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REVIEW ARTICLE

Risk–Benefit Profile of Direct-Acting Oral Anticoagulants in Established Therapeutic Indications: An Overview of Systematic Reviews and Observational Studies

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Abstract Since 2008, the direct-acting oral anticoagulants (DOACs) have expanded the therapeutic options of cardiovascular diseases with recognized clinical and epidemiological impact, such as non-valvular atrial fibrillation (NVAF) and venous thromboembolism (VTE), and also in the preventive setting of orthopedic surgical patients. The large body of evidence, not only from pivotal clinical trials but also from 'real-world' postmarketing observational findings (e.g. analytical epidemiological studies and registry data) gathered to date allow for a first attempt at verifying a posteriori whether or not the pharmacological advantages of the DOACs actually translate into therapeutic innovation, with relevant implications for clinicians, regulators and patients. This review aims to synthesize the risk–benefit profile of DOACs in the aforementioned consolidated indications through an 'evidence summary' approach gathering the existent evidence-based data, particularly systematic reviews with meta-analyses of randomized controlled trials, as well as observational studies, comparing DOACs with vitamin K antagonists. Clinical evidence will be discussed and compared with major international guidelines to identify whether an update is needed. Controversial clinically relevant safety issues will be also examined in order to highlight current challenges and unsettled questions (e.g. actual bleeding risk in susceptible populations). It is anticipated that the large number of publications on NVAF or VTE (44 systematic reviews with meta-analyses and 12 observational studies retained in our analysis) suggests the potential existence of overlapping studies and calls for common criteria to qualitatively and quantitatively assess discordances, thus guiding future research.

Key Points

Our systematic search retrieved 44 systematic reviews and 12 observational studies comparing direct-acting oral anticoagulants (DOACs) with vitamin K antagonists (VKAs) in non-valvular atrial fibrillation and/or venous thromboembolism patients, thus indicating the need to formally assess actual overlapping studies.

This body of evidence corroborates the general consensus that, overall, DOACs are comparable to VKAs in terms of safety, efficacy and effectiveness, and unequivocally indicates a consistent and clinically relevant reduced risk (more than 50 %) of intracranial bleeding.

A number of unsettled questions still require dedicated investigation by post-authorization safety studies (including head-to-head comparisons), particularly the actual magnitude of gastrointestinal bleeding risk in special populations, the impact of renal impairment on the risk–benefit profile of DOACs, and the risk of liver injury.

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1 Introduction

Anticoagulant therapy represents the mainstay for the prevention and treatment of venous thromboembolism (VTE), comprising deep vein thrombosis (DVT) and pulmonary embolism (PE) [1], as well as for the prevention of stroke in patients with atrial fibrillation (AF) [2–4]. For decades, heparins [especially low-molecular-weight heparins (LMWHs)] and vitamin K antagonists (VKAs; especially warfarin) have been the pillar of anticoagulant therapy.

Recently, the drug discovery paradigm has shifted towards rational design following a target-based approach, and resulted in the development of oral agents that directly inhibit the activity of thrombin [direct thrombin inhibitors (DTIs), such as dabigatran] or activated factor X (factor Xa inhibitors, such as rivaroxaban, apixaban, edoxaban), now referred to as direct-acting non-vitamin K oral anticoagulants (DOACs) [5–7].

Apart from the first-in-class drug ximelagatran, withdrawn early from the market because of liver toxicity, the launch of DOACs dates back to 2008 when dabigatran was licensed by the European Medicines Agency (EMA) through a priority review process based on results from a single phase III trial for the prevention of VTE in patients undergoing major orthopedic surgery (i.e. elective total hip replacement surgery or total knee replacement surgery). Dabigatran was also the first DOAC to receive approval from the EMA in October 2010 for stroke prevention in non-valvular AF (NVAF). Edoxaban, the latest DOAC to be approved, received marketing authorization from the EMA and Food and Drug Administration (FDA) in early 2015, both for NVAF and for the treatment (not prevention) of DVT and PE following 5–10 days of initial therapy with a parenteral anticoagulant. Notably, rivaroxaban is the only oral anticoagulant to receive specific indication in Europe for the prevention of recurrent atherothrombotic events in patients with acute coronary syndrome (ACS).

Discussing the comparative clinical pharmacology of DOACs versus VKAs, as well as their pros and cons, is beyond the aim of this review; for details, the reader may refer to recent review articles [8–10]. The DOACs have favorable pharmacological properties, which contributed to their relatively fast introduction in clinical practice, including predictable dose–response curve with fixed doses for most patients (minimizing the need for dose adjustment), and limited food and drug interactions. However, the variability in renal excretion among DOACs, the lack of widely available laboratory tests for measuring their anticoagulant activity, when required, and the currently limited clinical experience in case of overdose and/or severe bleeding should not be overlooked.

A large body of evidence, not only from pivotal clinical trials, but also from 'real-world' postmarketing observational findings (e.g. analytical epidemiological studies and registry data) has accrued in recent years and the question arises whether or not these theoretical pharmacological advantages of DOACs actually translate into therapeutic innovation, i.e. if this class of medicines represents just an additional therapeutic option or a real breakthrough [11].

In this context, our aim was to (i) summarize evidence on the efficacy, effectiveness, and safety of DOACs in established indications, namely NVAF and VTE, compared with VKAs; and (ii) highlight current challenges and future perspectives on the actual role of DOACs in these settings. This is also justified in light of the ongoing debate on whether or not results of randomized controlled trials (RCTs) can be safely transferred to the general population [12, 13].

2 Methods

This overview adopts an 'evidence summary' approach with the aim of assessing the risk–benefit profile of DOACs. This will be achieved by analyzing and summarizing the existent body of evidence, in particular using systematic reviews with meta-analyses of RCTs (i.e. the highest level/strength of evidence), as well as observational studies comparing DOACs with VKAs. Although rapid reviews cannot be formally considered as systematic analysis, they may share quality and reproducibility of systematic reviews (provided that the research question and criteria for study selection and appraisal are specified a priori) with the additional benefit of a descriptive summary/categorization of the data, thus highlighting areas of further research [14, 15].

To this end, and keeping in mind the importance of analyzing the best available evidence, we systematically performed a prespecified search strategy in MEDLINE/PubMed to extract the following.

(i) Systematic reviews of RCTs or observational studies, published as of 30 September 2015 (effective date the search was performed). Detailed criteria for article retrieval and eligibility are provided as supplementary material (electronic supplementary Table 1). We decided to include only direct comparisons between DOACs and VKAs and, therefore, exclude indirect network meta-analyses (NMAs) because their actual value and methodological quality is still a matter of debate [16]. In addition, a critical appraisal of 11 NMAs on the efficacy and safety of DOACs in NVAF has recently been published by the International

Society of Pharmacoeconomics and Outcomes Research [17].

(ii) Observational studies (used as a proxy of real-world data), published as of 31 January 2016. Detailed criteria for article retrieval and eligibility are provided as supplementary material (electronic supplementary Table 2). Considering the aim of assessing the safety and effectiveness in clinical practice, we selected analytical studies providing a clear epidemiological measure [i.e. relative risk, risk ratio (RR), odds ratio (OR)], excluding descriptive studies dealing with the management and treatment of AF and other forms of registry.

Article assessment for eligibility, data extraction and interpretation, as well as quality evaluation, were performed in blind by ER and MB through common criteria. All outcomes reported in the different studies were analyzed, regardless of clinical relevance and severity (i.e. both fatal and non-serious events were considered). Both efficacy (e.g. stroke, recurrent VTE, mortality) and safety [e.g. intracranial hemorrhage (ICH), major/fatal bleeding, gastrointestinal bleeding, renal/hepatic safety] endpoints were then extracted. Disagreements were solved by consensus. For both systematic reviews and observational studies, the most adjusted estimates were extracted. In case different data were provided for different doses, results from the highest dose were selected. For systematic reviews with meta-analysis, heterogeneity was also extracted and considered for the overall assessment.

In particular, the following prespecified criteria were applied to extracted data to assess individual outcome recorded by systematic review/observational study (i.e. without considering the conclusions provided by the authors in the original full text):

- Favor DOACs (↑): OR, RR, or hazard ratio (HR) extracted from relevant studies were statistically significant for DOACs, with low-to-moderate heterogeneity (i.e. $I^2 < 70$ % for meta-analysis);
- Favor VKAs (↓): OR, RR or HR extracted from relevant studies were statistically significant for VKAs, with low-to-moderate heterogeneity (i.e. $I^2 < 70$ % for meta-analysis);
- Neutral (↔): OR, RR or HR extracted from relevant studies were not statistically significant, or high heterogeneity was reported (i.e. $I^2 > 70$ % for meta-analysis).

Therefore, a study counts as many-fold as the number of outcomes/indications/DOACs/doses investigated.

Because multiple systematic reviews with meta-analyses emerged, we further assessed their quality by individually applying the 11 items of the validated AMSTAR tool [18]. We decided to exclude item number 8 ("Was the scientific quality of the included studies used appropriately in formulating conclusion?") from the evaluation for the following reasons: (i) only rarely was the scientific quality considered to draw conclusions and formulate recommendations in the majority of systematic reviews (with the exception of Cochrane reviews), especially due to the reduced number of studies; (ii) we did not use the conclusions posted in the manuscript by the authors in the text, instead we interpreted reported results according to our methodological criteria. Therefore, the maximum score was 10. Detailed criteria and final quality assessment are provided as supplementary material (electronic supplementary Table 3).

3 Results

Overall, from the initial 722 articles, 44 systematic reviews with meta-analysis [19–61] and 12 observational studies [62–73] were finally retained. A synopsis of the overall assessment is presented in Tables 1 and 2, whereas the full list of studies with relevant details are provided as supplementary material (electronic supplementary Tables 1 and 2).

The majority of systematic reviews addressed both efficacy and safety, whereas 13/44 focused only safety (mainly intracranial and gastrointestinal bleeding). Half of the included studies (21/44) enrolled AF patients only, 9/44 were carried out on VTE patients (3 in VTE patients with cancer) only, and 14/44 analyzed both AF and VTE populations. Eleven systematic reviews were specifically designed to evaluate one single endpoint, mainly safety outcomes: liver injury, renal damage, intraocular bleeding, ICH, drug tolerability, gastrointestinal bleeding, and myocardial infarction. A large proportion of systematic reviews (37/44) collected data from RCTs, four from observational studies and three from both randomized and non-randomized studies; these seven systematic reviews were conducted to evaluate the safety and efficacy of DOACs in the setting of AF ablation. The largest proportion of systematic reviews was published in 2014–2015 (30/44), both in general (e.g. *PLoS ONE*, *Lancet*, *BMJ*, *Annals of Internal Medicine*) and specialized journals (e.g. *Heart*), and in the *Cochrane Database of Systematic Reviews* archive.

Major bleeding, fatal bleeding and clinically relevant bleeding were the most frequently investigated safety outcomes, whereas ischemic stroke/systemic embolism were the preferred efficacy endpoints. With regard to special populations, three systematic reviews were performed to assess VTE risk in patients with cancer, whereas two studies analyzed the impact of renal injury on the risk–benefit profile of DOACs.

Table 1 Synopsis of the evidence-based evaluation of DOACs in consolidated therapeutic indications (NVAF and DVT/PE): systematic reviews and meta-analysis (see electronic supplementary Table 1 for details)

Risk–benefit profile	Outcome(s)	Assessment and number of studies			Best effect (95 % CI)[a]	Worst effect (95 % CI)[b]
		↑	↔	↓		
Safety	Major bleeding, fatal bleeding, clinically relevant bleeding	20	24		RR 0.53 (0.43–0.64) (fatal bleeding)	RR 1.27 (0.58–2.81) (major bleeding)
	Clinically relevant non-major bleeding	3[c]	5[d]		RR 0.58 (0.48–0.70) (dabigatran)	RR 0.94 (0.70–1.28)[d] (in patients with venous thromboembolism and cancer)
	Intracranial hemorrhage	13			RR 0.43 (0.37–0.50) (in patients with AF or venous thromboembolism)	RR 0.39 (0.16–0.94) (in patients with venous thromboembolism)
	Gastrointestinal bleeding/major gastrointestinal bleeding	1	11		RR 0.64 (0.41–0.99) (in patients with venous thromboembolism)	OR 1.68 (1.03–2.72) ($I^2 = 91$ %)
	Other bleeds (e.g. ocular) and safety issues (e.g. discontinuation due to ADR, tolerability)		8	3	RR 0.99 (0.89–1.10) (patient-related discontinuation rates)	OR 2.18 (1.82–2.61) (adverse events leading to discontinuation)
	Myocardial infarction		9	3	OR 0.87 (0.73–1.05) (in patients with AF)	RR 2.55 (1.14–5.69) (in patients with venous thomboembolism)
	Liver injury and renal impairment		5		RR 0.79 (0.70–0.90) (transaminases >3 ULN) RR 0.96 (0.87–1.07) (renal impairment)	RR 0.82 (0.56–1.18) (liver injury) RR 1.43 (0.63–3.24) (renal impairment, rivaroxaban)
Efficacy	Ischemic stroke/systemic embolism (including composite outcomes and hemorrhagic stroke, thromboembolic events, other cardiovascular events)	13	10	2	RR 0.77 (0.70–0.86) (NNT = 137)	OR 3.94 (1.54–10.08) (in AF ablation based on observational studies)
	Mortality (all-cause or vascular death)	9	11		RR 0.88 (0.81–0.94) (cardiovascular mortality)	RR 0.87 (0.24–3.08) (in patients undergoing cardioversion)
	Recurrent venous thromboembolism/DVT/PE (fatal/non-fatal)	1	14		OR 0.75 (0.57–0.98) (recurrent DVT for factor Xa inhibitors)	RR 0.97 (0.43–2.15) (recurrent thromboembolism)

A study counts as many-fold as the number of outcomes/indications/DOACs investigated

DOACs direct-acting oral anticoagulants, *NVAF* non-valvular atrial fibrillation, *DVT* deep vein thrombosis, *PE* pulmonary embolism, *ADR* adverse drug reaction, *AF* atrial fibrillation, *NNT* number needed to treat, *OR* odds ratio, *RR* risk ratio, *ULN* upper limit of normal, ↑ indicates favors DOACs, ↓ indicates favors VKAs, ↔ indicates neutral (as effective/safe as VKAs)

[a] Based on the upper limit of the confidence intervals

[b] Based on the lower (efficacy outcome) or upper (safety outcome) limit of the confidence intervals

[c] One study highlighted a favorable effect in the subgroup analysis for dabigatran

[d] One study analyzed clinically relevant bleeding + clinically relevant non-major bleeding

The quality of systematic reviews was ranked 'high' for 33 studies (i.e. the AMSTAR score was ≥9/10 for 75 % of the studies), of which 17 received the maximum score. The majority (76 %) analyzed more than one endpoint, with seven systematic reviews assessing at least four outcomes and documenting clinical benefit in terms of efficacy and safety issues. The inability to capture grey literature and evaluate the quality of included studies were the main reasons affecting the final score (electronic supplementary Table 3).

Observational studies were mainly performed on effectiveness and safety (7/12), rather than only on safety (5/12). Half analyzed dabigatran, four analyzed dabigatran and rivaroxaban, and two analyzed rivaroxaban only. The majority (9/12) were performed only on patients with AF, 2/12 were performed on both AF and VTE populations, and

Table 2 Synopsis of the evidence-based evaluation of DOACs in consolidated therapeutic indications (NVAF and DVT/PE): observational studies (see electronic supplementary Table 2 for details)

Risk–benefit profile	Outcome(s)	Assessment and number of studies			Best effect (95 % CI)[a]	Worst effect (95 % CI)[b]
		↑	↔	↓		
Safety	Major bleeding, fatal bleeding	2[c]	4	2	adjHR 0.59 (0.45–0.78) (dabigatran 150 mg in VKA-experienced patients)	HR 1.89 (1.54–2.32) (dabigatran, in users of antiplatelet agents)
	Intracranial hemorrhage	5[d]	1		adjHR 0.08 (0.01–0.40) (dabigatran 150 mg)	HR 1.17 (0.66–2.05) (rivaroxaban)
	Gastrointestinal bleeding	2[e]	8	3	HR 0.60 (0.37–0.93) (dabigatran 110 mg in VKA-naïve patients)	HR 2.91 (1.65–4.81) (rivaroxaban, aged >75 years)
	Other (e.g. hospitalization due to bleeding, all bleeding events)	1	6		adjHR 0.86 (0.79–0.93) (dabigatran 150 mg, hospitalization)	HR 0.98 (0.64–1.51) (rivaroxaban, hospitalization)
	Myocardial infarction	2	1		adjHR 0.40 (0.21–0.70) (dabigatran 150 mg)	adjHR 0.92 (0.78–1.08) (dabigatran)
Efficacy	Stroke/ischemic stroke/ systemic embolism	1	7		adjHR 0.70 (0.57–0.85) (dabigatran 150 mg)	adjHR 1.18 (0.85–1.64) (dabigatran)
	Mortality	2	1		adjHR 0.57 (0.40–0.80) (dabigatran 150 mg)	adjHR 0.51 (0.24–1.07) (rivaroxaban)
	Recurrent venous thromboembolism/DVT/PE	4	2		HR 0.33 (0.21–0.53) (rivaroxaban, patients with AF, DVT)	adjHR 0.91 (0.54–1.54) (rivaroxaban, recurrent venous thromboembolism)

A study counts as many-fold as the number of outcomes/indications/DOACs/doses investigated

DOACs direct-acting oral anticoagulants, *NVAF* non-valvular atrial fibrillation, *DVT* deep vein thrombosis, *PE* pulmonary embolism, *adjHR* adjusted hazard ratio, *HR* hazard ratio, *AF* atrial fibrillation, *VKA* vitamin K antagonist, ↑ indicates favors DOACs, ↓ indicates favors VKAs, ↔ indicates neutral (as effective/safe as VKAs)

[a] Based on the upper limit of the confidence intervals

[b] Based on the lower (efficacy outcome) or upper (safety outcome) limit of the confidence intervals

[c] For dabigatran 110 mg in VKA-naïve patients

[d] All for dabigatran

[e] For dabigatran 110 mg and dabigatran 110 mg in VKA-naïve patients

only one was performed on VTE patients only. Notably, only 2/12 studies were designed to assess a single outcome, i.e. gastrointestinal bleeding, which was also the most frequently investigated endpoint. A cohort study design was undertaken in all studies.

According to systematic reviews of RCTs, DOACs reduced the risk of ICH by approximately 50 % [data are consistent across the different meta-analyses, with the largest estimate being RR 0.43, 95 % confidence interval (CI) 0.37–0.50], whereas observational studies found an even larger benefit [adjusted HR (adjHR) 0.08, 95 % CI 0.01–0.40]. With regard to gastrointestinal bleeding, systematic reviews were in agreement overall and did not find a statistically significant increased risk; only one study documented a favorable effect compared with VKAs (RR 0.64, 95 % CI 0.41–0.99) in VTE patients with cancer. Observational studies instead demonstrated, in some cases, an increased risk (HR 1.85, 95 % CI 1.64–2.07). A similar pattern was observed for major bleeding, fatal bleeding and clinically relevant bleeding. Apart from bleeding issues, different systematic reviews assessed the potential risk of myocardial infarction, liver and renal injury. For myocardial infarction only, a statistically significant association emerged from systematic reviews (RR 2.55, 95 % CI 1.14–5.69), although this was not confirmed by observational studies, which documented a strong protective effect (adjHR 0.40, 95 % CI 0.21–0.70).

4 Discussion

We collapsed key findings from previous systematic reviews and observational studies, an approach that is only rarely performed in the literature [74]. In fact, the majority of recent meta-analyses actually neglect previous systematic reviews on the same topic [75]. Our overview retained 44 systematic reviews and 12 observational studies comparing DOACs with VKAs in NVAF and/or VTE patients, thus suggesting the potential existence of overlapping studies (i.e. the different systematic reviews may meta-

analyze the same original studies and the same outcomes), which require formal assessment to guide future research. The evaluation of this aspect requires an a priori study design and was beyond the aim of the present analysis.

This body of evidence (i) corroborates the general consensus that DOACs are, overall, comparable with VKAs in terms of safety, efficacy and effectiveness; (ii) highlights that results from meta-analysis of RCTs are in line with those from observational studies, both in terms of the overall direction of the effects and their estimates [76]; and (iii) unequivocally indicates a consistent and clinically relevant reduced risk of ICH, which emerged during pre-registration trials, was confirmed in systematic reviews, and was further corroborated by observational studies. All studies documenting this protective effect relate to dabigatran, whereas the only matched cohort study reporting no statistically significant protective effect on ICH (HR 1.17, 95 % CI 0.66–2.05) compared rivaroxaban with warfarin. The latest meta-analysis of observational studies on dabigatran (not included in our analysis) corroborated these findings by pooling seven cohort studies (HR 0.44, 95 % CI 0.34–0.59, $I^2 = 64$ % for dabigatran 150 mg) [77]. The mechanism behind a reduced ICH risk is still largely unknown, although in vivo studies pointed out that the potential anti-inflammatory properties of dabigatran may partially explain the observed clinical benefit [78, 79].

With regard to other bleeding complications, the actual risk and/or clinical benefit of DOACs appears to still be unresolved (lack of consistency among studies), which is the case for gastrointestinal, major and fatal bleeding. As expected, compared with systematic reviews of RCTs, observational studies documented a higher risk of gastrointestinal bleeding, which emerged for dabigatran (especially at a dose of 150 mg or in patients aged ≥75 years [65]) and rivaroxaban [64]. Different nationwide propensity-matched cohort studies reported no statistically significant differences for both drugs [70, 72], and a favorable effect for dabigatran 110 mg was reported in VKA-naïve patients.

Beyond bleeding complications, three safety issues deserve to be mentioned as they represent clinically important events per se, i.e. coronary risk, liver injury and renal impairment. As expected, our review did not identify these rare safety signals. A recent literature review, comprising case reports, concluded that, while the coronary risk (described for dabigatran) is not supported by a critical evaluation of the evidence, the unpredictable occurrence of liver injury and the potential for renal damage warrant a more precise characterization and call for awareness by clinicians (see below) [80].

With regard to efficacy, some differences exist among the different outcomes. This is especially the case for patients with NVAF. In this setting, some discordances across systematic reviews emerged on ischemic stroke/systemic embolism and mortality, whereas in patients with VTE, DOACs were comparable with VKAs (with the exception of one study, all were concordant in reporting a statistically non-significant reduced risk of recurrent VTE/PE). Notably, observational studies documented a potential benefit of high magnitude (60 % risk reduction); however, it is important to underline that these positive results were derived from an industry-sponsored study on rivaroxaban performed in NVAF patients and reporting a lower likelihood of VTE events and higher persistence compared with warfarin, despite no difference in terms of major effectiveness and safety outcomes [71].

In NVAF, the place in therapy of DOACs appears consolidated. A variety of recommendations have been formulated by several scientific societies. Among these, the American College of Cardiology (ACC) provided practical algorithm-based approaches to support the management of DOACs in clinical practice [81], and the updated European Heart Rhythm Association (EHRA) practical guide listed practical aspects in different common clinical scenarios [82]. We now have the opportunity to match an anticoagulant drug to the individual patient, who is unique for his/her genetic profile, comorbid conditions, concomitant medications, and adherence to treatment [83–86]. A simplified algorithm to facilitate the selection of preferred anticoagulant agents in AF is provided in Fig. 1.

Conversely, the precise role of DOACs in VTE is still a matter of debate and is a clinical research priority. In fact, the latest American College of Chest Physicians (ACCP) guideline was the first to recommend DOACs over VKAs for initial and long-term VTE treatment (in the absence of cancer) [87]. Our data supported comparable efficacy and safety of DOACs compared with VKAs [56], although the most comprehensive meta-analysis by Adam et al. compared DOACs with LMWHs (standard therapy in this setting) and demonstrated that, although effective for thromboprophylaxis after total hip or knee replacement, their clinical benefits are marginal over LMWHs and are offset by increased risk of major bleeding [88]. Acute-phase management of VTE may differ depending on the DOAC used. Dabigatran is administered after an initial treatment with LMWHs in the acute phase, before oral maintenance treatment with dabigatran is started. By contrast, rivaroxaban and apixaban are used in a single-agent approach (i.e. there is no need for initial acute-phase treatment with LMWHs, but they do require a dose change between initial and maintenance phases). Notably, in a phase III trial of rivaroxaban, the majority of patients (84 %) received prestudy heparins for a mean duration of 1 day before starting rivaroxaban, although no remarkable differences emerged in patients not receiving this bridge therapy [89]. It is still uncertain whether one approach has

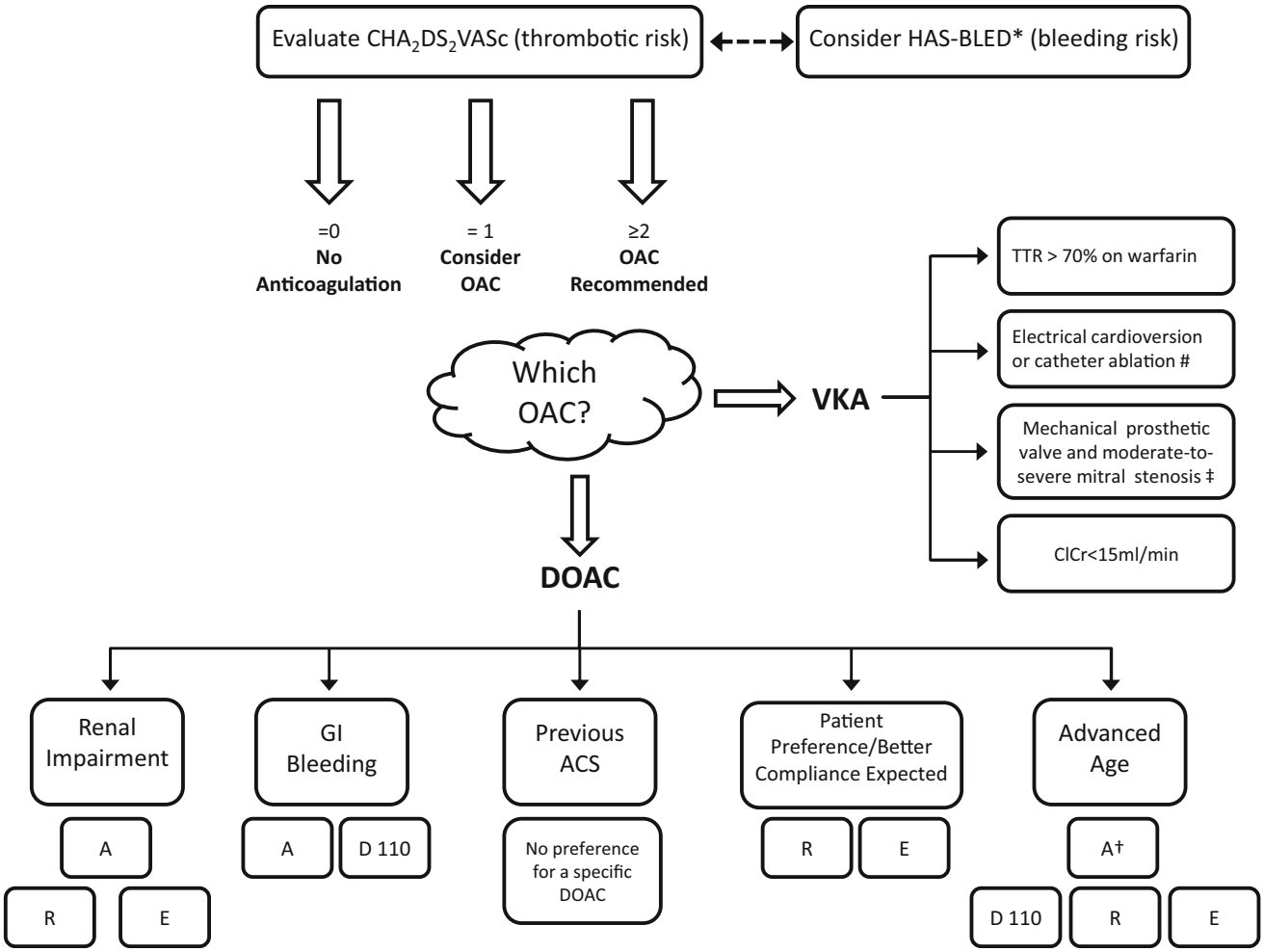

Fig. 1 Simplified approach to guide selection among oral anticoagulants. *Asterisk* If HAS-BLED ≥3, offer regular monitoring and amend risk factors for bleeding in any patients initiating OACs. *Hash* In patients with AF undergoing electrical cardioversion, VKAs remain the standard of care, although available data suggest that DOACs may be as safe and as effective. In patients undergoing catheter ablation, uninterrupted warfarin is preferred in many institutions [85, 86]. *Double dragger* For eligibility of DOACs in specific valvular indications, please refer to the ESC guidelines [82]. *Dragger* Dose adjustment required, especially in patients aged >80 years, body weight <60 kg, creatinine >1.5 mg/dl. For all DOACs, please refer to the relevant summary of product characteristics or product information to verify whether or not dose adjustment is needed, including the extent of renal impairment and concomitant use of P-glycoprotein inhibitors and/or CYP3A4 inhibitors. *A* apixaban, *D110* dabigatran 110 mg, *DOAC* direct-acting oral anticoagulant, *E* edoxaban, *OAC* oral anticoagulant, *R* rivaroxaban, *TTR* time in therapeutic range, *VKA* vitamin K antagonist, *ClCr* creatinine clearance, *GI* gastrointestinal, *ACS* acute coronary syndrome, *AF* atrial fibrillation, *ESC* European Society of Cardiology, *CYP* cytochrome P450

a clinical advantage over another. Future research should assess (i) the actual effectiveness of a single versus dual-agent approach, and (ii) the optimal length of VTE therapy and the need for extended treatment. In fact, the risk of recurrent VTE is highest soon after the VTE event, and declines thereafter, although some excess risk remains unless the initial event was associated with a transient risk factor. Thus, the net clinical benefit of prolonged VTE prophylaxis depends on the risk of recurrent VTE versus the risk of bleeding. Risk assessment tools are warranted to support decision making, especially in severely ill patients at high risk of hemorrhage [90].

From a research standpoint, a meta-analysis of individual patient data may theoretically provide novel information, although there are substantial difficulties, including time-consuming issues and technicalities to access original data. We believe there are no specific areas requiring further meta-analysis of RCTs, whereas 'real-world' data such as well-designed observational studies could help in resolving uncertainties surrounding safety issues, such as liver injury and use in patients with renal impairment. A recent tool is represented by post-authorization safety studies (PASSs) and, in particular, specialist cohort event monitoring (SCEM) studies enable a cohort of patients

prescribed a medicine in secondary care to be monitored; the Rivaroxaban Observational Safety Evaluation (ROSE) study was requested by the EMA to monitor the short-term (12-week) use and safety profile of rivaroxaban prescribed for the prevention of stroke and systemic embolism in adult patients with NVAF, treatment of DVT and PE, and prevention of recurrent DVT and PE in adult patients requiring anticoagulation [91]. Future observational studies should be designed to investigate special populations (e.g. patients with cancer or renal impairment) and newer agents such as apixaban and edoxaban, provided that their uptake reaches significant magnitude. In particular, for apixaban it is worth verifying whether the theoretical advantage of less renal clearance actually translates into actual clinical benefit in patients with renal impairment [92, 93].

Among the various unsettled issues, the impact of polypharmacy and drug–drug interactions is unclear and warrant further investigation, especially in frail elderly patients using DOACs in unconventional settings for evolving therapeutic uses (e.g. heparin-induced thrombocytopenia). In fact, although drug interactions are perceived to be less likely with DOACs, compared with VKAs, the precise incidence and significance of these interactions remain to be clearly defined as the activity of permeability glycoprotein (P-gp) varies greatly between individuals. In particular, clinicians should be reminded of the likelihood of interactions with drugs that inhibit both P-gp and cytochrome P450 (CYP) 3A4 as some DOACs (rivaroxaban, apixaban) are both substrates for P-gp and metabolized extensively by CYP3A4 [94].

Taken together, our review calls for the need to move from systematic reanalysis of the existent literature towards a new era of evidence-based medicine. In particular, registry data from PASSs can optimistically fill our gap in knowledge, especially considering the heterogeneity across populations prospectively recorded in these inception cohorts, which can be followed throughout a lifetime with clinically useful laboratory and clinical data. Among these, the Italian START-Register [95] was launched in 2011; only 109 of 5252 patients received a DOAC due to the relatively recent availability of drugs in the Italian market and limitations of prescriptions by the Italian Regulatory Agency. A number of global and country-specific registries have been set up; apart from monitoring drug use, they can provide a means of tracking uptake of guideline recommendations.

Finally, evidence from pharmacovigilance analyses [i.e. spontaneous reporting systems (SRSs)] should be carefully considered; when properly designed with the intent of addressing the actual safety profile in the postmarketing phase, these studies offer additional complementary evidence, compared with observational data and meta-analyses, because they are likely to reflect real clinical practice, where comorbidities, polypharmacotherapy and heterogeneity of diseases exist. Notably, international comparisons of adverse event reports highlighted that, for both dabigatran and rivaroxaban, a large proportion of spontaneous reports (from 34 % up to 89 %) were associated with the use of concomitant medicines with bleeding potential. This highlights the need for active vigilance by prescribers and the importance of assessing the patient's comorbidity and comedications to minimize risks in routine clinical practice [96, 97].

The risk of liver injury associated with DOACs is a recent safety issue (undetected in preclinical and clinical phases), which only emerged from postmarketing analysis of SRSs, especially for rivaroxaban [98]. Current data suggest that most patients are characterized by a hepatocellular or mixed liver injury pattern, usually recovering rapidly after drug discontinuation, although hepatic failure has been reported. Overall, hepatotoxicity associated with DOACs is idiosyncratic, appears at therapeutic doses and cannot be explained by the pharmacological action of these drugs. For rivaroxaban, currently available data are compatible with both an allergic and non-allergic (metabolic) toxicity. Although incidence cannot be derived from SRSs, the estimated frequency is clearly rarer compared with ximelagatran; therefore, recommending close monitoring of liver function in patients treated with DOACs is not justified. However, the time to onset from published case reports suggests that early evaluation of hepatic enzymes (i.e. within the first month) may be considered, at least in patients under complex treatment regimens with comorbidities; subsequently, liver function can be monitored on a yearly basis [80]. Therefore, vigilance should be maintained by both clinicians, pharmacovigilance experts and patients, who should timely communicate early clinical signs/symptoms, consider on a case-by-case basis the role of DOACs as well as concomitant therapies, and report suspect cases to the national pharmacovigilance services [99].

5 Summary and Perspectives

Potential overlapping studies exist comparing DOACs with VKAs for consolidated therapeutic indications, namely NVAF and VTE. The 44 systematic reviews retained in our evidence-based review call for common criteria to reduce redundant literature and facilitate both clinicians and regulators in the decision-making process. Overall, we can confirm the comparable efficacy and effectiveness of DOACs in comparison with VKAs in these consolidated therapeutic indications. With regard to safety, systematic reviews of RCTs and observational studies strongly agree on the superiority of DOACs in terms of ICH, with similar

data for gastrointestinal and major bleeding. However, no direct head-to-head comparisons have been reported for the four available DOACs, and individual choice among different drugs and doses is therefore challenging for clinicians [85, 86]. The agenda is rich of still unresolved research issues (Table 3).

To address these challenging, unmet clinical needs, comparative effectiveness and safety studies are warranted. To date, only one Danish nationwide cohort study has compared dabigatran, rivaroxaban and apixaban with warfarin in patients with NVAF who were naïve to oral anticoagulants [100]. Apart from differential prescribing patterns (with dabigatran preferentially used in younger patients with a lower risk of stroke and less renal impairment, likely to reflect perceived differences among DOACs from preapproval trials), no significant differences have emerged between DOACs and warfarin with regard to ischemic stroke only; apixaban and dabigatran were associated with a significantly lower risk of death and major bleeding compared with rivaroxaban or warfarin (these last

Table 3 Key aspects still to be addressed

Research issues	Comments
Overlapping systematic reviews	The existence of actual redundant systematic reviews should be formally quantified. Future systematic reviews must be consistently designed, registered and reported, especially by reconciling the conclusions of prior reviews, along with a summary table of included studies [75]
Actual risk of gastrointestinal bleeding (magnitude and anatomical site)	This is especially the case for rivaroxaban, apixaban and edoxaban. For rivaroxaban, recent postmarketing data identified possible increased risk, thus strengthening the importance of minimizing modifiable risk factors [103]. It is also important to determine whether and how upper gastrointestinal bleeding is influenced by the use of medications such as proton pump inhibitors
Effectiveness and safety in special populations	Elderly vulnerable patients with cancer should be closely monitored for adverse events because they are at higher risk of bleeding complications. The use of DOACs in patients with renal impairment is also debated (they are all excreted via the kidney, at least partially) and insufficiently investigated. The 2015 EHRA practical guide suggested a 3-month interval monitoring of renal function, using the Cockcroft–Gault method, in elderly patients [82]
Other safety issues beyond bleeding complications	While, for coronary risk, recent data, including observational studies, are partially reassuring [104], evidence on the risk of liver injury is accruing (case series and disproportionality analysis) [98, 99]. With regard to renal injury, fewer data exist; a meta-analysis of ten RCTs found no differences in the risk of renal failure (compared with VKAs), although rivaroxaban showed a trend for increased risk and an increased risk of creatinine elevation (RR 1.25, 95 % CI 1.08–1.45; $I^2 = 0$ %) [25]
The impact of polypharmacy and drug–drug interactions	Post-analyses of ROCKET-AF (rivaroxaban) and ARISTOTLE (apixaban) revealed that two-thirds and three-quarters of patients had polypharmacy, respectively. This subgroup had a higher risk of bleeding but not stroke (rivaroxaban), increased mortality, and higher rates of thromboembolic and bleeding complications (apixaban) [105, 106]. The precise magnitude and impact of drug–drug interactions requires database analysis in the near future, when the use of DOACs reaches a plateau [94]
The need for measuring anticoagulant activity	At the time of approval, no need for INR monitoring was promoted as a key advantage favoring DOACs over VKAs. However, for both dabigatran and rivaroxaban, there is an ongoing debate with regulators and companies on the actual importance of having laboratory data as an early indicator of the efficacy/safety of the drug, especially in settings such as polypharmacotherapy and emergency bleeding
The optimal incorporation of antidotes in clinical practice	Idarucizumab is the only specific antidote designed to reverse the effect of dabigatran, licensed by the EMA and US FDA in October 2015, but other antidotes are underway and will be marketed in the near future for factor Xa inhibitors [107]. Cohort studies in 'real-life' conditions are warranted [108]
The existence of a cardiovascular protection beyond anticoagulation	A subanalysis of RE-LY [109] showed that the use of dabigatran is associated with a reduction in plasma apoB levels, although the underlying mechanism is only speculative
The risk–benefit profile in emerging arterial and venous diseases	A number of trials are underway to test and confirm the efficacy and safety of DOACs in emerging (cirrhosis, heparin-induced thrombocytopenia, antiphospholipid syndrome) and evolving uses (patients with valvular heart disease, triple therapy, heart failure, catheter ablation, electrical cardioversion) [102, 110]

EHRA European Heart Rhythm Association, *RCTs* randomized controlled trials, *VKAs* vitamin K antagonists, *RR* risk ratio, *DOACs* direct-acting oral anticoagulants, *INR* international normalized ratio, *EMA* European Medicines Agency, *FDA* Food and Drug Administration, *apoB* apolipoprotein B

two drugs having similar profiles for bleeding risk). All DOACs have lower rates of ICH than warfarin, but only dabigatran consistently showed statistically significant reduced risk in main and sensitivity analyses.

Current guidelines are incorporating emerging evidence and, with minor differences, are recommending DOACs over VKAs in several clinical scenarios. Only in a minority of settings are VKAs preferred over DOACs, i.e. patients with mechanical valves, time in therapeutic range >70 % (provided that careful monitoring is maintained), those with AF undergoing cardioversion or ablation, and patients with AF on hemodialysis or with severe renal impairment (Fig. 1). When choosing a particular type or dose of DOAC, various clinical considerations can be summarized by the mnemonic 'ABCDE': abnormally low weight (dose reduction might be needed); bleeding risk, especially previous or recent gastrointestinal bleeding; creatinine clearance (i.e. renal function); drug interactions (e.g. P-glycoprotein and/or CYP3A4 inhibitors); and elderly age (dose reduction might be needed) [101]. Clarifying the potential role and proper use of DOACs in these subgroups (i.e. actual contraindication or lack of data) is a topic for further research. In addition, the emerging use of DOACs in unconventional prothrombotic settings (evolving and emerging indications) warrants additional 'real-world' data [102]. In this context, PASSs have started and country-specific registries are collecting useful data.

6 Conclusions

Real-world data from observational studies are in line with those from RCTs, and support the notion that, in NVAF and VTE, DOACs are as effective as VKAs and safer in terms of ICH. However, the actual benefit (or risk) in terms of gastrointestinal bleeding still represents an unsolved issue, which deserves head-to-head comparisons in the real-world setting, especially in susceptible subpopulations such as elderly patients, patients with cancer, and those with multimorbidities (coexistence of NVAF with multi-organ impairment) under polypharmacotherapy. Continued monitoring by regulators, pharmacovigilance experts and clinicians is mandatory.

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Compliance with Ethical Standards

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