EFFETTI DELLA PRESCRIZIONE DI ANTICOAGULANTI ORALI DIRETTI A DOSAGGIO NON RACCOMANDATO:

RISULTATI DI UNA METANALISI

BACKGROUND

- Atrial fibrillation is the most common arrhythmia, affecting 1-2% of the population and is associated with a 5-fold increased risk of ischemic stroke (IS).
- RCTs have reported that direct oral anticoagulants (DOACs) are noninferior to VKAs in preventing IS, TIA and systemic embolism (SE), but superior concerning bleeding risk reduction.
- While adherence to the recommended dose was guaranteed in the major RCTs, recent real-world registries have reported cases of nonrecommended doses of DOAC prescription.
- The efficacy and safety profiles of nonrecommended DOAC doses in patients with nonvalvular atrial fibrillation are still undefined.

BACKGROUND- ASIAN ETHNICITY

- Asian patients carry higher risk of ischemic and haemorrhagic events than Western populations.
- IS and bleeding risk scores have not been well validated in Asians.
- An increased bleeding risk in Asians treated with VKAs is well-known from RCTs.
- Conversely, when DOACs were used in Asians, this bleeding risk excess was not found.

Effects of Direct Oral Anticoagulants' Nonrecommended Dose in Atrial Fibrillation: A Meta-Analysis

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Eur Neurol, 2022 Sep 13;1-12.

AIM OF THE STUDY

To compare efficacy and safety profile of nonrecommended doses of DOAC to those recommended in patients with nonvalvular atrial fibrillation.

Eur Neurol, 2022 Sep 13;1-12.

METHODS

- The authors searched for randomized controlled trials and observational studies that compared nonrecommended versus recommended doses of DOACs, published up to December 2021.
- Primary study outcomes were ischemic stroke/transient ischemic attack/systemic embolism (IS/TIA/SE) and major bleeding (MB).
- All-cause mortality was a secondary outcome.
- Pooled odds ratios (ORs) between groups of patients were determined with a random-effect model.

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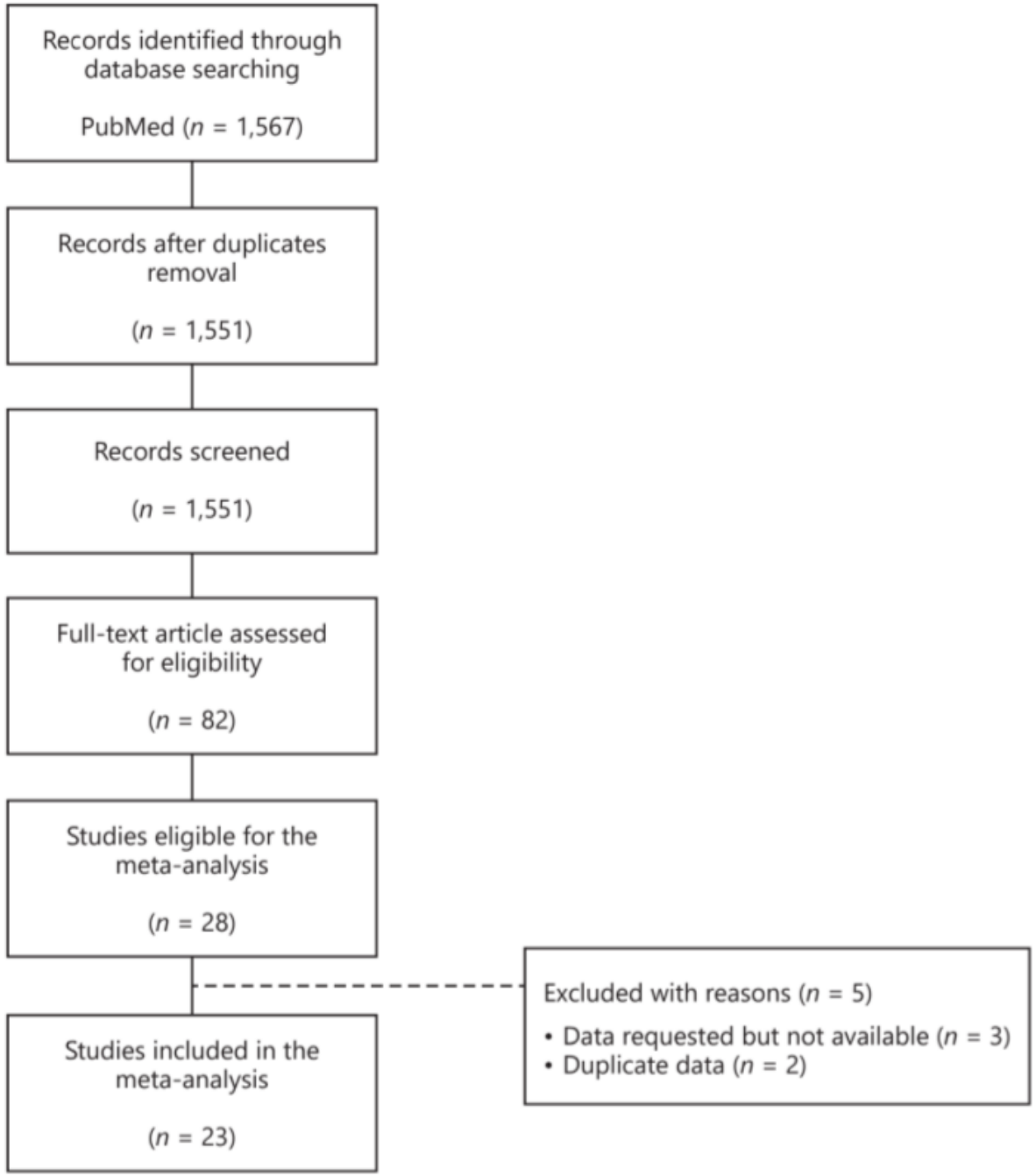

STUDY SELECTION FLOW

TOTAL: 175,801 patients

Non recommended doses more common in:

- older patients
- more comorbidities
- higher CHA2DS2VASc
- worse renal function

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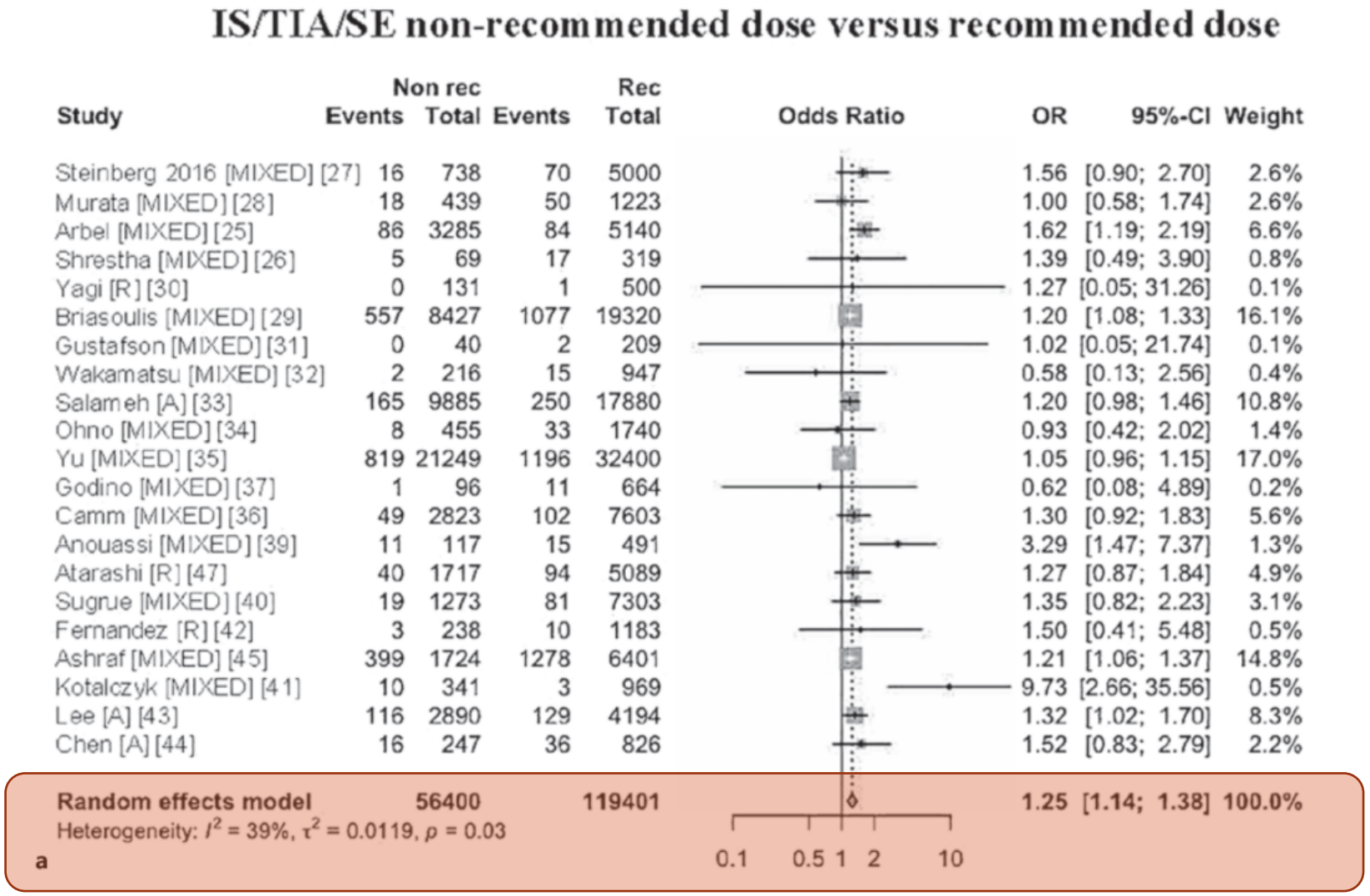
IS/TIA/SE



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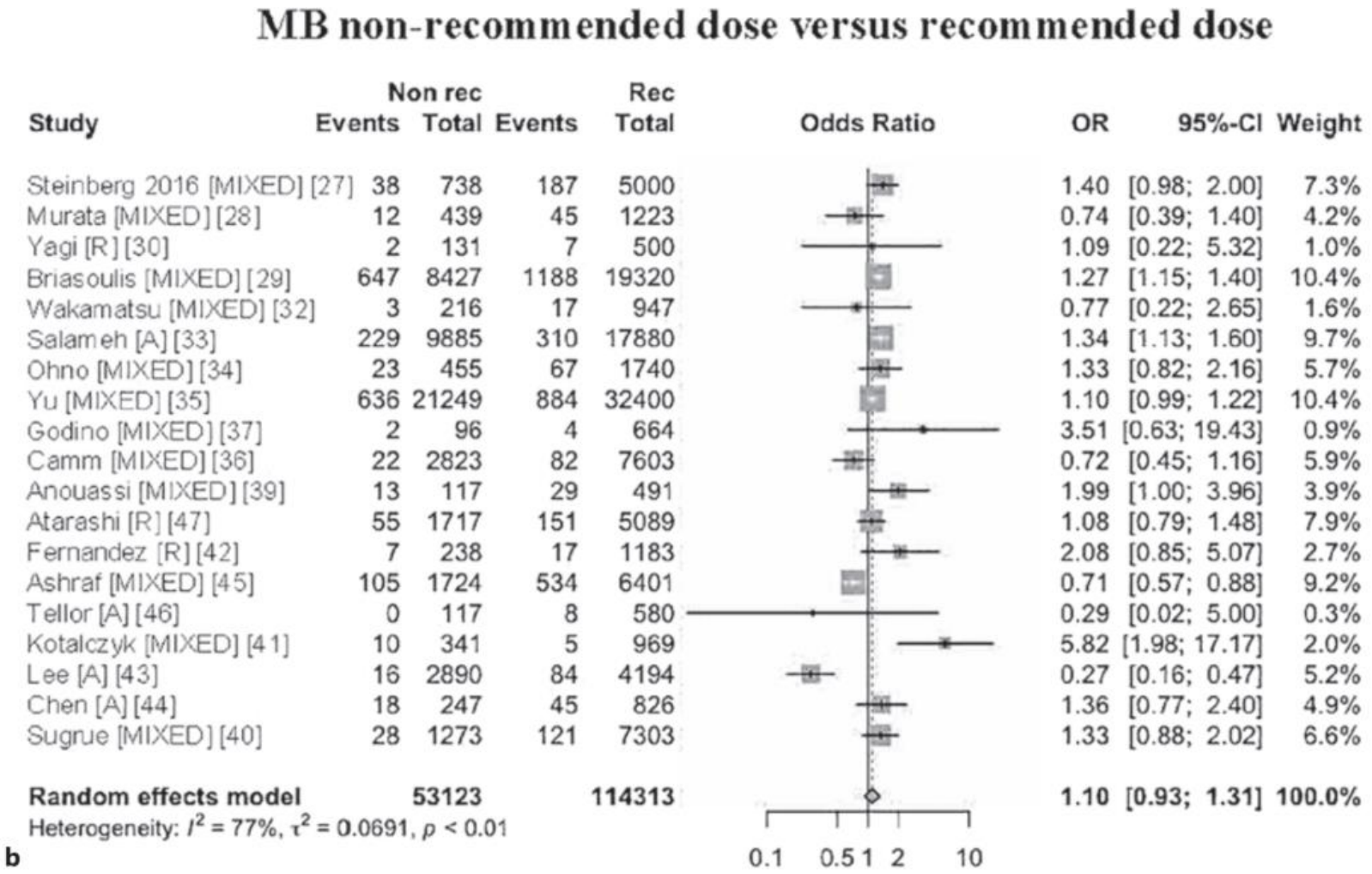
MAJOR BLEEDING



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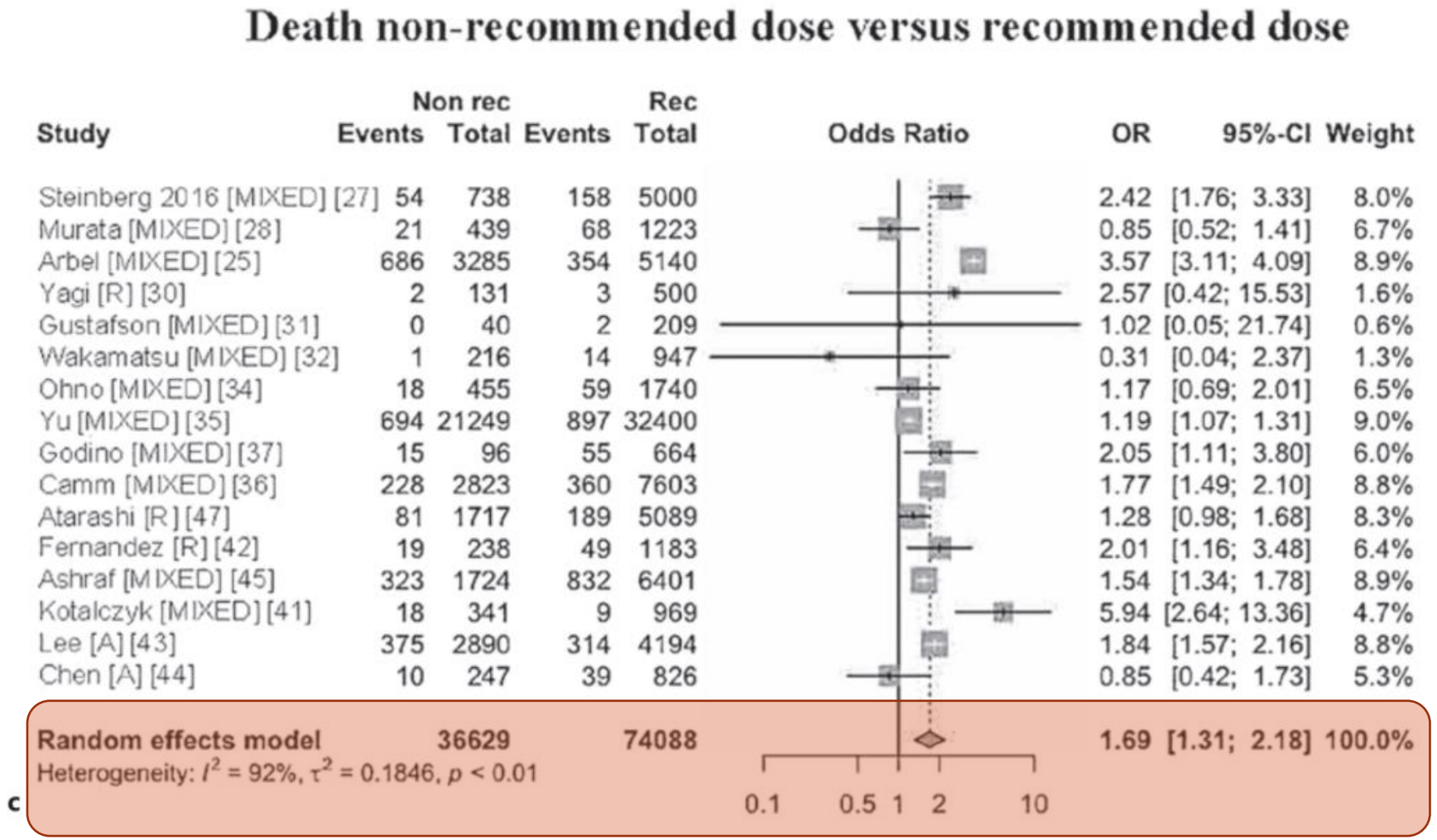
ALL-CAUSE DEATH



LOW NON-RECOMMENDED DOSES

IS/TIA/SE non-recommended low dose versus recommended dose

Study	Non rec Events	Non rec Total	Rec Events	Rec Total	OR	95%-CI	Weight
Arbel [MIXED] [25]	86	3285	84	5140	1.62	[1.19; 2.19]	9.4%
Shrestha [MIXED] [26]	4	51	17	319	1.51	[0.49; 4.69]	1.5%
Steinberg 2016 [MIXED] [27]	16	689	91	5895	1.52	[0.89; 2.59]	4.9%
Murata [MIXED] [28]	11	369	50	1223	0.72	[0.37; 1.40]	3.6%
Yagi [R] [30]	0	123	1	500	1.35	[0.05; 33.30]	0.2%
Briasoulis [MIXED] [29]	148	3564	776	19320	1.04	[0.87; 1.24]	13.0%
Wakamatsu [MIXED] [32]	2	216	15	947	0.58	[0.13; 2.56]	0.9%
Salameh [A] [33]	165	9885	250	17880	1.20	[0.98; 1.46]	12.5%
Ohno [MIXED] [34]	6	338	33	1740	0.93	[0.39; 2.25]	2.3%
Yu [MIXED] [35]	584	16757	1196	32400	0.94	[0.85; 1.04]	15.2%
Camm [MIXED] [36]	39	2423	102	7603	1.20	[0.83; 1.74]	7.8%
Atarashi [R] [47]	36	1609	94	5089	1.22	[0.82; 1.79]	7.4%
Sugrue [MIXED] [40]	16	1071	81	7303	1.35	[0.79; 2.32]	4.9%
Kotalczyk [MIXED] [41]	10	341	3	969	9.73	[2.66; 35.56]	1.1%
Fernandez [R] [42]	1	138	10	1183	0.86	[0.11; 6.74]	0.5%
Lee [A] [43]	116	2890	129	4194	1.32	[1.02; 1.70]	10.8%
Chen [A] [44]	16	247	36	826	1.52	[0.83; 2.79]	4.1%
Random effects model		**43996**		**112531**	**1.21**	**[1.05; 1.39]**	**100.0%**

Heterogeneity: $I^2 = 55\%$, $\tau^2 = 0.0324$, $p < 0.01$

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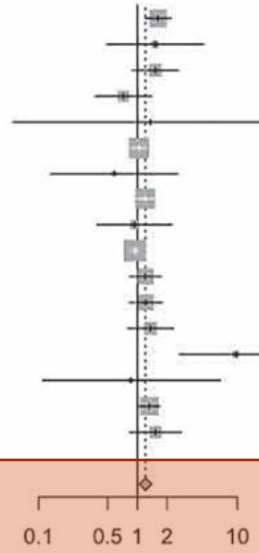

MB non-recommended low dose versus recommended dose

Study	Non rec Events	Non rec Total	Rec Events	Rec Total	OR	95%-CI	Weight
Steinberg 2018 [MIXED] [38]	32	689	189	5895	1.47	[1.00; 2.16]	8.7%
Murata [MIXED] [28]	7	369	45	1223	0.51	[0.23; 1.13]	4.1%
Yagi [R] [30]	2	123	7	500	1.16	[0.24; 5.67]	1.4%
Briasoulis [MIXED] [29]	229	3564	1188	19320	1.05	[0.91; 1.21]	12.2%
Wakamatsu [MIXED] [32]	3	216	17	947	0.77	[0.22; 2.65]	2.1%
Salameh [A] [33]	229	9885	310	17880	1.34	[1.13; 1.60]	11.8%
Ohno [MIXED] [34]	15	338	67	1740	1.16	[0.65; 2.06]	6.1%
Yu [MIXED] [35]	442	16757	884	32400	0.97	[0.86; 1.08]	12.5%
Camm [MIXED] [36]	15	2423	82	7603	0.57	[0.33; 0.99]	6.4%
Atarashi [R] [47]	46	1609	151	5089	0.96	[0.69; 1.35]	9.4%
Kotalczyk [MIXED] [41]	10	341	5	969	5.82	[1.98; 17.17]	2.6%
Fernandez [R] [42]	3	138	17	1183	1.52	[0.44; 5.27]	2.1%
Lee [A] [43]	16	2890	84	4194	0.27	[0.16; 0.47]	6.6%
Chen [A] [44]	18	247	45	826	1.36	[0.77; 2.40]	6.2%
Tellor [A] [46]	0	98	8	580	0.34	[0.02; 5.97]	0.4%
Sugrue [MIXED] [40]	21	1071	121	7303	1.19	[0.74; 1.90]	7.5%
Random effects model		**40758**		**107652**	**1.01**	**[0.83; 1.22]**	**100.0%**

Heterogeneity: $I^2 = 74\%$, $\tau^2 = 0.0761$, $p < 0.01$

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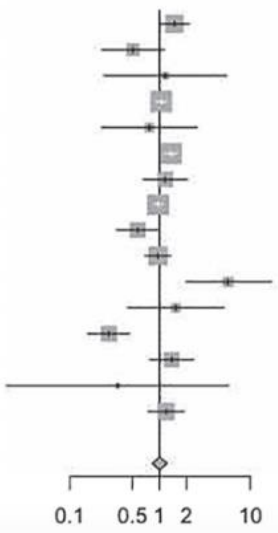

Death non-recommended low dose versus recommended dose

Study	Non rec Events	Non rec Total	Rec Events	Rec Total	OR	95%-CI	Weight
Arbel [MIXED] [25]	686	3285	354	5140	3.57	[3.11; 4.09]	9.9%
Steinberg 2018 [MIXED] [38]	52	689	177	5895	2.64	[1.92; 3.63]	9.3%
Murata [MIXED] [28]	14	369	68	1223	0.67	[0.37; 1.21]	7.8%
Yagi [R] [30]	2	123	3	500	2.74	[0.45; 16.57]	2.7%
Wakamatsu [MIXED] [32]	1	216	14	947	0.31	[0.04; 2.37]	2.3%
Ohno [MIXED] [34]	15	338	59	1740	1.32	[0.74; 2.36]	7.9%
Yu [MIXED] [35]	472	16757	897	32400	1.02	[0.91; 1.14]	10.0%
Camm [MIXED] [36]	195	2423	360	7603	1.76	[1.47; 2.11]	9.8%
Atarashi [R] [47]	68	1609	189	5089	1.14	[0.86; 1.52]	9.4%
Kotalczyk [MIXED] [41]	18	341	9	969	5.94	[2.64; 13.36]	6.5%
Fernandez [R] [42]	13	138	49	1183	2.41	[1.27; 4.56]	7.5%
Lee [A] [43]	375	2890	314	4194	1.84	[1.57; 2.16]	9.9%
Chen [A] [44]	10	247	39	826	0.85	[0.42; 1.73]	7.1%
Random effects model		**29425**		**67709**	**1.66**	**[1.18; 2.35]**	**100.0%**

Heterogeneity: $I^2 = 95\%$, $\tau^2 = 0.3102$, $p < 0.01$

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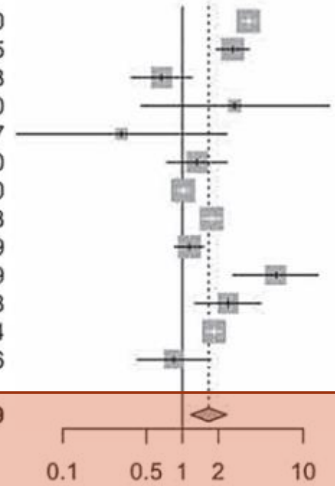

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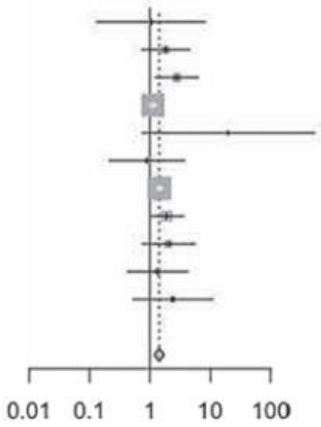
HIGH NON-RECOMMENDED DOSES

IS/TIA/SE non-recommended high dose versus recommended dose

Study	Non rec Events	Non rec Total	Rec Events	Rec Total	OR	95%-CI	Weight
Shrestha [MIXED] [26]	1	18	17	319	1.04	[0.13; 8.32]	0.9%
Steinberg 2016 [MIXED] [27]	5	197	70	5000	1.83	[0.73; 4.60]	4.1%
Murata [MIXED] [28]	7	66	50	1223	2.78	[1.21; 6.40]	4.9%
Briasoulis [MIXED] [29]	218	4863	776	19320	1.12	[0.96; 1.31]	35.9%
Yagi [R] [30]	0	8	1	500	19.59	[0.74; 516.23]	0.4%
Ohno [MIXED] [34]	2	117	33	1740	0.90	[0.21; 3.80]	1.8%
Yu [MIXED] [35]	235	4492	1196	32400	1.44	[1.25; 1.66]	36.9%
Camm [MIXED] [36]	10	400	102	7603	1.89	[0.98; 3.64]	7.4%
Atarashi [R] [47]	4	108	94	5089	2.04	[0.74; 5.66]	3.4%
Sugrue [MIXED] [40]	3	202	81	7303	1.34	[0.42; 4.29]	2.7%
Fernandez [R] [42]	2	100	10	1183	2.39	[0.52; 11.08]	1.6%
Random effects model		**10571**		**81680**	**1.42**	**[1.17; 1.73]**	**100.0%**

Heterogeneity: $I^2 = 32\%$, $\tau^2 = 0.0217$, $p = 0.14$



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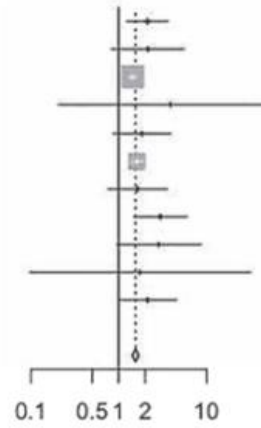
MB non-recommended high dose versus recommended dose

Study	Non rec Events	Non rec Total	Rec Events	Rec Total	OR	95%-CI	Weight
Steinberg 2016 [MIXED] [27]	15	197	187	5000	2.12	[1.23; 3.66]	2.7%
Murata [MIXED] [28]	5	66	45	1223	2.15	[0.82; 5.60]	0.9%
Briasoulis [MIXED] [29]	418	4863	1188	19320	1.44	[1.28; 1.61]	58.6%
Yagi [R] [30]	0	8	7	500	3.87	[0.20; 73.36]	0.1%
Ohno [MIXED] [34]	8	117	67	1740	1.83	[0.86; 3.91]	1.4%
Yu [MIXED] [35]	194	4492	884	32400	1.61	[1.37; 1.89]	31.4%
Camm [MIXED] [36]	7	400	82	7603	1.63	[0.75; 3.56]	1.3%
Atarashi [R] [47]	9	108	151	5089	2.97	[1.47; 5.99]	1.6%
Fernandez [R] [42]	4	100	17	1183	2.86	[0.94; 8.66]	0.6%
Tellor [A] [46]	0	19	8	580	1.73	[0.10; 31.00]	0.1%
Sugrue [MIXED] [40]	7	202	121	7303	2.13	[0.98; 4.63]	1.3%
Random effects model		**10572**		**81941**	**1.55**	**[1.42; 1.69]**	**100.0%**

Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.50$



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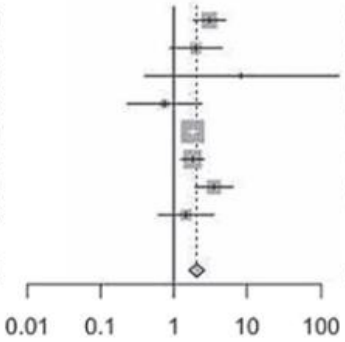
Death non-recommended high dose versus recommended dose

Study	Non rec Events	Non rec Total	Rec Events	Rec Total	OR	95%-CI	Weight
Steinberg 2016 [MIXED] [27]	18	197	158	5000	3.08	[1.85; 5.13]	14.8%
Murata [MIXED] [28]	7	66	68	1223	2.02	[0.89; 4.58]	7.5%
Yagi [R] [30]	0	8	3	500	8.36	[0.40; 174.75]	0.7%
Ohno [MIXED] [34]	3	117	59	1740	0.75	[0.23; 2.43]	4.0%
Yu [MIXED] [35]	222	4492	897	32400	1.83	[1.57; 2.12]	33.6%
Camm [MIXED] [36]	33	400	360	7603	1.81	[1.25; 2.62]	20.7%
Atarashi [R] [47]	13	108	189	5089	3.55	[1.95; 6.45]	12.0%
Fernandez [R] [42]	6	100	49	1183	1.48	[0.62; 3.54]	6.7%
Random effects model		**5488**		**54738**	**2.06**	**[1.61; 2.65]**	**100.0%**

Heterogeneity: $I^2 = 40\%$, $\tau^2 = 0.0425$, $p = 0.11$



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ASIAN SUBGROUP

	Asian population	Non asian population
Non-recommended dose vs recommended dose		
IS/TIA/SE	OR 1.22 (95% CI: 0.98–1.52, I^2=52%)	OR 1.24 (95% CI: 1.16–1.33, I^2=0%)
Major bleeding	OR 1.01 (95% CI: 0.71–1.44, I^2=79%)	OR 1.19 (95% CI: 0.96–1.48, I^2=76%)
All-cause mortality	OR 1.37 (95% CI: 1.04–1.79, I^2=81%)	OR 2.13 (95% CI: 1.49–3.05, I^2=92%)
Non-recommended LOW dose vs recommended dose		
IS/TIA/SE	OR 1.17 (95% CI: 0.89–1.54,I^2=64%)	OR 1.21 (95% CI: 1.07–1.36, I^2=7%)
Major bleeding	OR 0.93 (95% CI: 0.64–1.34, I^2=78%)	OR 1.14 (95% CI: 0.93–1.40, I^2=55%)
All-cause mortality	OR 1.30 (95% CI: 0.93–1.81, I^2=86%)	OR 2.53 (95% CI: 1.65–3.88, I^2=92%)
Non-recommended HIGH dose vs recommended dose		
IS/TIA/SE	OR 1.71 (95% CI: 1.12–2.61, I^2=29%)	OR 1.18 (95% CI: 1.02–1.36, I^2=0%)
Major bleeding	OR 1.68 (95% CI: 1.45–1.95, I^2=0%)	OR 1.48 (95% CI: 1.33–1.66, I^2=0%)
All-cause mortality	OR 2.06 (95% CI: 1.33–3.18, I^2=49%)	OR 2.10 (95% CI: 1.40–3.17, I^2=42%)

LIMITATIONS

- Criteria to define recommended doses and nonrecommended doses of DOACs are not uniform among the studies (ex Japanese guidelines).
- Subgroup analyses based on a single DOAC are of limited value due to the small number of studies with this data.
- Data on patients' compliance, adherence, switch to another DOAC or dose adjustments from the first prescribed treatment were not collected.
- All eligible studies not included because data were unavailable, and most authors did not share disaggregated data.

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CONCLUSIONS

- Compared with recommended doses, nonrecommended low doses of DOACs increase the risk of ischemic events without decreasing the risk of bleeding.
- For Asians, the efficacy of DOACs seemed preserved despite the nonrecommended low-dose prescription.
- Clinicians should carefully adhere to recommended DOAC prescription advice in managing NVAF patients.

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