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SYSTEMATIC REVIEW

Efficacy and Safety of Direct Oral Anticoagulants Versus Warfarin in Patients with Atrial Fibrillation Across BMI Categories: A Systematic Review and Meta-Analysis

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Background

- It has been established that overweight and moderately obese patients with cardiovascular diseases have a better prognosis than patients with normal body mass index (BMI), giving rise to what is known as an “obesity paradox”
- More recently, several post hoc analyses of randomized controlled trials (RCTs) and observational studies have examined the associations between BMI and clinical outcomes in AF patients treated with DOACs or warfarin, but their results remain controversial.

Aim of the study

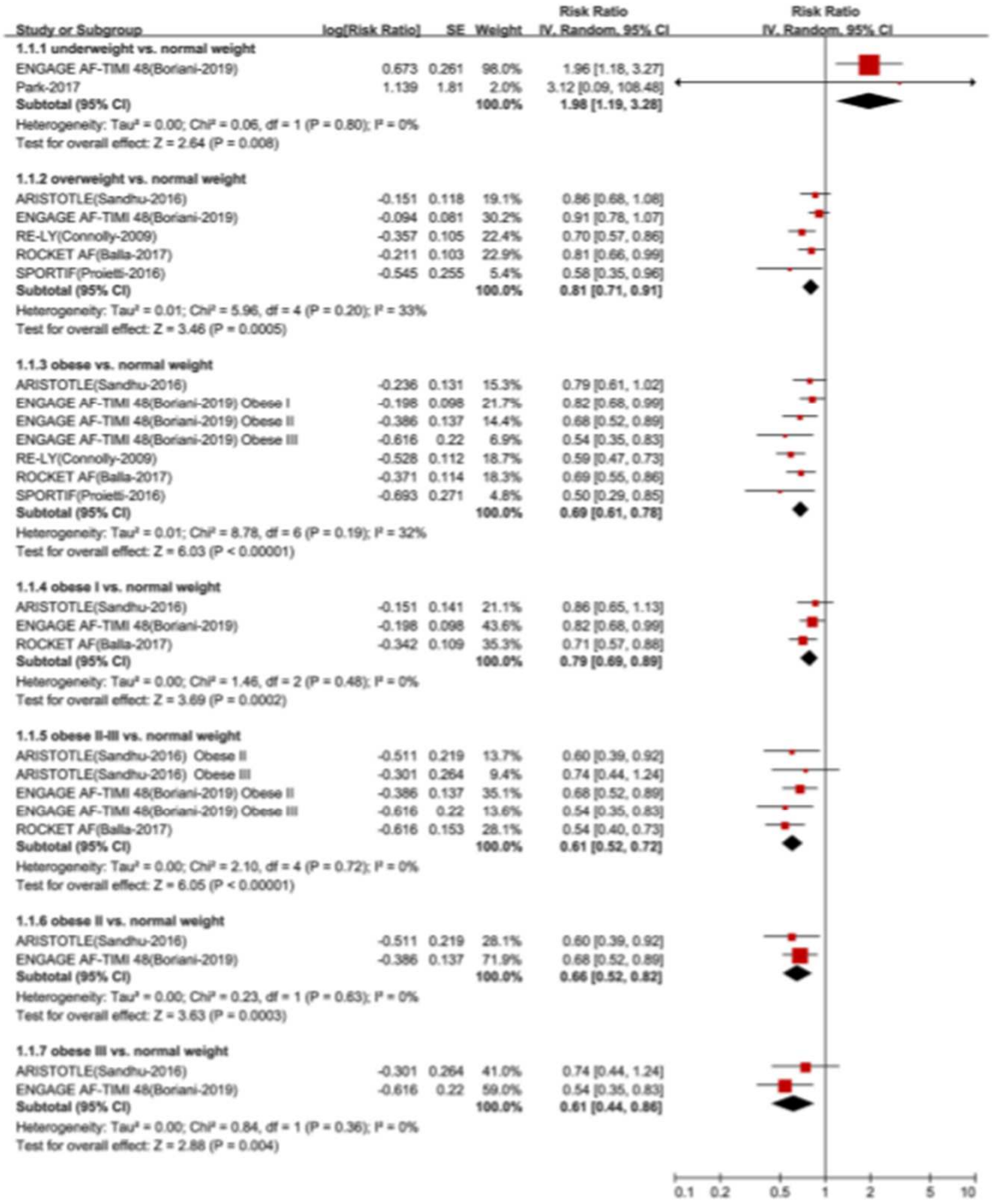
- This meta-analysis aimed to explore if there is an obesity paradox in anticoagulated AF patients, and compare the treatment effects between DOACs and warfarin in AF patients across BMI categories.

Methods

- The authors systematically searched the PubMed and Embase databases until February 26, 2019 for eligible studies reporting the outcomes in anticoagulated AF patients classified by BMI categories.
- Nine studies were included in the analysis.

Results (I)

- Compared with normal weight, underweight was associated with an increased risk of stroke or systemic embolism (SSE) (RR 1.98, 95% CI 1.19–3.28), whereas either overweight or obesity was related with reduced rates of SSE (overweight: RR 0.81, 95% CI 0.71–0.91; obesity: RR 0.69, 95% CI 0.61–0.78) and all-cause death (overweight: RR 0.73, 95% CI 0.64–0.83; obesity: RR 0.72, 95% CI 0.66–0.79).


Study or Subgroup
log[Risk Ratio]
SE
Weight
Risk Ratio
IV, Random, 95% CI
Risk Ratio
IV, Random, 95% CI
1.1.1 underweight vs. normal weight
ENGAGE AF-TIMI 48(Boriani-2019) 0.673 0.261 98.0% 1.96 [1.18, 3.27]
Park-2017 1.139 1.81 2.0% 3.12 [0.09, 108.48]
Subtotal (95% CI) 100.0% 1.98 [1.19, 3.28]
Heterogeneity: Tau² = 0.00; Chi² = 0.06, df = 1 (P = 0.80); I² = 0%
Test for overall effect: Z = 2.64 (P = 0.008)
1.1.2 overweight vs. normal weight
ARISTOTLE(Sandhu-2016) -0.151 0.118 19.1% 0.86 [0.68, 1.08]
ENGAGE AF-TIMI 48(Boriani-2019) -0.094 0.081 30.2% 0.91 [0.78, 1.07]
RE-LY(Connolly-2009) -0.357 0.105 22.4% 0.70 [0.57, 0.86]
ROCKET AF(Balla-2017) -0.211 0.103 22.9% 0.81 [0.66, 0.99]
SPORTIF(Proietti-2016) -0.545 0.255 5.4% 0.58 [0.35, 0.96]
Subtotal (95% CI) 100.0% 0.81 [0.71, 0.91]
Heterogeneity: Tau² = 0.01; Chi² = 5.96, df = 4 (P = 0.20); I² = 33%
Test for overall effect: Z = 3.46 (P = 0.0005)
1.1.3 obese vs. normal weight
ARISTOTLE(Sandhu-2016) -0.236 0.131 15.3% 0.79 [0.61, 1.02]
ENGAGE AF-TIMI 48(Boriani-2019) Obese I -0.198 0.098 21.7% 0.82 [0.68, 0.99]
ENGAGE AF-TIMI 48(Boriani-2019) Obese II -0.386 0.137 14.4% 0.68 [0.52, 0.89]
ENGAGE AF-TIMI 48(Boriani-2019) Obese III -0.616 0.22 6.9% 0.54 [0.35, 0.83]
RE-LY(Connolly-2009) -0.528 0.112 18.7% 0.59 [0.47, 0.73]
ROCKET AF(Balla-2017) -0.371 0.114 18.3% 0.69 [0.55, 0.86]
SPORTIF(Proietti-2016) -0.693 0.271 4.8% 0.50 [0.29, 0.85]
Subtotal (95% CI) 100.0% 0.69 [0.61, 0.78]
Heterogeneity: Tau² = 0.01; Chi² = 8.78, df = 6 (P = 0.19); I² = 32%
Test for overall effect: Z = 6.03 (P < 0.00001)
1.1.4 obese I vs. normal weight
ARISTOTLE(Sandhu-2016) -0.151 0.141 21.1% 0.86 [0.65, 1.13]
ENGAGE AF-TIMI 48(Boriani-2019) -0.198 0.098 43.6% 0.82 [0.68, 0.99]
ROCKET AF(Balla-2017) -0.342 0.109 35.3% 0.71 [0.57, 0.88]
Subtotal (95% CI) 100.0% 0.79 [0.69, 0.89]
Heterogeneity: Tau² = 0.00; Chi² = 1.46, df = 2 (P = 0.48); I² = 0%
Test for overall effect: Z = 3.69 (P = 0.0002)
1.1.5 obese II-III vs. normal weight
ARISTOTLE(Sandhu-2016) Obese II -0.511 0.219 13.7% 0.60 [0.39, 0.92]
ARISTOTLE(Sandhu-2016) Obese III -0.301 0.264 9.4% 0.74 [0.44, 1.24]
ENGAGE AF-TIMI 48(Boriani-2019) Obese II -0.386 0.137 35.1% 0.68 [0.52, 0.89]
ENGAGE AF-TIMI 48(Boriani-2019) Obese III -0.616 0.22 13.6% 0.54 [0.35, 0.83]
ROCKET AF(Balla-2017) -0.616 0.153 28.1% 0.54 [0.40, 0.73]
Subtotal (95% CI) 100.0% 0.61 [0.52, 0.72]
Heterogeneity: Tau² = 0.00; Chi² = 2.10, df = 4 (P = 0.72); I² = 0%
Test for overall effect: Z = 6.05 (P < 0.00001)
1.1.6 obese II vs. normal weight
ARISTOTLE(Sandhu-2016) -0.511 0.219 28.1% 0.60 [0.39, 0.92]
ENGAGE AF-TIMI 48(Boriani-2019) -0.386 0.137 71.9% 0.68 [0.52, 0.89]
Subtotal (95% CI) 100.0% 0.66 [0.52, 0.82]
Heterogeneity: Tau² = 0.00; Chi² = 0.23, df = 1 (P = 0.63); I² = 0%
Test for overall effect: Z = 3.63 (P = 0.0003)
1.1.7 obese III vs. normal weight
ARISTOTLE(Sandhu-2016) -0.301 0.264 41.0% 0.74 [0.44, 1.24]
ENGAGE AF-TIMI 48(Boriani-2019) -0.616 0.22 59.0% 0.54 [0.35, 0.83]
Subtotal (95% CI) 100.0% 0.61 [0.44, 0.86]
Heterogeneity: Tau² = 0.00; Chi² = 0.84, df = 1 (P = 0.36); I² = 0%
Test for overall effect: Z = 2.88 (P = 0.004)
0.1
0.2
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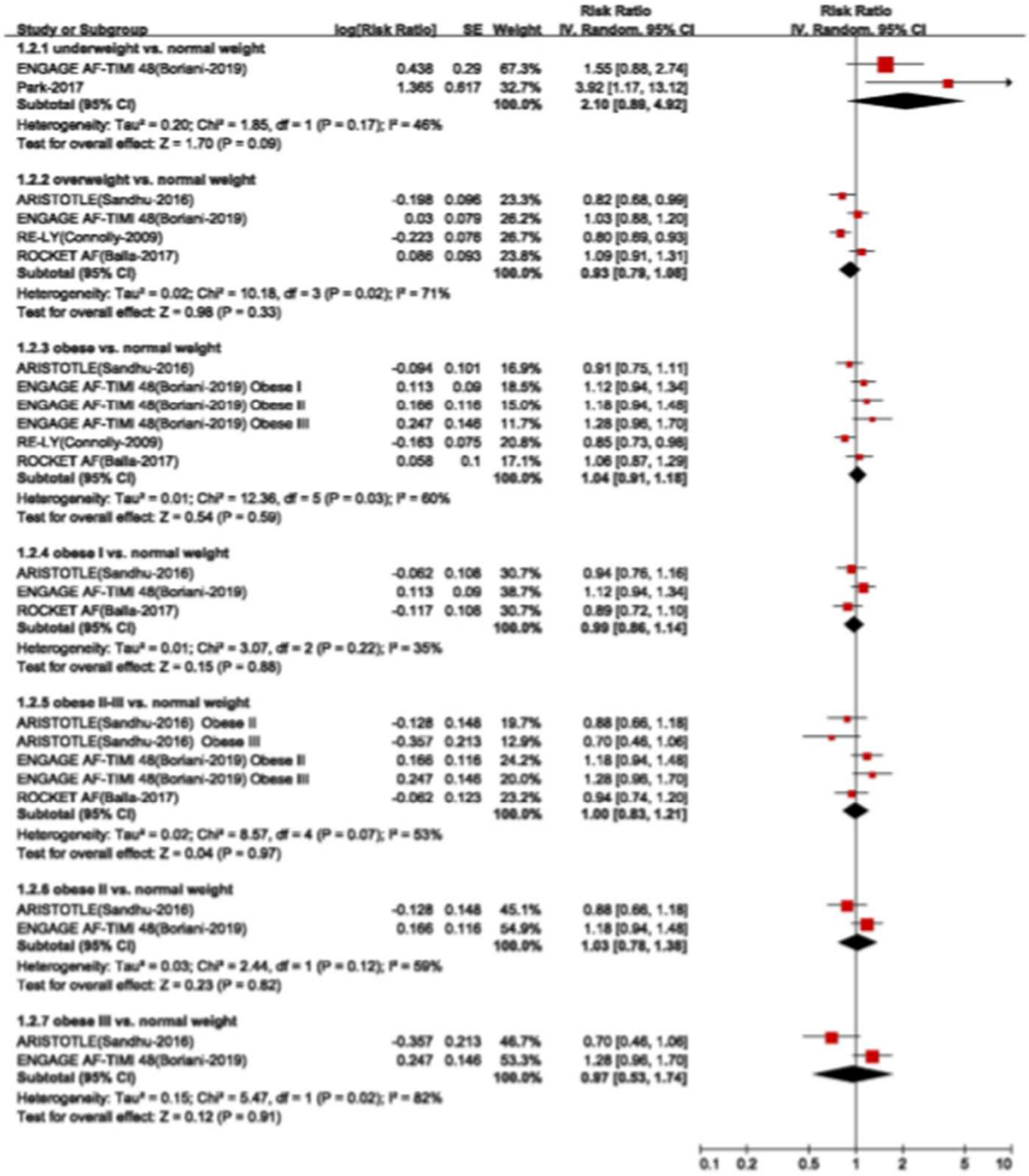
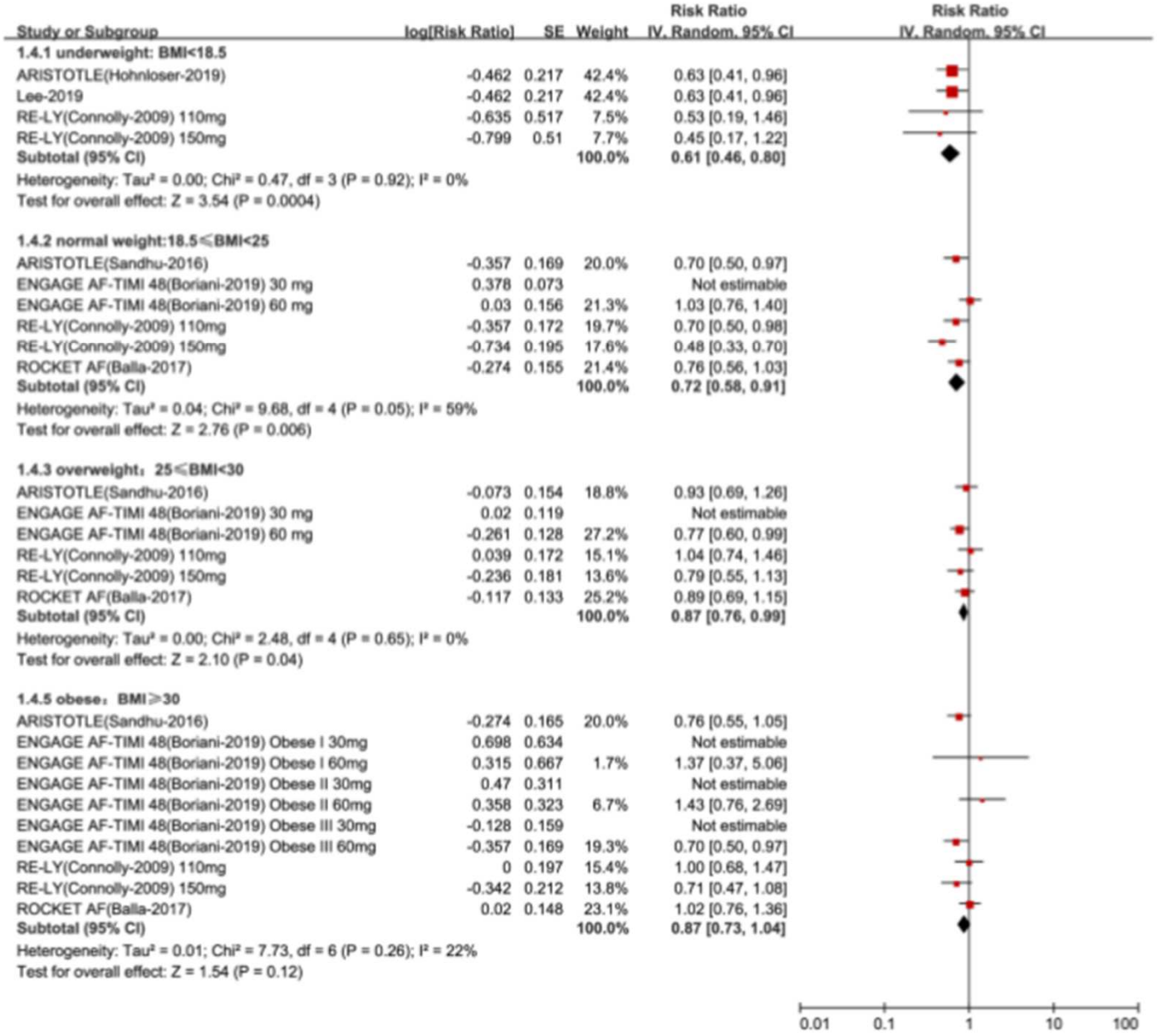
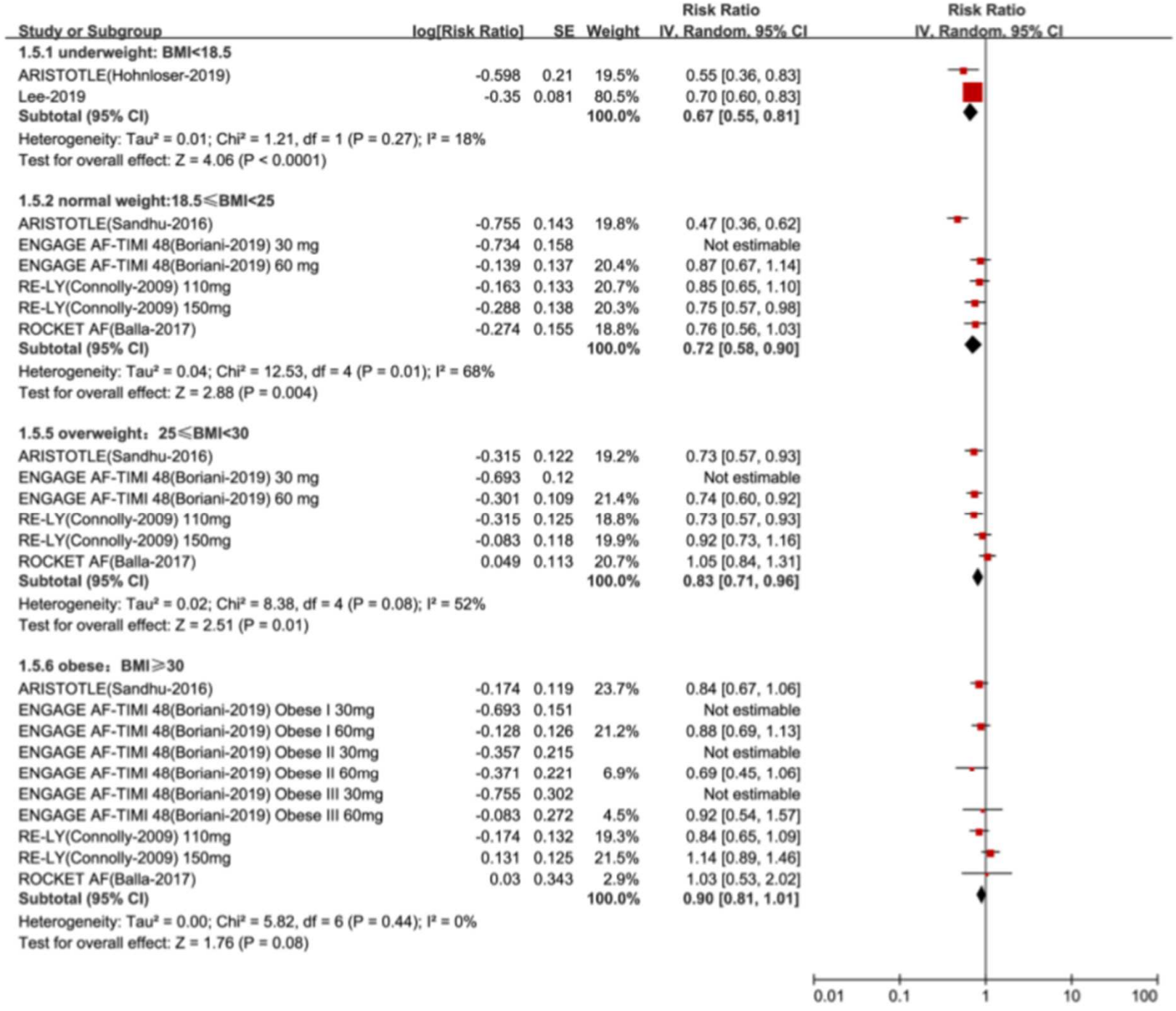
2
5
10


Study or Subgroup
log[Risk Ratio]
SE
Weight
Risk Ratio
IV, Random, 95% CI
Risk Ratio
IV, Random, 95% CI
1.2.1 underweight vs. normal weight
ENGAGE AF-TIMI 48(Boriani-2019) 0.438 0.29 67.3% 1.55 [0.88, 2.74]
Park-2017 1.365 0.617 32.7% 3.92 [1.17, 13.12]
Subtotal (95% CI) 100.0% 2.10 [0.89, 4.92]
Heterogeneity: Tau² = 0.20; Chi² = 1.85, df = 1 (P = 0.17); I² = 46%
Test for overall effect: Z = 1.70 (P = 0.09)
1.2.2 overweight vs. normal weight
ARISTOTLE(Sandhu-2016) -0.198 0.096 23.3% 0.82 [0.68, 0.99]
ENGAGE AF-TIMI 48(Boriani-2019) 0.03 0.079 26.2% 1.03 [0.88, 1.20]
RE-LY(Connolly-2009) -0.223 0.076 26.7% 0.80 [0.69, 0.93]
ROCKET AF(Balla-2017) 0.086 0.093 23.8% 1.09 [0.91, 1.31]
Subtotal (95% CI) 100.0% 0.93 [0.79, 1.08]
Heterogeneity: Tau² = 0.02; Chi² = 10.18, df = 3 (P = 0.02); I² = 71%
Test for overall effect: Z = 0.98 (P = 0.33)
1.2.3 obese vs. normal weight
ARISTOTLE(Sandhu-2016) -0.094 0.101 16.9% 0.91 [0.75, 1.11]
ENGAGE AF-TIMI 48(Boriani-2019) Obese I 0.113 0.09 18.5% 1.12 [0.94, 1.34]
ENGAGE AF-TIMI 48(Boriani-2019) Obese II 0.166 0.116 15.0% 1.18 [0.94, 1.48]
ENGAGE AF-TIMI 48(Boriani-2019) Obese III 0.247 0.146 11.7% 1.28 [0.96, 1.70]
RE-LY(Connolly-2009) -0.163 0.075 20.8% 0.85 [0.73, 0.98]
ROCKET AF(Balla-2017) 0.058 0.1 17.1% 1.06 [0.87, 1.29]
Subtotal (95% CI) 100.0% 1.04 [0.91, 1.18]
Heterogeneity: Tau² = 0.01; Chi² = 12.36, df = 5 (P = 0.03); I² = 60%
Test for overall effect: Z = 0.54 (P = 0.59)
1.2.4 obese I vs. normal weight
ARISTOTLE(Sandhu-2016) -0.062 0.108 30.7% 0.94 [0.76, 1.16]
ENGAGE AF-TIMI 48(Boriani-2019) 0.113 0.09 38.7% 1.12 [0.94, 1.34]
ROCKET AF(Balla-2017) -0.117 0.108 30.7% 0.89 [0.72, 1.10]
Subtotal (95% CI) 100.0% 0.99 [0.86, 1.14]
Heterogeneity: Tau² = 0.01; Chi² = 3.07, df = 2 (P = 0.22); I² = 35%
Test for overall effect: Z = 0.15 (P = 0.88)
1.2.5 obese II-III vs. normal weight
ARISTOTLE(Sandhu-2016) Obese II -0.128 0.148 19.7% 0.88 [0.66, 1.18]
ARISTOTLE(Sandhu-2016) Obese III -0.357 0.213 12.9% 0.70 [0.46, 1.06]
ENGAGE AF-TIMI 48(Boriani-2019) Obese II 0.166 0.116 24.2% 1.18 [0.94, 1.48]
ENGAGE AF-TIMI 48(Boriani-2019) Obese III 0.247 0.146 20.0% 1.28 [0.96, 1.70]
ROCKET AF(Balla-2017) -0.062 0.123 23.2% 0.94 [0.74, 1.20]
Subtotal (95% CI) 100.0% 1.00 [0.83, 1.21]
Heterogeneity: Tau² = 0.02; Chi² = 8.57, df = 4 (P = 0.07); I² = 53%
Test for overall effect: Z = 0.04 (P = 0.97)
1.2.6 obese II vs. normal weight
ARISTOTLE(Sandhu-2016) -0.128 0.148 45.1% 0.88 [0.66, 1.18]
ENGAGE AF-TIMI 48(Boriani-2019) 0.166 0.116 54.9% 1.18 [0.94, 1.48]
Subtotal (95% CI) 100.0% 1.03 [0.78, 1.38]
Heterogeneity: Tau² = 0.03; Chi² = 2.44, df = 1 (P = 0.12); I² = 59%
Test for overall effect: Z = 0.23 (P = 0.82)
1.2.7 obese III vs. normal weight
ARISTOTLE(Sandhu-2016) -0.357 0.213 46.7% 0.70 [0.46, 1.06]
ENGAGE AF-TIMI 48(Boriani-2019) 0.247 0.146 53.3% 1.28 [0.96, 1.70]
Subtotal (95% CI) 100.0% 0.97 [0.53, 1.74]
Heterogeneity: Tau² = 0.15; Chi² = 5.47, df = 1 (P = 0.02); I² = 82%
Test for overall effect: Z = 0.12 (P = 0.91)
0.1
0.2
0.5
1
2
5
10

Results (II)

- Compared with patients receiving warfarin, patients receiving DOACs who were underweight, normal weight or overweight all had decreased risks of SSE (underweight: RR 0.61, 95% CI 0.46–0.80; normal weight: RR 0.72, 95% CI 0.58–0.91; overweight: RR 0.87, 95% CI 0.76–0.99) and major bleeding (underweight: RR 0.67, 95% CI 0.55–0.81; normal weight: RR 0.72, 95% CI 0.58–0.90; overweight: RR 0.83, 95% CI 0.71–0.96).
- Obese DOAC users were at no higher risks for SSE and major bleeding.


Study or Subgroup
log[Risk Ratio]
SE
Weight
Risk Ratio
IV, Random, 95% CI
Risk Ratio
IV, Random, 95% CI
1.4.1 underweight: BMI<18.5
ARISTOTLE(Hohnloser-2019) -0.462 0.217 42.4% 0.63 [0.41, 0.96]
Lee-2019 -0.462 0.217 42.4% 0.63 [0.41, 0.96]
RE-LY(Connolly-2009) 110mg -0.635 0.517 7.5% 0.53 [0.19, 1.46]
RE-LY(Connolly-2009) 150mg -0.799 0.51 7.7% 0.45 [0.17, 1.22]
Subtotal (95% CI) 100.0% 0.61 [0.46, 0.80]
Heterogeneity: Tau² = 0.00; Chi² = 0.47, df = 3 (P = 0.92); I² = 0%
Test for overall effect: Z = 3.54 (P = 0.0004)
1.4.2 normal weight:18.5⩽BMI<25
ARISTOTLE(Sandhu-2016) -0.357 0.169 20.0% 0.70 [0.50, 0.97]
ENGAGE AF-TIMI 48(Boriani-2019) 30 mg 0.378 0.073 Not estimable
ENGAGE AF-TIMI 48(Boriani-2019) 60 mg 0.03 0.156 21.3% 1.03 [0.76, 1.40]
RE-LY(Connolly-2009) 110mg -0.357 0.172 19.7% 0.70 [0.50, 0.98]
RE-LY(Connolly-2009) 150mg -0.734 0.195 17.6% 0.48 [0.33, 0.70]
ROCKET AF(Balla-2017) -0.274 0.155 21.4% 0.76 [0.56, 1.03]
Subtotal (95% CI) 100.0% 0.72 [0.58, 0.91]
Heterogeneity: Tau² = 0.04; Chi² = 9.68, df = 4 (P = 0.05); I² = 59%
Test for overall effect: Z = 2.76 (P = 0.006)
1.4.3 overweight：25⩽BMI<30
ARISTOTLE(Sandhu-2016) -0.073 0.154 18.8% 0.93 [0.69, 1.26]
ENGAGE AF-TIMI 48(Boriani-2019) 30 mg 0.02 0.119 Not estimable
ENGAGE AF-TIMI 48(Boriani-2019) 60 mg -0.261 0.128 27.2% 0.77 [0.60, 0.99]
RE-LY(Connolly-2009) 110mg 0.039 0.172 15.1% 1.04 [0.74, 1.46]
RE-LY(Connolly-2009) 150mg -0.236 0.181 13.6% 0.79 [0.55, 1.13]
ROCKET AF(Balla-2017) -0.117 0.133 25.2% 0.89 [0.69, 1.15]
Subtotal (95% CI) 100.0% 0.87 [0.76, 0.99]
Heterogeneity: Tau² = 0.00; Chi² = 2.48, df = 4 (P = 0.65); I² = 0%
Test for overall effect: Z = 2.10 (P = 0.04)
1.4.5 obese：BMI⩾30
ARISTOTLE(Sandhu-2016) -0.274 0.165 20.0% 0.76 [0.55, 1.05]
ENGAGE AF-TIMI 48(Boriani-2019) Obese I 30mg 0.698 0.634 Not estimable
ENGAGE AF-TIMI 48(Boriani-2019) Obese I 60mg 0.315 0.667 1.7% 1.37 [0.37, 5.06]
ENGAGE AF-TIMI 48(Boriani-2019) Obese II 30mg 0.47 0.311 Not estimable
ENGAGE AF-TIMI 48(Boriani-2019) Obese II 60mg 0.358 0.323 6.7% 1.43 [0.76, 2.69]
ENGAGE AF-TIMI 48(Boriani-2019) Obese III 30mg -0.128 0.159 Not estimable
ENGAGE AF-TIMI 48(Boriani-2019) Obese III 60mg -0.357 0.169 19.3% 0.70 [0.50, 0.97]
RE-LY(Connolly-2009) 110mg 0 0.197 15.4% 1.00 [0.68, 1.47]
RE-LY(Connolly-2009) 150mg -0.342 0.212 13.8% 0.71 [0.47, 1.08]
ROCKET AF(Balla-2017) 0.02 0.148 23.1% 1.02 [0.76, 1.36]
Subtotal (95% CI) 100.0% 0.87 [0.73, 1.04]
Heterogeneity: Tau² = 0.01; Chi² = 7.73, df = 6 (P = 0.26); I² = 22%
Test for overall effect: Z = 1.54 (P = 0.12)
0.01
0.1
1
10
100


Study or Subgroup
log[Risk Ratio]
SE
Weight
Risk Ratio
IV, Random, 95% CI
Risk Ratio
IV, Random, 95% CI
1.5.1 underweight: BMI<18.5
ARISTOTLE(Hohnloser-2019) -0.598 0.21 19.5% 0.55 [0.36, 0.83]
Lee-2019 -0.35 0.081 80.5% 0.70 [0.60, 0.83]
Subtotal (95% CI) 100.0% 0.67 [0.55, 0.81]
Heterogeneity: Tau² = 0.01; Chi² = 1.21, df = 1 (P = 0.27); I² = 18%
Test for overall effect: Z = 4.06 (P < 0.0001)
1.5.2 normal weight:18.5≤BMI<25
ARISTOTLE(Sandhu-2016) -0.755 0.143 19.8% 0.47 [0.36, 0.62]
ENGAGE AF-TIMI 48(Boriani-2019) 30 mg -0.734 0.158 Not estimable
ENGAGE AF-TIMI 48(Boriani-2019) 60 mg -0.139 0.137 20.4% 0.87 [0.67, 1.14]
RE-LY(Connolly-2009) 110mg -0.163 0.133 20.7% 0.85 [0.65, 1.10]
RE-LY(Connolly-2009) 150mg -0.288 0.138 20.3% 0.75 [0.57, 0.98]
ROCKET AF(Balla-2017) -0.274 0.155 18.8% 0.76 [0.56, 1.03]
Subtotal (95% CI) 100.0% 0.72 [0.58, 0.90]
Heterogeneity: Tau² = 0.04; Chi² = 12.53, df = 4 (P = 0.01); I² = 68%
Test for overall effect: Z = 2.88 (P = 0.004)
1.5.5 overweight：25≤BMI<30
ARISTOTLE(Sandhu-2016) -0.315 0.122 19.2% 0.73 [0.57, 0.93]
ENGAGE AF-TIMI 48(Boriani-2019) 30 mg -0.693 0.12 Not estimable
ENGAGE AF-TIMI 48(Boriani-2019) 60 mg -0.301 0.109 21.4% 0.74 [0.60, 0.92]
RE-LY(Connolly-2009) 110mg -0.315 0.125 18.8% 0.73 [0.57, 0.93]
RE-LY(Connolly-2009) 150mg -0.083 0.118 19.9% 0.92 [0.73, 1.16]
ROCKET AF(Balla-2017) 0.049 0.113 20.7% 1.05 [0.84, 1.31]
Subtotal (95% CI) 100.0% 0.83 [0.71, 0.96]
Heterogeneity: Tau² = 0.02; Chi² = 8.38, df = 4 (P = 0.08); I² = 52%
Test for overall effect: Z = 2.51 (P = 0.01)
1.5.6 obese：BMI≥30
ARISTOTLE(Sandhu-2016) -0.174 0.119 23.7% 0.84 [0.67, 1.06]
ENGAGE AF-TIMI 48(Boriani-2019) Obese I 30mg -0.693 0.151 Not estimable
ENGAGE AF-TIMI 48(Boriani-2019) Obese I 60mg -0.128 0.126 21.2% 0.88 [0.69, 1.13]
ENGAGE AF-TIMI 48(Boriani-2019) Obese II 30mg -0.357 0.215 Not estimable
ENGAGE AF-TIMI 48(Boriani-2019) Obese II 60mg -0.371 0.221 6.9% 0.69 [0.45, 1.06]
ENGAGE AF-TIMI 48(Boriani-2019) Obese III 30mg -0.755 0.302 Not estimable
ENGAGE AF-TIMI 48(Boriani-2019) Obese III 60mg -0.083 0.272 4.5% 0.92 [0.54, 1.57]
RE-LY(Connolly-2009) 110mg -0.174 0.132 19.3% 0.84 [0.65, 1.09]
RE-LY(Connolly-2009) 150mg 0.131 0.125 21.5% 1.14 [0.89, 1.46]
ROCKET AF(Balla-2017) 0.03 0.343 2.9% 1.03 [0.53, 2.02]
Subtotal (95% CI) 100.0% 0.90 [0.81, 1.01]
Heterogeneity: Tau² = 0.00; Chi² = 5.82, df = 6 (P = 0.44); I² = 0%
Test for overall effect: Z = 1.76 (P = 0.08)
0.01
0.1
1
10
100

Conclusions

- Overall, these results indicate the existence of an “obesity paradox” in anticoagulated AF patients.
- In comparison with warfarin, DOACs have superior efficacy and safety in the treatment of underweight, normal weight or overweight AF patients and are non-inferior in obese patients.
- Altogether, DOAC treatment is as good as or better than warfarin in the prevention of stroke in AF patients irrespective of BMI.