## Efficacy and safety of direct oral anticoagulants with diabetes and nonvalvular atrial fibrillation: a systematic review and meta-analysis

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**Background:** Diabetes Mellitus (DM) is an independent risk factor for stroke and atrial fibrillation (AF). Therefore, the risk/benefit profile of the direct oral anticoagulants (DOAC) is of clinical interest.

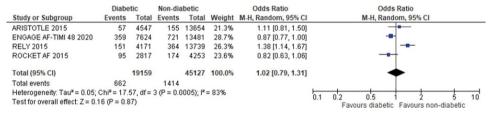
**Purpose:** To compare efficacy and safety outcomes of DOAC for nonvalvular AF in patients with DM versus without DM.

**Methods:** We systematically searched PubMed, Embase and Cochrane databases, in January 2020, for interventional studies comparing DOAC efficacy and safety in patients with AF and diabetes versus without diabetes.

**Results:** Four randomized clinical trials were included, providing a total of 63987 patients, 18860 with DM and 45127 without DM. In terms of efficacy, our meta-analysis revealed a similar rate of stroke/systemic embolism (pooled OR 1.02 [0.79, 1.31], P=0.87, I<sup>2</sup>=83%), stroke (pooled OR 1.98 [0.68, 1.40], P=0.90, I<sup>2</sup>=90%) and all-cause mortality (pooled OR 1.18 [0.97, 1.43], P=0.10, I<sup>2</sup>=87%), albeit with a significant heterogeneity.

However, in direct factor Xa inhibitors sub analysis, diabetic patients had a lower trend of systemic embolism/stroke (pooled OR 0.90 [0.79, 1.02], P=0.09,  $I^2=18\%$ ), significantly lower stroke rate (pooled OR 0.82 [0.73, 0.93], P<0.01,  $I^2=0\%$ ), but a higher all-cause mortality (pooled OR 1.08 [1.00, 1.16], P<0.01,  $I^2=0\%$ ). In terms of safety, the diabetic patients receiving DOAC had higher rates of major bleeding events (pooled OR 1.28 [1.14, 1.45], P<0.01,  $I^2=50\%$ ), although with significant heterogeneity. Direct factor Xa inhibitors sub analysis also revealed a higher rate of major bleeding events (pooled OR 1.22 [1.08, 1.38], P<0.01,  $I^2=24\%$ ), but a similar intracranial bleeding events (pooled OR 1.03 [0.86, 1.24], P=0.72,  $I^2=0\%$ )

**Conclusion:** Our pooled analysis suggests that diabetic patients on DOAC have an higher bleeding risk on DOAC, although with a superior embolic protection.



Systemic Embolism/Stroke in DM vs. NonDM

	Diabetic		Non-diabetic		Odds Ratio		Odds Ratio
Study or Subgroup	<b>Events</b>	Total	<b>Events</b>	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
ARISTOTLE 2015	57	4547	155	13654	16.2%	1.11 [0.81, 1.50]	
ENGAGE AF-TIMI 48 2020	359	7624	721	13481	61.4%	0.87 [0.77, 1.00]	<b>=</b>
RELY 2015	151	4171	364	13739	0.0%	1.38 [1.14, 1.67]	
ROCKET AF 2015	95	2817	174	4253	22.4%	0.82 [0.63, 1.06]	-
Total (95% CI)		14988		31388	100.0%	0.90 [0.79, 1.02]	•
Total events	511		1050				
Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 2.43, df = 2 (P = 0.30); I <sup>2</sup> = 18%							0.1 0.2 0.5 1 2 5 10
Test for overall effect: Z = 1.67 (P = 0.09)							Favours diabetic Favours non-diabetic