Direct oral anticoagulants and advanced liver disease: A systematic review and meta-analysis

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Background

- Direct oral anticoagulants (DOACs) are recommended for stroke prevention in patients with atrial fibrillation (AF) or for treatment of deep vein thrombosis, although some concerns about safety and efficacy were raised on the use of these drugs in patients with advanced liver disease (ALD).
- Due to lack of evidence, DOACs are not recommended in class C of Child-Pugh-Turcotte score (rivaroxaban also in class B).

Aim of the study

The aim of the study was to evaluate the ischemic and bleeding risk profile of DOACs compared to VKAs in patients with AF or DVT and with ALD or cirrhosis.

Methods

- Systematic review of the literature.
- Observational (both prospective and retrospective n = 10) cohort studies and 2 randomized controlled trials (RCT) were included.
- Definition of ALD: all type of liver disease that was excluded by phase III clinical trials. Patients with diagnosis of cirrhosis, independently from Child-Pugh score, patients with serum aspartate aminotransferase or alanine aminotransferase >twofold the upper limit of normal or total bilirubin >1,5-fold the upper limit of normal and patients with FIB-4 >3.25 were included.
- Primary endpoint: any bleeding, major bleeding, GI bleeding and ICH.
- Secondary endpoint: the efficacy of DOACs in reducing overall mortality, new onset of IS/SE and recurrence or progression of DVT or pulmonary embolism.

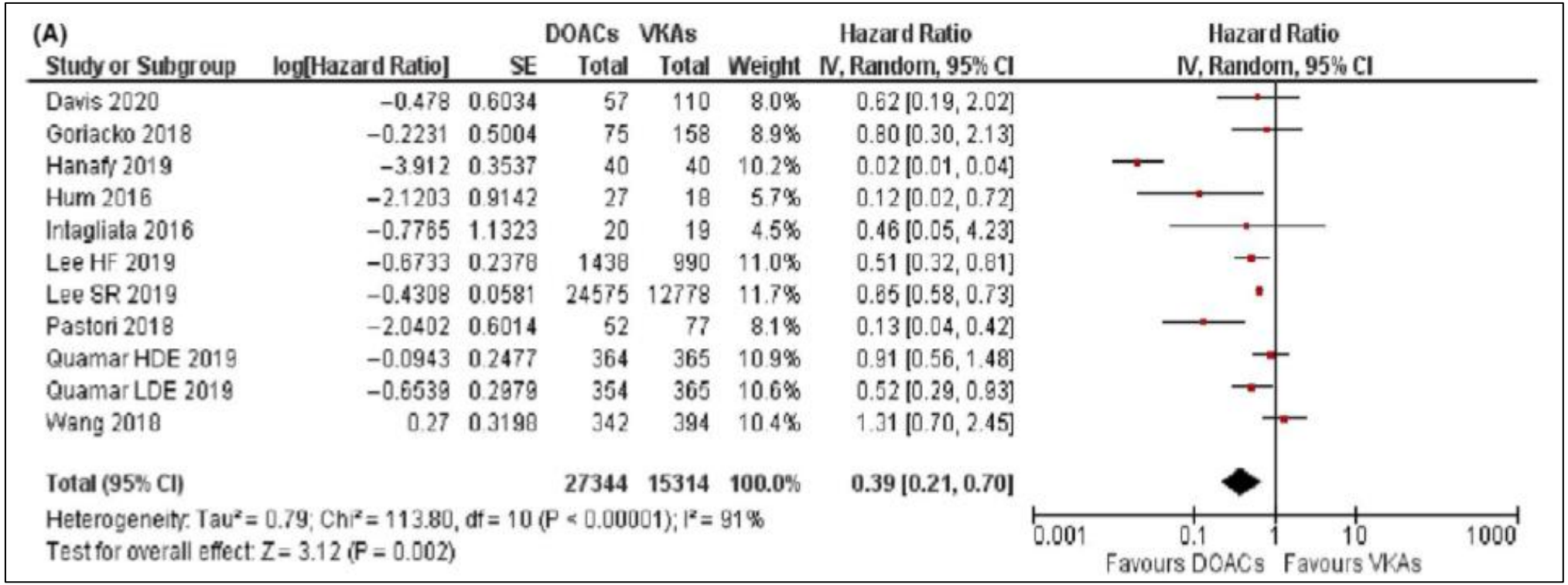
TABLE 2 Definition of advanced liver disease in each study

Author	Year	Definition of Liver disease
Pastori	2018	FIB-4 > 3,25
Wang	2018	Serum AST or ALT > twofold the upper limit of normal or total bilirubin > 1,5-fold the upper limit of normal (exclusion criteria of clinical registration trial)
Lee SR	2019	liver cirrhosis, viral hepatitis, or AST or ALT > 2 times ULN (exclusion criteria of clinical registration trial)
Lee HF	2019	Liver cirrhosis (ICD-9 definition)
Goriacko	2018	Chronic liver disease (ICD-9 definition)
Intagliata	2016	Liver cirrhosis (ICD – 9 definition)
Quamar	2019	Hystory of liver disease
Hum	2016	Chronic liver disease and cirrhosis (ICD-9 definition)
Nagaoki	2018	Liver cirrhosis
Davis	2020	Liver cirrhosis (ICD-0 definition)
Serper	2020	Liver cirrhosis (ICD-9 definition)
Hanafy	2019	HCV-related compensated cirrhosis

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; ICD-0, international classification of disease - 10° revision; ICD-9, international classification of disease - 9° evision.

Results (I)

- DOACs treatment showed a net benefit reducing major bleeding (about 61%).



(A)

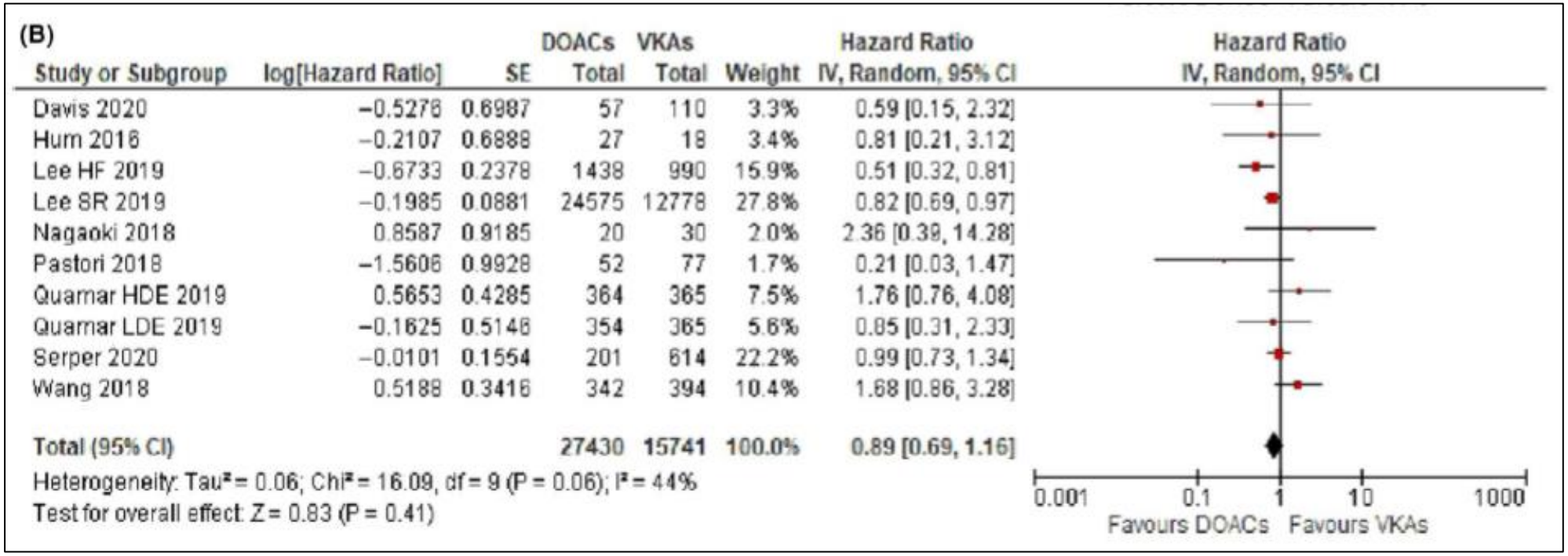
Study or Subgroup	log[Hazard Ratio]	SE	DOACs Total	VKAs Total	Weight	Hazard Ratio IV, Random, 95% CI
Davis 2020	−0.478	0.6034	57	110	8.0%	0.62 [0.19, 2.02]
Goriacko 2018	−0.2231	0.5004	75	158	8.9%	0.80 [0.30, 2.13]
Hanafy 2019	−3.912	0.3537	40	40	10.2%	0.02 [0.01, 0.04]
Hum 2016	−2.1203	0.9142	27	18	5.7%	0.12 [0.02, 0.72]
Intagliata 2016	−0.7765	1.1323	20	19	4.5%	0.46 [0.05, 4.23]
Lee HF 2019	−0.6733	0.2378	1438	990	11.0%	0.51 [0.32, 0.81]
Lee SR 2019	−0.4308	0.0581	24575	12778	11.7%	0.65 [0.58, 0.73]
Pastori 2018	−2.0402	0.6014	52	77	8.1%	0.13 [0.04, 0.42]
Quamar HDE 2019	−0.0943	0.2477	364	365	10.9%	0.91 [0.56, 1.48]
Quamar LDE 2019	−0.6539	0.2979	354	365	10.6%	0.52 [0.29, 0.93]
Wang 2018	0.27	0.3198	342	394	10.4%	1.31 [0.70, 2.45]
Total (95% CI)			**27344**	**15314**	**100.0%**	**0.39 [0.21, 0.70]**

Heterogeneity: Tau² = 0.79; Chi² = 113.80, df = 10 (P < 0.00001); I² = 91%

Test for overall effect: Z = 3.12 (P = 0.002)

Results (II)

- DOACs treatment showed no difference compared to VKAs in GI bleeding risk.



(B)

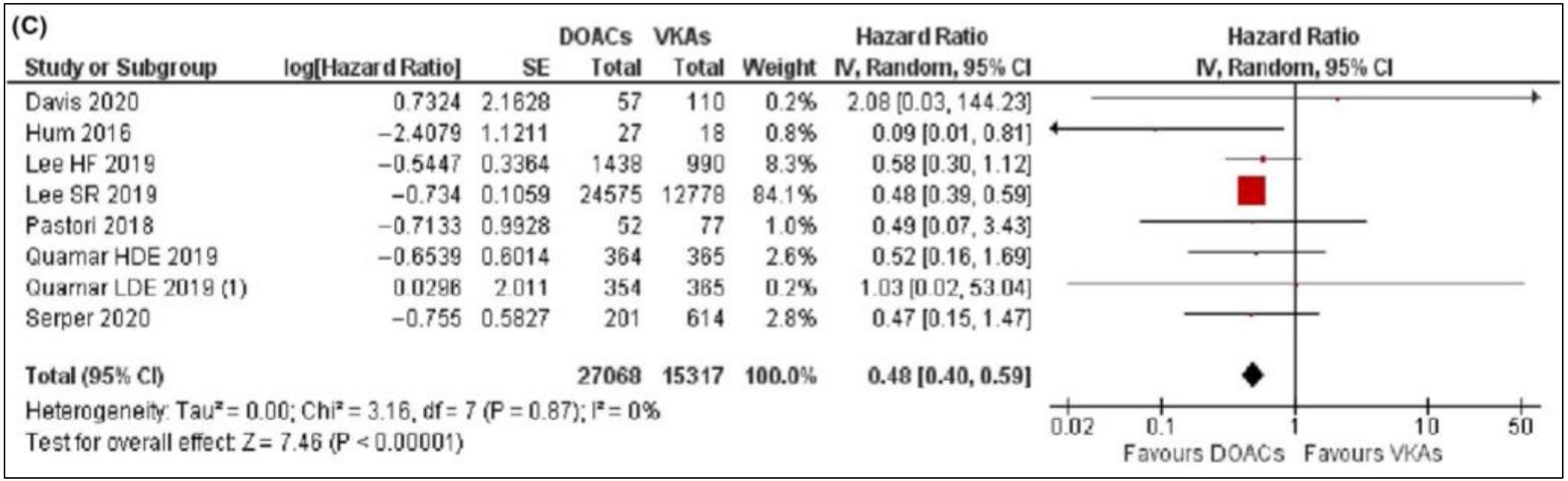
Study or Subgroup	log[Hazard Ratio]	SE	DOACs Total	VKAs Total	Weight	Hazard Ratio IV, Random, 95% CI
Davis 2020	−0.5276	0.6987	57	110	3.3%	0.59 [0.15, 2.32]
Hum 2016	−0.2107	0.6888	27	18	3.4%	0.81 [0.21, 3.12]
Lee HF 2019	−0.6733	0.2378	1438	990	15.9%	0.51 [0.32, 0.81]
Lee SR 2019	−0.1985	0.0881	24575	12778	27.8%	0.82 [0.69, 0.97]
Nagaoki 2018	0.8587	0.9185	20	30	2.0%	2.36 [0.39, 14.28]
Pastori 2018	−1.5606	0.9928	52	77	1.7%	0.21 [0.03, 1.47]
Quamar HDE 2019	0.5653	0.4285	364	365	7.5%	1.76 [0.76, 4.08]
Quamar LDE 2019	−0.1625	0.5146	354	365	5.6%	0.85 [0.31, 2.33]
Serper 2020	−0.0101	0.1554	201	614	22.2%	0.99 [0.73, 1.34]
Wang 2018	0.5188	0.3416	342	394	10.4%	1.68 [0.86, 3.28]
Total (95% CI)			**27430**	**15741**	**100.0%**	**0.89 [0.69, 1.16]**

Heterogeneity: Tau² = 0.06; Chi² = 16.09, df = 9 (P = 0.06); I² = 44%

Test for overall effect: Z = 0.83 (P = 0.41)

Results (III)

- DOACs treatment showed a net benefit in preventing ICH (about 52%)



(C)

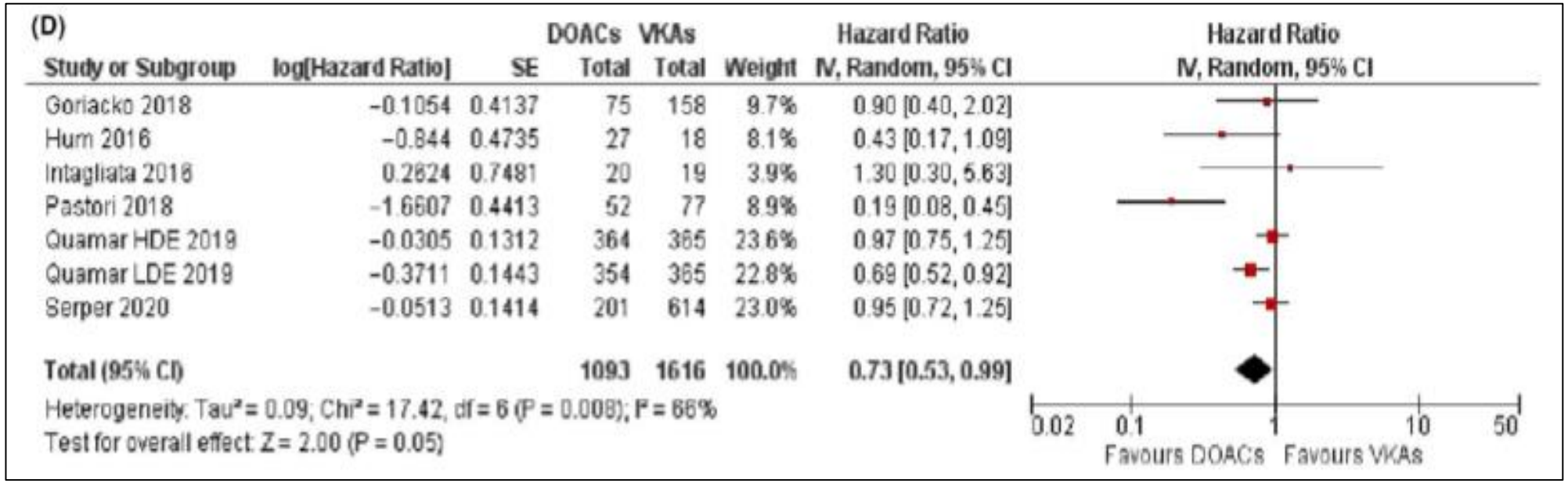
Study or Subgroup	log[Hazard Ratio]	SE	DOACs Total	VKAs Total	Weight	Hazard Ratio IV, Random, 95% CI
Davis 2020	0.7324	2.1628	57	110	0.2%	2.08 [0.03, 144.23]
Hum 2016	−2.4079	1.1211	27	18	0.8%	0.09 [0.01, 0.81]
Lee HF 2019	−0.5447	0.3364	1438	990	8.3%	0.58 [0.30, 1.12]
Lee SR 2019	−0.734	0.1059	24575	12778	84.1%	0.48 [0.39, 0.59]
Pastori 2018	−0.7133	0.9928	52	77	1.0%	0.49 [0.07, 3.43]
Quamar HDE 2019	−0.6539	0.6014	364	365	2.6%	0.52 [0.16, 1.69]
Quamar LDE 2019 (1)	0.0296	2.011	354	365	0.2%	1.03 [0.02, 53.04]
Serper 2020	−0.755	0.5827	201	614	2.8%	0.47 [0.15, 1.47]
Total (95% CI)			**27068**	**15317**	**100.0%**	**0.48 [0.40, 0.59]**

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 3.16$, $df = 7$ ($P = 0.87$); $I^2 = 0\%$

Test for overall effect: $Z = 7.46$ ($P < 0.00001$)

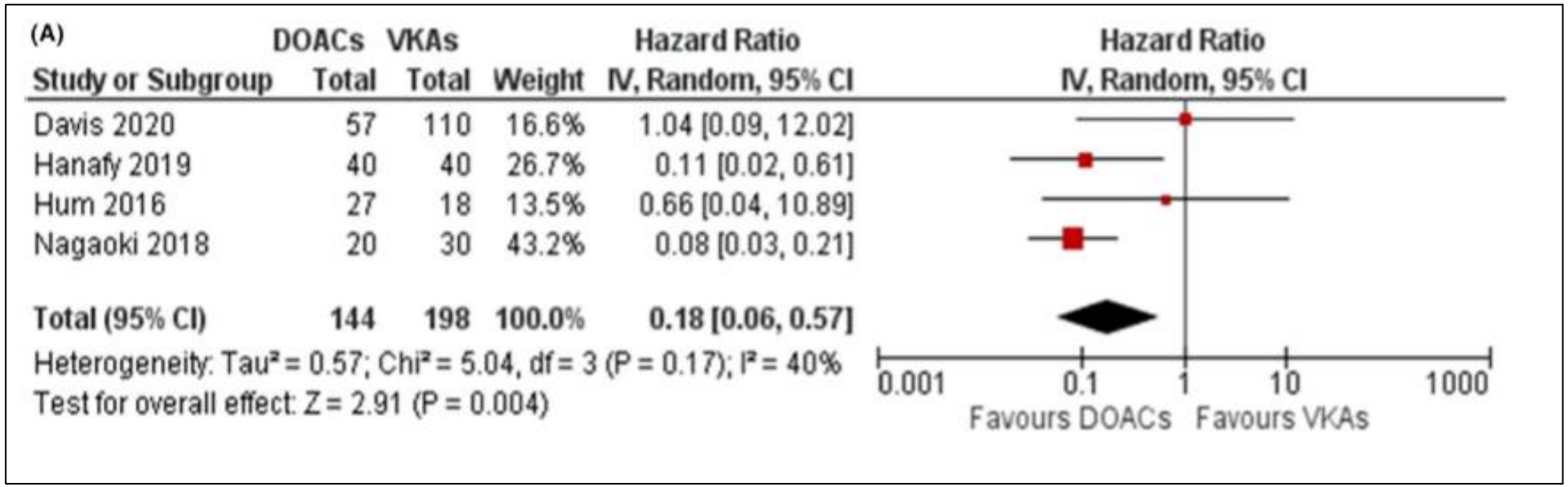
Results (IV)

- DOACs treatment showed a benefit in preventing all type of bleeding.



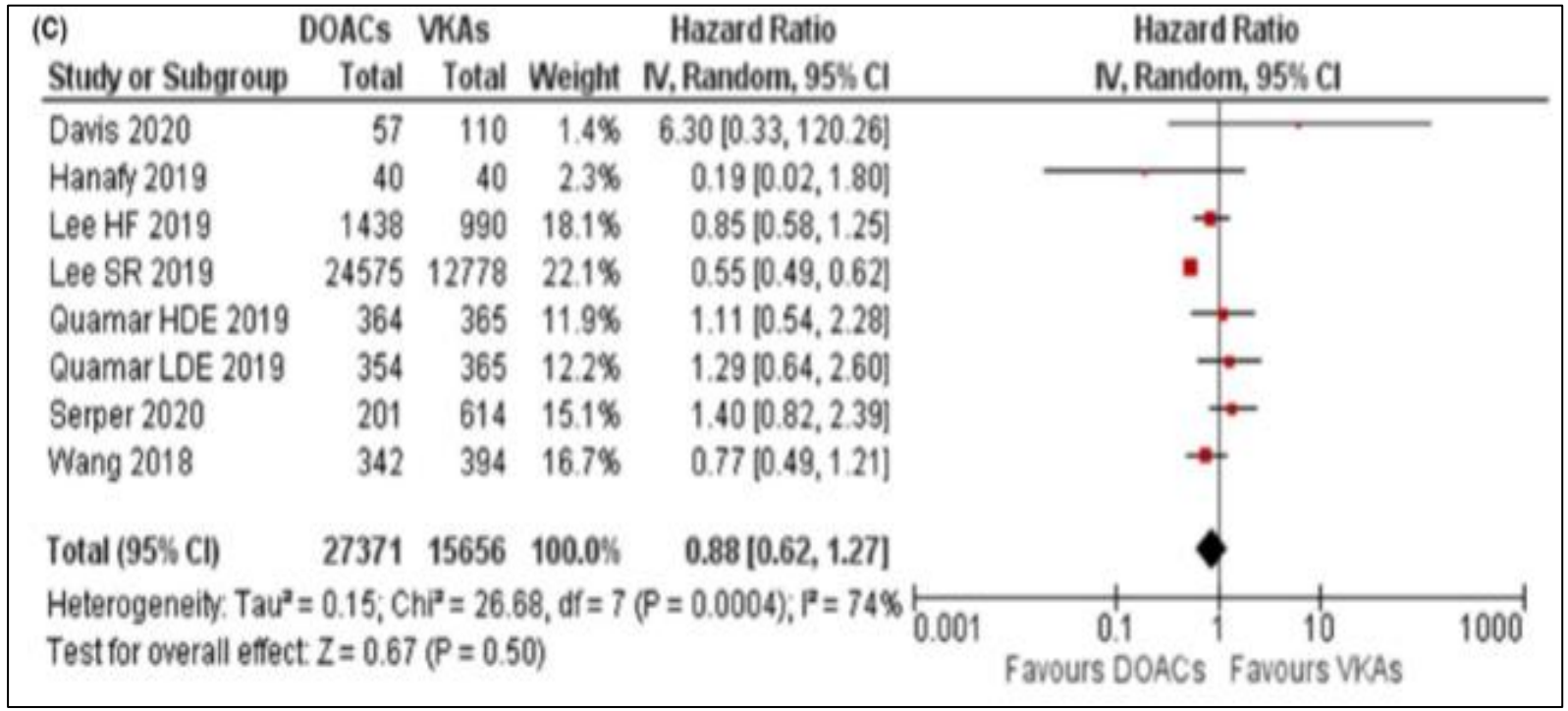
Results (V)

- DOACs showed a minor progression/recurrence of DVTs compared to VKAs with a mean reduction of recurrence/progression of DVTs about 82%.



Results (VI)

- No difference in IS/SE was shown in the analysis.



Results (VII)

- In AF patients, the net benefit of DOACs comparing to VKAs persisted in reduction of major bleeding and ICH. Furthermore, a reduction in overall mortality was found in this subgroup of patients.
- In patients with cirrhosis, no difference in safety and efficacy outcomes were shown between DOACs and VKAs groups, except for ICH and recurrence/progression of DVTs.

Conclusions

- This meta-analysis shows that DOACs cause significant reductions in the risk of major bleeding, ICH and recurrence/ progression of DVTs by ensuring, at the same time, adequate protection from IS/SE and not increasing GI bleeding risk compared to VKAs.
- Thus, DOACs may be an attractive therapeutic option helpful in the management of patients with ALD or cirrhosis.