received a diagnosis of AF (Ing Lorenzini et al., 2016), but it remains unclear in that study if patients ≥75 years had a higher bleeding risk than younger patients, and if the bleeding risk was influenced by the dabigatran dose. No other information on DIs of DOACs with lovastatin are currently available. There are several case-reports of fluvastatin – another lipid modifying agent and a CYP2C9-inhibitor - in association with rivaroxaban and resulting in bleeding events in patients with AF, one of these patients being over 75 years (Raschi et al., 2015). Finally, among other lipid-lowering medications known to affect activity of CYP3A4, CYP2C9 or *P*-gp, no reports of potential DIs of DOACs with pravastatin, rosuvastatin, ezetimibe or fenofibrate were found.

Concomitant use of drugs affecting hemostasis might increase the risk of bleeding. Drugs which inhibit platelet function - and widely used in both primary and secondary cardiovascular prevention - comprise acetylsalicylic acid (ASA), ticlopidine, clopidogrel, ticagrelor and prasugrel (Shah et al., 2016; Held et al., 2015; Scharf, 2012). Particularly, diabetic patients have increased platelet reactivity warranting use of platelet-inhibiting strategies in order to reduce their ischemic risk (Angiolillo, 2009). In the RE-LY study, 38% of patients at some point received ASA or clopidogrel in addition to VKA or dabigatran. Risk of major bleedings increased proportionally with the concomitant use of single or dual antiplatelet agents, in all treatment arms (Dans et al., 2013). However, the lowest absolute risks for all bleedings were noted among patients taking dabigatran 110 mg twice daily, and this is the reason why this lower dose is recommended, in many countries, for patients over the age of 80 years, or for those 75 years or older with risk of bleeding. Noteworthy, nearly 25% of patients concomitantly taking dabigatran (at any doses) and platelet inhibitor(s) were reported to be diabetics, but this condition turned out not to interfere with the absolute risk of bleedings. Similarly, in the ENGAGE AF-TIMI 48 trial, patients receiving a single platelet-inhibitor (32%) in addition to warfarin or edoxaban (both high and lower dose) were at similar risk of stroke or embolism but with higher rates of bleeding than those not taking antiplatelet therapy (Xu et al., 2016). Unfortunately, the impact of older age on the occurrence of bleedings under concomitant antiplatelet therapy was not investigated in either the RE-LY or the ENGAGE AF-TIMI 48 trial. An observational prospective analysis on 2 216 patients with AF from the DIRECT registry (mean age 71.6 years), showed that patients treated with antiplatelet agents and DOACs had significantly higher bleeding risk than those using DOACs only. However, after adjustment for patient's baseline characteristics (including older age and renal impairment), add-on antiplatelet therapy to DOAC itself did not influence bleeding risk (Sotomi et al., 2019). Noteworthy, all the current available DOACs were equally represented in this analysis, and no differences between drugs or relative dosages emerged from this study. Finally, a case report described spinal subarachnoid hemorrhage in cortical superficial siderosis after apixaban 2.5 mg bid and clopidogrel therapy in a 78-year-old patient (Heckmann, 2016).

4. Concluding remarks

In the present review we have tried to provide a list of drugs in the cardiometabolic area known to affect CYP3A4-, CYP2C9- and *P*-gp activity, which can therefore interfere with the anti-coagulation activity of DOACs in patients with AF and cardiometabolic comorbidities (Table 2). Besides these side-effects attributable to interactions with other drugs commonly used in the cardiometabolic area, this narrative review cannot overlook the undisputed benefits of DOACs even in elderly people. This is a crucial point since real world evidence suggest that less than half of older patients requiring anticoagulant therapy are actually treated (Damanti et al., 2017; Zoni-Berisso et al., 2013). The introduction of DOACs has been a major therapeutic advance even for elderly patients for whom the balance between thromboembolic and bleeding risk is challenging. In general, these agents afford clinicians a more predictable anti-coagulation effect and lower risk of intracranial hemorrhages with comparable or superior efficacy when compared with VKAs (Deng et al., 2020).

In general, DIs with DOACs are mostly reported as bleeding or ischemic events, the occurrence of whom is suspected to relate to the co-administration of potentially interacting drugs. A major drawback in all these reports is, however, the lack of validated tests to confirm a coagulation impairment attributable to the DI. This issue is undoubtedly of relevance for those drugs (e.g. statins) which are widely used concomitantly with DOACs to reduce the risk of cardiovascular events. Due to the age-related decline of renal function, presence of multiple comorbidities and comedications, DIs of DOACs are expectedly more frequently reported in elderly than in younger patients. However, it is not known whether certain types of DIs occur more frequently in elderly and, in general, detailed reports in patients ≥75 years are quite limited. Additionally, the dosage of DOAC was often not provided by authors of the publications included in the present review. It appears that bleeding complications occur more frequently with higher DOACs doses, especially with concomitant renal impairment, but we found no systematic analysis of DIs in relation to DOACs dose dependence. On the basis of the available data, it cannot also be ascertained whether the DOACs dabigatran, apixaban, rivaroxaban and edoxaban vary regarding their DIs with drugs used for cardiometabolic diseases. We observed that DIs with dabigatran were most frequently reported, probably because dabigatran was the first DOAC approved for clinical use in AF. However, it cannot be conclusively determined if the higher number of observations about DIs with dabigatran than with other DOACs, is due to its longer duration of use or to an actual higher rate of adverse events attributable to DIs.

Finally, we acknowledge some limitations of our research. First, we restricted our literature analysis to publications included in PubMed. Therefore, publications in journals not included in PubMed have not been covered. As well, manuscripts in language other than English were not considered. Second, three is remarkable heterogeneity in the scientific quality of data retrieved. This because most of the observations are provided by case reports with their inherent methodological limitations, or derive from subgroup-analyses of RCTs and registries which have been sponsored and carried out by DOACs manufacturers themselves (Stöllberger et al., 2014; Li et al., 2020).

In conclusion, there are a number of signals for clinically relevant interactions between DOACs and certain drugs commonly used in patients with cardiometabolic diseases. Elderly patients appear to be at particular risk of adverse events due to these interactions, especially in presence of renal impairment and multiple comorbidities. Further studies

should be carried out to properly investigate the role of these drugs potentially interacting with DOACs in elderly patients, with particular focus on differences between DOACs and the impact of different dosages.

CRediT authorship contribution statement

Alfonso Bellia: Conceptualization, Methodology, Writing – original draft. **David Della-Morte:** Conceptualization, Methodology, Writing – original draft. **Nicola Di Daniele:** Writing – review & editing. **Davide Lauro:** Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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