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ORIGINAL ARTICLE
Atrial Fibrillation

Risk of bleeding with the concurrent use of amiodarone and DOACs: a systematic review and meta-analysis

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Background and Aims Amiodarone is frequently prescribed alongside direct oral anticoagulants (DOACs) in atrial fibrillation. There are concerns regarding drug-drug interactions (DDIs) between amiodarone and DOACs. The literature is conflicting on the clinical implications of this DDI, hence we conducted a meta-analysis to compare bleeding risk among patients receiving DOACs, with and without concurrent amiodarone.

Methods and results A systematic search was conducted for studies published between 1 January 2009 and 26 June 2024 in MEDLINE via PubMed, Embase, and CENTRAL. Included studies compared major bleeding in patients on concurrent amiodarone and DOACs to those on DOACs without amiodarone. Event rates were used to calculate odds ratios (ORs), which were pooled with a random-effects model. Nine studies were identified, which included 124 813 patients on amiodarone/DOACs, and 314 074 on DOACs. The average age was 77.2 years in the amiodarone/DOAC group, compared to 74.4 years in the DOAC group ($P = 0.21$). Among DOAC patients, there was a statistically significant increase in major bleeding with concurrent amiodarone (OR 1.22, 95% confidence interval (CI) 1.03–1.44, $P = 0.02$, $I^2 = 88\%$). Intracranial bleeding rate was numerically higher in the amiodarone/DOAC group (1.0 vs. 0.4%), but the difference did not reach statistical significance (OR 2.20, 95% CI 0.53–9.06, $P = 0.27$, $I^2 = 100\%$). There were no significant differences in gastrointestinal bleeding (OR 1.10, 95% CI 0.98–1.23, $P = 0.12$, $I^2 = 62\%$) and all-cause mortality (OR 1.38, 95% CI 0.70–2.73, $P = 0.35$, $I^2 = 99\%$).

Conclusion Concurrent use of amiodarone and DOACs was associated with an increase in major bleeding. This should be considered when co-prescribing these medications.

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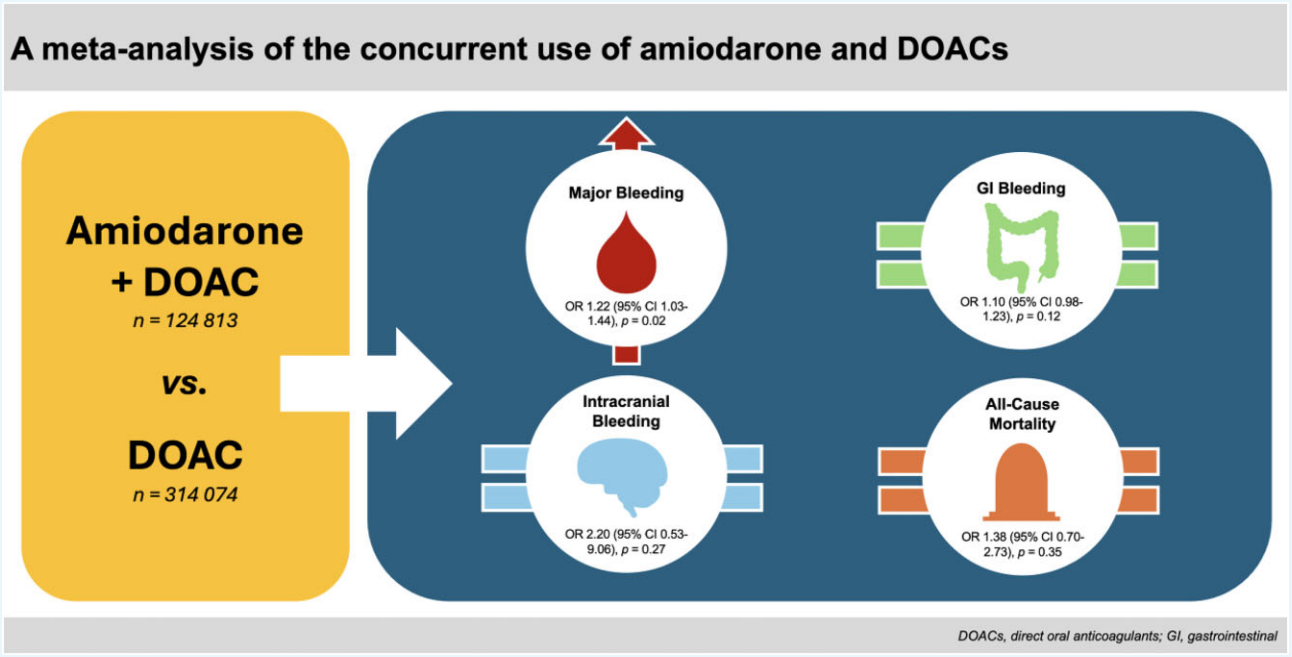
Graphical Abstract



Keywords DOAC • Amiodarone • Drug-drug interaction • Bleeding

Introduction

Direct oral anticoagulants (DOACs) were assumed to have fewer drug-drug interactions (DDIs) in patients with atrial fibrillation (AF) in comparison to vitamin K antagonists (VKAs).[1] However, there is increasing evidence on potential DDIs between DOACs and many drugs, with one important interaction being with amiodarone.[2,3] It is estimated that 6–10% of AF patients on DOACs are on amiodarone.[4–6] Therefore, a DDI with DOACs is of major concern.

Amiodarone is a moderate inhibitor of cytochrome P450 3A4 (CYP3A4) and P-glycoprotein (P-gp) enzymes.[7] Accordingly, pharmacokinetic studies have shown increased DOAC drug levels with concurrent amiodarone.[8,9] While all DOACs are metabolized by P-gp, only rivaroxaban and apixaban undergo significant CYP3A4 metabolism.[10] Accordingly, the risk of bleeding in the presence of amiodarone may vary across DOACs.

The interaction between warfarin and amiodarone is well-established, with early case series identifying a mean increase in prothrombin time by 44%.[11,12] A more recent retrospective study of 754 patients on warfarin found the proportion of patients with an international normalized ratio (INR) above 3.0 increased from 12 to 37% with the addition of amiodarone.[13] Accordingly, a 25% dose reduction of warfarin is suggested when amiodarone is initiated.[13]

The interaction between DOACs and amiodarone compared to warfarin has been evaluated in subgroup analyses of landmark randomized controlled trials (RCTs). ROCKET-AF and ENGAGE-AF TIMI 48 found similar risks of major bleeding between the groups. However, ARISTOTLE identified less major bleeding with apixaban/amiodarone, compared to warfarin/amiodarone [hazard ratio (HR) 0.61, 95% confidence interval (CI) 0.39–0.96].

There is also discrepant observational data on real world bleeding risk. Hill *et al.* conducted a retrospective cohort study comparing 4872 patients on amiodarone/DOACs to 21 853 patients on metoprolol/DOACs.[14] Interestingly, a lower risk of major bleeding was identified in the amiodarone group. This differs from a larger retrospective cohort study by Ray *et al.* of 91 590 patients that compared AF patients on DOACs and amiodarone, to those on DOACs with either flecainide or sotalol.[15] The risk of major bleeding was found to be higher in the amiodarone group.[15]

Therefore, the evidence on the risk of bleeding with concurrent DOACs and amiodarone is conflicting. Accordingly, the objective of our meta-analysis was to compare bleeding among patients on DOACs with and without concurrent amiodarone.

Methods

Registration

This study was prospectively registered on PROSPERO (CRD42024562816).

Literature search and data sources

A systematic search was conducted on MEDLINE via PubMed, Embase, and Cochrane Central Register of Controlled Trials (CENTRAL) for studies published between 1 January 2009 and 26 June 2024. The search start date of 2009 was selected as it preceded the approval of DOACs for AF by regulatory bodies. No language restrictions were applied. The PubMed search strategy is available in Supplementary material online, Appendix S1. The PubMed search strategy was adapted for other databases. A grey literature search was conducted including databases, conference proceedings, and manual web searches. The reference lists of relevant articles were hand searched.

Study selection and quality assessment

Eligible studies compared major bleeding in patients on concurrent amiodarone and DOACs, to patients on DOACs (which may be accompanied by a non-amiodarone drug that is not a strong CYP3A4 or P-gp inhibitor, such as, a beta-blocker). Non-comparative studies were excluded, such as

case reports and case series. Abstracts, systematic reviews, meta-analyses, and clinical guidelines were also excluded. Articles were independently screened by three investigators (F.M., T.Q., S.M.). Disagreements were resolved through discussion, and when necessary, in consultation with a fourth author (M.S.).

The quality of primary studies was assessed in duplicate (F.M., T.Q.). The Newcastle-Ottawa Scale was used to evaluate case-control and cohort studies, where a study can receive a maximum of 9 points.[16]

Data extraction

Two investigators (F.M., T.Q.) independently extracted the following data in duplicate from included studies: study design, sample size, intervention and control medications, demographics (age, sex, comorbidities, concurrent medications), outcome data (length of follow-up, rate and type of bleeding, rate of all-cause mortality), and definitions of outcomes. Disagreements were resolved through discussion, and when necessary, in consultation with a third author (M.S.). The primary outcome was major bleeding as defined by the included studies. Secondary outcomes were gastrointestinal (GI) bleeding, intracranial bleeding, and all-cause mortality. GI and intracranial bleeding were summed to comprise major bleeding in the study by Wong *et al.*[17] Definitions of outcomes are summarized in *Table 1*, where provided by primary studies.

Statistical analysis

The RevMan (version 5) software package by the Cochrane Collaboration was used for statistical analysis. Baseline characteristics were pooled using weighted averages. Data presented in person quarters in primary studies were used as reported in our analyses. Outcomes were pooled with a random-effects model as described by DerSimonian and Laird.[18] Summary estimates and 95% CIs were reported for dichotomous variables as odds ratios (ORs). An adjusted analysis was also conducted reporting calculated HRs. Heterogeneity was assessed with Cochran's Q X^2 and I^2. An I^2 above 50% represented substantial heterogeneity.[19] A *P*-value below 0.05 indicated statistical significance. Comparisons between both groups were performed using the Student's *t*-test. Results of meta-analysis and summary estimates were presented in forest plots.

Results

Literature search and characteristics of included studies

The literature search yielded 3180 studies (1604 from PubMed, 1355 from Embase, 220 from CENTRAL, and 1 from handsearching). Duplicates were removed, and we excluded 2530 studies during title and abstract review. The remaining 32 studies were assessed in full text. Nine studies met inclusion criteria and were included in this meta-analysis. *Figure 1* summarizes the literature search and study selection according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standards.[20]

We included one nested case-control study,[21] two prospective cohort studies,[22,23] five retrospective cohort studies,[14,15,24–26] and one retrospective cohort and case-crossover study.[17] Follow-up ranged from a median of 29 days to up to 6 years. The individual definition of major bleeding in each study was summarized in *Table 1*. While all definitions required presentation to medical attention for bleeding, or death due to bleeding, definitions varied across studies.

The quality of all included studies using the Newcastle-Ottawa scale scored a minimum of 7 points, out of a maximum possible 9 points (*Table 2*).[16]

Baseline characteristics of included patients

We included 438 887 patients on DOACs, of which 124 813 received amiodarone, and 314 074 did not receive amiodarone. Rivaroxaban was the most common DOAC in both groups (44.7% amiodarone/DOAC vs. 43.9% DOAC). Edoxaban was only used in one study.[17] The average age was 77.2 years in the amiodarone/DOAC group, compared to 74.4 years in the DOAC group ($P = 0.21$). The mean CHA_2DS_2-VASc score was 4.7 in the amiodarone/DOAC group and 4.0 in the DOAC group ($P = 0.21$). HAS-BLED scores were similar between groups, with a mean of 3.2 in the amiodarone/DOAC group and 2.8 in the DOAC group ($P = 0.7$). AF/atrial flutter was present in 97.4% of the patients in the amiodarone/DOAC group and 92.5% of the patients in the DOAC group ($P = 0.10$). Baseline characteristics of patients are summarized in *Table 3*. Additional information is available in Supplementary material online, Appendix S2.

Outcomes

Primary outcome

Major bleeding occurred in 2.4% of patients on amiodarone with DOACs, compared to 2.1% of patients on DOACs without amiodarone. Among patients on DOACs, there was a statistically significant increase in major bleeding in those on concurrent amiodarone (OR 1.22, 95% CI 1.03–1.44, $P = 0.02$, $I^2 = 88\%$; *Figure 2*). To explore possible sources of heterogeneity, influencer analysis was performed, and suggested heterogeneity was driven by Chang *et al.* and Ray *et al.*[15,24]

Secondary outcomes

GI bleeding occurred at similar rates among DOAC patients on amiodarone (1.4%) compared to those not on amiodarone (1.3%). The difference was not statistically significant (OR 1.10, 95% CI 0.98–1.23, $P = 0.12$, $I^2 = 62\%$; *Figure 3*). Intracranial bleeding was numerically higher among patients on amiodarone and DOAC (1.0%), compared to those not on amiodarone (0.4%). However, the difference did not reach statistical significance (OR 2.20, 95% CI 0.53–9.06, $P = 0.27$, $I^2 = 100\%$; *Figure 4*). Finally, all-cause mortality was similar among patients on amiodarone and DOAC, compared to those not on amiodarone (8.7% vs. 7.3%; OR 1.38, 95% CI 0.70–2.73, $P = 0.35$, $I^2 = 99\%$; *Figure 5*).

Adjusted analysis

An adjusted analysis was conducted reporting HRs. Five studies reported risk estimates for major bleeding and were included in the adjusted analysis.[14,15,21,24,26] There was a statistically significant increase in major bleeding among patients on DOACs and amiodarone, compared to patients on DOACs alone, consistent with the original analysis (HR 1.25, 95% CI 1.08–1.45, $P = 0.003$, $I^2 = 83\%$; Supplementary material online, Appendix S3). Three studies presented risk estimates for GI bleeding.[17,24,26] Differing from the original analysis, those on concurrent DOACs and amiodarone were found to have significantly increased risk of GI bleeding, compared to those not on amiodarone (HR 1.21, 95% CI 1.14–1.28, $P < 0.001$, $I^2 = 0\%$; Supplementary material online, Appendix S4). The same three studies reported risk estimates for intracranial bleeding, which remained similar between groups (HR 1.55, 95% CI 1.00–2.40, $P = 0.05$, $I^2 = 91\%$; Supplementary material online, Appendix S5).[17,24,26] Finally, four studies reported risk estimates for all-cause mortality, which also remained similar between groups (HR 1.14, 95% CI 1.00–1.29, $P = 0.05$, $I^2 = 62\%$; Supplementary material online, Appendix S6).[15,17,25,26]

Discussion

Our meta-analysis of nine studies has shown that patients on concurrent amiodarone and DOACs have higher odds of major bleeding. There were no statistically significant differences in our secondary outcomes of GI bleeding, intracranial bleeding, and all-cause mortality.

Table 1 Characteristics of included studies

Author	Study design	Intervention	Control	Length of follow-up	Definition of major bleeding
Chang (2017)[20]	Retrospective cohort	Amiodarone & DOAC ($n = 94\,170$[a]) Dabigatran (40%), rivaroxaban (51%), apixaban (9%)	DOAC ($n = 352\,867$[a]) Dabigatran (44%), rivaroxaban (48%), apixaban (8%)	Up to 4 years	Hospitalization or an ED visit with primary diagnosis of intracranial, GI, urogenital, or other bleeding (including urogenital, pleural, or peritoneal bleeding)
Chiou (2021)[21]	Retrospective cohort	Amiodarone & rivaroxaban ($n = 177$)	Rivaroxaban ($n = 1205$)	Mean 31 months	Bleeding accompanied by haemoglobin fall of $\geq$2 g/dL, transfusion of $\geq$2 units of packed red blood cells, critical site bleeding, or resulting in death, as per ISTH criteria
Grymonprez (2023)[22]	Retrospective cohort	Amiodarone and DOAC ($n = 37\,180$)	DOAC ($n = 143\,018$)	Up to 6 years	Hospitalized bleeding event in a critical area or organ (e.g. intracranial), fatal bleeding or bleeding event with medical procedure code for blood transfusion $\leq$10 days after admission, which is adapted from ISTH definition due to a lack of data on haemoglobin and blood transfusion
Hill (2022)[10]	Retrospective cohort	Amiodarone and DOAC ($n = 4872$) Dabigatran (26%), rivaroxaban (37%), apixaban (37%)	Metoprolol and DOAC ($n = 21\,853$) Dabigatran (23%), rivaroxaban (43%), apixaban (34%)	Median 193 days (intervention), 233 days (control)	Hospitalization or ED visit with GI, intracerebral, subarachnoid, and other non-traumatic intracranial bleeding
Ray (2023)[11]	Retrospective cohort	Amiodarone and DOAC ($n = 54\,977$) Apixaban (57%), rivaroxaban (43%)	Flecainide/sotalol and DOAC ($n = 36\,613$) Apixaban (57%), rivaroxaban (43%)	Median 159 days	Intracranial (fatal or non-fatal) bleeding or fatal extracranial bleeding, with death within 30 days of bleeding onset
Shurrab (2023)[17]	Nested case-control	Amiodarone and DOAC ($n = 2766$)	DOAC ($n = 5532$)	–	Hospitalization with primary diagnosis of subarachnoid, intracerebral/intracranial, or GI bleeding
Wang (2023)[18]	Prospective cohort	Amiodarone and rivaroxaban ($n = 154$)	Rivaroxaban ($n = 154$)	3 months	Fatal bleeding, bleeding in a critical area or organ (intracranial, intraspinal, intraocular, retroperitoneal, intraarticular, pericardial, or intramuscular with compartment syndrome), bleeding that led to a decrease in haemoglobin by $\geq$2 g/dL or required transfusion of $\geq$2 units of whole blood or red cells

Table 1 Continued

Author	Study design	Intervention	Control	Length of follow-up	Definition of major bleeding
Wong (2024)[13]	Retrospective cohort and case-crossover	Amiodarone and DOAC ($n = 9075$) Dabigatran (8%), rivaroxaban (40%), apixaban (47%), edoxaban (5%)	Beta blocker and DOAC ($n = 116\,566$) Dabigatran (6%), rivaroxaban (41%), apixaban (48%), edoxaban (5%)	Median 29 days	–
Zhang (2022)[19]	Prospective cohort	Amiodarone and rivaroxaban ($n = 41$)	Dronedarone and rivaroxaban ($n = 41$)	3 months	Fatal or associated with any of the following: (a) a fall in haemoglobin of 2 g/dL or more, or transfusion of ≥2 units of packed red blood cells, (b) involvement of a critical anatomical site (intracranial, spinal, ocular, pericardial, articular, intramuscular with compartment syndrome, retroperitoneal), or (c) BARC types 3–5

BARC, Bleeding Academic Research Consortium; DOAC, direct oral anticoagulant; ED, emergency department; GI, gastrointestinal; ISTH, International Society on Thrombosis and Hemostasis.
[a] Person quarters.

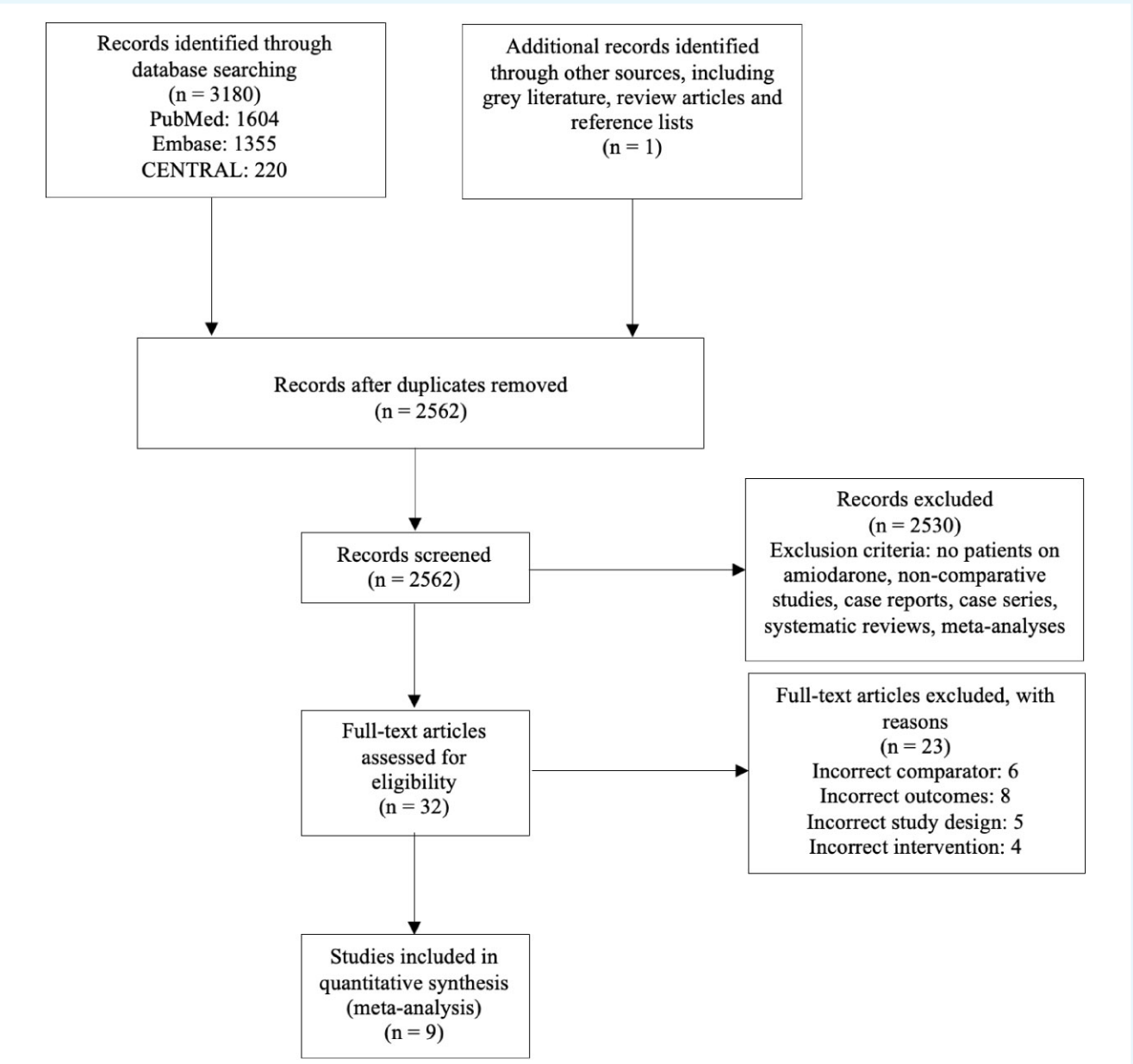


Figure 1 Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram of literature search and study selection.

In our meta-analysis, concurrent amiodarone and DOACs was associated with a 23% increase in the odds of major bleeding, compared with patients on a DOAC without amiodarone (OR 1.22, 95% CI 1.03–1.44). While the increase is modest in magnitude, this DDI should be recognized given frequent co-prescriptions.[4–6] To date, individual studies have shown conflicting results. Our previous work of AF patients on DOACs identified a significant association between major bleeding and current amiodarone use (OR of 1.53, 95% CI 1.24–1.89).[21] Other studies included in this meta-analysis have shown similar results.[15,24,26] In contrast, Hill *et al.* found a reduced risk of major bleeding (HR 0.77, 95% CI 0.61–0.97). However, this may be due to a smaller sample size, low event rates, and shorter duration of follow-up.[14]

We found no difference in the odds of GI bleeding (OR 1.10, 95% CI 0.98–1.23) or all-cause mortality (OR 1.38, 95% CI 0.70–2.73) between the groups. The rate of intracranial bleeding was higher in the amiodarone/DOAC group, but the difference did not reach statistical significance (OR 2.20, 95% CI 0.53–9.06). The two retrospective cohorts in our meta-analysis that found similar rates of GI bleeding have notable limitations. The median length of follow-up in Wong *et al.* was 29 days, which may be insufficient to observe the risks of DDI.[17] The remaining studies that reported on GI bleeding followed patients for at least 2.5 years. Furthermore, in Chiou *et al.*, 53.6% of patients in the DOAC group and 57.6% in the DOAC-amiodarone group were on prophylactic dosing of rivaroxaban at 10 mg.[25] This may have impacted the rates of GI bleeding found in the study. Further research is required since event rates were generally low across studies and confidence intervals are wide.

We also conducted an adjusted analysis. The risk of major bleeding remained elevated among those on amiodarone and DOACs, compared to DOACs alone, supporting the original analysis (HR 1.25, 95% CI 1.08–1.45, $P = 0.003$). All-cause mortality (HR 1.14, 95%

Table 2 **Risk of bias assessment of included studies**

	Selection					Outcome		
Study	**Representativeness of exposed cohort**	**Selection of non-exposed cohort**	**Ascertainment of exposure**	**Demonstration that outcome of interest was not present at start of study**	**Comparability of cohorts on basis of design or analysis**	**Assessment of outcome**	**Follow-up duration adequate**	**Adequacy of follow up**
Chang (2017)	*	*	*	*	**		*	*
Chiou (2021)	*	*	*	*	**	*	*	*
Grymonprez (2023)	*	*	*	*	**	*	*	*
Hill (2022)	*	*	*	*	**		*	*
Ray (2023)	*	*	*	*	**			*
Wang (2023)	*	*	*	*	**			*
Wong (2024)	*	*	*	*	**	*		*
Zhang (2022)	*	*	*	*	**			*
	Adequate case definition	Representativeness of cases	Selection of controls	Definition of controls	Comparability of cohorts on basis of design or analysis	Ascertainment of exposure	Same method of ascertainment for cases and controls	Non-response rate
Shurrab (2023)	*	*	*	*	**		*	*

Asterisks (*) indicate the star rating according to the Newcastle-Ottawa Scale. A study can be awarded a Maximum of 4 stars for selection, 2 stars for comparability, and 3 stars for outcome.

Table 3 Characteristics of included patients

	DOAC (n = 314 074)	Amiodarone & DOAC (n = 124 813)	P-value
Age	74.4 ± 5.9	77.2 ± 7.4	0.21
Male	45 116 (50.0)	22 767 (52.2)	0.41
Dabigatran	20 065 (22.6)	6657 (30.7)	0.25
Rivaroxaban	38 520 (43.9)	17 555 (44.7)	0.27
Apixaban	30 564 (34.7)	19 522 (42.3)	0.41
Concurrent antiplatelet	2650 (7.5)	8034 (14.7)	0.43
Hypertension	26 663 (86.8)	47 361 (92.8)	0.89
Diabetes mellitus	23 273 (27.4)	17 188 (35.9)	0.50
Stroke/TIA	14 853 (13.4)	692 (8.3)	0.36
Atrial fibrillation/flutter	100 973 (92.5)	41 222 (97.4)	0.10
History of bleeding	41 094 (37.7)	8465 (20.9)	0.43
CHA_2DS_2-VASc score	4.0 ± 1.2	4.7 ± 1.5	0.21
HAS-BLED score	2.8 ± 0.9	3.2 ± 1.3	0.70

Baseline characteristics were not available for the following studies: Chang, Grymonprez, and Shurrab.
Values are presented as mean ± standard deviation or n (%).
TIA, transient ischaemic attack.

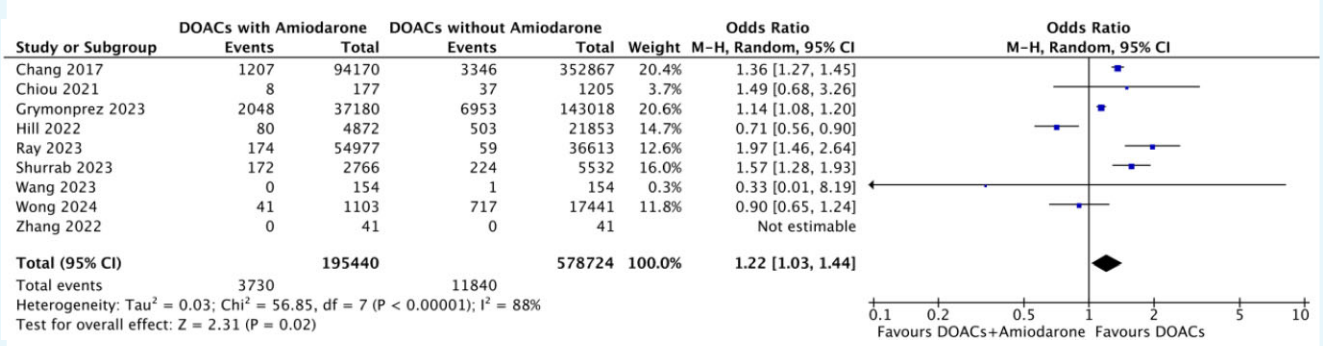


Figure 2 Forest plot of the individual and combined rates of major bleeding. CI, confidence interval; df, degrees of freedom; M-H, Mantel-Haenszel.

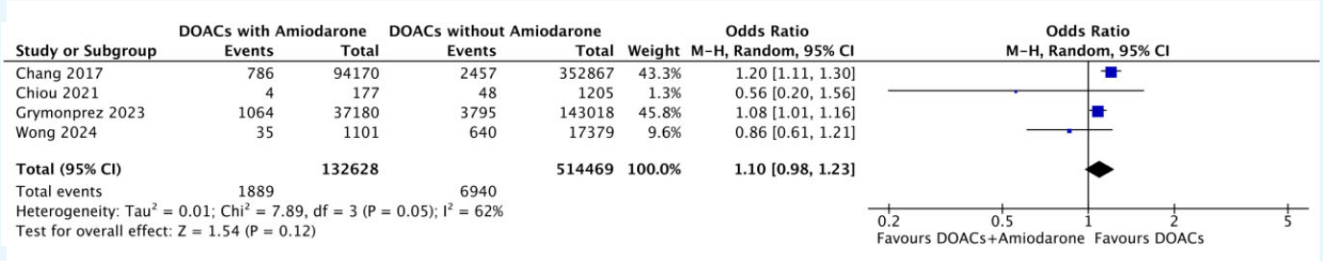


Figure 3 Forest plot of the individual and combined rates of gastrointestinal bleeding. CI, confidence interval; df, degrees of freedom; M-H, Mantel-Haenszel.

CI 1.00–1.29, P = 0.05) and intracranial bleeding (HR 1.55, 95% CI 1.00–2.40, P = 0.05) remained similar between groups in the adjusted analysis. However, there was a concerning trend (P = 0.05), warranting evaluation in subsequent studies. Finally, while GI bleeding was similar between groups in the original analysis, the adjusted analysis demonstrated a significant increase in the amiodarone/DOAC group, compared to the DOAC group (HR 1.21, 95% CI 1.14–1.28, P < 0.001). This discrepancy may be explained by the removal of the retrospective cohort by Chiou *et al.* from the adjusted analysis due to the lack of risk estimate for GI bleeding.[25] Contrary to other included studies, Chiou *et al.* found a higher proportion of GI bleeding in patients on DOACs alone (4.0%), compared to those on concurrent

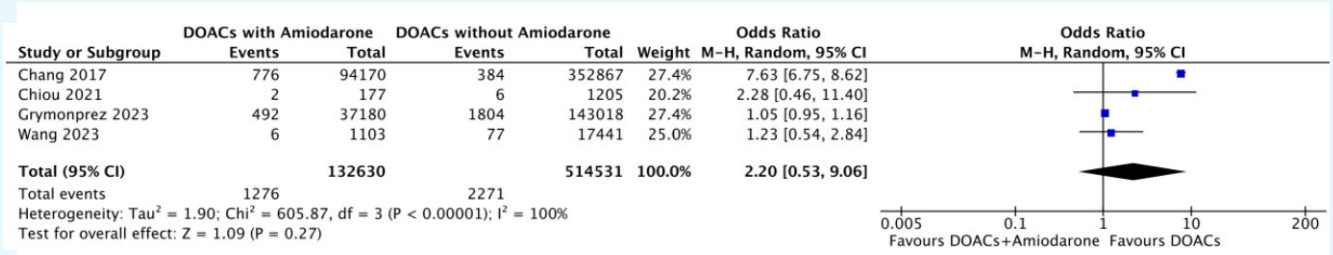


Figure 4 Forest plot of the individual and combined rates of intracranial bleeding. CI, confidence interval; df, degrees of freedom; M-H, Mantel-Haenszel.

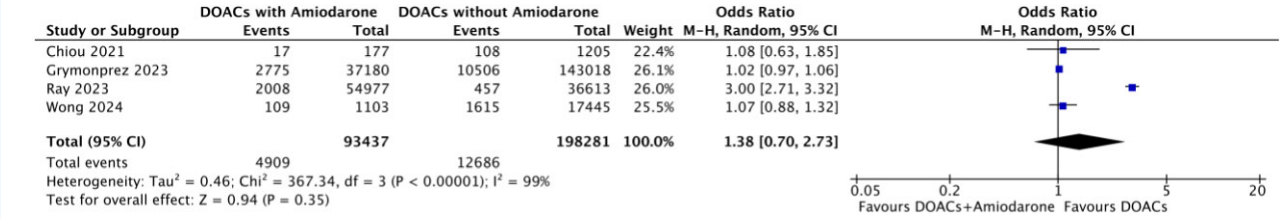


Figure 5 Forest plot of the individual and combined rates of all-cause mortality. CI, confidence interval; df, degrees of freedom; M-H, Mantel-Haenszel.

amiodarone (2.3%).[25] However, these findings are limited by sample size, and a more frequent history of major bleeding in the DOAC group.

Currently, product monographs for DOACs acknowledge the DDI with amiodarone, but indicate that dose adjustments are not required.[27–30] Similarly, guidelines by Thrombosis Canada and European Heart Rhythm Association advise caution on the combination of DOACs and amiodarone, but provide no further guidance to clinicians.[31,32] Our meta-analysis of over 400 000 patients demonstrated higher odds of major bleeding with concurrent amiodarone and DOACs, compared to DOAC-treated patients. This provides further insight into the interaction and quantifies the risk. In patients who are on both amiodarone and DOACs, clinicians may wish to avoid the use of other P-gp and CYP3A4 inhibitors, address underlying bleeding risk factors, or intensify follow-up to monitor for bleeding. A practical disadvantage of DOACs compared to VKAs in this setting, is the lack of reliable measurement of anticoagulation intensity, as INR allows for VKAs.[33]

Our meta-analysis has a number of strengths. This is the first meta-analysis on the risk of bleeding with concurrent amiodarone and DOACs. We included nine studies and nearly 440 000 patients, making this the most comprehensive review of the literature to date. The included studies were of good quality, with all scoring at least 7 points on the 9-point Newcastle-Ottawa scale.

Limitations

The limitations of our meta-analysis are related to the primary studies. All included studies are observational in design, with most being retrospective, which are inherently prone to residual confounding and selection bias. RCTs evaluating the clinical risks of concurrent amiodarone and DOAC use will greatly advance knowledge of the interaction. Baseline characteristics were not reported by three studies.[21,24,26] Four primary studies used databases, which record the prescription of medications, but not adherence.[14,15,17,21] However, non-adherence would bias results towards the null. Reporting of relevant bleeding risk factors, such as renal and liver function and concomitant medications, was inconsistent. Additionally, the dose of DOACs was rarely reported, preventing analysis of whether under- or overdosing contributed to our findings. Furthermore, outcome data was not reported for individual DOACs and thus this analysis could not be performed. Finally, our results may not be generalizable to edoxaban since it was only used in one study.[17] These important factors may be further assessed in future studies.

Supplementary material

Supplementary material is available at *European Heart Journal—Cardiovascular Pharmacotherapy* online.

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Data availability

The data underlying this article will be shared on reasonable request with the corresponding author.

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