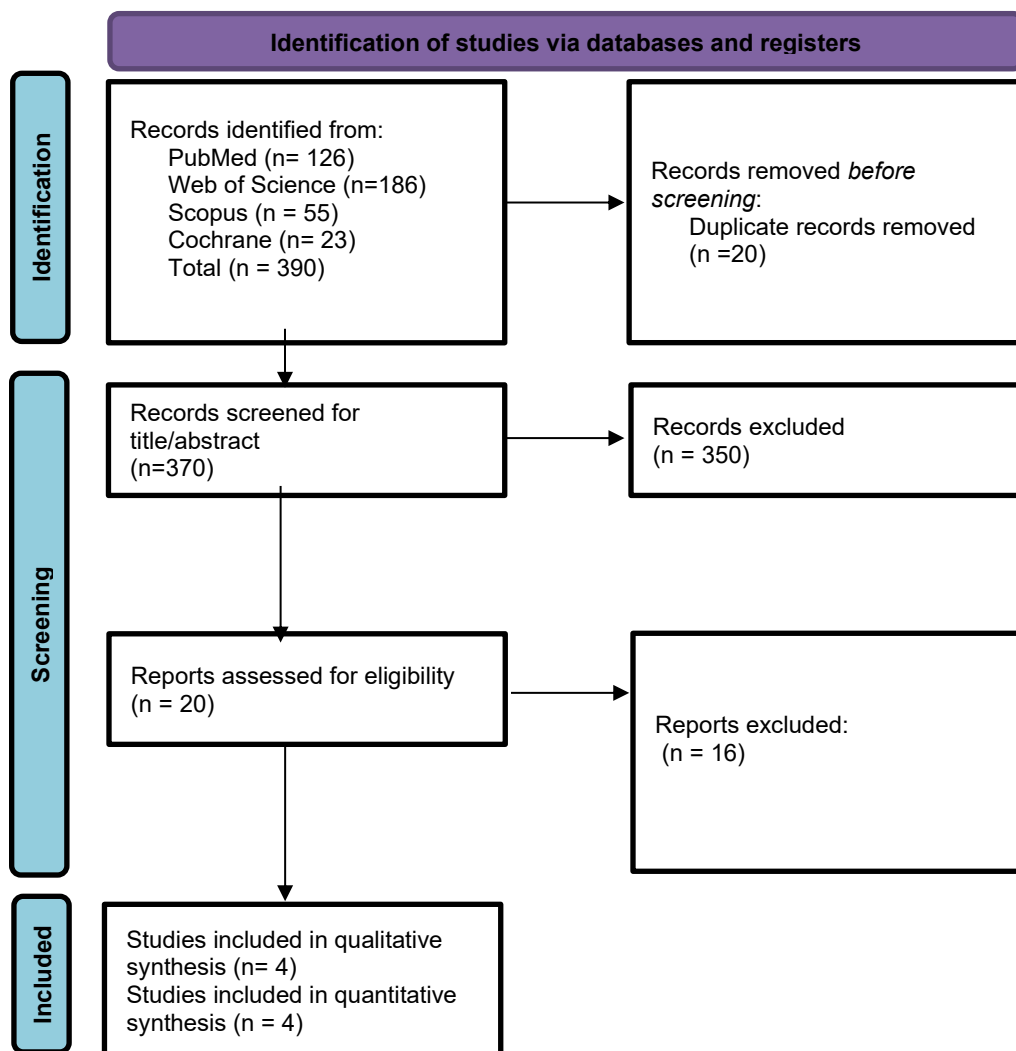


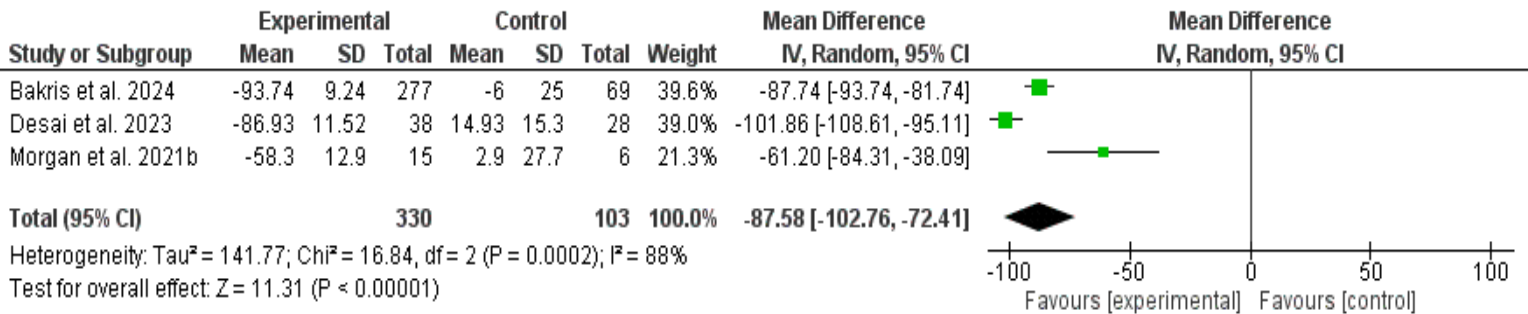
Data bases	Search strategy	Result
Pubmed	Title-abstract ((Zilebesiran OR Ionis AGT-LRx OR Ionis-AGT-LRx OR “Ionis AGT” OR “RNA interference therapeutic” OR “RNA interference drug”) AND (Hypertension OR “High Blood Pressure”.))	126
Wos	Topics ((Zilebesiran OR Ionis AGT-LRx OR Ionis-AGT-LRx OR “Ionis AGT” OR “RNA interference therapeutic” OR “RNA interference drug”) AND (Hypertension OR “High Blood Pressure”.))	186
Scopus	((Zilebesiran OR Ionis AGT-LRx OR Ionis-AGT-LRx OR “Ionis AGT” OR “RNA interference therapeutic” OR “RNA interference drug”) AND (Hypertension OR “High Blood Pressure”.))	55
Cochrane Central Register of Controlled Trials	((Zilebesiran OR Ionis AGT-LRx OR Ionis-AGT-LRx OR “Ionis AGT” OR “RNA interference therapeutic” OR “RNA interference drug”) AND (Hypertension OR “High Blood Pressure”.))	23
Total		390

**Online Resource 1.** A detailed search strategy for each database.

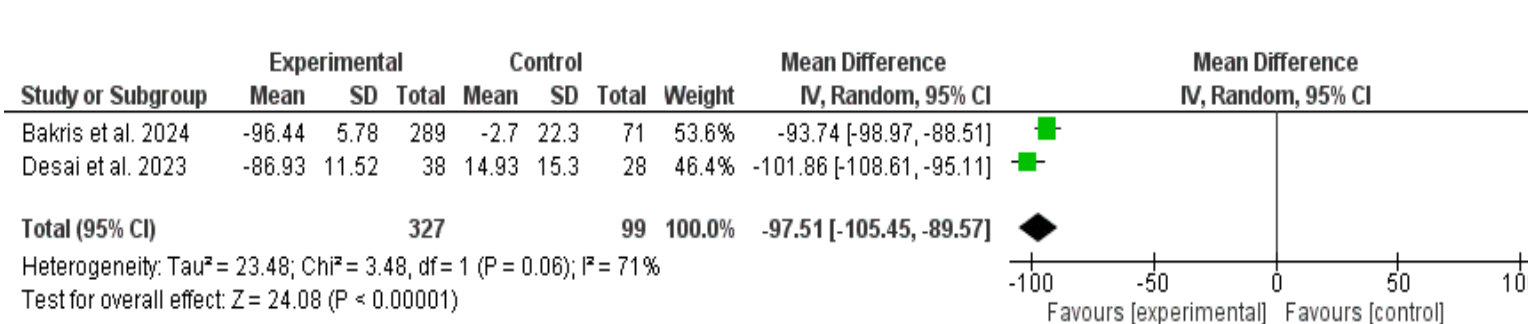


**Online Resource 2.** PRISMA flow diagram

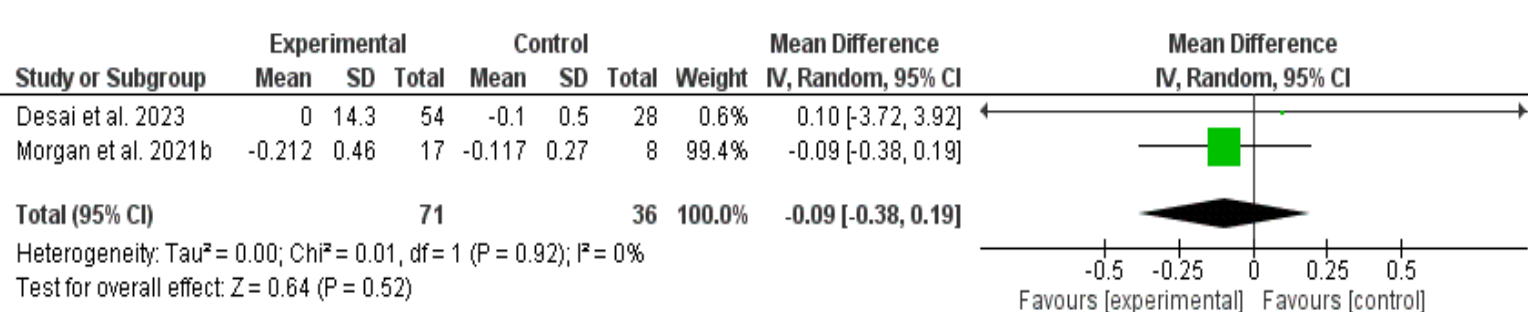
(A)



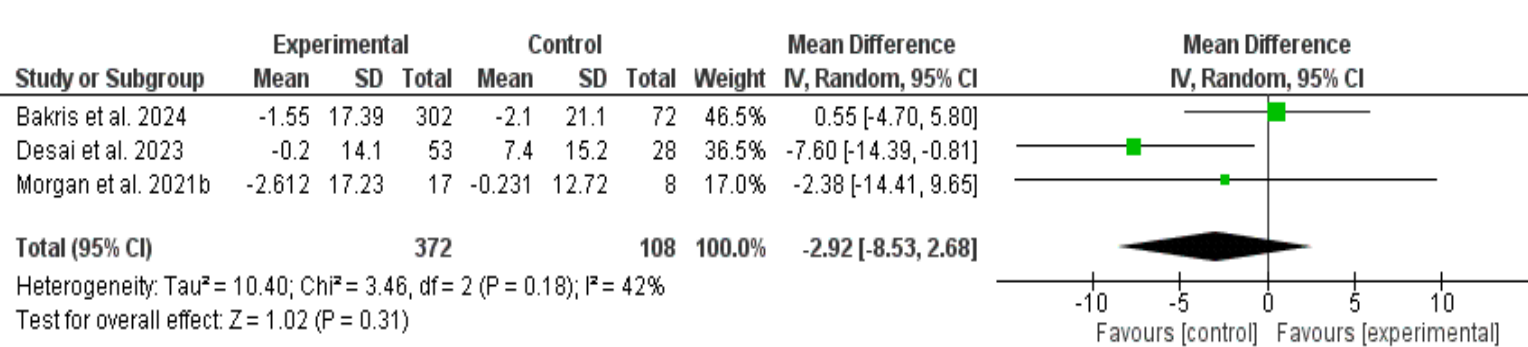
(B)



(C)

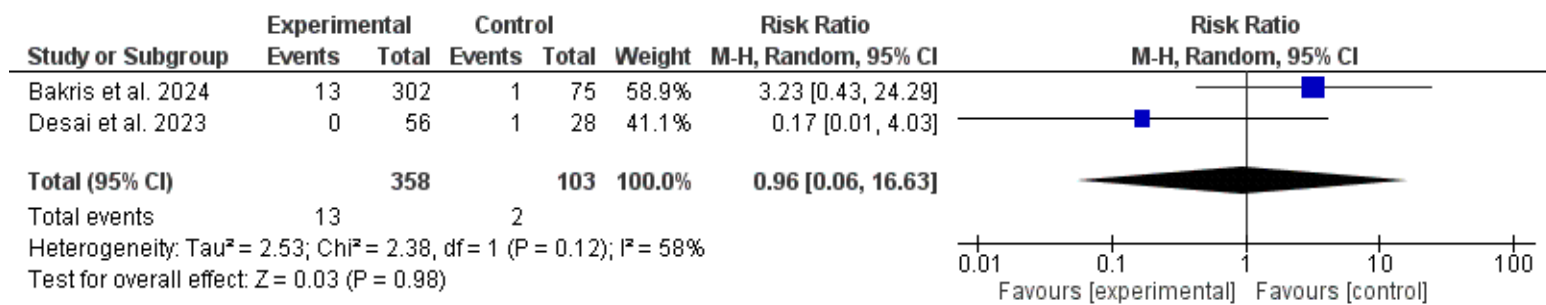


(D)

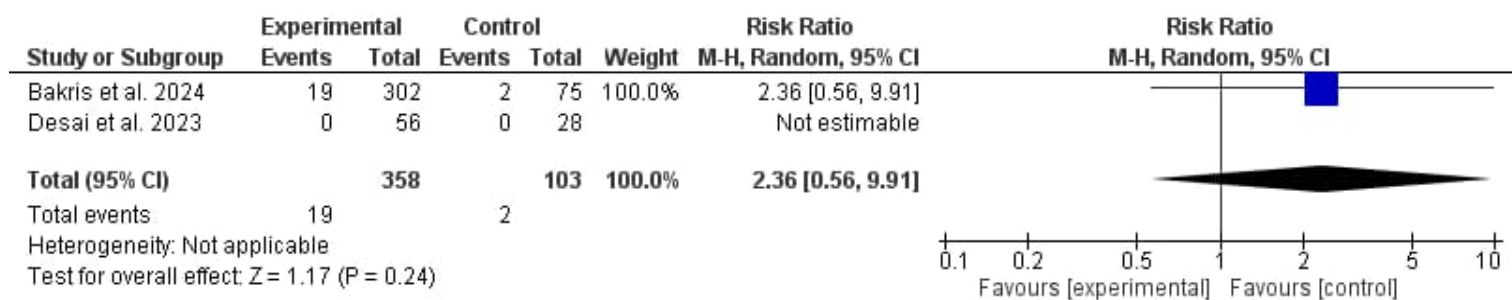


**Online Resource 3:** shows difference between siRNA therapy and placebo in **(A)** mean percent change in AGT at end of follow-up **(B)** mean percent change in AGT at the 3-month endpoint **(C)** mean change in potassium level **(D)** mean change in eGFR.

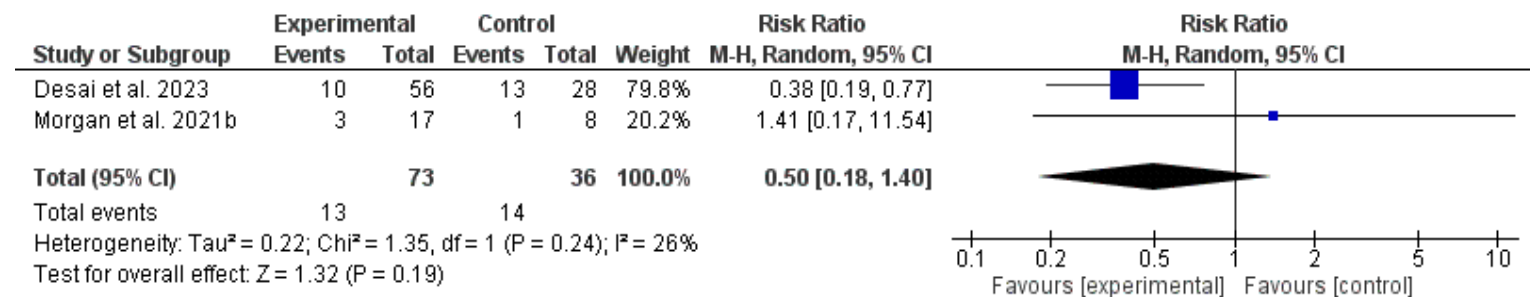
(A)



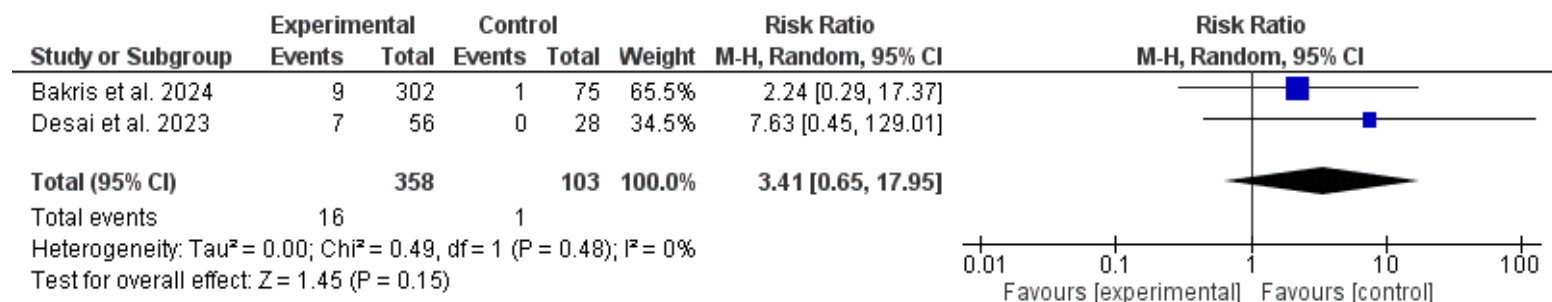
(B)



(C)

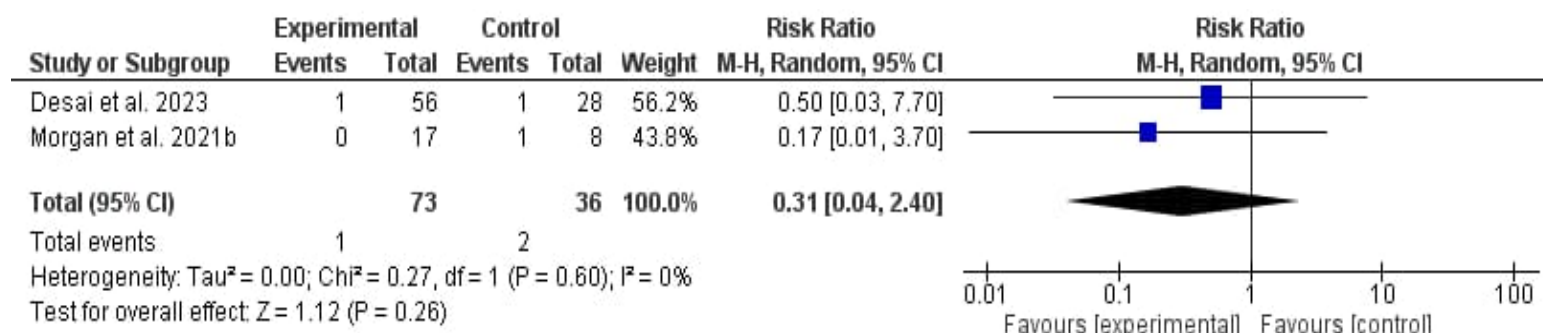


(D)

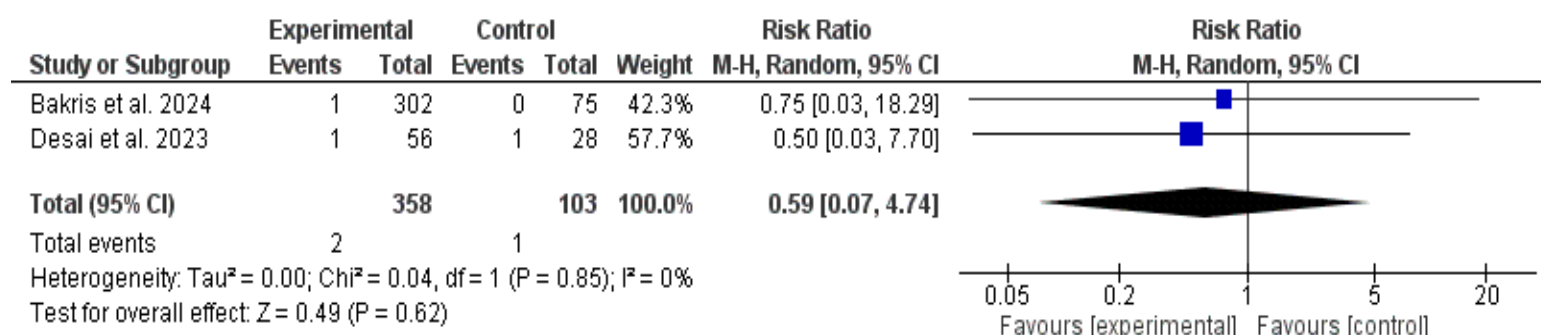


**Online Resource 4:** shows difference between siRNA therapy and placebo in risk ratio of adverse effects (A) hypotension (B) hyperkalemia (C) headache (D) hepatic adverse effects.

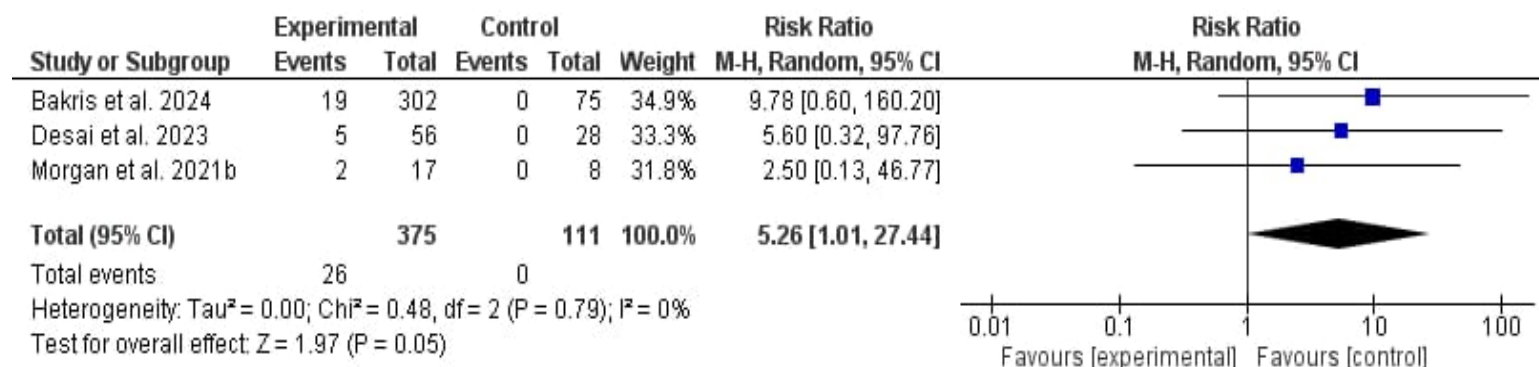
(A)



(B)

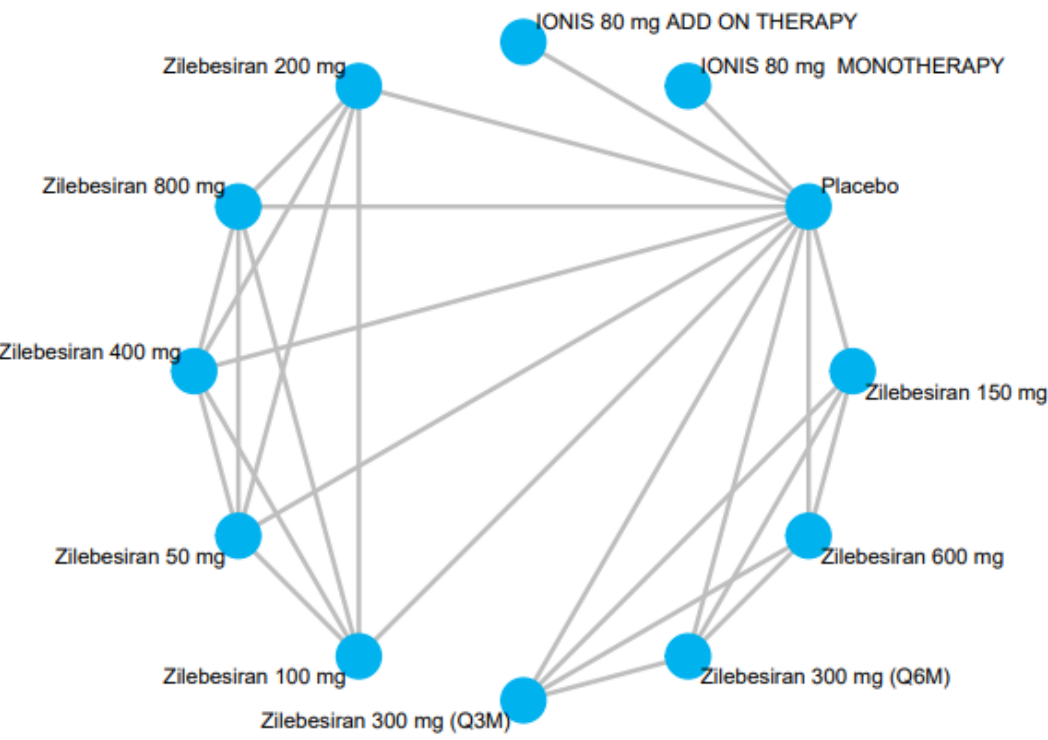


(C)

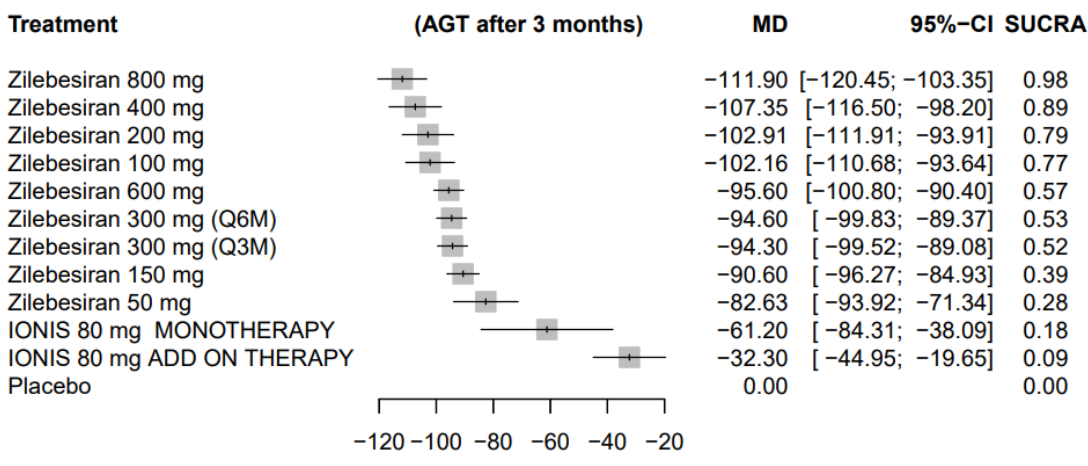


**Online Resource 5:** shows difference between siRNA therapy and placebo in risk ratio of  
(A) serious side effects (B) death (C) injection site reactions.

(A)

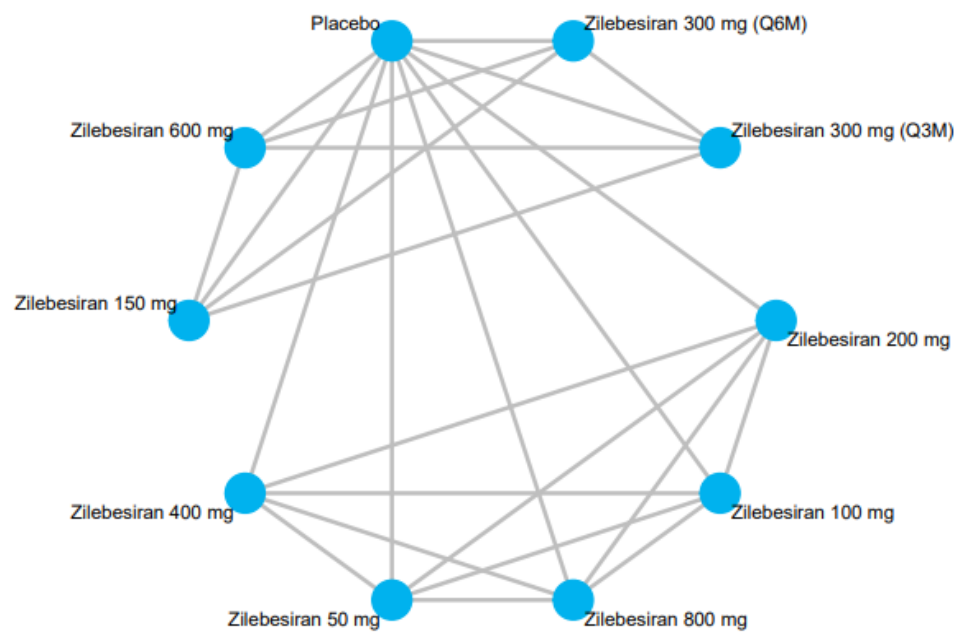


(B)

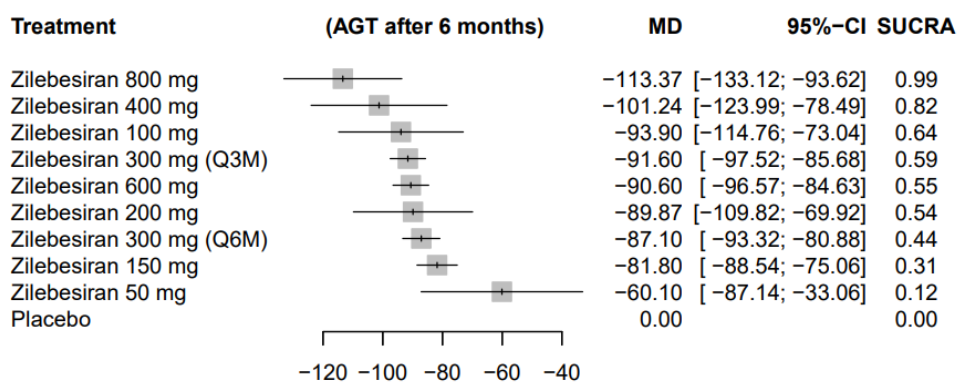


**Online Resource 6.** Network Plots and Forest Plots for Angiotensinogen (AGT) Levels at 3 months: (A) Network plot for AGT, (B) Network Forest plot for AGT.

(A)



(B)



**Online Resource 7.** Network Plots and Forest Plots for Angiotensinogen (AGT) Levels at 6 months: (A) Network plot for AGT, (B) Network Forest Plot for AGT.

(A)

Zilebesiran 800 mg	-4.55 ( -9.34; 0.24)	-8.99 (-13.49; -4.49)	-9.74 (-13.18; -6.30)	.	.	.	.	-29.27 ( -37.44; -21.10)	.	.	-111.90 (-120.45;-103.35)
-4.55 ( -9.34; 0.24)	Zilebesiran 400 mg	-4.44 ( -9.98; 1.10)	-5.19 ( -9.92; -0.46)	.	.	.	.	-24.72 ( -33.51; -15.93)	.	.	-107.35 (-116.50; -98.20)
-8.99 ( -13.49; -4.49)	-4.44 ( -9.98; 1.10)	Zilebesiran 200 mg	-0.75 ( -5.18; 3.68)	.	.	.	.	-20.28 ( -28.91; -11.65)	.	.	-102.91 (-111.91; -93.91)
-9.74 ( -13.18; -6.30)	-5.19 ( -9.92; -0.46)	-0.75 ( -5.18; 3.68)	Zilebesiran 100 mg	.	.	.	.	-19.53 ( -27.66; -11.40)	.	.	-102.16 (-110.68; -93.64)
-16.30 ( -26.31; -6.29)	-11.75 ( -22.27; -1.23)	-7.31 (-17.70; 3.08)	-6.56 (-16.54; 3.42)	Zilebesiran 600 mg	-1.00 ( -1.75; -0.25)	-1.30 ( -2.03; -0.57)	-5.00 ( -7.31; -2.69)	.	.	.	-95.60 (-100.80; -90.40)
-17.30 ( -27.32; -7.28)	-12.75 ( -23.28; -2.22)	-8.31 (-18.71; 2.09)	-7.56 (-17.55; 2.43)	-1.00 ( -1.75; -0.25)	Zilebesiran 300 mg (Q6M)	-0.30 ( -1.20; 0.60)	-4.00 ( -6.37; -1.63)	.	.	.	-94.60 ( -99.83; -89.37)
-17.60 ( -27.62; -7.58)	-13.05 ( -23.58; -2.52)	-8.61 (-19.01; 1.79)	-7.86 (-17.85; 2.13)	-1.30 ( -2.03; -0.57)	-0.30 ( -1.20; 0.60)	Zilebesiran 300 mg (Q3M)	-3.70 ( -6.06; -1.34)	.	.	.	-94.30 ( -99.52; -89.08)
-21.30 ( -31.56; -11.04)	-16.75 ( -27.51; -5.99)	-12.31 (-22.94; -1.68)	-11.56 (-21.79; -1.33)	-5.00 ( -7.31; -2.69)	-4.00 ( -6.37; -1.63)	-3.70 ( -6.06; -1.34)	Zilebesiran 150 mg	.	.	.	-90.60 ( -96.27; -84.93)
-29.27 ( -37.44; -21.10)	-24.72 ( -33.51; -15.93)	-20.28 ( -28.91; -11.65)	-19.53 ( -27.66; -11.40)	-12.97 ( -25.40; -0.54)	-11.97 ( -24.41; 0.47)	-11.67 ( -24.11; 0.77)	-7.97 ( -20.60; 4.66)	Zilebesiran 50 mg	.	.	-82.63 ( -93.92; -71.34)
-50.70 ( -75.34; -26.06)	-46.15 ( -71.00; -21.30)	-41.71 ( -66.51; -16.91)	-40.96 ( -65.59; -16.33)	-34.40 ( -58.08; -10.72)	-33.40 ( -57.09; -9.71)	-33.10 ( -56.79; -9.41)	-29.40 ( -53.19; -5.61)	-21.43 ( -47.15; 4.29)	IONIS 80 mg MONOTHERAPY	.	-61.20 ( -84.31; -38.09)
-79.60 ( -94.87; -64.33)	-75.05 ( -90.66; -59.44)	-70.61 ( -86.14; -55.08)	-69.86 ( -85.11; -54.61)	-63.30 ( -76.98; -49.62)	-62.30 ( -75.99; -48.61)	-62.00 ( -75.69; -48.31)	-58.30 ( -72.16; -44.44)	-50.33 ( -67.29; -33.37)	-28.90 ( -55.24; -2.56)	IONIS 80 mg ADD ON THERAPY	-32.30 ( -44.95; -19.65)
-111.90 (-120.45;-103.35)	-107.35 (-116.50; -98.20)	-102.91 (-111.91; -93.91)	-102.16 (-110.68; -93.64)	-95.60 (-100.80; -90.40)	-94.60 ( -99.83; -89.37)	-94.30 ( -99.52; -89.08)	-90.60 ( -96.27; -84.93)	-84.93 -82.63 ( -93.92; -71.34)	-61.20 ( -84.31; -38.09)	.	Placebo

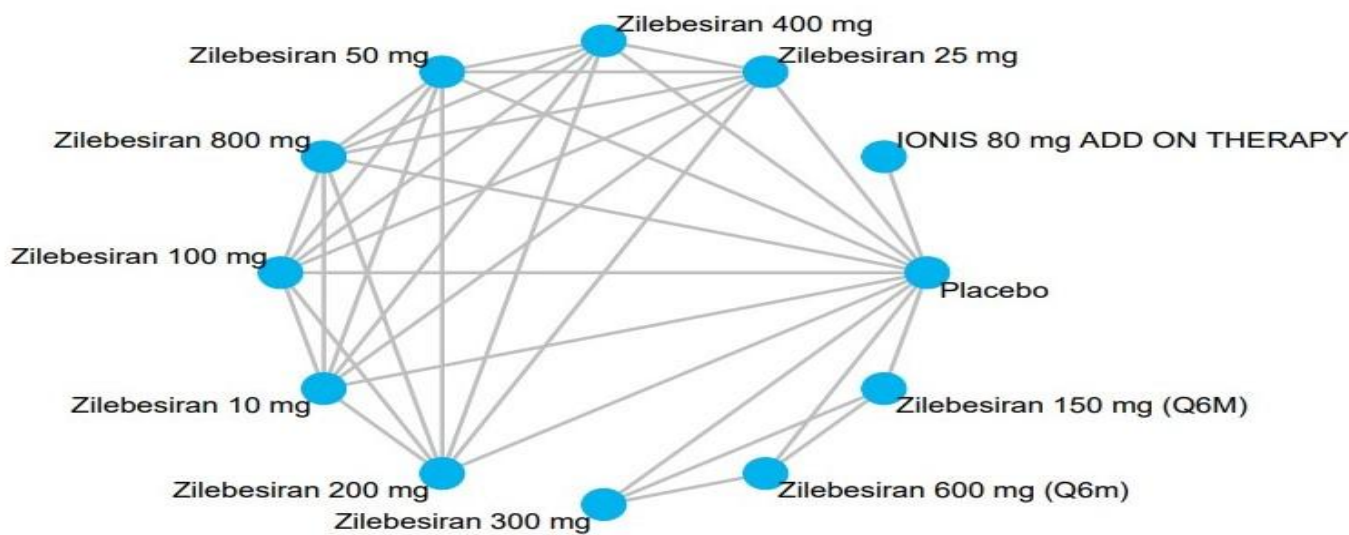
(B)

Zilebesiran 800 mg	-12.13 ( -23.83; -0.43)	.	-19.47 ( -26.85;-12.09)	.	-23.50 ( -27.67;-19.33)	.	.	-53.27 ( -71.99;-34.55)	-113.37 (-133.12;-93.62)
-12.13 ( -23.83; -0.43)	Zilebesiran 400 mg	.	-7.34 ( -20.83; 6.15)	.	-11.37 ( -23.41; 0.67)	.	.	-41.14 ( -63.00;-19.28)	-101.24 (-123.99;-78.49)
-21.77 ( -42.39; -1.15)	-9.64 ( -33.15; 13.87)	Zilebesiran 300 mg (Q3M)	.	-1.00 ( -2.05; 0.05)	.	-4.50 ( -6.52; -2.48)	-9.80 ( -13.09; -6.51)	.	-91.60 ( -97.52;-85.68)
-19.47 ( -26.85;-12.09)	-7.34 ( -20.83; 6.15)	2.30 ( -19.39; 23.99)	Zilebesiran 100 mg	.	-4.03 ( -11.94; 3.88)	.	.	-33.80 ( -53.69;-13.91)	-93.90 (-114.76;-73.04)
-22.77 ( -43.40; -2.14)	-10.64 ( -34.17; 12.89)	-1.00 ( -2.05; 0.05)	-3.30 ( -25.00; 18.40)	Zilebesiran 600 mg	.	-3.50 ( -5.68; -1.32)	-8.80 ( -12.19; -5.41)	.	-90.60 ( -96.57;-84.63)
-23.50 ( -27.67;-19.33)	-11.37 ( -23.41; 0.67)	-1.73 ( -22.54; 19.08)	-4.03 ( -11.94; 3.88)	-0.73 ( -21.56; 20.10)	Zilebesiran 200 mg	.	.	-29.77 ( -48.70;-10.84)	-89.87 (-109.82;-69.92)
-26.27 ( -46.98; -5.56)	-14.14 ( -37.73; 9.45)	-4.50 ( -6.52; -2.48)	-6.80 ( -28.57; 14.97)	-3.50 ( -5.68; -1.32)	-2.77 ( -23.67; 18.13)	Zilebesiran 300 mg (Q6M)	-5.30 ( -9.10; -1.50)	.	-87.10 ( -93.32;-80.88)
-31.57 ( -52.44;-10.70)	-19.44 ( -43.17; 4.29)	-9.80 ( -13.09; -6.51)	-12.10 ( -34.02; 9.82)	-8.80 ( -12.19; -5.41)	-8.07 ( -29.13; 12.99)	-5.30 ( -9.10; -1.50)	Zilebesiran 150 mg	.	-81.80 ( -88.54;-75.06)
-53.27 ( -71.99;-34.55)	-41.14 ( -63.00;-19.28)	-31.50 ( -59.18; -3.82)	-33.80 ( -53.69;-13.91)	-30.50 ( -58.19; -2.81)	-29.77 ( -48.70;-10.84)	-27.00 ( -54.75; 0.75)	-21.70 ( -49.57; 6.17)	Zilebesiran 50 mg	-60.10 ( -87.14;-33.06)
-113.37 ( -133.12;-93.62)	-101.24 ( -123.99;-78.49)	-91.60 ( -97.52;-85.68)	-93.90 (-114.76;-73.04)	-90.60 ( -96.57;-84.63)	-89.87 ( -109.82;-69.92)	-87.10 ( -93.32;-80.88)	-81.80 ( -88.54;-75.06)	-60.10 ( -87.14;-33.06)	Placebo

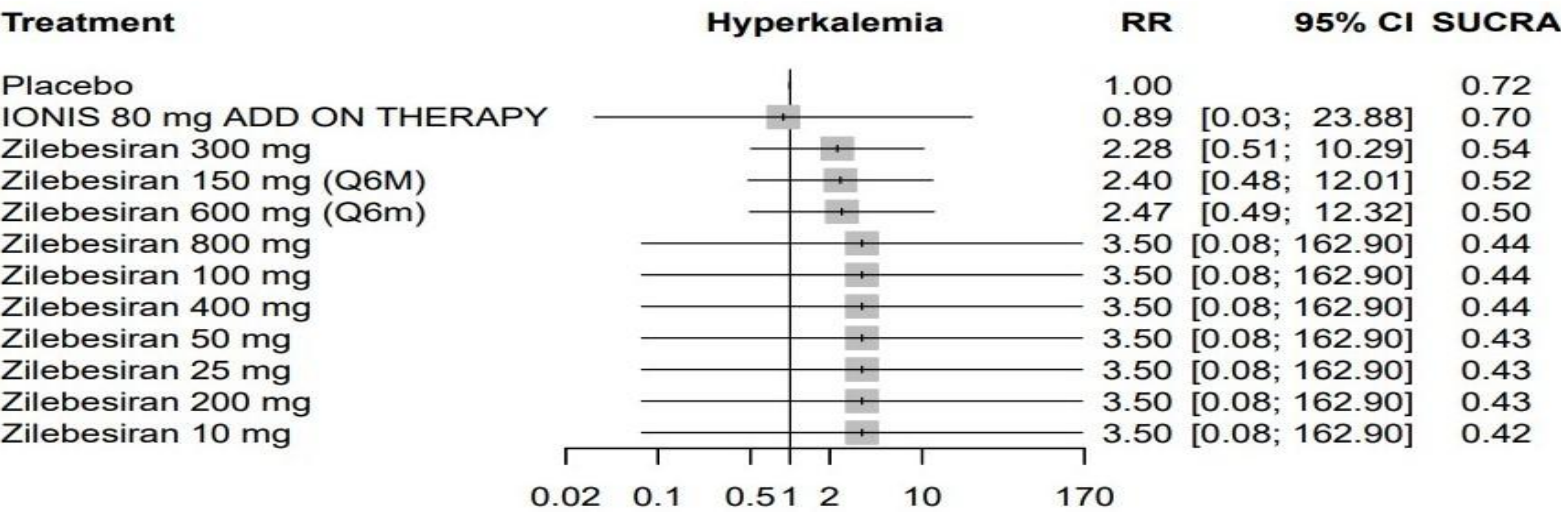
Online Resource 8. League Tables for Angiotensinogen (AGT) Levels: (A) League table for AGT at 3 months (B) League table for AGT at 6 months



(A)



(B)

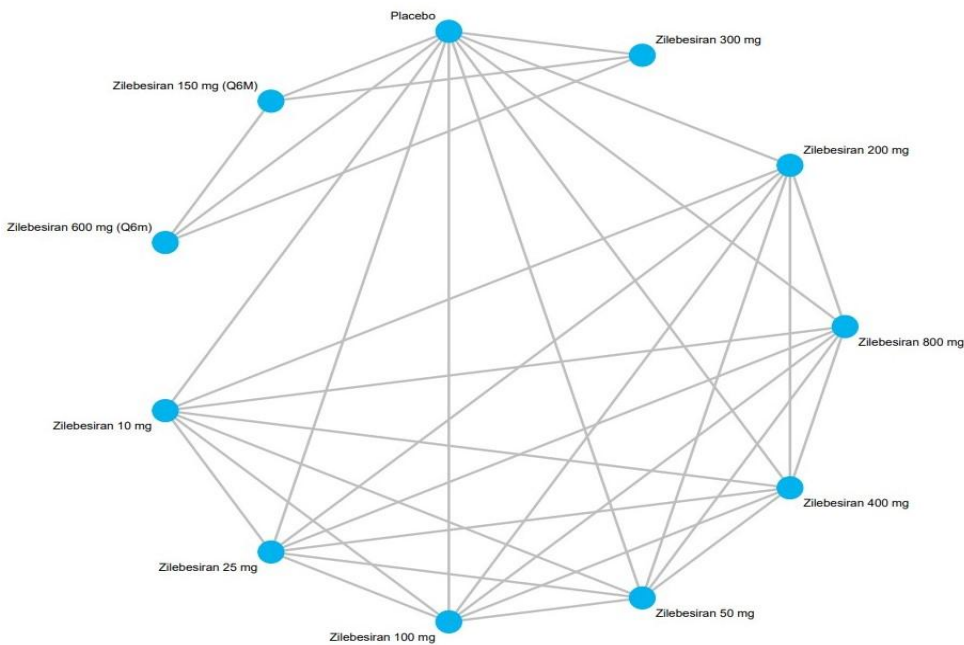


(C)

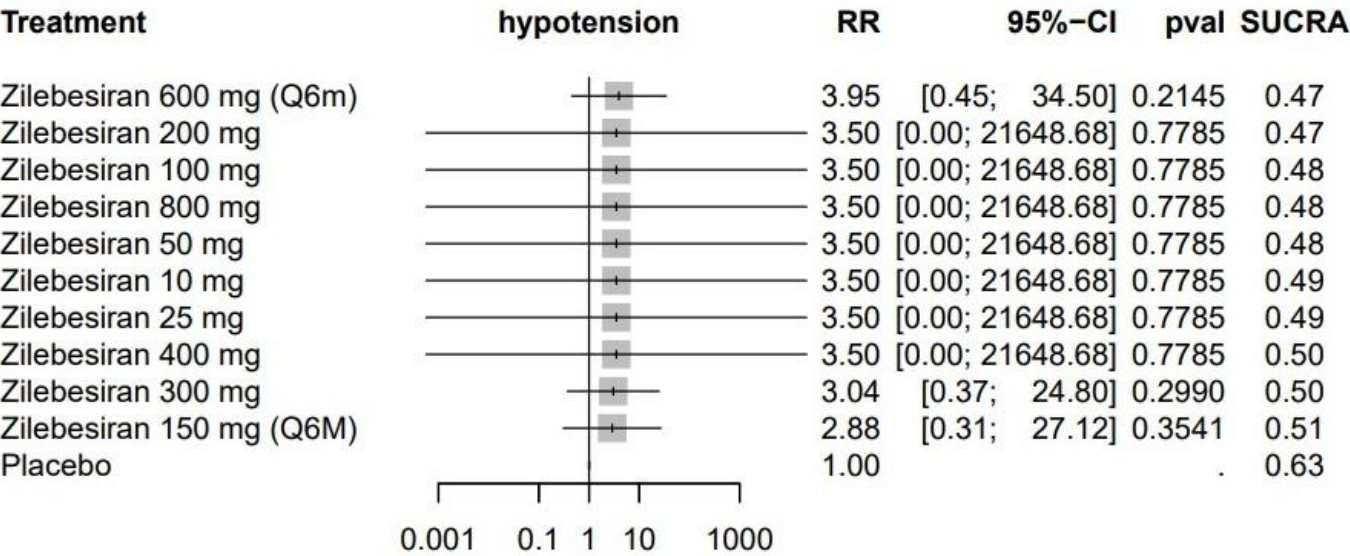
IONIS 80 mg ADD ON THERAPY	0.89 (0.03; 23.88)	.	.	.	.	.	.	.	.	.	.
0.89 (0.03; 23.88)	Placebo	0.29 (0.01; 13.30)	0.29 (0.01; 13.30)	0.42 (0.08; 2.08)	0.29 (0.01; 13.30)	0.29 (0.01; 13.30)	0.44 (0.10; 1.98)	0.29 (0.01; 13.30)	0.29 (0.01; 13.30)	0.41 (0.08; 2.02)	0.29 (0.01; 13.30)
0.25 (0.00; 39.93)	0.29 (0.01; 13.30)	Zilebesiran 10 mg	1.00 (0.02; 44.50)	.	1.00 (0.02; 44.50)	1.00 (0.02; 44.50)	.	1.00 (0.02; 44.50)	1.00 (0.02; 44.50)	.	1.00 (0.02; 44.50)
0.25 (0.00; 39.93)	0.29 (0.01; 13.30)	1.00 (0.02; 44.50)	Zilebesiran 100 mg	.	1.00 (0.02; 44.50)	1.00 (0.02; 44.50)	.	1.00 (0.02; 44.50)	1.00 (0.02; 44.50)	.	1.00 (0.02; 44.50)
0.37 (0.01; 14.42)	0.42 (0.08; 2.08)	1.46 (0.02; 93.64)	1.46 (0.02; 93.64)	Zilebesiran 150 mg (Q6M)	.	.	1.05 (0.37; 3.04)	.	.	0.97 (0.29; 3.23)	.
0.25 (0.00; 39.93)	0.29 (0.01; 13.30)	1.00 (0.02; 44.50)	1.00 (0.02; 44.50)	0.69 (0.01; 44.17)	Zilebesiran 200 mg	1.00 (0.02; 44.50)	.	1.00 (0.02; 44.50)	1.00 (0.02; 44.50)	.	1.00 (0.02; 44.50)
0.25 (0.00; 39.93)	0.29 (0.01; 13.30)	1.00 (0.02; 44.50)	1.00 (0.02; 44.50)	0.69 (0.01; 44.17)	1.00 (0.02; 44.50)	Zilebesiran 25 mg	.	1.00 (0.02; 44.50)	1.00 (0.02; 44.50)	.	1.00 (0.02; 44.50)
0.39 (0.01; 14.55)	0.44 (0.10; 1.98)	1.53 (0.02; 94.99)	1.53 (0.02; 94.99)	1.05 (0.37; 3.04)	1.53 (0.02; 94.99)	1.53 (0.02; 94.99)	Zilebesiran 300 mg	.	.	0.92 (0.32; 2.66)	.
0.25 (0.00; 39.93)	0.29 (0.01; 13.30)	1.00 (0.02; 44.50)	1.00 (0.02; 44.50)	0.69 (0.01; 44.17)	1.00 (0.02; 44.50)	1.00 (0.02; 44.50)	0.65 (0.01; 40.33)	Zilebesiran 400 mg	1.00 (0.02; 44.50)	.	1.00 (0.02; 44.50)
0.25 (0.00; 39.93)	0.29 (0.01; 13.30)	1.00 (0.02; 44.50)	1.00 (0.02; 44.50)	0.69 (0.01; 44.17)	1.00 (0.02; 44.50)	1.00 (0.02; 44.50)	0.65 (0.01; 40.33)	1.00 (0.02; 44.50)	Zilebesiran 50 mg	.	1.00 (0.02; 44.50)
0.36 (0.01; 14.04)	0.41 (0.08; 2.02)	1.42 (0.02; 91.23)	1.42 (0.02; 91.23)	0.97 (0.29; 3.23)	1.42 (0.02; 91.23)	1.42 (0.02; 91.23)	0.92 (0.32; 2.66)	1.42 (0.02; 91.23)	1.42 (0.02; 91.23)	Zilebesiran 600 mg (Q6m)	.
0.25 (0.00; 39.93)	0.29 (0.01; 13.30)	1.00 (0.02; 44.50)	1.00 (0.02; 44.50)	0.69 (0.01; 44.17)	1.00 (0.02; 44.50)	1.00 (0.02; 44.50)	0.65 (0.01; 40.33)	1.00 (0.02; 44.50)	1.00 (0.02; 44.50)	0.70 (0.01; 45.33)	Zilebesiran 800 mg

Online Resource 9: (A) network plot for hyperkalemia (B) network forest plot for risk ratio of hyperkalemia (C) league table for hyperkalemia.

(A)



(B)



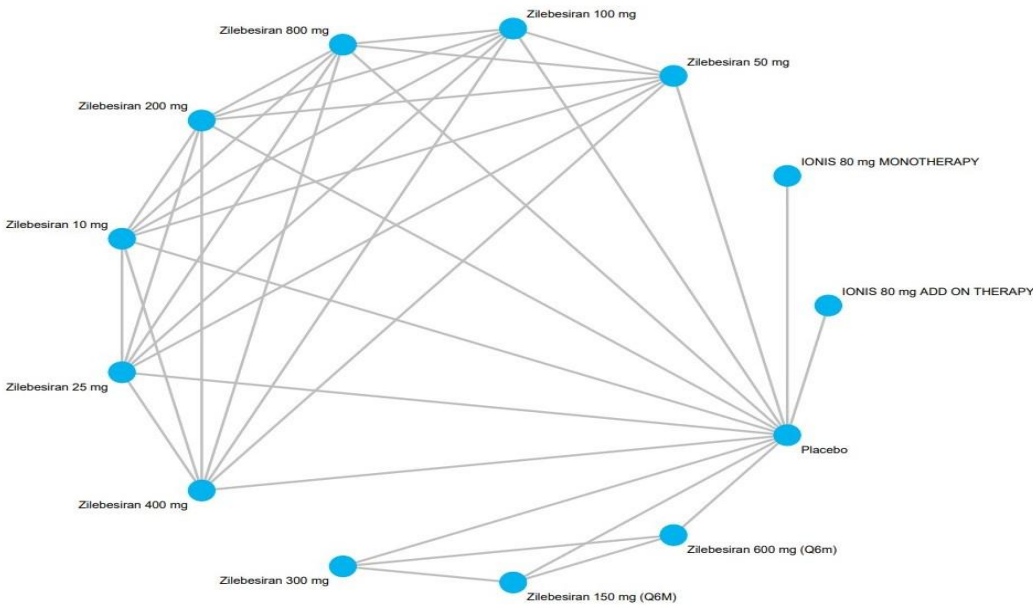
(C)

Placebo	0.29 (0.00; 1767.24)	0.29 (0.00; 1767.24)	0.35 (0.04; 3.26)	0.29 (0.00; 1767.24)	0.29 (0.00; 1767.24)	0.33 (0.04; 2.68)	0.29 (0.00; 1767.24)	0.29 (0.00; 1767.24)	0.25 (0.03; 2.21)	0.29 (0.00; 1767.24)
0.29 (0.00; 1767.24)	Zilebesiran 10 mg	1.00 (0.00; 6064.88)	.	1.00 (0.00; 6064.88)	1.00 (0.00; 6064.88)	.	1.00 (0.00; 6064.88)	1.00 (0.00; 6064.88)	.	1.00 (0.00; 6064.88)
0.29 (0.00; 1767.24)	1.00 (0.00; 6064.88)	Zilebesiran 100 mg	.	1.00 (0.00; 6064.88)	1.00 (0.00; 6064.88)	.	1.00 (0.00; 6064.88)	1.00 (0.00; 6064.88)	.	1.00 (0.00; 6064.88)
0.35 (0.04; 3.26)	1.21 (0.00; 9959.90)	1.21 (0.00; 9959.90)	Zilebesiran 150 mg (Q6M)	.	.	0.95 (0.24; 3.69)	.	.	0.73 (0.17; 3.16)	.
0.29 (0.00; 1767.24)	1.00 (0.00; 6064.88)	1.00 (0.00; 6064.88)	0.82 (0.00; 6765.42)	Zilebesiran 200 mg	1.00 (0.00; 6064.88)	.	1.00 (0.00; 6064.88)	1.00 (0.00; 6064.88)	.	1.00 (0.00; 6064.88)
0.29 (0.00; 1767.24)	1.00 (0.00; 6064.88)	1.00 (0.00; 6064.88)	0.82 (0.00; 6765.42)	1.00 (0.00; 6064.88)	Zilebesiran 25 mg	.	1.00 (0.00; 6064.88)	1.00 (0.00; 6064.88)	.	1.00 (0.00; 6064.88)
0.33 (0.04; 2.68)	1.15 (0.00; 9130.60)	1.15 (0.00; 9130.60)	0.95 (0.24; 3.69)	1.15 (0.00; 9130.60)	1.15 (0.00; 9130.60)	Zilebesiran 300 mg	.	.	0.77 (0.22; 2.65)	.
0.29 (0.00; 1767.24)	1.00 (0.00; 6064.88)	1.00 (0.00; 6064.88)	0.82 (0.00; 6765.42)	1.00 (0.00; 6064.88)	1.00 (0.00; 6064.88)	0.87 (0.00; 6890.73)	Zilebesiran 400 mg	1.00 (0.00; 6064.88)	.	1.00 (0.00; 6064.88)
0.29 (0.00; 1767.24)	1.00 (0.00; 6064.88)	1.00 (0.00; 6064.88)	0.82 (0.00; 6765.42)	1.00 (0.00; 6064.88)	1.00 (0.00; 6064.88)	0.87 (0.00; 6890.73)	1.00 (0.00; 6064.88)	Zilebesiran 50 mg	.	1.00 (0.00; 6064.88)
0.25 (0.03; 2.21)	0.89 (0.00; 7149.63)	0.89 (0.00; 7149.63)	0.73 (0.17; 3.16)	0.89 (0.00; 7149.63)	0.89 (0.00; 7149.63)	0.77 (0.22; 2.65)	0.89 (0.00; 7149.63)	0.89 (0.00; 7149.63)	Zilebesiran 600 mg (Q6m)	.
0.29 (0.00; 1767.24)	1.00 (0.00; 6064.88)	1.00 (0.00; 6064.88)	0.82 (0.00; 6765.42)	1.00 (0.00; 6064.88)	1.00 (0.00; 6064.88)	0.87 (0.00; 6890.73)	1.00 (0.00; 6064.88)	1.00 (0.00; 6064.88)	1.13 (0.00; 9094.16)	Zilebesiran 800 mg

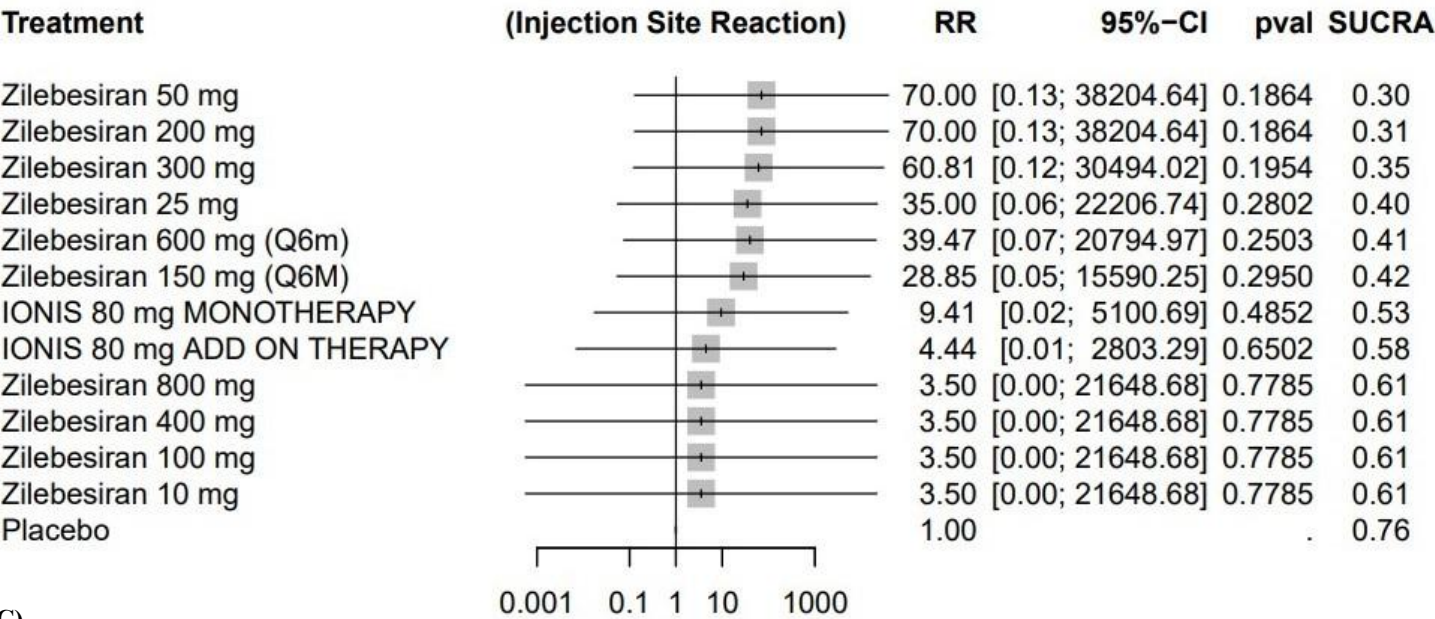
**Online Resource 10: (A) network plot for hypotension (B) network forest plot for risk ratio of hypotension (C) league table for hypotension.**



(A)



(B)

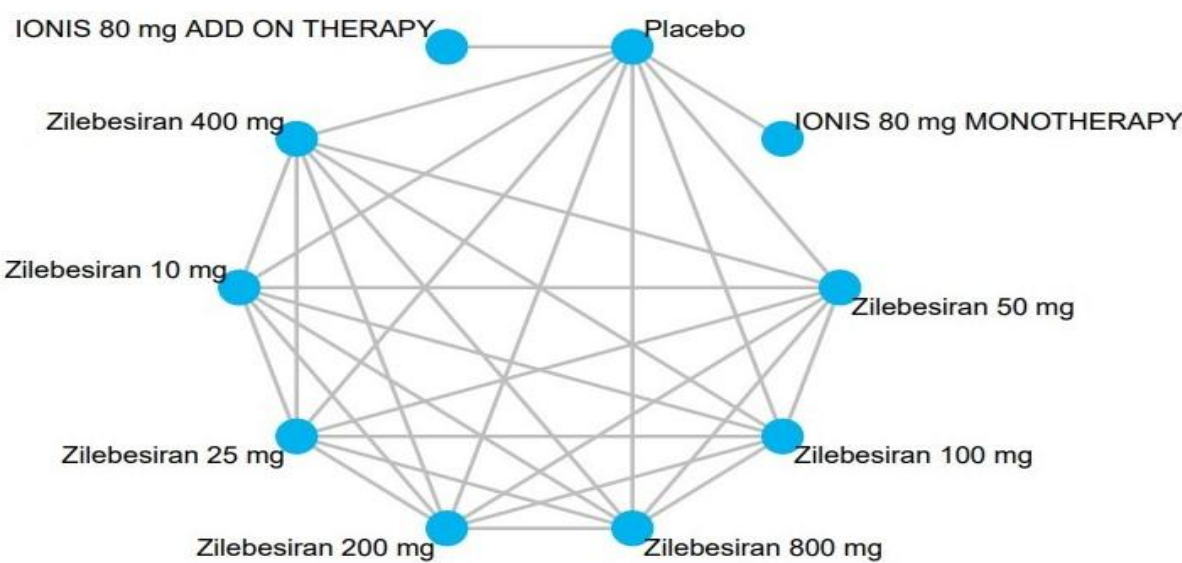


(C)

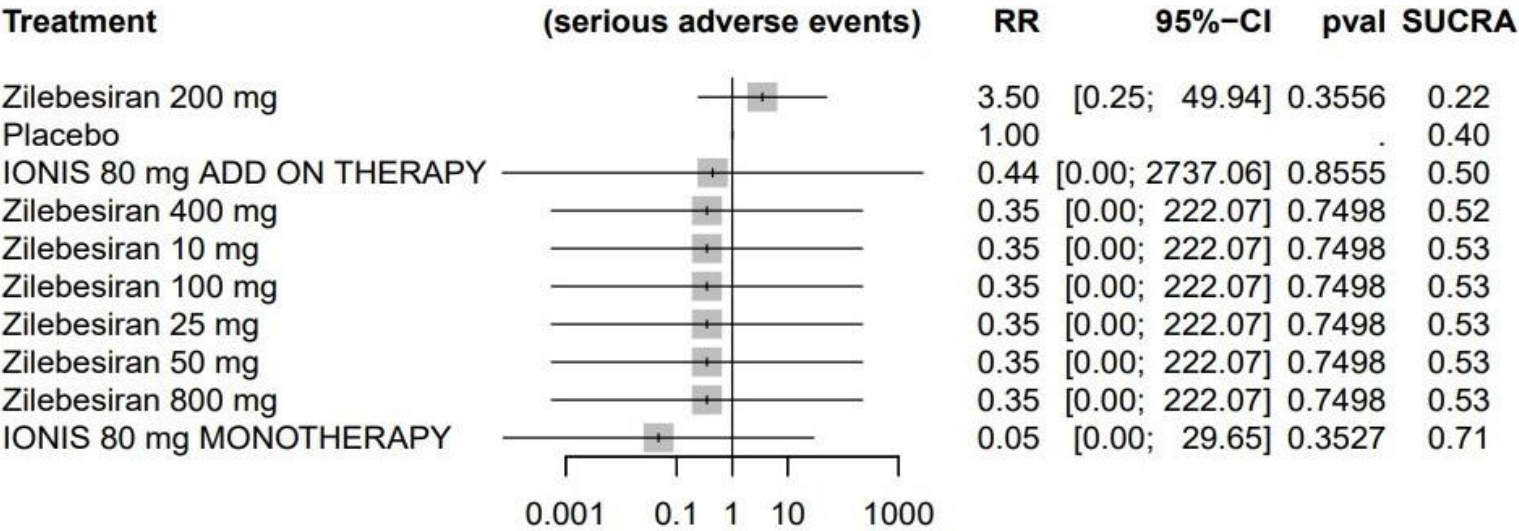
IONIS 80 mg ADD ON THERAPY	.	4.44 (0.01; 2803.29)	.	.	.	.	.	.	.	.	.	.	.
0.47 (0.00; 3867.38)	IONIS 80 mg MONOTHERAPY	9.41 (0.02; 5100.69)	.	.	.	.	.	.	.	.	.	.	.
4.44 (0.01; 2803.29)			Placebo	0.29 (0.00; 1767.24)	0.29 (0.00; 1767.24)	0.03 (0.00; 18.74)	0.01 (0.00; 7.80)	0.03 (0.00; 18.13)	0.02 (0.00; 8.25)	0.29 (0.00; 1767.24)	0.01 (0.00; 7.80)	0.03 (0.00; 13.35)	0.29 (0.00; 1767.24)
1.27 (0.00; 65596.42)			0.29 (0.00; 1767.24)	Zilebesiran 10 mg	1.00 (0.00; 6064.88)	.	0.05 (0.00; 26.55)	0.10 (0.00; 61.78)	.	1.00 (0.00; 6064.88)	0.05 (0.00; 26.55)	.	1.00 (0.00; 6064.88)
1.27 (0.00; 65596.42)			0.29 (0.00; 1767.24)	1.00 (0.00; 6064.88)	Zilebesiran 100 mg	.	0.05 (0.00; 26.55)	0.10 (0.00; 61.78)	.	1.00 (0.00; 6064.88)	0.05 (0.00; 26.55)	.	1.00 (0.00; 6064.88)
0.15 (0.00; 1259.41)			0.33 (0.00; 2394.09)	0.03 (0.00; 18.74)	0.12 (0.00; 5722.29)	0.12 (0.00; 5722.29)	Zilebesiran 150 mg (Q6M)	.	0.47 (0.14; 1.63)	.	.	0.73 (0.17; 3.16)	.
0.06 (0.00; 522.55)			0.13 (0.00; 993.43)	0.01 (0.00; 7.80)	0.05 (0.00; 26.55)	0.05 (0.00; 26.55)	0.41 (0.00; 3038.87)	Zilebesiran 200 mg	2.00 (0.22; 17.89)	.	20.00 (0.04; 10621.96)	1.00 (0.18; 5.46)	20.00 (0.04; 10621.96)
0.13 (0.00; 1161.85)			0.27 (0.00; 2211.62)	0.03 (0.00; 18.13)	0.10 (0.00; 61.78)	0.10 (0.00; 61.78)	0.82 (0.00; 6765.42)	2.00 (0.22; 17.89)	Zilebesiran 25 mg	.	10.00 (0.02; 6178.04)	0.50 (0.06; 4.47)	10.00 (0.02; 6178.04)
0.07 (0.00; 567.05)			0.15 (0.00; 1077.25)	0.02 (0.00; 8.25)	0.06 (0.00; 2598.54)	0.06 (0.00; 2598.54)	0.47 (0.14; 1.63)	1.15 (0.00; 8052.36)	0.58 (0.00; 4484.56)	Zilebesiran 300 mg	.	1.54 (0.51; 4.62)	.
1.27 (0.00; 65596.42)			2.69 (0.00; 127025.31)	0.29 (0.00; 1767.24)	1.00 (0.00; 6064.88)	1.00 (0.00; 6064.88)	8.24 (0.00; 388695.73)	20.00 (0.04; 10621.96)	10.00 (0.02; 6178.04)	17.37 (0.00; 784432.52)	Zilebesiran 400 mg	0.05 (0.00; 26.55)	1.00 (0.00; 6064.88)
0.06 (0.00; 522.55)			0.13 (0.00; 993.43)	0.01 (0.00; 7.80)	0.05 (0.00; 26.55)	0.05 (0.00; 26.55)	0.41 (0.00; 3038.87)	1.00 (0.18; 5.46)	0.50 (0.06; 4.47)	0.87 (0.00; 6076.99)	0.05 (0.00; 26.55)	Zilebesiran 50 mg	20.00 (0.04; 10621.96)
0.11 (0.00; 904.05)			0.24 (0.00; 1718.19)	0.03 (0.00; 13.35)	0.09 (0.00; 4119.65)	0.09 (0.00; 4119.65)	0.73 (0.17; 3.16)	1.77 (0.00; 12843.03)	0.89 (0.00; 7149.63)	1.54 (0.51; 4.62)	0.09 (0.00; 4119.65)	1.77 (0.00; 12843.03)	Zilebesiran 600 mg (Q6m)
1.27 (0.00; 65596.42)			2.69 (0.00; 127025.31)	0.29 (0.00; 1767.24)	1.00 (0.00; 6064.88)	1.00 (0.00; 6064.88)	8.24 (0.00; 388695.73)	20.00 (0.04; 10621.96)	10.00 (0.02; 6178.04)	17.37 (0.00; 784432.52)	1.00 (0.00; 6064.88)	20.00 (0.04; 10621.96)	11.28 (0.00; 524009.66)
													Zilebesiran 800 mg

Online Resource 11: (A) network plot for injection site reaction (B) network forest plot for risk ratio of injection site reaction (C) league table for injection site reaction.

(A)



(B)



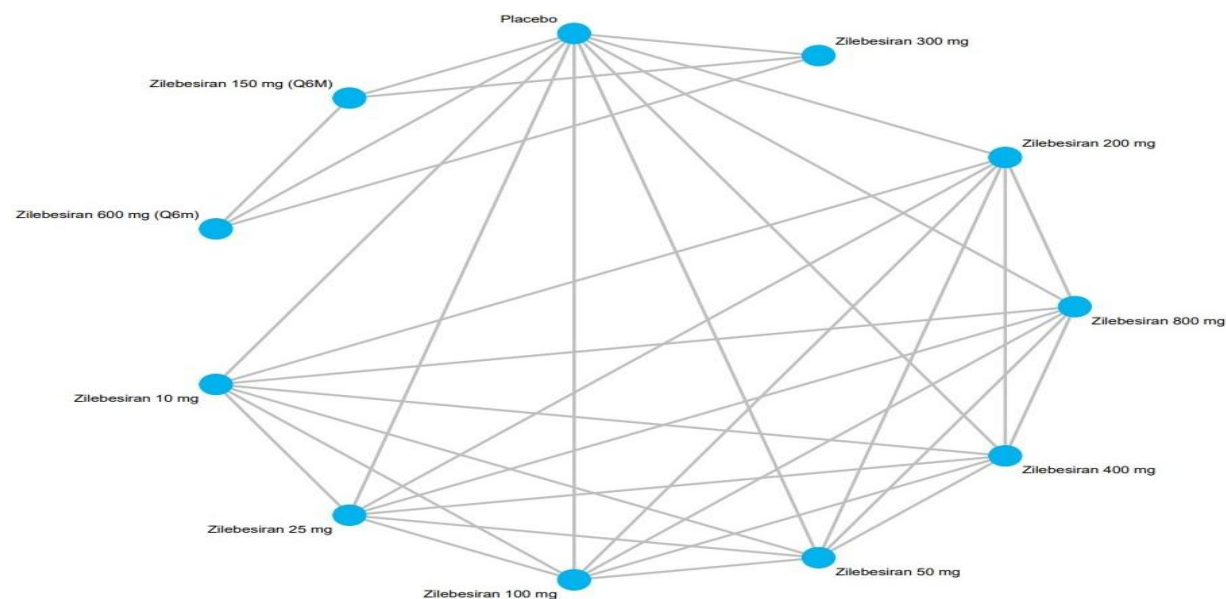
(C)

IONIS 80 mg ADD ON THERAPY	.	0.44 (0.00; 2737.06)	.	.	.	.	.	.	.
9.44 (0.00; 485881.66)	IONIS 80 mg MONOTHERAPY	0.05 (0.00; 29.65)	.	.	.	.	.	.	.
0.44 (0.00; 2737.06)	0.05 (0.00; 29.65)	Placebo	2.86 (0.00; 1812.80)	2.86 (0.00; 1812.80)	0.29 (0.02; 4.08)	2.86 (0.00; 1812.80)	2.86 (0.00; 1812.80)	2.86 (0.00; 1812.80)	2.86 (0.00; 1812.80)
1.27 (0.00; 65596.42)	0.13 (0.00; 1229.35)	2.86 (0.00; 1812.80)	Zilebesiran 10 mg	1.00 (0.00; 6064.88)	0.10 (0.00; 61.78)	1.00 (0.00; 6064.88)	1.00 (0.00; 6064.88)	1.00 (0.00; 6064.88)	1.00 (0.00; 6064.88)
1.27 (0.00; 65596.42)	0.13 (0.00; 1229.35)	2.86 (0.00; 1812.80)	1.00 (0.00; 6064.88)	Zilebesiran 100 mg	0.10 (0.00; 61.78)	1.00 (0.00; 6064.88)	1.00 (0.00; 6064.88)	1.00 (0.00; 6064.88)	1.00 (0.00; 6064.88)
0.13 (0.00; 1161.85)	0.01 (0.00; 14.34)	0.29 (0.02; 4.08)	0.10 (0.00; 61.78)	0.10 (0.00; 61.78)	Zilebesiran 200 mg	10.00 (0.02; 6178.04)	10.00 (0.02; 6178.04)	10.00 (0.02; 6178.04)	10.00 (0.02; 6178.04)
1.27 (0.00; 65596.42)	0.13 (0.00; 1229.35)	2.86 (0.00; 1812.80)	1.00 (0.00; 6064.88)	1.00 (0.00; 6064.88)	10.00 (0.02; 6178.04)	Zilebesiran 25 mg	1.00 (0.00; 6064.88)	1.00 (0.00; 6064.88)	1.00 (0.00; 6064.88)
1.27 (0.00; 65596.42)	0.13 (0.00; 1229.35)	2.86 (0.00; 1812.80)	1.00 (0.00; 6064.88)	1.00 (0.00; 6064.88)	10.00 (0.02; 6178.04)	1.00 (0.00; 6064.88)	Zilebesiran 400 mg	1.00 (0.00; 6064.88)	1.00 (0.00; 6064.88)
1.27 (0.00; 65596.42)	0.13 (0.00; 1229.35)	2.86 (0.00; 1812.80)	1.00 (0.00; 6064.88)	1.00 (0.00; 6064.88)	10.00 (0.02; 6178.04)	1.00 (0.00; 6064.88)	1.00 (0.00; 6064.88)	Zilebesiran 50 mg	1.00 (0.00; 6064.88)
1.27 (0.00; 65596.42)	0.13 (0.00; 1229.35)	2.86 (0.00; 1812.80)	1.00 (0.00; 6064.88)	1.00 (0.00; 6064.88)	10.00 (0.02; 6178.04)	1.00 (0.00; 6064.88)	1.00 (0.00; 6064.88)	1.00 (0.00; 6064.88)	Zilebesiran 800 mg

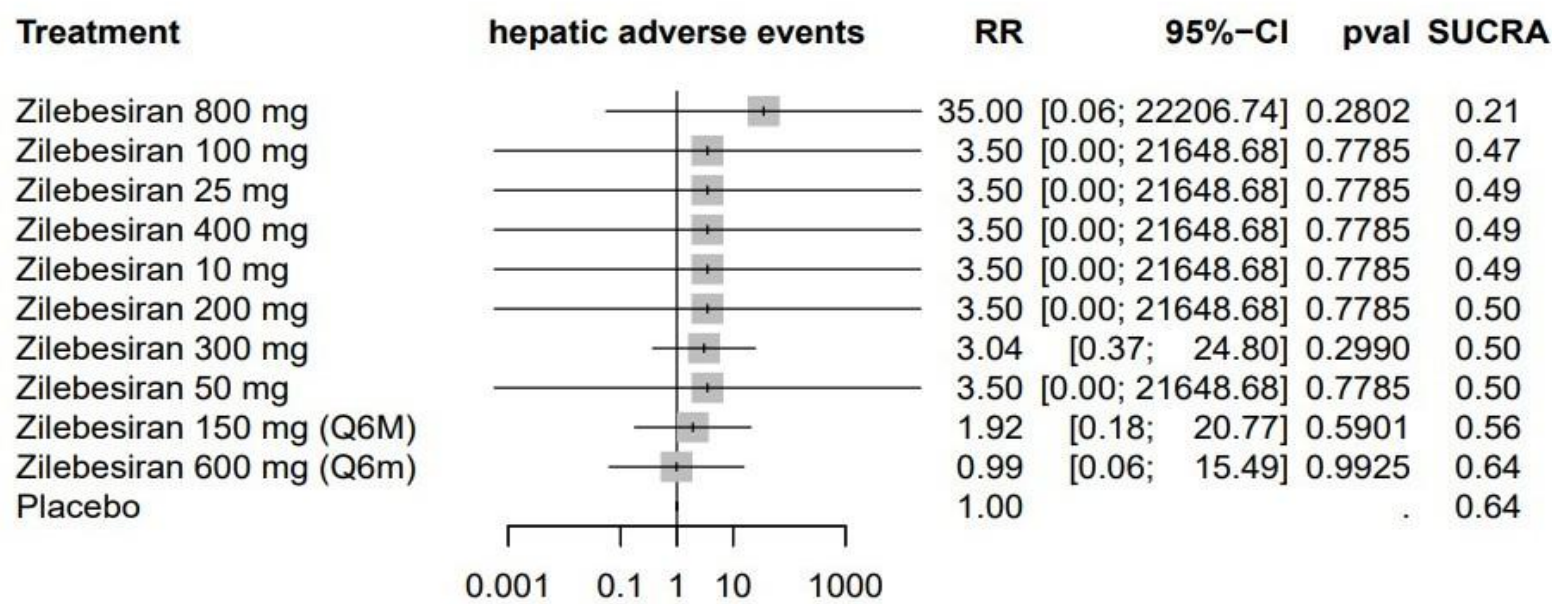
Online Resource 12: (A) network plot for serious adverse effects (B) network forest plot for risk ratio of serious adverse effects (C) league table for serious adverse effects.



(A)



(B)

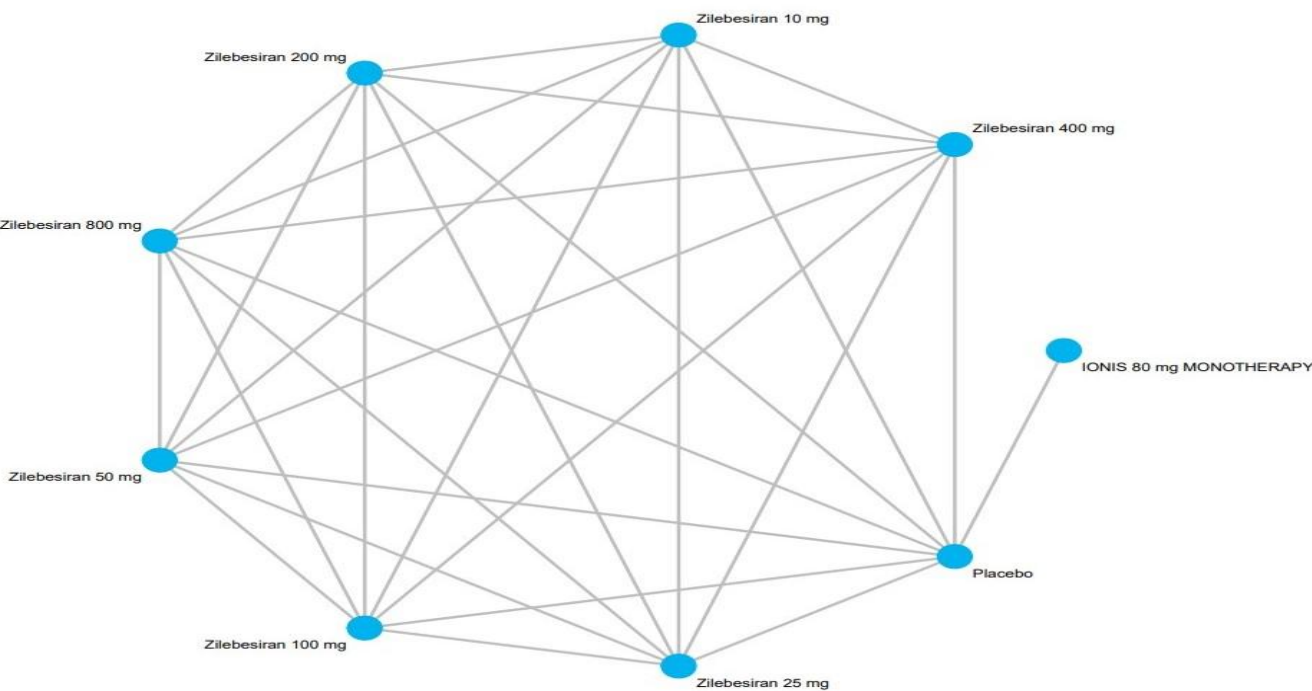


(C)

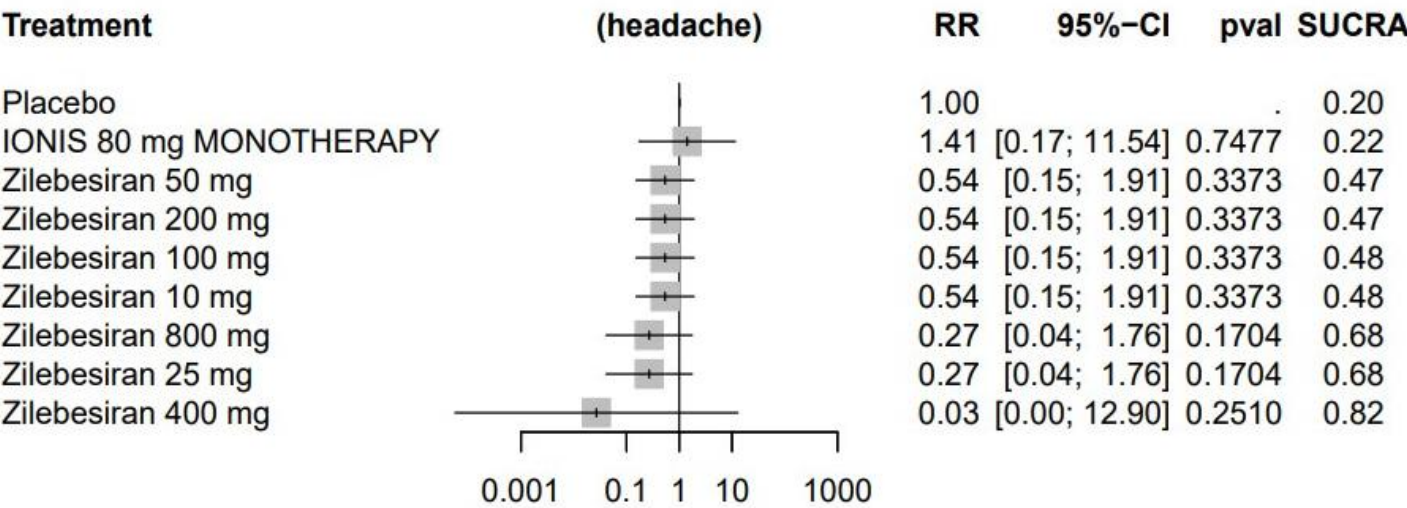
Placebo	0.29 (0.00; 1767.24)	0.29 (0.00; 1767.24)	0.52 (0.05; 5.62)	0.29 (0.00; 1767.24)	0.29 (0.00; 1767.24)	0.33 (0.04; 2.68)	0.29 (0.00; 1767.24)	0.29 (0.00; 1767.24)	1.01 (0.06; 15.91)	0.03 (0.00; 18.13)
0.29 (0.00; 1767.24)	Zilebesiran 10 mg	1.00 (0.00; 6064.88)	.	1.00 (0.00; 6064.88)	1.00 (0.00; 6064.88)	.	1.00 (0.00; 6064.88)	1.00 (0.00; 6064.88)	.	0.10 (0.00; 61.78)
0.29 (0.00; 1767.24)	1.00 (0.00; 6064.88)	Zilebesiran 100 mg	.	1.00 (0.00; 6064.88)	1.00 (0.00; 6064.88)	.	1.00 (0.00; 6064.88)	1.00 (0.00; 6064.88)	.	0.10 (0.00; 61.78)
0.52 (0.05; 5.62)	1.82 (0.00;15478.93)	1.82 (0.00;15478.93)	Zilebesiran 150 mg (Q6M)	.	.	0.63 (0.13; 3.06)	.	.	1.95 (0.18; 21.05)	.
0.29 (0.00; 1767.24)	1.00 (0.00; 6064.88)	1.00 (0.00; 6064.88)	0.55 (0.00; 4673.03)	Zilebesiran 200 mg	1.00 (0.00; 6064.88)	.	1.00 (0.00; 6064.88)	1.00 (0.00; 6064.88)	.	0.10 (0.00; 61.78)
0.29 (0.00; 1767.24)	1.00 (0.00; 6064.88)	1.00 (0.00; 6064.88)	0.55 (0.00; 4673.03)	1.00 (0.00; 6064.88)	Zilebesiran 25 mg	.	1.00 (0.00; 6064.88)	1.00 (0.00; 6064.88)	.	0.10 (0.00; 61.78)
0.33 (0.04; 2.68)	1.15 (0.00; 9130.60)	1.15 (0.00; 9130.60)	0.63 (0.13; 3.06)	1.15 (0.00; 9130.60)	1.15 (0.00; 9130.60)	Zilebesiran 300 mg	.	.	3.08 (0.38; 25.13)	.
0.29 (0.00; 1767.24)	1.00 (0.00; 6064.88)	1.00 (0.00; 6064.88)	0.55 (0.00; 4673.03)	1.00 (0.00; 6064.88)	1.00 (0.00; 6064.88)	0.87 (0.00; 6890.73)	Zilebesiran 400 mg	1.00 (0.00; 6064.88)	.	0.10 (0.00; 61.78)
0.29 (0.00; 1767.24)	1.00 (0.00; 6064.88)	1.00 (0.00; 6064.88)	0.55 (0.00; 4673.03)	1.00 (0.00; 6064.88)	1.00 (0.00; 6064.88)	0.87 (0.00; 6890.73)	1.00 (0.00; 6064.88)	Zilebesiran 50 mg	.	0.10 (0.00; 61.78)
1.01 (0.06; 15.91)	3.55 (0.00;33518.65)	3.55 (0.00;33518.65)	1.95 (0.18; 21.05)	3.55 (0.00;33518.65)	3.55 (0.00;33518.65)	3.08 (0.38; 25.13)	3.55 (0.00;33518.65)	3.55 (0.00;33518.65)	Zilebesiran 600 mg (Q6m)	.
0.03 (0.00; 18.13)	0.10 (0.00; 61.78)	0.10 (0.00; 61.78)	0.05 (0.00; 53.31)	0.10 (0.00; 61.78)	0.10 (0.00; 61.78)	0.09 (0.00; 76.88)	0.10 (0.00; 61.78)	0.10 (0.00; 61.78)	0.03 (0.00; 31.41)	Zilebesiran 800 mg

Online Resource 13: (A) network plot for hepatic adverse effects (B) network forest plot for risk ratio of hepatic adverse effects (C) league table for hepatic adverse effects.

(A)



(B)



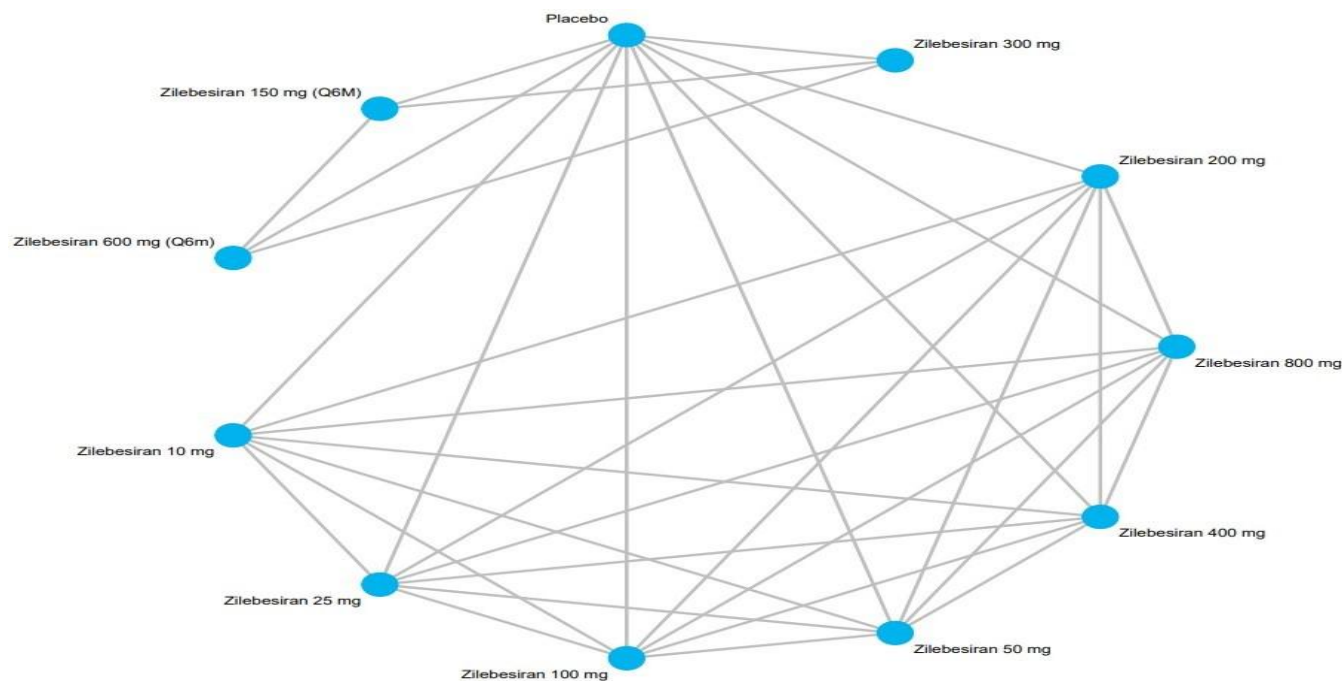
(C)

IONIS 80 mg MONOTHERAPY	1.41 (0.17; 11.54)	.	.	.	.	.	.	.
1.41 (0.17; 11.54)	Placebo	1.86 (0.52; 6.58)	1.86 (0.52; 6.58)	1.86 (0.52; 6.58)	3.71 (0.57; 24.25)	37.14 (0.08;17795.49)	1.86 (0.52; 6.58)	3.71 (0.57; 24.25)
2.62 (0.23; 30.46)	1.86 (0.52; 6.58)	Zilebesiran 10 mg	1.00 (0.18; 5.46)	1.00 (0.18; 5.46)	2.00 (0.22; 17.89)	20.00 (0.04;10621.96)	1.00 (0.18; 5.46)	2.00 (0.22; 17.89)
2.62 (0.23; 30.46)	1.86 (0.52; 6.58)	1.00 (0.18; 5.46)	Zilebesiran 100 mg	1.00 (0.18; 5.46)	2.00 (0.22; 17.89)	20.00 (0.04;10621.96)	1.00 (0.18; 5.46)	2.00 (0.22; 17.89)
2.62 (0.23; 30.46)	1.86 (0.52; 6.58)	1.00 (0.18; 5.46)	1.00 (0.18; 5.46)	Zilebesiran 200 mg	2.00 (0.22; 17.89)	20.00 (0.04;10621.96)	1.00 (0.18; 5.46)	2.00 (0.22; 17.89)
5.24 (0.31; 87.71)	3.71 (0.57; 24.25)	2.00 (0.22; 17.89)	2.00 (0.22; 17.89)	2.00 (0.22; 17.89)	Zilebesiran 25 mg	10.00 (0.02; 6178.04)	0.50 (0.06; 4.47)	1.00 (0.07; 13.37)
52.44 (0.08;35577.42)	37.14 (0.08;17795.49)	20.00 (0.04;10621.96)	20.00 (0.04;10621.96)	20.00 (0.04;10621.96)	10.00 (0.02; 6178.04)	Zilebesiran 400 mg	0.05 (0.00; 26.55)	0.10 (0.00; 61.78)
2.62 (0.23; 30.46)	1.86 (0.52; 6.58)	1.00 (0.18; 5.46)	1.00 (0.18; 5.46)	1.00 (0.18; 5.46)	0.50 (0.06; 4.47)	0.05 (0.00; 26.55)	Zilebesiran 50 mg	2.00 (0.22; 17.89)
5.24 (0.31; 87.71)	3.71 (0.57; 24.25)	2.00 (0.22; 17.89)	2.00 (0.22; 17.89)	2.00 (0.22; 17.89)	1.00 (0.07; 13.37)	0.10 (0.00; 61.78)	2.00 (0.22; 17.89)	Zilebesiran 800 mg

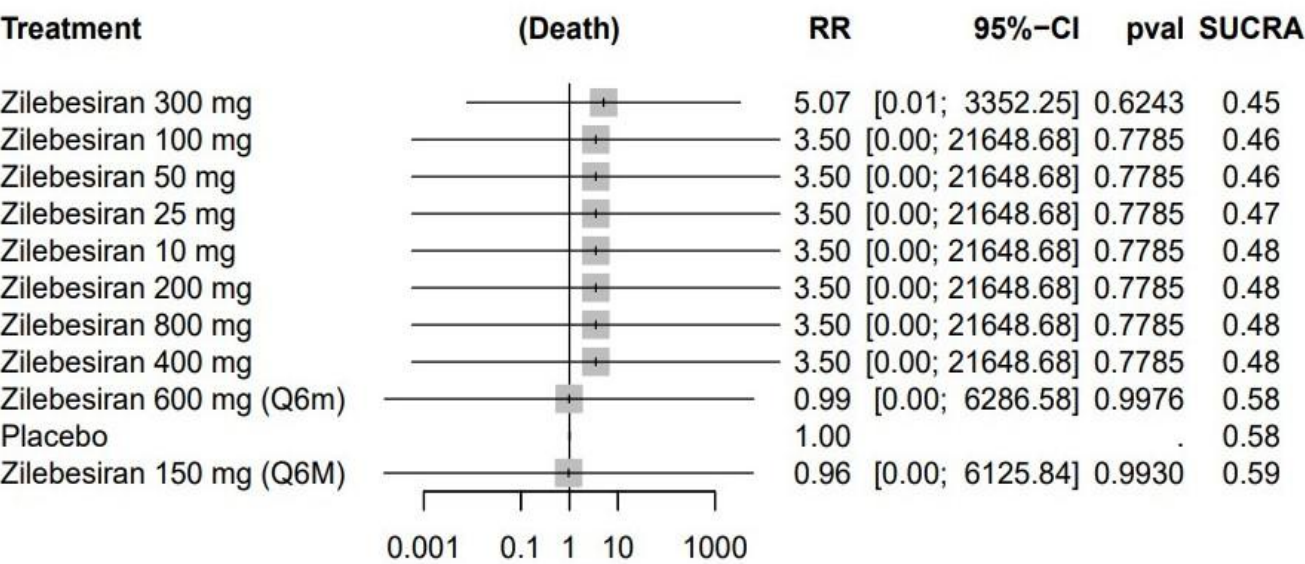
Online Resource 14: (A) network plot for headache (B) network forest plot for risk ratio of headache (C) league table



(A)



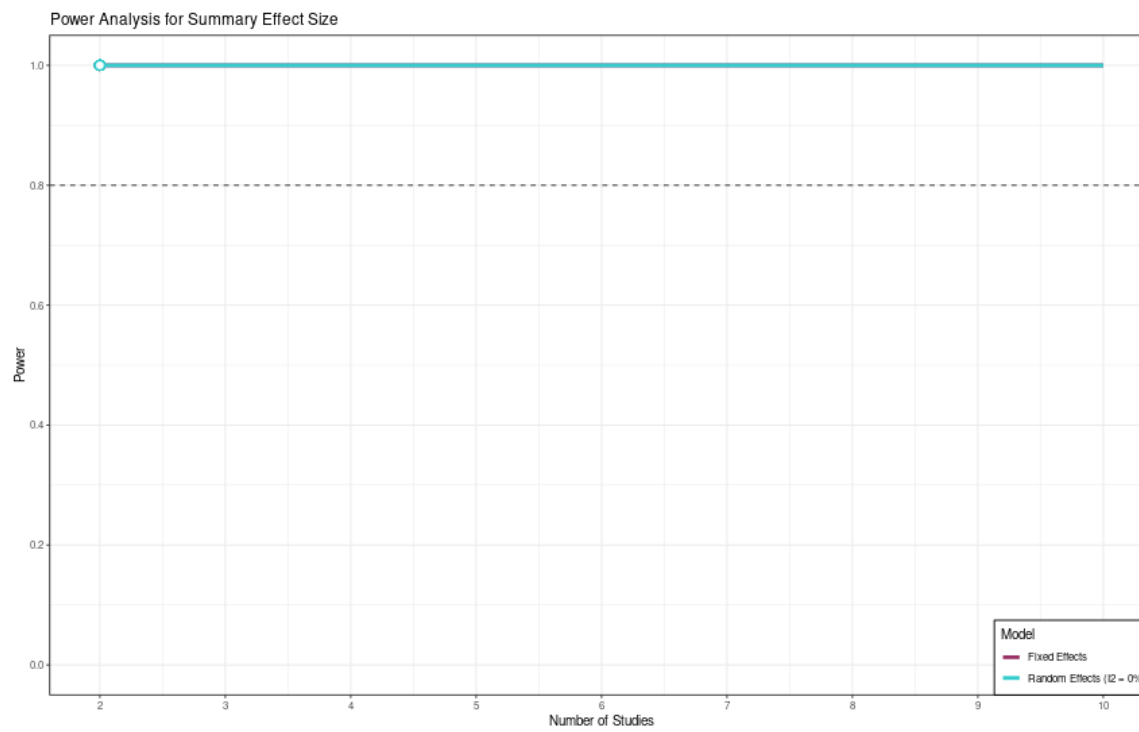
(B)



(C)

Placebo	0.29 (0.00; 1767.24)	0.29 (0.00; 1767.24)	1.04 (0.00; 6625.71)	0.29 (0.00; 1767.24)	0.29 (0.00; 1767.24)	0.20 (0.00; 130.54)	0.29 (0.00; 1767.24)	0.29 (0.00; 1767.24)	1.01 (0.00; 6455.34)	0.29 (0.00; 1767.24)
0.29 (0.00; 1767.24)	Zilebesiran 10 mg	1.00 (0.00; 6064.88)	.	1.00 (0.00; 6064.88)	1.00 (0.00; 6064.88)	.	1.00 (0.00; 6064.88)	1.00 (0.00; 6064.88)	.	1.00 (0.00; 6064.88)
0.29 (0.00; 1767.24)	1.00 (0.00; 6064.88)	Zilebesiran 100 mg	.	1.00 (0.00; 6064.88)	1.00 (0.00; 6064.88)	.	1.00 (0.00; 6064.88)	1.00 (0.00; 6064.88)	.	1.00 (0.00; 6064.88)
1.04 (0.00; 6625.71)	3.64 (0.00; 855033.09)	3.64 (0.00; 855033.09)	Zilebesiran 150 mg (Q6M)	.	.	0.19 (0.00; 125.54)	.	.	0.97 (0.00; 6207.76)	.
0.29 (0.00; 1767.24)	1.00 (0.00; 6064.88)	1.00 (0.00; 6064.88)	0.27 (0.00; 64532.75)	Zilebesiran 200 mg	1.00 (0.00; 6064.88)	.	1.00 (0.00; 6064.88)	1.00 (0.00; 6064.88)	.	1.00 (0.00; 6064.88)
0.29 (0.00; 1767.24)	1.00 (0.00; 6064.88)	1.00 (0.00; 6064.88)	0.27 (0.00; 64532.75)	1.00 (0.00; 6064.88)	Zilebesiran 25 mg	.	1.00 (0.00; 6064.88)	1.00 (0.00; 6064.88)	.	1.00 (0.00; 6064.88)
0.20 (0.00; 130.54)	0.69 (0.00; 36704.32)	0.69 (0.00; 36704.32)	0.19 (0.00; 125.54)	0.69 (0.00; 36704.32)	0.69 (0.00; 36704.32)	Zilebesiran 300 mg	.	.	5.14 (0.01; 3397.12)	.
0.29 (0.00; 1767.24)	1.00 (0.00; 6064.88)	1.00 (0.00; 6064.88)	0.27 (0.00; 64532.75)	1.00 (0.00; 6064.88)	1.00 (0.00; 6064.88)	1.45 (0.00; 76944.96)	Zilebesiran 400 mg	1.00 (0.00; 6064.88)	.	1.00 (0.00; 6064.88)
0.29 (0.00; 1767.24)	1.00 (0.00; 6064.88)	1.00 (0.00; 6064.88)	0.27 (0.00; 64532.75)	1.00 (0.00; 6064.88)	1.00 (0.00; 6064.88)	1.45 (0.00; 76944.96)	1.00 (0.00; 6064.88)	Zilebesiran 50 mg	.	1.00 (0.00; 6064.88)
1.01 (0.00; 6455.34)	3.55 (0.00; 833065.51)	3.55 (0.00; 833065.51)	0.97 (0.00; 6207.76)	3.55 (0.00; 833065.51)	3.55 (0.00; 833065.51)	5.14 (0.01; 3397.12)	3.55 (0.00; 833065.51)	3.55 (0.00; 833065.51)	Zilebesiran 600 mg (Q6m)	.
0.29 (0.00; 1767.24)	1.00 (0.00; 6064.88)	1.00 (0.00; 6064.88)	0.27 (0.00; 64532.75)	1.00 (0.00; 6064.88)	1.00 (0.00; 6064.88)	1.45 (0.00; 76944.96)	1.00 (0.00; 6064.88)	1.00 (0.00; 6064.88)	0.28 (0.00; 66227.51)	Zilebesiran 800 mg

Online Resource 15: (A) network plot for death (B) network forest plot for risk ratio of death (C) league table for death.



**Online Resource 16: Formal power calculations for primary outcomes ( ambulatory SBP, ambulatory DBP, office SBP, and office DBP).**