

Supplementary material

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Oral Anticoagulation challenges and therapeutic dilemmas in the very elderly: To treat and how to treat octogenarians and nonagenarians?

Supplementary Table S1. Observational studies and randomized trials or sub-studies of randomized trials assessing the effectiveness and safety of different oral anticoagulation strategies in the elderly

Study (year)	Country	Type of study	Comparison of drugs	Population	Efficacy (IS/SE)	Safety (Intracranial hemorrhage or major bleeding)
Halvorsen S. et al., 2014 [S123]	Norway	Post-hoc analysis of an RCT	Apixaban versus warfarin	2,436 AF patients aged ≥80 years	Apixaban compared with warfarin reduced the risk of thromboembolism or mortality	Reduced risk of major bleeding with apixaban compared with
Wolff A. et al., 2015 [S124]	Canada	Retrospective cohort study	DOAC versus antiplatelet medication	561 AF patients aged ≥85 years	Antiplatelet monotherapy associated with increased risk of stroke and mortality rates compared to OAC	N/A
Chan PH et al., 2016 [S125]	China	Retrospective cohort study	Dabigatran vs warfarin with time in therapeutic range (TTR) ≥55%	571 AF patients aged ≥80 years	Dabigatran achieved superior stroke risk reduction compared with warfarin with TTR ≥55%	Dabigatran achieved similar risk of intracranial hemorrhage compared with warfarin with TTR ≥55%
Ng K. et al., 2016 [S126]	Canada	Retrospective cohort study	Apixaban versus aspirin	366 AF patients ≥85 years	Increased thromboembolic risk in patients under aspirin compared with those under apixaban	Similar risk of bleeding with apixaban versus aspirin
Yamasita Y. et al., 2016 [S127]	Japan	Prospective cohort study	DOAC versus no DOAC	479 AF patients aged ≥85 years	Higher thromboembolic risk in patients receiving DDOAC than those without DOAC	Similar risk of bleeding with OAC and without OAC
Lauw M. et al., 2017 [46]	Canada	Post-hoc analysis of an RCT	Dabigatran versus warfarin	3,027 AF patients aged ≥ 80years	Dabigatran was superior to warfarin regarding stroke occurrence	Dabigatran was superior to warfarin regarding ICH occurrence; dabigatran 150mg BID was linked with increased extracranial bleeding incidence compared to dabigatran 110mg BID.
Patti G. et., 2017 [1]	Italy	Retrospective cohort study	VKA, apixaban, rivaroxaban or dabigatran) versus no anticoagulant or antiplatelet therapy	551 AF patients aged ≥85 years	Non-significantly lower risk of thromboembolism between anticoagulant and no-anticoagulant or antiplatelet therapy	Similar risk of major bleeding between anticoagulant and no-anticoagulant or antiplatelet therapy
Lai CL et al., 2018 [45]	Taiwan	Retrospective cohort study	Dabigatran 110mg, rivaroxaban 15mg, and warfarin	54,722 AF patients >85 years	Reduced-dose dabigatran or rivaroxaban were associated with lower all-cause and cardiovascular mortality than warfarin; the risk of thromboembolism rates did not differ	Reduced-dose dabigatran was also associated with lower risk of intracranial hemorrhage than warfarin

Poli D. et al., 2019 [S128]	Italy	Propensity score matched prospective cohort study	DOACs (dabigatran, rivaroxaban, apixaban, or edoxaban) vs warfarin	1,124 AF patients aged ≥85 years	Higher thromboembolic risk and lower risk of mortality under DOACS compared to warfarin	Similar risk of major bleeding under DOACs and warfarin.
Deitelzweig S. et al., 2019 [S129]	USA	Post-hoc analysis of RCT	DOACs (apixaban, dabigatran or rivaroxaban) vs warfarin	88,582 AF patients aged ≥80 years	All DOACs had lower risk of thromboembolism compared to warfarin; Consistent results in both low- and standard- dose sub-analyses.	Apixaban associated with lower risk of major bleeding versus warfarin; Dabigatran associated with similar risk of major bleeding versus warfarin; Rivaroxaban associated with higher risk of MB; Dabigatran associated with lower risk of MB compared to rivaroxaban; Consistent results in both low- and standard- dose sub-analyses.
Kim HM et al., 2019 [S130]	Korea	Retrospective cohort study	DOACs (apixaban, rivaroxaban or dabigatran) versus warfarin	687 AF patients aged ≥80 years	DOACs associated with lower risk of thromboembolic events, and all-cause death than warfarin	DOACs associated with lower risk of major bleeding than warfarin
Shinohara M. et al., 2019 [S131]	Japan	Retrospective cohort study	DOACs (apixaban, rivaroxaban or dabigatran) versus warfarin	354 AF patients aged ≥80 years	Similar risk of thromboembolism between DOACs and warfarin	Reduced risk of bleeding with DOACs versus warfarin
Giustozzi M. et al., 2019 [S132]	Italy	Retrospective cohort study	DOACs (apixaban, rivaroxaban or dabigatran) versus warfarin	546 AF patients aged ≥90 years	Similar risk of thromboembolism between DOACs and warfarin	Similar risk of major bleeding with DOACs versus warfarin
Nishida T. et al., 2019 [S133]	Japan	Prospective cohort study	DOACs versus warfarin	264 AF patients aged ≥ 85 years	Similar risk of thromboembolism and mortality with DOACs versus warfarin	Decreased risk of major bleeding in DOACs compared to warfarin
Russo V. et al., 2020 [S134]	Italy	Propensity score matched prospective cohort study	DOACs (apixaban, dabigatran or rivaroxaban) vs warfarin	774 AF patients aged ≥ 80 years	No significant difference in terms of thromboembolic events; significantly lower all-cause mortality rates under DOACs	There was no significant difference in terms of major bleeding events and intracranial hemorrhage under DOACs vs under warfarin
Raposeiras SR et al., 2020 [31]	Spain	Propensity score matched retrospective cohort study	Non-OAC versus DOACs versus VKA	1,750 AF patients aged ≥90 years	DOACs were associated with lower risk of death and thromboembolism compared to non-OAC	VKA were associated with increased risk of ischemic hemorrhage and major bleeding compared to DOACs
Papanastasiou A., 2021 [S135]	Greece	Retrospective cohort study	DOACs (dabigatran, rivaroxaban, apixaban, or edoxaban) vs warfarin	330 AF patients aged ≥80years	No difference in the risk of stroke or mortality	No difference in the risk of major bleeding
Tsai CT et al., 2021 [S136]	Taiwan	Propensity score matched cohort study	DOACs (dabigatran, rivaroxaban or apixaban) vs warfarin	15,361 AF patients aged ≥ 85 years	Rivaroxaban associated with reduced risk of stroke compared to warfarin; All DOACs were at least as effective as warfarin for stroke prevention and associated with a lower risk of all-cause mortality and composite adverse events	Dabigatran and rivaroxaban were associated with reduced risk of ICH compared to warfarin. Major bleeding rates did not differ significantly among the prescribed OAC
Hanon O. et al., 2021 [S137]	France	Propensity score-matched prospective cohort study	Rivaroxaban vs warfarin	1,903 AF patients aged ≥80 years	Similar risk of thromboembolism	bleeding risk, largely driven by lower risk of intracerebral bleeding, is lower with rivaroxaban than with VKA

Cbao TF et al., 2021 [105]	Taiwan	Propensity score matched retrospective cohort study	DOACs (dabigatran, rivaroxaban, apixaban, or edoxaban) vs non-OAC and warfarin	7,362 AF patients aged ≥ 90 years	DOACs associated with a lower risk of a net clinical endpoint of ischemic stroke, intracranial hemorrhage, major bleeding, or mortality	DOACs associated with a lower risk of a net clinical endpoint of ischemic stroke, intracranial hemorrhage, major bleeding, or mortality
Coleman CI et al., 2022 [S138]	USA	Propensity score-matched retrospective cohort study	Rivaroxaban versus warfarin	31,941 AF patients aged ≥80 years	Similar risk of thromboembolism between rivaroxaban and warfarin	Similar risk of major or CRNM bleeding between rivaroxaban and warfarin
Taoutel R. et al., 2022 [S139]	USA	Retrospective cohort study	Full vs reduced dose of DOACs (apixaban, rivaroxaban or dabigatran)	713 AF patients aged ≥80 years	DOACs effectively reduced stroke and systemic embolization rates independent of DOAC dose.	DOACs yielded a low risk of CNS bleeding, independent of DOAC dose.
Okumura K. et al., 2022 [30]	Japan	Retrospective cohort study	DOACs (dabigatran, rivaroxaban, apixaban, or edoxaban) versus non-use of OACs or warfarin	7,104 AF patients aged ≥80 years with high bleeding risk	DOACs were associated with reduced incidence of thromboembolism compared to the non-use of OAC agents, and were superior to warfarin effectiveness	DOACs were associated with major bleeding compared to non-use of OACs; DOACs had superior safety compared to warfarin
Yoshida T. et al., 2022 [47]	Japan	Post-hoc analysis of RCT	Edoxaban versus placebo	984 AF patients aged ≥80 years	Edoxaban reduced the incidence of thromboembolism regardless of the level of renal dysfunction	There was no increase in intracranial hemorrhage or fatal bleeding events in the edoxaban group

*RCT, randomized controlled trial; AF, atrial fibrillation; VKA, Vitamin-K antagonist; DOAC, direct oral anticoagulants

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