BUKTI KORESPONDENSI

Judul Artikel : Non-coding RNA therapeutics in cardiovascular diseases and risk factors: Systematic review

Jurnal : Non Coding RNA Research

Author : Meity Ardiana a,b*, Asiyah Nurul Fadila a,b, Zakirah Zuhra a,b, Nabilla Merdika Kusuma, Made Edgard Surya Erlangga Rurus d, Delvac Oceandy e

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No.	Perihal	Tanggal	Komentar Editor Jurnal	Komentar Penulis
1	Pengiriman Artikel	4 April 2023	Editor mengirim pesan otomatis. PDF untuk naskah referensi telah dibuat dan memerlukan persetujuan. Harap tinjau PDF dengan cermat, sebelum menyetujuinya, untuk mengonfirmasi bahwa PDF telah benar melalui login website jurnal. **Email :** 4 April 2023 pukul 13.55 Editor telah menerima naskah referensi dan untuk melacak status naskah Anda, silakan masuk sebagai penulis di https://www.editorialmanager. com/ncrna/ **Email :** 4 April 2023 pukul 13.58; 4 April 2023 pukul 14.16	-

2	Pengiriman Revisi	18 Mei 2023 8 Juni 2023	Saya telah menerima komentar dari pengulas pada naskah. Makalah harus dapat diterima untuk diterbitkan sambil menunggu revisi moderat dan modifikasi artikel sesuai dengan komentar pengulas terlampir. Komentar dari Reviewer: **Peninjau #1:** Dalam naskah ini, penulis secara sistematis menganalisis dampak aktual dan potensi masa depan dari terapi yang melibatkan beragam kelas RNA non-coding dalam pengobatan penyakit kardiovaskular. Metode yang dijelaskan untuk penggalian literatur dan pemilihan kriteria seleksi cukup ketat, dan kualitas naskah secara keseluruhan baik. Tinjauan ini mencakup topik mutakhir dan menawarkan sinopsis berguna mengenai status uji klinis terkini yang melibatkan terapi RNA untuk pencegahan dan pengobatan penyakit kardiovaskular. Meskipun demikian, beberapa penyesuaian kecil diperlukan untuk meningkatkan keterbacaan dan kualitas naskah:	Penulis telah memperbaiki naskah dan mengirimkan melalui dashboard jurnal. (lampiran dengan highlight)

			- Pada halaman 8, penyakit kardiovaskular yang paling banyak diteliti sebagai target ASO adalah hiperkolesterolemia, amiloidosis transthyretin, penyakit jantung aterosklerotik, dan fibrilasi atrium. Saya sarankan menjaga urutan yang sama untuk paragraf berikut, karena akan lebih logis dan mudah diikuti. - Pada kalimat pertama pendahuluan, saya menyarankan untuk mengutip referensi yang lebih tepat mengenai dampak CVD sebagai penyebab utama kematian. Apalagi ref. 1 dan 2 terus-menerus diingat dalam seluruh pendahuluan, dan dalam beberapa kasus, sumber lain yang lebih tepat untuk dikutip dapat ditemukan. - Halaman 7: menyatakan bahwa tindakan ASO dengan menghambat penerjemahan tidak sepenuhnya benar; ASO juga telah banyak digunakan untuk melewatkan ekson dan untuk menutupi rangkaian regulasi lain dari berbagai kelas molekul RNA. Selain itu, penulis menyatakan bahwa ASO juga dapat menargetkan RNA non-coding, dan ini berbeda dengan mekanisme penghambatan translasi.	

			Karena ASO dapat bertindak dengan berbagai macam mekanisme tindakan, saya sangat menyarankan untuk merevisi bagian naskah ini termasuk penjelasan yang lebih tepat dan rinci. - Halaman 9: disebutkan bahwa Mipomersen menghambat sintesis dan sekresi apoB; penulis harus menjelaskan mekanisme kerjanya dengan lebih baik. - Halaman 9: di akhir halaman, beberapa referensi dilaporkan dengan nama yang diperluas, bukan dikutip dengan nomor. - Halaman 10: paragraf mengenai dampak CPR pada fibrilasi atrium memerlukan referensi lebih lanjut. - Halaman 11, baris 3: tidak jelas apakah dosis yang dilaporkan mengacu pada ASO atau enoxaparin. - Halaman 11, paragraf ATTR: diperlukan lebih banyak referensi di bagian pendahuluan. - Halaman 12-13: di bagian "Aptamer", ref. 5 terus dikutip dalam banyak kalimat. Akan lebih baik jika mengutip makalah tertentu yang datanya dilaporkan, daripada	

			mengingat ulasan yang sama berulang kali. - Halaman 14: bagian ini kurang organik dan berulang-ulang, dengan penarikan terus menerus ke referensi. 28. Saya sarankan untuk merevisinya karena dapat membingungkan pembaca. - Halaman 15: referensi. 33 di luar konteks, saya sarankan untuk menghapusnya. **Peninjau #2:** Ardiana dan rekannya secara sistematis meninjau RNA non-coding (ncRNA), oligonukleotida antisense (ASO), dan aptamers dalam CVD. Ini adalah tinjauan yang terencana dan dilaksanakan dengan baik. Berikut lihat saran saya, * Memberikan representasi grafis dari mode tindakan untuk ncRNA, ASO, dan aptamers. * Berikan ringkasan grafis tentang bagaimana ncRNA, ASO, dan aptamers cocok dengan model penyakit molekuler CVD dan penyakit molekuler yang diterima saat ini faktor risiko.	

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Supplementary material 1 : Research keywords

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AND

(non coding rna[MeSH Terms]) AND (cardiovascular diseases[MeSH Terms]) AND (clinicaltrial[Filter]) AND (Therapy) Filters: Clinical Trial, Randomized Controlled Trial
("rna, untranslated"[MeSH Terms] AND "cardiovascular diseases"[MeSH Terms] AND "clinical trial"[Publication Type] AND ("therapeutics"[MeSH Terms] OR "therapeutics"[All Fields] OR "therapies"[All Fields] OR "therapy"[MeSH Subheading] OR "therapy"[All Fields] OR "therapy s"[All Fields] OR "therapys"[All Fields])) AND (clinicaltrial[Filter] OR randomizedcontrolledtrial[Filter])

AND

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#1 MeSH descriptor: [Cardiovascular Diseases] explode all trees 119552
#2 (cardiovascular disease*):ti,ab,kw OR (heart NEXT (disorder OR disease)):ti,ab,kw OR (cardiovascular risk factor*):ti,ab,kw OR ((cardiac OR vascular) NEXT (disorder* OR disease*)):ti,ab,kw (Word variations have been searched) 81891
#3 #1 OR #2 173705
#4 MeSH descriptor: [RNA] explode all trees 4178
#5 (non-coding RNA):ti,ab,kw OR (microRNA):ti,ab,kw OR (siRNA):ti,ab,kw OR (aptamer):ti,ab,kw OR (antisense oligonucleotide*):ti,ab,kw (Word variations have been searched) 1902
#6 #4 OR #5 5772
#7 #3 AND #6 539
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#9 (therapy*):ti,ab,kw OR (management):ti,ab,kw (Word variations have been searched) 861658
#10 #8 OR #9 951586
#11 #7 and #10 391

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Supplementary material 2: Included Studies

Study registration number (ref)	Study Population	Age Group	Intervention Arm	n	Comparator arm	n	Time to follow Up	Primary Endpoint	Outcome: Mean Difference (Treatment vs Placebo)	Outcome: Change from Baseline (95% CI)		Adverse Events
										Placebo	Study Drug	
Aptamers												
Povsic et al. 2013	Non-ST-elevation ACS patients with planned early cardiac catheterization via femoral access <24h. Past medical history of CHF, MI, Previous PCI, Previous CABG, HTN, T2DM, Renal Insuficiency, Stroke, Current tobacco use.	25 to 75	Pegnivacogin 1mg/kg and Anivamersen reversal 0.075, 0.20, 0.40, 1.00 mg/kg	REG1 25 to 100% (n= 40,113 ,119,1 94)	Heparin	(n=161)	30 days	Primary endpoint: total ACUITY bleeding. Secondary endpoints: major bleeding and ischaemic event.	Total bleeding (%) 33.7, 2.7, 3.7, -1.3; Major bleeding (%) 10, 1, -2, -3; Ischaemic event (%) -2.7 (0.2,1.4)	Total bleeding 31.3%. Major bleeding 10%. Ischaemic event 5.7%. Incidence of the composite ischaemic endpoint (n=9) (death (n=1), non-fatal myocardial infarction (n=7), urgent target vessel revascularization (n=1), or recurrent ischaemia in the target vessel distribution) through a 30-day follow-up of patient with Heparin.	Total bleeding 65, 34, 35, 30 (p=0.1 when discharge and 0.9 in 30-day follow up); major bleeding 20, 11, 8, 7 ; ischaemic event 3.0 (ischaemic event 95% CI = 0.2-1.4) in REG1. Incidence of the composite ischaemic endpoint REG1 (n=3, 1, 5, 5) (death (n= 0, 0, 1, 0) , non-fatal myocardial infarction (n= 3, 1, 4, 4), urgent target vessel revascularization, or recurrent ischaemia in the target vessel distribution (n= 1, 0, 1, 1)) through a 30-day follow-up	REG1 n=60. Heparin n=55. 3 incidence of allergic-like adverse events within 24 h of drug administration, 2 of 3 are SAE. REG 1 (hives 0.2%, hypotension 2.4%, rash 0%, dyspnoea 0.9%). Heparin (hives 0%, hypotension 1.9%, rash 0.7%, dyspnoea 0%)

Arzamendi et al. 2011	CAD patient on double antiplatelet therapy and normal volunteers (CAD patient n=27 (Male (n=22), Hypertension (n=9), Hypercholesterolemia (n=16), T2DM (n=4), Smoker (n=10), ACS (STEMI n=17; NSTEMI n=1; UA=9)), Healthy volunteers n=5)	18 to 75	ex vivo treated pretherapy (incubated 5 minutes before the onset of perfusion) or 10 min post therapy on damage arteries with: ARC1779 (25, 83, and 250 nmol/L), or Abciximab (100 nmol/L), or placebo	n=27	placebo	n	15 min	Platelet function		Pretherapy with placebo in healthy patients (n=5) effect on platelet adhesion: 81.9 ± 23.6 × 10^6 platelets/cm2		
Staudacher et al. 2019	Healthy volunteers and patient with ACS	≥ 18 (whole blood sample)	Pegnivacogin or Pegnivacogin 1 mg/kg +Anivamersen (RNA Aptamer reversal agent)	n	Placebo	n	20 min	CD62P-expression, PAC-1 binding	Pegnivacogin vs placebo CD62P expression 20 mikroM ADP (n=9): -13.38 p=0.027 1 mikroM ADP (n=24): -6.59 p=0.031 PACbinding 20 mikroM ADP (n=11): -16.98 p=0.0098 1 mikroM ADP (n= 25): -9.59 p=0.0008 20 mikroM ADP (n=10): -2.42 p=0.922 1 mikroM ADP (n=3): -2.38 p=0.449 Blood from healthy subject after ex-vivo incubation with 150 µl pegnivacogin: platelet aggregation -3.66% p=0.002, n=10 Patient CAD treated dual antiplatelet after 20min iv 1 mg/kg pegnivacogin: platelet aggregation -56.79% p=0.020, n=3		
Chan et al. 2008	subjects with stable CAD	50 -75	aptamer (RB006) sd 1 min iv ASO (RB007) sd 3h iv	Group 1 = 28; Group 2 (+ placebo antidote) = 14	placebo	8	day 7	safety, tolerability, pharmacodynamic	RB006 increased the activated partial thromboplastin time dose dependently; the median activated partial thromboplastin time at 10 minutes after a single intravenous bolus of 15, 30, 50, and 75 mg RB006 was 29.2, 34.6, 46.9, and 52.2 seconds, P<0.0001. RB007 reversed the activated partial thromboplastin time to baseline levels within a median of 1 minute with no rebound increase through 7 days.		

Cohen et al. 2010	undergo non-urgent PCI have a prior indication for PCI pre-treatment with aspirin and clopidrogel	18-80 adult	RB006 1 mg/kg / IV, SD RB007 0.2:1 (50% efficacy)/ 2:1 (100%), SD	20	UFH IV treated	4	48 hours 14 days	major bleeding 48 hrs/ hospital discharge all-cause death, MI- events, urgent revasc 14 days	1.0 Median (0.9, 1,1) p< 0.001			A total of 4 AEs, 2 patients from treatment group 2 patients from control/comparison group
Antisense Oligonucleotides (ASOs)												
Furtado et al. 2012	hypercholesterolemic LDL−C ≥130mg/dL and TG≤400mg/dL BMI 25-32kg/m2	18 to 65 yo	Mipomersen once a week. Doses A: 100 mg B: 200 mg C: 300 mg For a total of 13 weeks	A:8 B:8 C:6(apo CIII)	Placebo	2 2 2	Day 99	Total cholesterol; Concentration of ApoCIII; concentration of apoB	Total Cholesterol 100 mg = -33.3 (-60.6, -5.9) p=0.004 200 mg = -78.4 (-105.7, -51.1) p<0.001 300 mg = -108.5 (-136.9, -81.0) p<0.001 ApoB 100 mg = -30.3 (-46.2, -14.3) p=0.001 200 mg = -57.3 (-72.3, -42.3) p<0.001 300 mg = -84.5 (-100.3, -68.7) p<0.001 ApoCIII 100 mg = 0.97 (-3.1, 5.1) p=0.6 200 mg = -5.81 (-10.1, -1.5) p=0.01 300 mg = -6.03 (-8.9, -3.2) p<0.001			Not reported
Viney et al. 2016	64 participants to the phase 2 trial (35 in IONIS-APO(a)Rx and 29 in placebo in June 25, 2014, to Nov 18, 2015). 58 healthy volunteers to the phase 1/2a trial of IONIS-APO(a)-LRx (28 in sd group and 30 in md group in April 15, 2015, to Jan 11, 2016)	Adult	A: IONIS-APO(a)Rx 100 mg SC, once a week for 4 weeks, 200 mg SC, once a week for 4 weeks, then 300 mg SC, once a week for 4 weeks B: IONIS-APO(a)-LRx 6 doses of 10 mg, 20 mg, or 40 mg at days 1, 3, 5, 8, 15, and 22, for a total dose exposure in the active arms of 60 mg, 120 mg, or 240 mg per cohort.	A: 51 B: 13	Placebo	A: 26 B: 3	A: day 85 or 99 B: day 30	A: reduction of Lp(a) plasma concentration B: reduction of Lp(a) plasma concentration	A: 66.8% (61.6, 72) B: 24·8% (3·1, 67·1) for 10 mg, 35·1% (2·2, 8·8) for 20 mg, 48·2% (10·9, 78·4) for 40 mg, 82·5% (50·5, 109·2) for 80 mg, 84·5% (65·2, 112·6) for 120 mg			There were two serious adverse events (myocardial infarctions) in the IONIS-APO(a)Rx phase 2 trial, one in the IONIS-APO(a)Rx and one in the placebo group, but neither were thought to be treatment related. 12% of injections with IONIS-APO(a)Rx were associated with injection-site reactions. IONIS-APO(a)-LRx was associated with no injection-site reactions.

Tsimikas et al. 2015	healthy adults, BMI less than 32•0 kg/m(2), Lp(a) 25 nmol/L (100 mg/L) or more	18-65 years	ISIS-APO(a)Rx, Single dose, SC injection A: 50 mg B: 100 mg C: 200 mg D; 400 mg ISIS-APO(a)Rx, Multi dose, SC injection A: 100 mg for a total dose exposure of 600 mg B: 200 mg for a total dose exposure of 1200 mg C: 300 mg for a total dose exposure of 1800 mg	I A:3 B:3 C:3 D:3 II A:8 B:8 C:8	Placebo	Single dose: 4 Multi dose: 6	day 30 day 36	Lp(A) reduction	Single doses of ISIS-APO(a)Rx (50–400 mg) did not decrease Lp(a) concentrations at day 30.	5% (-8,15)	Multidose ISIS-APO(a)Rx 100 mg 39.6% , p=0.005 200 mg 59.0%, p=0.001 300 mg 77.8%, p=0.001	Mild injection site reactions were the most common adverse events. 2 volunteers excluded due to AE (one each in ISIS-APO(a)Rx 200 mg md (ec injection site adverse event) and 300 mg md (ec flu-like syndrome that resolved without sequelae). No SAE. Mild injection site reactions were the most common adverse events. ≥10% of participant in ISIS-APO(a)Rx group got headache and fatigue, no significantly different compared to Placebo.
Waldman et al. 2017	Established atherosclerosis, LDL >= 3.4 mmol/L (130 mg/dL) despite on stable maximal possible lipid lowering therapy for more than >= 3 months, BMI <= 40 kg/m2, women had to be postmenopausal or on highly	> 18 yo, mean 42-72 yo	Mipomersen 200 mg, SC injection, weekly for 26 weeks (at least 12 weaks)	11	none	4	26 weeks, or between 12-26 weeks for discontinued patients (n=4)	pre apheresis LDL cholesterol	-0.02 (-1.1, 1.1) p=0.002	-1.6 (-10.7, 7.51)	-22.6 (-32.6, -12.6)	Of the 11 patients randomized to mipomersen, 3 discontinued the drug early due to side effects (2 for injection site reactions and 1 for flu-like symptoms) and were replaced. Further 4 patients discontinued mipomersen during treatment weeks 12e26, again for side effects (1 due to elevations of liver enzymes, the other 3 due to moderate to rather severe injection site reactions (ISR) and flu-like symptoms (FLS)) and were not replaced.

	effective contraceptive regimen, and fulfilled German criteria for lipoprotein apheresis											
Büller et al. 2015	undergoing elective primary unilateral total knee arthroplasty	18 to 80 yo	FXI-ASO, SC injection 200 mg 300 mg 9 times at day 1,3,5,8,15,22,29,36,39	134 71	enoxaparin 40mg	69	3 months	Incidence of adjudicated total thromboembolism which was a composite of asymptomatic DVT, objectively confirmed symptomatic venous thromboemolism, fatal PE, unexplained death which PE could not be ruled out.	Efficacy (Total Venous Thromboembolism) 200 mg = -15 (-37, 7) p=0.59 300 mg = -18 (-16, -29) p<0.001			Total 12 AE (bleeding), 6 of which related to treatment.
Dasgupta et al. 2020	Biopsy proven ATTR amyloidosis (hereditary or wild type) with clinical signs and symptoms of CHF (NYHA I - III), a left ventricular wall thickness >= 1.3 cm on TEE, stable renal function (GFR > 35) and stable thyroid function (TSH < 10 or	No age restriction (mean 63.4 - 76.2 yo)	Inotersen 300 mg/1.5 ml subcutaneous/week	33	None	None	Every 6 months, published)	Decrease of LV mass (MRI), Decrease in left ventricular septal thickness (TEE), Increase of exercise tolerance (6MWT), Stable LVEF, Steady decline of BNP.				Total 8 AE, all related to treatment. AEs: Inflammation & Induration on the site of injection

	normal serum T4)											
Tsimikas et al. 2020	elevated screening plasma lipoprotein (a) level (≥60 mg per deciliter [150 nmol per liter]). Confounding factors: CAD, Overweigh, HT, DMT2, Familial Hypercholesterolemia, smoking	Adult >18-80	APO(a)-LRx, SC injection 20 mg every 4 weeks, 40 mg every 4 weeks, 60 mg every 4 weeks, 20 mg every 2 weeks for 6 months	48, 48, 47, 48, 48	Placebo normal saline per week	47	6 months	percent change in Lipo(a) at 6 monts exposure, safety and efficacy	20 mg/4 weeks = 80.7 (1.2, 21) p=0.003 ; 40 mg/4 weeks = 101.7 (7.3, 131.4) p<0.001; 20 mg/2 weeks = 115.1 (9.8, 195) p<0.001; 60 mg/ 4 weeks = 134.3 (24, 627.4) p<0.001; 20 mg/1 weeks = 172.6 (109.3, 11.571)p<0.001			Total 253 AE, 212 of which related to treatment. 2 deaths due to traffic accident and suicide. AEs:. influenza like symptoms, injection site reaction
Santos et al. 2015	HoFH, Severe-HC, HeFH-CAD, HC-CHD	>= 12 y	Mipomersen 200 mg, SC injection, weekly for 26 weeks	Total 261 HoFH 51, Severe-HC 58, HeFH-CAD 124, HC-CHD 157	placebo	129	week 28 - week 28+24	LDL-C	HoFH = 0.3 (0.04, 0.6), p=0.002 ; Severe-HC = 0.6 (0.4, 0.8) p=0.002 ; HeFH-CAD = 0 (-0.2, 0.2) p=0.001 ; HC-CHD = 0.6 (0.4, 0.8) p<0.001			injection site reaction (+). N= ??

Santos et al. 2015	HoFH, Severe-HC, HeFH-CAD, HC-CHD Comorbidites: smoker, metabolic syndrome, overweight-obese		Mipomersen 200 mg, SC injection, weekly for 26 weeks	382 HoFH 51, Severe-HC 57, HeFH-CAD123, HC-CHD 151,	placebo	126	week 28	Lp(a)	-26.4 (-32.1, -20.7) p<0.001 median (interquartile range)			
Thomas et al. 2013	HC, CHD Comorbidities: DMT2	>=18	Mipomersen 200 mg SC injection weekly, for 28 weeks	101	placebo	50	week 28 - week 24	LDL-C	-38 (-49.3824, -26.6176) p<0.001	−4.5 ± 24.22	−36.9 ± 26.85	A total of 139 patietns experiencing AEs, 97 of which related to treatment. AEs: injectio site reaction, flu-like symptoms, ALD increased, hepatic stetosis
Luigetti et al. 2022	hereditary aTTR		inotersen 14.6 ± 5.9 months (range, 6–24 months)	23	none	none	6 to 14.6 months	troponin, NTpro BNP, intervent septum thickness, BMI safety --> number of dropouts	Troponin 0.01 (-0.0052, 0.0252) p=0.19 ; NTpro BNP -45.6 (-703.82, 612.62) p=0.88 IVS 1.5 (-0.46, 3.46) p=0.12			5 dropouts, 2 of which related to treatment. 20 AEs are all related to treatment, which are: 4: severe thrombocytopenia 9: mid trombocytopenia 7: mild thrombocytopenia
Yang et al. 2016	hyperTAG cohort 1: FCS cohort 2: hyperTAG of varying causes cohort 3: stable fibrate therapy	adult	Volanesorsen 100 mg, 200 mg, 300 mg weekly for 13 weeks	11, 13, 11	Placebo	16	176 days	apoCIII-apoB	apoCIII-ApoB 100 mg -31 (-17005, 16943) apoCIII-ApoB 200 mg 21026 (8505, 33547) p <0.001 apoCIII-ApoB 300 mg -626803 (-640678, -612928) p <0.001			not reported
Benson et al. 2017	hereditary and wild-type ATTR with moderate-severe cardiomyopathy biopsy-proven	adult/elderly >55 years	IONIS-TTR])									10 patients experiencing AEs

Reeskamp et al. 2018	high risk and severe HeFH persistent hyperchol maximal LDL-lowering therapy Comorbidities: Smoking Alcohol consumption HoFH CHD other atherosclerotic disease Hypertension DM statin	Adult>18 yo	Mimopersen 200 mg SQ 1x/week 70 mg SQ 3x/week for 60 weeks	133 --> 104 73 --> 102	Placebo	67 --> 57 38 --> 25	84 weeks	percent change LDL	-20.96 (-29.5085, -12.4115) p<0.001 -18.80 (-20.7270, -16.8730) p<0.001			A total of 259 AEs, 178 of which related to treatment
Sugihara et al. 2015	dual chamber PPM and AF burden 1-10 comorbidities: Use of dabigatran/warfarin HT DM Hyperlipidemia Hypothyroidism Prior stroke Use of card meds as indicated above	adult >18 yrs	ISIS-CRPRx 200 mg in 1 mL solution/SC in two injection 3x/wk for 1 week 1x/wk for 3 wks Total intervention: 4 weeks	7	none	none	every visit during drug administration; 4 week; and 8 week	change in AF burden before and after			MD: 1.6% (-1.45% to 4.65%) p=0.37 CRP: -2.9 (-5.95, 0.15) mg/L p=0.031	

Viney et al. 2021	healthy, non-pregnant,/lactating, BMI <32, able to take vitamin A	18-65 adults	AKCEA-TTR-LRx (ION-682884) 120 mg SD/SC 45 mg 4x dose/SC, 1x/month for 4 months 60 mg 4x dose/SC, 1x/month for 4 months 90 mg 4x dose/SC, 1x/month for 4 months	9 10 10 10	placebo	2 2 2 2		safety assesment : AEs --> physical and lab findings PK parameters PD parameters	TTR SD: -80.40 (-94.0 to -66.8) 45 mg : -79.80 (-95 to -64.6), p<0.001 60 mg: -84.60 (-98.9 to -70.3), p<0.001 90 mg: -87.90 (-97.4 to -78.4), p<0.001			A total of 7 AEs, 6 of which related to treatment.
Benson et al. 2018	stage 1 and 2 hereditary TTR amyloidosis comorbidities: Val30Met TTR mutation stage 1 vs stage 2 Previous treatment with tafamidis and diflusinal	adults	inotersen 300 mg, SC injection, 3 injection for the 1st week, followed by weekly injection up to 65 wks (67 doses)	87	placebo	52	1 week after initiation 35 wks after initiation 66 week post treatment	"mNIS+7 score Norfolk QOLD-DN score"	mNIS+7: -19.70 (-21.3 to -18.1) p<0.001 norfolk QOL-DN: -.17(xxxxx) p<0.001			A total of 199 AEs, 119 of which related to treatment. 110 --> any AEs 9 --> serious AEs.
sIRNA												
INCLISIRAN												
Fitzgerald et al. 2014	Healthy adults with LDL-C higher than 3.00mmol/L	18-65	ALN-PCS one dose IV 0.015 mg/kg 0.045 mg/kg 0.090 mg/kg 0.150 mg/kg 0.250 mg/kg 0.400 mg/kg	Total 24 3 3 3 3 6 6	Placebo (NS)	8	Data for adverse event : 28 days Other data : 180 days	Safety, tolerability, and adverse event	Mean percentage change vs placebo: PCSK9 (-45.3 , -86.0, -71.5, -96.2, -98.3, -114.5); LDL-C (-6.6 , -13.4 , -27.2 , -24.0 , -30.1 , -47,2)	PCSK9 change from baseline (-8.7%); LDL-C (-24.0%)	PCSK9 change from baseline (-30.8 , -52.9 , -45.9, -64.2, -58.5, -58.6%); LDL-C (-14.4 , -19.3 , -30.4 , -35.0 , -35.5 , -36.1%)	Treatment-emergent adverse events (TEAE) (rash, headache, hiccups, cold symptoms, paraesthesia, polyuria or dysuria, infusion-site hematoma) ALN-PCS n=19 (79%) Placebo n=7 (88%)

Fitzgerald et al. 2017	Healthy volunteers with LDL cholesterol level >=100 mg/dl, TG level <=400 mg/dl	18 to 65 yo sd phase, 18 to 75 yo md phase	Single dose phase: sc inclisiran (n=4 each) 25 mg 100 mg 300 mg 500 mg 800 mg (two cohorts for the 800-mg dose). Multi-dose phase: (n=4-8 each) 125mg/w for 4 weeks, 250mg/2 weeks for 4 weeks, 300mg/month for 2 months with and without statin, 500mg/month for 2 months with and without statin	SD 4 each MD 4-8 each	Placebo	SD n=6, MD phase n=11 (8 in md phase without statin group and 3 in md phase with statin group)	56 days for sd phase, ≤84 days for md phase. PD end point were evaluated for an additional month (until 180 days after last dose of therapy) after completion of safety and side effect profile assessment	Safety, side effect profile	sd phase: PCSK9 (-46.0 ; -31.4 ; -73.9 ; -69.3 ; -72.5) sd phase: PCSK9 (<0.05 ; n/a ; <0.001 ; <0.001 ; 0.001)	in sd phase: reduce PCSK9 (-0.6%)	sd phase: reduced in PCSK9 (-46.6 ; -32.0 ; -74.5 ; -69.9 ; -73.1)	No SAE, most common adverse events were cough, musculoskeletal pain, nasopharyngitis, headache, back pain, and diarrhea. in sd phase (≥5% participant in inclisiran group): 2 of 18 cough, musculoskeletal pain, nasopharyngitis. In md phase (≥10% participant in inclisiran group) 6 of 33 headache, 5 (15%) diarrhea, 5 (15%) back pain, 4 (12%) nasopharyngitis
Ray et al. 2017	LDL > 70mg/dL for patient with history ASCVD/ >100 mg/dL without history ASCVD max statin therapy	62-74	SD : - Placebo - 200mg - 300mg - 500mg DD : - Placebo - 100mg - 200mg - 300mg	370	Placebo	127	Primary 180 days Other data 210-240 days	Percentage change from baseline in LDL-Cholesterol level		SD 2.1 DD 1.8	Percentage change from baseline LDL - C Levels (Data are Least-squares means) SD -27.9 ; -38.4 ; -41.9 DD -35.5 ; -44.9 ; -52.6	Serious Adverse events Intervention group SD 200mg 6 (10%); 300mg 5 (8%) ; 500mg 6 (9%) ; DD 100mg 11 (18%) ; 6 (10%) ; 7 (11%) Placebo SD placebo 3 (5%) ; DD placebo 6 (10%)

Raal et al. 2020	Diagnosed with heterozygous familial hypercholesterolemia LDL at least 100mg/dL despite max statin therapy	47-64	Inclisiran SC 300mg Day 1, 90, 270, 450	242	Placebo	240	Day 30, 150, 330, 510, 540	I = Percentage change from baseline LDL - C levels on day 510 II = time-averaged percent change in the LDL - C level between day 90 and day 540	I = -47.9% (95% CI, -53.5 to -42.3; P<0.001) II = -44.3% (95% CI, -48.5 to -40.1; P <0.001)	I = 8.2% (4.3 to 12.2) II = 6.2% (3.3 to 9.2)	I = -39.7% (-43.7 to -35.7) II = - 38.1% (-41.1 to -35.1)	Patients with >= 1 serious adverse event - Intervention group 18 (7.5%) , 1 death from cardiovascular cause 1 (0.4%) - Control 33 (13.8%)
Ray et al. 2022	high risk, primary prevention patients or those with ASCVD (secondary prevention)	≥18	Inclisiran 300mg SD SC Day 1, 90, 270, 450	98	Placebo	105	up to day 540	Percentage change in LDL-C from baseline at day 510 and time adjusted percentage change in LDL-C from baseline after day 90 and up to day 540	LDL-C changes from baseline to day 510 (-43.7%). Time adjusted change in LDL-C from baseline after day 90 up to day 540 (-41.0%). Absolute change difference of LDL-C is -.5mmol/dL (-58.4mg/dL) between groups P <0.0001 , <0.0001 , <0.0001	The mean percentage changes in LDL-C levels from baseline to day 510 was +1.8% with placebo. Mean baseline LDL-C= 3.6mmol/L. The mean time adjusted percentage change in LDL-C from baseline after day 90 up to day 540 was +0.6% for placebo. The absolute change in LDL-C from baseline to day 510 was -0.06% (-2.3mg/dL) in placebo group.	The mean percentage changes in LDL-C levels from baseline to day 510 was -41.9% with inclisiran. The mean time adjusted percentage change in LDL-C from baseline after day 90 up to day 540 was -40.4% for inclisiran. The absolute change in LDL-C from baseline to day 510 was -.1,6mmol/L (-60.7mg/dL) in inclisiran group	SAE, AE at injection site Intervention : SAE (n=20), AE at injection site (n=4) Control : SAE (n=13), AE at injection site (n=0)

Wright et al .2021	ITT Population (For efficacy analyses: Pooled analysis of ORION-9,-10 and -11, included patients with heterozygous familial hypercholesterolaemia, atherosclerotic CV disease (ASCVD), or ASCVD risk equivalent on maximally tolerated statin-therapy Population (for Safety analyses) : All patients who received at least 1 dose of Inclisiran / placebo	54 - 73	Inclisiran 284mg SD SC Day 1, 90 and 6-monthly until 18months	1833	Placebo	1827	540	Change in LDL- C Levels & Safety population (risk of cardiovascular events)	Change in LDL-C levels day 90 : - 50.6% [95% CI (−52.3 to −49.0); P<0.0001] day 540 : − 51.4% [95% CI (−53.4 to −49.4); P<0.0001] Inclisiran significantly reduced MACE (OR[95%CI] : 0.74 [0.58−0.94]), but not fatal and non−fatal MI (OR [95% CI] : 0.80 [0.50−1.27]) and fatal and non−fatal stroke (OR [95% CI] : 0.86 [0.41−1.81]).			- MACE Intervention : 131 Control :171 - Fatal and non-fatal MI Intervention : 33 Control :41 - Fatal and non-fatal stroke Intervention : 13 Control :15
Ray et al. 2020	ASCVD, LDL >70, statin and lipid lowering therapy use, GFR >30	adult >18 years	Inclisiran 284 mg/SC	ORION 10 : 781 ORION 11 : 810	Placebo	780 807	day 30 day 150 day 330 day 510 day 540	Percentage change in LDL time adjusted LDL change (throughout the follow-up period)	-52.3 P <0.001 -49.9 P <0.001	ORION 10: 1.0% ORION 11: 4%	ORION 10: -51.3 ORION 11: -45.8%	Total AEs : 1156 Serious AEs : ORION 10: 175 ORION 11: 181

Wright et al. 2020	Participant with normal renal function and mild, moderate and severe RI from phase 1 ORION -7 renal study and the phase 2 ORION-1 study; BMI 18-40kg/m2 and BW >50kg	18 < age <80	(ORION 7) = SD Placebo and 300mg ; DD Placebo and 300mg (ORION 1)1 = Normal Function, 2 = Mild RI, 3= Moderate RI, 4= Severe RI	ORION 1 = 122 ORION 7 = 31	Placebo	ORION 1 = 125 ORION 7 = 0	180 days atau max 360 days	ORION 7 : PK, Safety, PD ORION 1 : PK, Safety				Participants with at least 1 TEAE (treatment-emergent adverse event) Intervention : 126 Control : 101
Raal et al. 2022	HeFH ASCVD ASCVD-risk equivalent	adults	Inclisiran 284 mg/SC	148	Placebo	150	510 days	LDL percentage change at day 510 time-averaged percentage LDL change	-54.2% P <0.0001	0.077 SD 2.9- 12.6	-46.5% SD -51.7 - 41.3	Participants with ≥1 TEAEs : 233 Serious TEAEs : Intervention: 32 Placebo: 37
PATISIRAN												
Coelho et al. 2013	ALLN 01:biopsy-confirmed TTR amyloidosis mild-moderate neuropathy karnofsky performance status >60 BMI 18.5-33 NYHA II or less adequate liver, renal, thyroid function not pregnant/childbearing potential ALLN 2: 18-45, healthy, BMI 18-31.5.	adults >18 yr	ALN-TTR01 (0.01 to 1.0 mg/kg) - IV ALN-TTR02 (0.01 to 0.5 mg/kg) - IV	24 13	Placebo	8 4	70 days	reduction in TTR level	-38% (dosage 1.0 mg/kg) P 0.01 ALLN 02 0.15 = -85.7% P 0.001 0.3 = -87.6% P 0.001 0.5:= -93.8% P 0.001	0.01 0.001 0.001 0.001		ALN-TTR01 Infusion Reaction : 5 Fatigue : 2 Placebo : 0 ALN-TTR02 Skin Erythema : 6 Infusion Reaction : 1 Placebo : 2 (Skin Erythema)

Coelho et al. 2020	hATTR amyloidosis	29 to 77	Patisiran 0.3 mg/kgbb - IV once / 3 weeks	Patisiran alone (n=7)	Patisiran + TTR tetramer stabilizer	n=19	24 months	The primary objective was to evaluate the safety and tolerability of long-term dosing with patisiran.	(-0.28)	(-7.03) SE 2.11	(-6.75) SE 5.24	SAE 7, death 2, any AE leading to discontinuation 2. None of which were considered related to Patisiran flushing (n=7), infusion-related reactions (n=6), diarrhea (n=3)
Minamisawa et al. 2019	Patients with hereditary transthyretin-mediated (hATTR) amyloidosis with polyneuropathy and cardiac amyloidosis	61 (54-67)	Patisiran 0.3 mg/kgbb - IV once / 3 weeks	90 (71.4%) patisiran	Placebo	36 (28.6%) placebo	18 months	improved left ventricular (LV) global longitudinal strain (LV GLS)	Patisiran improved the absolute GLS (least-squares mean [SE] difference, 1.4% [0.6%]; 95% CI, 0.3%-2.5%; P = .02) compared with placebo at 18 months, with the greatest differential increase observed in the basal region (overall least-squares mean [SE] difference, 2.1% [0.8%]; 95% CI, 0.6%-3.6%; P = .006) and no significant differences in the mid and apical regions among groups			

Solomon et al. 2019	Had a diagnosis of hATTR amyloidosis with a documented TTR mutatiom and symptomatic neuropathy, were ambulatory, had adequate liver function and adequate renal function, and were included in the prespecified cardiac subpopulation (baseline LV wall thickness > 13 mm, no history of aortic valve disease or hypertension) Enrolled participants which did not fulfill criteria to be included in prespecified cardiac subpopulation	18 - 85 yo	Patisiran 0.3 mg/kgbb - IV once / 3 weeks	Cardiac subpopulation 90	Placebo	36	Echo parameters at 18 months NTproBNP and 10MWT gait speed at 9 months and 18 months	Reduction of left ventricular wall thickness, interventricular septal wall thickness, posterior wall thickness, and relative wall thickness. Increase of end diastolic volume, decrease of global longitudinal strain, increase of cardiac output. Decrease of NT pro BNP. Increase of 10MWT gait speed. No significant outcome in echo parameters. Decrease of NTproBNP. Increase of 10MWT gait speed.	Reduction in mean LV wall thickness (least-squares mean difference±SEM, –0.9±0.4 mm; P=0.017) was observed with patisiran compared with placebo. In patisiran treated patients compared with placebo, global longitudinal strain was decreased (–1.4%±0.6%, P=0.015), cardiac output was increased (0.38±0.19 L/min, P=0.044), and LVEDV was increased (8.31±3.91 mL, P=0.036) Patisiran reduced NT-proBNP compared with placebo at 9 months (ratio of fold change patisiran/placebo, 0.63; 95% CI, 0.50–0.80) and 18 months (ratio of fold change patisiran/placebo, 0.45; 95% CI, 0.34–0.59; P=7.7×10–8), corresponding to a 55% reduction relative to placebo			Cardiac serious adverse events Intervention : 20 Control : 10
Adams et al. 2018	hereditary transthyretin amyloidosis with polyneuropathy, some patients has cardiac abn (NYHA I dan II)	18 - 85 years	Patisiran 0.3 mg/kgbb - IV once / 3 weeks	148	Placebo	77	18 months	mNIS+7, LVthickness, LVLStrain	-34; -0.9 ; -1.37 <0.001; 0.02; 0.02	28; -0.1; 1.46	mNIS+7 -6 LVWT (mm) -1 LVLS (%) 0.08	diarrhea, edema, nausea, cough, asthenia, death, etc Intervention : 143 Control : 75

Obici et al. 2020	hereditary transthyretin amyloidosis with polyneuropathy, some patients has cardiac abn (NYHA I dan II)	18 - 85 years	Patisiran 0.3 mg/kgbb - IV once/ 3 weeks	148 (90 with cardiac proble ms)	Placebo	77 (36 with cardiac diseases)	18 months	measures of overall QoL		14.4 ; 0.6	Norfolk-6.7; EQ +2	Not reported
REVUSIRAN												
Judge et al. 2020	TTR mutation and amyloid deposits, hx of hf and cardiac involvement on echo	18 - 90 years	Revusiran 500mg/SC	140	Placebo	66	18 months	6MWT, Troponin I, NTpBNP		-17.6	6MWT -21.4	the study was prematurely discontinued due to an imbalance of deaths observed in the revusiran group (18 patients, 12.9%) compared with the placebo group (2 patients, 3.0%) during the on-treatment period
SLN360												
Nissen et al. 2022	no known CVDs Lp(a) conc >150 nmol/L BMI 18-45 kg/m2	adults 36-63 years	SLN360 SD 30 mg/SC 100 mg/SC 300 mg/SC 600 mg/SC	24 (6 each dose)	Placebo	8	150 days	Safety and tolerability				Participants with any treatment-emergent adverse event intervention group : 100% placebo group : 75%

Supplementary material 3: Risk of Bias Assessment (ROBVIS)

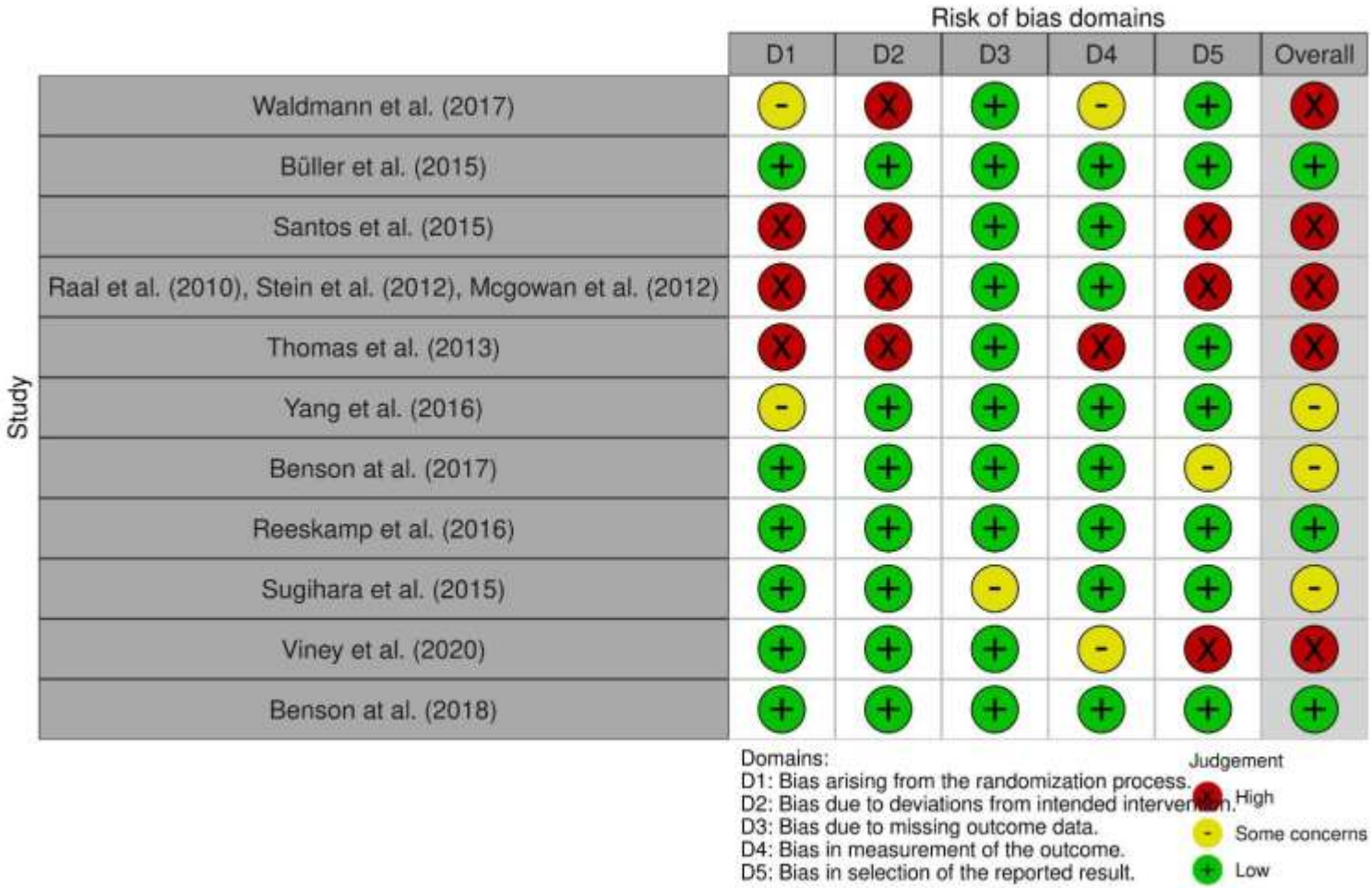

Table 1. ASO

No	Study registration number (ref)	Study Population	Age Group	Intervention Arm	n	Comparator arm	n	Time to follow Up	Primary Endpoint	Outcome: Mean Difference (Treatment vs Placebo)	Adverse Events
1	NCT00216463 (Furtado , 2012)	hypercholesterolemic LDL-C ≥130mg/dL and TG≤4oomg/dL BMI 25-32kg/m2	18 to 65 yo	Mipomersen once a week. Doses 100 mg 200 mg 300 mg For a total of 13 weeks	88 8 -->6 (apo CIII)	Placebo	22 2	Day 99	Total cholesterol; Concentration of ApoCIII; concentration of apoB	Total Cholesterol 100 mg = -33.3 (-60.6, -5.9) p=0.004 200 mg = -78.4 (-105.7, -51.1) p<0.001 300 mg = -108.5 (-136.9, -81.0) p<0.001 ApoB 100 mg = -30.3 (-46.2, -14.3) p=0.001 200 mg = -57.3 (-72.3, -42.3) p<0.001 300 mg = -84.5 (-100.3, -68.7) p<0.001 ApoCIII 100 mg = 0.97 (-3.1, 5.1) p=0.6 200 mg = -5.81 (-10.1, -1.5) p=0.01 300 mg = -6.03 (-8.9, -3.2) p<0.001	Not reported
2	NCT02160899 NCT02414594 (Viney, 2016)	64 participants to the phase 2 trial (35 in IONIS-APO(a)Rx and 29 in placebo in June 25, 2014, to Nov 18, 2015). 58 healthy volunteers to the phase 1/2a trial of IONIS-APO(a)-LRx (28 in sd group	Adult	A: IONIS-APO(a)Rx 100 mg SC, once a week for 4 weeks, 200 mg SC, once a week for 4 weeks, then 300 mg SC, once a week for 4 weeks	A: 51 B: 13	Placebo	A: 26 B: 3	A: day 85 or 99 B: day 30	A: reduction of Lp(a) plasma concentration B: reduction of Lp(a) plasma concentration	A: 66.8% (61.6, 72) B: 24·8% (3·1, 67·1) for 10 mg, 35·1% (2·2, 8·8) for 20 mg, 48·2% (10·9, 78·4) for 40 mg, 82·5% (50·5, 109·2) for 80 mg, 84·5% (65·2, 112·6) for 120 mg	There were two serious adverse events (myocardial infarctions) in the IONIS-APO(a)Rx phase 2 trial, one in the IONIS-APO(a)Rx and one in the placebo group, but neither

		and 30 in md group in April 15, 2015, to Jan 11, 2016)		B: IONIS-APO(a)-LRx 6 doses of 10 mg, 20 mg, or 40 mg at days 1, 3, 5, 8, 15, and 22, for a total dose exposure in the active arms of 60 mg, 120 mg, or 240 mg per cohort							were thought to be treatment related. 12% of injections with IONIS-APO(a)Rx were associated with injection-site reactions. IONIS-APO(a)-LRx was associated with no injection-site reactions.
3	European Clinical Trial Database 2012-004909-27 (Tsimikas et al, 2015)	healthy adults, BMI less than 32•0 kg/m(2), Lp(a) 25 nmol/L (100 mg/L) or more	18-65 years	ISIS-APO(a)Rx, Single dose, SC injection 50 mg 100 mg 200 mg 400 mg ISIS-APO(a)Rx, Multi dose, SC injection 100 mg for a total dose exposure of 600 mg 200 mg for a total dose exposure of 1200 mg 300 mg for a total dose exposure of 1800 mg	3 3 3 3 8 8 8 7	Placebo	Single dose : 4 Multi dose : 6	day 30 day 36	Lp(A) reduction	Single doses of ISIS-APO(a)Rx (50–400 mg) did not decrease Lp(a) concentrations at day 30. Placebo outcome change from baseline: 5% (-8,15) Multidose ISIS-APO(a)Rx 100 mg 39.6% , p=0.005 200 mg 59.0%, p=0.001 300 mg 77.8%, p=0.001	Mild injection site reactions were the most common adverse events. 2 volunteers excluded due to AE (one each in ISIS-APO(a)Rx 200 mg md (ec injection site adverse event) and 300 mg md (ec flu-like syndrome that resolved without sequelae). No SAE. Mild injection site reactions were the most common adverse events. ≥10% of participant in ISIS-APO(a)Rx group got headache and fatigue, no significantly

											different compared to Placebo.
4	Waldman, E (2017)	Established atherosclerosis, LDL >= 3.4 mmol/L (130 mg/dL) despite on stable maximal possible lipid lowering therapy for more than >= 3 months, BMI <= 40 kg/m2, women had to be postmenopausal or on highly effective contraceptive regimen, and fulfilled German criteria for lipoprotein apheresis	> 18 yo, mean 42-72 yo	Mipomersen 200 mg, SC injection, weekly for 26 weeks (at least 12 weaks)	11	none	4	26 weeks, or betwe en 12-26 weeks for discon tinued patient s (n=4)	pre apheresis LDL cholesterol	-0.02 (-1.1, 1.1) p=0.002	Of the 11 patients randomized to mipomersen, 3 discontinued the drug early due to side effects (2 for injection site reactions and 1 for flu-like symptoms) and were replaced. Further 4 patients discontinued mipomersen during treatment weeks 12e26, again for side effects (1 due to elevations of liver enzymes, the other 3 due to moderate to rather severe injection site reactions (ISR) and flu-like symptoms (FLS)) and were not replaced.
5	NCT01713361 (Büller et al, 2015)	undergoing elective primary unilateral total knee arthroplasty	18 to 80 yo	FXI-ASO, SC injection 200 mg 300 mg 9 times at day 1,3,5,8,15,22,29, 36,39	134 71	enoxapari n 40mg	69	3 month s	Incidence of adjudicated total thromboembolis m which was a composite of asymptomatic DVT, objectively	Efficacy (Total Venous Thromboembolism) 200 mg = -15 (-37, 7) p=0.59 300 mg = -18 (-16, -29) p<0.001	Total 12 AE (bleeding), 6 of which related to treatment.

									confirmed symptomatic venous thromboemolism, fatal PE, unexplained death which PE could not be ruled out.		
6	Dasgupta et al. (2019)	Biopsy proven ATTR amyloidosis (hereditary or wild type) with clinical signs and symptoms of CHF (NYHA I - III), a left ventricular wall thickness >= 1.3 cm on TEE, stable renal function (GFR > 35) and stable thyroid function (TSH < 10 or normal serum T4)	No age restriction (mean 63.4 - 76.2 yo)	Inotersen 300 mg/1.5 ml subcutaneous/week	33	None	None	Every 6 months, MRI every year if there is no contraindication Still ongoing (3 years by the time this journal was published)	Decrease of LV mass (MRI), Decrease in left ventricular septal thickness (TEE), Increase of exercise tolerance (6MWT), Stable LVEF, Steady decline of BNP.	Total 8 AE, all related to treatment. AEs: Inflamation & Induration on the site of injection	
7	NCT01713361 (Tsimikas et al, 2020)	elevated screening plasma lipoprotein(a) level (≥60 mg per deciliter [150 nmol per liter]). Confounding	Adult >18-80	APO(a)-LRx, SC injection 20 mg every 4 weeks, 40 mg every 4 weeks,	48, 48, 47, 48, 48	Placebo normal saline per week	47	6 months	percent change in Lipo(a) at 6 monts exposure, safety and efficacy	20 mg/4 weeks = 80.7 (1.2, 21) p=0.003 ; 40 mg/4 weeks = 101.7 (7.3, 131.4) p<0.001; 20 mg/2 weeks = 115.1 (9.8,	Total 253 AE, 212 of which related to treatment. 2 deaths due to traffic accident

		factors: CAD, Overweigh, HT, DMT2, Familial Hypercholesterolemia, smoking		60 mg every 4 weeks, 20 mg every 2 weeks for 6 months						195) p<0.001; 60 mg/ 4 weeks = 134.3 (24, 627.4) p<0.001; 20 mg/1 weeks = 172.6 (109.3, 11.571)p<0.001	and suicide. AEs:. influenza like symptoms, injection site reaction
8	Santos, Raul D (2015)	HoFH, Severe-HC, HeFH-CAD, HC-CHD	>= 12 y	Mipomersen 200 mg, SC injection, weekly for 26 weeks	Total 261 HoFH 51, Severe-HC 58, HeFH-CAD 124, HC-CHD 157	placebo	129	week 28 - week 28+24	LDL-C	HoFH = 0.3 (0.04, 0.6), p=0.002 ; Severe-HC = 0.6 (0.4, 0.8) p=0.002 ; HeFH-CAD = 0 (-0.2, 0.2) p=0.001 ; HC-CHD = 0.6 (0.4, 0.8) p<0.001	injection site reaction (+).
9	NCT00607373 NCT00706849 NCT00770146 NCT00794664. (Raal et al 2010, Stein et al 2012, Mcgowan	HoFH, Severe-HC, HeFH-CAD, HC-CHD Comorbidites: smoker, metabolic syndrome, overweight-obese		Mipomersen 200 mg, SC injection, weekly for 26 weeks	382 HoFH 51, Severe-HC 57, HeFH-CAD123,	placebo	126	week 28	Lp(a)	-26.4 (-32.1, -20.7) p<0.001 median (interquartile range)	

	et al 2012)				HC-CHD 151,						
10	NCT00770146 (thomas et al 2013)	HC, CHD Comorbidities: DMT2	>=18	Mipomersen 200 mg SC injection weekly, for 28 weeks	101	placebo	50	week 28 - week 24	LDL-C	-38 (-49.3824, -26.6176) p<0.001	A total of 139 patietns experiencing AEs, 97 of which related to treatment. AEs: injectio site reaction, flu-like symptoms, ALD increased, hepatic stetosis
11	Luigetti, M, et.al. (2022)	hereditary aTTR		inotersen 14.6 ± 5.9 months (range, 6–24 months)	23	none	none	6 to 14.6 months	troponin, NTpro BNP, intervent septum thickness, BMI safety --> number of dropouts	Troponin 0.01 (-0.0052, 0.0252) p=0.19 ; NTpro BNP -45.6 (-703.82, 612.62) p=0.88 IVS 1.5 (-0.46, 3.46) p=0.12	5 dropouts, 2 of which related to treatment. 20 AEs are all related to treatment, which are: 4: severe thrombocytopenia 9: mid trombocytopenia 7: mild thrombocytopenia
12	Yang, X, et.al. (2016)	hyperTAG cohort 1: FCS cohort 2: hyperTAG of varying causes cohort 3: stable fibrate therapy	adult	Volanesorsen 100 mg, 200 mg, 300 mg weekly for 13 weeks	11, 13, 11	Placebo	16	176 days	apoCIII-apoB	apoCIII-ApoB 100 mg -31 (-17005, 16943) apoCIII-ApoB 200 mg 21026 (8505, 33547) p <0.001 apoCIII-ApoB 300 mg -626803 (-640678, -612928) p <0.001	not reported

13	Benson, MD, et. al. (2017)	hereditary and wild-type ATTR with moderate-severe cardiomyopathy biopsy-proven	adult /elderly >55 years	IONIS-TTR])							10 patients experiencing AEs
14	Reeskamp, L, et.. al. (2018)	high risk and severe HeFH persistent hypercholmaximal LDL-lowering therapy Comorbidities: Smoking Alcohol consumption HoFH CHD other atherosclerotic disease Hypertension DM statin	Adult>18 yo	Mimopersen 200 mg SQ 1x/week 70 mg SQ 3x/week for 60 weeks	133 --> 104 73 --> 102	Placebo	67 --> 57 38 --> 25	84 weeks	percent change LDL	-20.96 (-29.5085, -12.4115) p<0.001 -18.80 (-20.7270, -16.8730) p<0.001	A total of 259 AEs, 178 of which related to treatment
15	Sugihara, C, et.al. (2015)	dual chamber PPM and AF burden 1-10 comorbidities: Use of dabigatran/warfarin HT DM Hyperlipidemia Hypothyroidism Prior stroke Use of card meds as indicated above	adult >18 yrs	ISIS-CRPRx 200 mg in 1 mL solution/SC in two injection 3x/wk for 1 week 1x/wk for 3 wks Total intervention: 4 weeks	7	none	none	every visit during drug administration; 4 week; and 8 week	change in AF burden before and after	MD: 1.6% (-1.45% to 4.65%) p=0.37 CRP: -2.9 (-5.95, 0.15) mg/L p=0.031	

16	NCT03728634 (Viney et al 2020)	healthy, non-pregnant,/lactating, BMI <32, able to take vitamin A	18-65 adults	AKCEA-TTR-LRx (ION-682884) 120 mg SD/SC 45 mg 4x dose/SC, 1x/month for 4 months 60 mg 4x dose/SC, 1x/month for 4 months 90 mg 4x dose/SC, 1x/month for 4 months	9 10 10 10	placebo	2 2 2 2		safety assesment : AEs --> physical and lab findings PK parameters PD parameters	TTR SD: -80.40 (-94.0 to -66.8) 45 mg : -79.80 (-95 to -64.6), p<0.001 60 mg: -84.60 (-98.9 to -70.3), p<0.001 90 mg: -87.90 (-97.4 to -78.4), p<0.001	A total of 7 AEs, 6 of which related to treatment.
17	NCT01737398 (Benson et al 2018)	stage 1 and 2 hereditary TTR amyloidosis comorbidites: Val30Met TTR mutation stage 1 vs stage 2 Previous treatment with tafamidis and diflusinal	adults	inotersen 300 mg, SC injection, 3 injection for the 1st week, followed by weekly injection up to 65 wks (67 doses)	87	placebo	52	1 week after initiation 35 wks after initiation 66 week post treatment	"mNIS+7 score Norfolk QOLD-DN score"	mNIS+7: -19.70 (-21.3 to -18.1) p<0.001 norfolk QOL-DN: -.17(xxxxx) p<0.001	A total of 199 AEs, 119 of which related to treatment. 110 --> any AEs 9 --> serious AEs.

Table 2. Aptamer

No	Study registration number (ref)	Study Population	Age Group	Intervention Arm	n	Comparator arm	n	Time to follow Up	Primary Endpoint	Outcome: Mean Difference (Treatment vs Placebo)	Adverse Events
1	10.1093/eurheartj/ehs232 NCT00932100 (Povsic, TJ, et al, 2013)	Non-ST-elevation ACS patients with planned early cardiac catheterization via femoral access <24h. Past medical history of CHF, MI, Previous PCI, Previous CABG, HTN, T2DM, Renal Insuficiency, Stroke, Current tobacco use.	25 to 75	Pegnivacogin 1mg/kg and Anivamersen reversal 0.075, 0.20, 0.40, 1.00 mg/kg	REG1 25 to 100% (n= 40,113,119,194)	Heparin	161	30 days	Primary endpoint: total ACUITY bleeding. Secondary endpoints: major bleeding and ischaemic event.	Total bleeding (%) 33.7, 2.7, 3.7, -1.3; Major bleeding (%) 10, 1, -2, -3; Ischaemic event (%) -2.7 (0.2,1.4)	REG1 n=60. Heparin n=55. 3 incidence of allergic-like adverse events within 24 h of drug administration, 2 of 3 are SAE. REG 1 (hives 0.2%, hypotension 2.4%, rash 0%, dyspnoea 0.9%). Heparin (hives 0%, hypotension 1.9%, rash 0.7%, dyspnoea 0%)
2	10.1177/1076029610384114 (Arzamendi D, et al 2011)	CAD patient on double antiplatelet therapy and normal volunteers (CAD patient n=27 (Male (n=22), Hypertension (n=9), Hypercholestrolemia (n=16), T2DM (n=4), Smoker (n=10),	18 to 75	exvivo treated pretherapy (incubated 5 minutes before the onset of perfusion) or 10 min posttherapy on damaege arteries with: ARC1779 (25, 83, and	n=27	placebo	n	15 min	Platelet function	Platelet adhesion: Pretherapy with ARC1779 or Abciximab in patients taking ASA and CPG (n CAD= 17) effect on platelet adhesion (unit: platelets × 10^6/cm2). ARC1779 83nmol/L: 4.8 ($p<0.05$) ARC1779 250nmol/L: 3.8 ($p<0.05$) Abciximab 100nmol/L: 2.9 ($p<0.05$) Placebo: 7.3 ($p<0.05$) Pretherapy with placebo in healthy patient (n=5) effect on platelet adhesion: 81.9 ± 23.6 × 10^6 platelets/cm2 Posttherapy with ARC1779 in CAD (n=10) $p>0.05$ in platelet adhesion compared to placebo. Platelet aggregation Abciximab abolished platelet aggregation in response	

		ACS (STEMI n=17; NSTEMI n=1; UA=9)), Healthy volunteers n=5)		250 nmol/L), or Abciximab (100 nmol/L), or placebo						to TRAP-1, ADP, and AA both in healthy volunteers and in patients. Collagen-induced aggregation: in healthy volunteers; averaged 18 Ω reduce to 2 Ω with abciximab, but unaffected by ARC1779 (18 Ω) in CAD patient; reduced to 3 Ω by abciximab, and unaffected by ARC1779 (4 Ω). Platelet activation This was done on blood samples from healthy volunteers after the perfusion experiments. Neither abciximab nor ARC1779 has a significant effect on P-selectin or vWF expression. Platelet–leukocyte binding increased after blood perfusion (control) compared with nonperfused blood (baseline), not significantly affected by ARC1779 or abciximab.	
3	10.1177/2048872617703065 (Staudacher DL, et al, 2019)	Healthy volunteers and patient with ACS	≥ 18 (whole blood sample)	Pegnivacogin or Pegnivacogin 1 mg/kg +Anivamersen (RNA Aptamer reversal agent)	n	Placebo	n	20 min	CD62P-expression, PAC-1 binding	Pegnivacogin when compared with placebo CD62P expression 20 mikroM ADP (n=9): -13.38 p=0.027 1 mikroM ADP (n=24): -6.59 p=0.031 PACbinding 20 mikroM ADP (n=11): -16.98 p=0.0098 1 mikroM ADP (n= 25): -9.59 p=0.0008 Pegnivacogin effect on ADP-activated platelets could be completely negated by Anivamersen, compared with Placebo CD62P expression 20 mikroM ADP (n=10): -2.42 p=0.922 1 mikroM ADP (n=3): -2.38 p=0.449 Blood from healthy subject after ex-vivo incubation with 150 µl pegnivacogin: platelet aggregation -3.66% p=0.002, n=10 Patient CAD treated dual antiplatelet after 20min iv 1 mg/kg pegnivacogin: platelet aggregation -56.79% p=0.020, n=3	
4	10.1161/CIRCULATI	Subjects with stable CAD	50 -75	aptamer (RB006) sd 1 min iv	Group 1 = 28;	placebo	8	day 7	safety, tolerability, pharmacodyn	RB006 increased the activated partial thromboplastin time dose	No major bleeding. 10% experienced non–dose-dependent and

	ONAHA.107.745687 (Chan, MY, et al, 2008)			ASO (RB007) sd 3h iv	6,6,8,8 (RB006 15,30,50,75mg with RB007 30,60,100,150mg) Group 2 = RB006+Placebo antidote = 14; 3,3,4,4				amic	dependently; the median activated partial thromboplastin time at 10 minutes after a single intravenous bolus of 15, 30, 50, and 75 mg RB006 was 29.2, 34.6, 46.9, and 52.2 seconds, P<0.0001. RB007 reversed the activated partial thromboplastin time to baseline levels within a median of 1 minute with no rebound increase through 7 days.	mainly mucocutaneous bleeding.
5	NCT00715455	undergo non-urgent PCI have a prior indication for PCI pre-treatment with aspirin and CPG	18-80 adult	RB006 1 mg/kg / IV, SD RB007 0.2:1 (50% efficacy)/ 2:1 (100%), SD	20	UFH IV treated	4	48 hours 14 days	major bleeding 48 hrs/ hospital discharge all-cause death, MI-event, urgent revasc 14 days	1.0 Median (0.9, 1,1) p< 0.001	A total of 4 AEs, 2 patients from treatment group 2 patients from control/comparison group

Table 3. siRNA

No	Study registration number (ref)	Study Population	Age Group	Intervention Arm	n	Comparator arm	n	Time to follow Up	Primary Endpoint	Outcome: Mean Difference (Treatment vs Placebo)	Adverse Events
INCLISIRAN											
1	NCT01437059 (Fitzgerald et al 2014)	Healthy adults with LDL-C higher than 3.00mmol/L	18-65	ALN-PCS one dose IV 0.015 mg/kg 0.045 mg/kg 0.090 mg/kg 0.150 mg/kg 0.250 mg/kg 0.400 mg/kg	Total 24 3 3 3 3 6 6	Placebo (NS)	8	Data for adverse event : 28 days Other data : 180 days	Safety, tolerability, and adverse event	Mean percentage change vs placebo: PCSK9 (-45.3 , -86.0, -71.5, -96.2, -98.3, -114.5); LDL-C (-6.6 , -13.4 , -27.2 , -24.0 , -30.1 , -47,2)	Treatment-emergent adverse events (TEAE) (rash, headache, hiccups, cold symptoms, paraesthesia, polyuria or disuria, infusion-site hematoma) ALN-PCS n=19 (79%) Placebo n=7 (88%)
2	NCT02314442 (Fitzgerald et al 2016)	Healthy volunteers with LDL cholesterol level >=100 mg/dl, TG level <=400 mg/dl	18 to 65 yo sd phase, 18 to 75 yo md phase	Single dose phase: sc inclisiran (n=4 each) 25 mg 100 mg 300 mg 500 mg 800 mg (two cohorts for the 800-mg dose). Multi-dose phase: (n=4-8 each) 125mg/w for 4 weeks, 250mg/2 weeks for 4 weeks, 300mg/month for 2 months with	SD 4 each MD 4-8 each	Placebo	SD n=6, MD phase n=11 (8 in md phase without statin group and 3 in md phase with statin group)	56 days for sd phase, ≤84 days for md phase. PD end point were evaluated for an additional month (until 180 days after last dose of therapy) after	Safety, side effect profile	sd phase: PCSK9 (-46.0 ; -31.4 ; -73.9 ; -69.3 ; -72.5) sd phase: PCSK9 (<0.05 ; n/a ; <0.001 ; <0.001 ; 0.001)	No SAE, most common adverse events were cough, musculoskeletal pain, nasopharyngitis, headache, back pain, and diarrhea. in sd phase (≥5% participant in inclisiran group): 2 of 18 cough, musculoskeletal pain, nasopharyngitis. In md phase (≥10% participant in inclisiran group) 6 of 33 headache, 5 (15%) diarrhea, 5 (15%) back pain, 4 (12%) nasopharyngitis

				and without statin, 500mg/month for 2 months with and without statin				completion of safety and side effect profile assessment			
3	NCT02597127 (Ray et al 2017)	LDL > 70mg/dL for patient with history ASCVD/ >100mg/dL without history ASCVD max statin therapy	62-74	SD : - Placebo - 200mg - 300mg - 500mg DD : - Placebo - 100mg - 200mg - 300mg	370	Placebo	127	Primary 180 days Other data 210-240 days	Percentage change from baseline in LDL-Cholesterol level	Serious Adverse events Intervention group SD 200mg 6 (10%); 300mg 5 (8%) ; 500mg 6 (9%) ; DD 100mg 11 (18%) ; 6 (10%) ; 7 (11%) Placebo SD placebo 3 (5%) ; DD placebo 6 (10%)	
4	NCT03397121 (Raal et al 2020)	Diagnosed with heterozygous familial hypercholesterolemia LDL at least 100mg/dL despite max statin therapy	47-64	Inclisiran SC 300mg Day 1, 90, 270, 450	242	Placebo	240	Day 30, 150, 330, 510, 540	I = Percentage change from baseline LDL - C levels on day 510 II = time-averaged percent change in the LDL - C level between day 90 and day 540	I = -47.9% (95% CI, -53.5 to -42.3; P<0.001) II = -44.3% (95% CI, -48.5 to -40.1; P <0.001)	Patients with >= 1 serious adverse event - Intervention group 18 (7.5%) , 1 death from cardiovascular cause 1 (0.4%) - Control 33 (13.8%)

5	NCT03400800 (Ray et al 2020)	high risk, primary prevention patients or those with ASCVD (secondary prevention)	≥18	Inclisiran 300mg SD SC Day 1, 90, 270, 450	98	Placebo	105	up to day 540	Percentage change in LDL-C from baseline at day 510 and time adjusted percentage change in LDL-C from baseline after day 90 and up to day 540	LDL-C changes from baseline to day 510 (-43.7%). Time adjusted change in LDL-C from baseline after day 90 up to day 540 (-41.0%). Absolute change difference of LDL-C is -.5mmol/dL (-58.4mg/dL) between groups P <0.0001 , <0.0001 , <0.0001	SAE, AE at injection site Intervention : SAE (n=20), AE at injection site (n=4) Control : SAE (n=13), AE at injection site (n=0)
6	Ray et al (2022)	ITT Population (For efficacy analyses: Pooled analysis of ORION-9,-10 and -11, included patients with heterozygous familial hypercholesterolaemia, atherosclerotic CV disease (ASCVD), or ASCVD risk	54 - 73	Inclisiran 284mg SD SC Day 1, 90 and 6-monthly until 18months	1833	Placebo	1827	540	Change in LDL- C Levels & Safety population (risk of cardiovascular events)	Change in LDL-C levels day 90 : - 50.6% [95% CI (−52.3 to −49.0); P<0.0001] day 540 : - 51.4% [95% CI (−53.4 to −49.4); P<0.0001] Inclisiran significantly reduced MACE (OR[95%CI] : 0.74 [0.58-0.94]), but not fatal and non-fatal MI (OR [95% CI] : 0.80 [0.50−1.27]) and fatal and non-fatal	- MACE Intervention : 131 Control :171 - Fatal and non-fatal MI Intervention : 33 Control :41 - Fatal and non-fatal stroke Intervention : 13 Control :15

		equivalent on maximally tolerated statin-therapy Population (for Safety analyses) : All patients who received at least 1 dose of Inclisiran / placebo								stroke (OR [95% CI] : 0.86 [0.41−1.81]).	
7	NCT03399370 and NCT03400800 (Ray et al 2020)	ASCVD, LDL >70, statin and lipid lowering therapy use, GFR >30	adult >18 years	Inclisiran 284 mg/SC	ORION 10 : 781 ORION 11 : 810	Placebo	780 807	day 30 day 150 day 330 day 510 day 540	Percentage change in LDL time adjusted LDL change (throughout the follow-up period)	-52.3 P <0.001 -49.9 P <0.001	Total AEs : 1156 Serious AEs : ORION 10: 175 ORION 11: 181
8	NCT02597127 and NCT03159416 (Wright et al 2020)	Participant with normal renal function and mild, moderate and severe RI from phase 1 ORION -7 renal study and the	18 < age <80	(ORION 7) = SD Placebo and 300mg ; DD Placebo and 300mg (ORION 1)1 = Normal Function, 2 = Mild RI, 3= Moderate RI, 4= Severe RI	ORION 1 = 122 ORION 7 = 31	Placebo	ORION 1 = 125 ORION 7 = 0	180 days atau max 360 days	ORION 7 : PK, Safety, PD ORION 1 : PK, Safety	Participants with at least 1 TEAE (treatment-emergent adverse event) Intervention : 126 Control : 101	

		phase 2 ORION-1 study; BMI 18-40kg/m2 and BW >50kg									
9	Raal et al PMID: 36217872	HeFH ASCVD ASCVD-risk equivalent	adults	Inclisiran 284 mg/SC	148	Placebo	150	510 days	LDL percentage change at day 510 time-averaged percentage LDL change	-54.2% P <0.0001	Participants with ≥1 TEAEs : 233 Serious TEAEs : Intervention: 32 Placebo: 37
PATISIRAN											
1	NCT01148953 and NCT01559077 (Coelho et al 2013)	ALLN 01:biopsy-confirmed TTR amyloidosis mild-moderate neuropathy karnofsky performance status >60 BMI 18.5-33 NYHA II or less adequate liver, renal, thyroid function	adults >18 yr	ALN-TTR01 (0.01 to 1.0 mg/kg) - IV ALN-TTR02 (0.01 to 0.5 mg/kg) - IV	24 13	Placebo	8 4	70 days	reduction in TTR level	-38% (dosage 1.0 mg/kg) P 0.01 ALLN 02 0.15 = -85.7% P 0.001 0.3 = -87.6% P 0.001 0.5:= -93.8% P 0.001	ALN-TTR01 Infusion Reaction : 5 Fatigue : 2 Placebo : 0 ALN-TTR02 Skin Erythema : 6 Infusion Reaction : 1 Placebo : 2 (Skin Erythema)

		not pregnant/childbearing potential ALLN 2: 18-45, healthy, BMI 18-31.5.									
2	NCT01961921 (Coelho 2020)	hATTR amyloidosis	29 to 77	Patisiran 0.3 mg/kgbb - IV once / 3 weeks	Patisiran alone (n=7)	Patisiran + TTR tetramer stabilizer	n=19	24 months	The primary objective was to evaluate the safety and tolerability of long-term dosing with patisiran.	(-0.28)	SAE 7, death 2, any AE leading to discontinuation 2. None of which were considered related to Patisiran flushing (n=7), infusion-related reactions (n=6), diarrhea (n=3)
3	NCT01960348 (Solomon et al 2019)	Patients with hereditary transthyretin-mediated (hATTR) amyloidosis with polyneuropathy and cardiac amyloidosis	61 (54-67)	Patisiran 0.3 mg/kgbb - IV once / 3 weeks	90 (71.4%) patisiran	Placebo	36 (28.6%) placebo	18 months	improved left ventricular (LV) global longitudinal strain (LV GLS)	Patisiran improved the absolute GLS (least-squares mean [SE] difference, 1.4% [0.6%]; 95% CI, 0.3%-2.5%; P = .02) compared with placebo at 18 months, with the greatest differential increase observed in the basal region (overall least-squares mean [SE] difference, 2.1% [0.8%]; 95% CI, 0.6%-3.6%; P = .006) and no significant differences in the mid and apical regions among groups	

4	NCT01960348	Had a diagnosis of hATTR amyloidosis with a documented TTR mutatiom and symptomatic neuropathy, were ambulatory, had adequate liver function and adequate renal function, and were included in the prespecified cardiac subpopulation (baseline LV wall thickness > 13 mm, no history of aortic valve disease or hypertension) Enrolled participants	18 - 85 yo	Patisiran 0.3 mg/kgbb - IV once / 3 weeks	Cardiac subpopulation 90	Placebo	36	Echo parameters at 18 months NTproBNP and 10MWT gait speed at 9 months and 18 months	Reduction of left ventricular wall thickness, interventricular septal wall thickness, posterior wall thickness, and relative wall thickness. Increase of end diastolic volume, decrease of global longitudinal strain, increase of cardiac output. Decrease of NT pro BNP. Increase of 10MWT gait speed. No significant outcome in echo parameters. Decrease of NTproBNP.	Reduction in mean LV wall thickness (least-squares mean difference±SEM, –0.9±0.4 mm; P=0.017) was observed with patisiran compared with placebo. In patisirantreated patients compared with placebo, global longitudinal strain was decreased (–1.4%±0.6%, P=0.015), cardiac output was increased (0.38±0.19 L/min, P=0.044), and LVEDV was increased (8.31±3.91 mL, P=0.036) Patisiran reduced NT-proBNP compared with placebo at 9 months (ratio of fold change patisiran/placebo, 0.63; 95% CI, 0.50–0.80) and 18 months (ratio of fold change patisiran/placebo, 0.45; 95% CI,	Cardiac serious adverse events Intervention : 20 Control : 10

		which did not fulfill criteria to be included in prespecified cardiac subpopulation							Increase of 10MWT gait speed.	0.34–0.59; P=7.7×10–8), corresponding to a 55% reduction relative to placebo	
5	NCT01960348	hereditary transthyretin amyloidosis with polyneuropathy, some patients has cardiac abn (NYHA I dan II)	18 - 85 years	Patisiran 0.3 mg/kgbb - IV once / 3 weeks	148	Placebo	77	18 months	mNIS+7, LVthickness, LVLStrain	-34; -0.9 ; -1.37 <0.001; 0.02; 0.02	diarreha, edema, nausea, cough, asthenia, death, etc Intervention : 143 Control : 75
6	NCT01960348	Hereditary transthyretin amyloidosis with polyneuropathy, some patients has cardiac abn (NYHA I dan II)	n/a	Patisiran 0.3 mg/kgbb - IV once/ 3 weeks	148 (90 yg cardiac)	Placebo	77 (36 yang cardiac)	18 months	measures of overall QoL	AEs not reported	

REVUSIRAN										
1	NCT02319005 (Judge et al 2020)	TTR mutation and amyloid deposits, hx of hf and cardiac involvement on echo	18 - 90 years	Revusiran 500mg/SC	140	Placebo	66	18 months	6MWT, Troponin I, NTpBNP	the study was prematurely discontinued due to an imbalance of deaths observed in the revusiran group (18 patients, 12.9%) compared with the placebo group (2 patients, 3.0%) during the on-treatment period
SLN360										
1	NCT04606602 or 2020-002471-35 (Nissen et al 2022)	no known CVDs Lp(a) conc >150 nmol/L BMI 18-45 kg/m2	adults 36-63 years	SLN360 SD 30 mg/SC 100 mg/SC 300 mg/SC 600 mg/SC	24 (6 each dose)	Placebo	8	150 days	Safety and tolerability	Participants with any treatment-emergent adverse event intervention group : 100% placebo group : 75%

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Decision on submission to Non-coding RNA Research

2 pesan

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Department of Cardiology and Vascular Medicine, Airlangga University – Soetomo General Hospital, Surabaya, Indonesia
+62812-5980-8492

meityardiana@fk.unair.ac.id

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Kepada: meityardiana@fk.unair.ac.id

Our reference: NCRNA 213
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Article title: Non-Coding RNA Therapeutics in Cardiovascular Diseases and Risk Factors: Systematic Review
To be published in: Non-coding RNA Research

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Best regards,

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To be published in: Non-coding RNA Research

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Our reference: NCRNA 213
Article reference: NCRNA_NCRNA-D-23-00035
Article title: Non-Coding RNA Therapeutics in Cardiovascular Diseases and Risk Factors: Systematic Review
To be published in: Non-coding RNA Research

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Cc: r.ramalingam@elsevier.com
Bcc: "Asiyahnurul@gmail.com" <Asiyahnurul@gmail.com>

Dear Mr Somasundaram,

Attached in this email is the supplementary file of my manuscript entitled **"Non-Coding RNA Therapeutics in Cardiovascular Diseases and Risk Factors: Systematic Review",** article reference NCRNA 213.
Hope this fulfilled the requirements. We are very sorry for the inconvenience.

Warm Regards,

Dr. dr. Meity Ardiana, Sp.JP(K), FIHA

Department of Cardiology and Vascular Medicine, Airlangga University – Soetomo General Hospital, Surabaya, Indonesia
+62812-5980-8492
meityardiana@fk.unair.ac.id

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Supplementary material 1 _ RNA.docx
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Cc: "Ramalingam, Rajinikanth (ELS-CHN)" <r.ramalingam@elsevier.com>

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Fax: not available
E-mail: meityardiana@fk.unair.ac.id

MY REFERENCE NUMBER is NCRNA 213

Best Regards,
Dr. dr. Meity Ardiana, Sp.JP(K), FIHA
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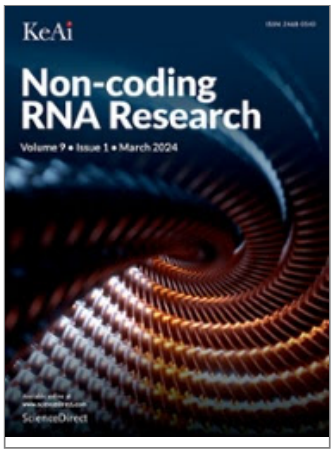

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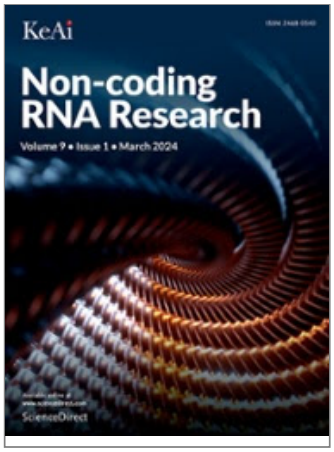

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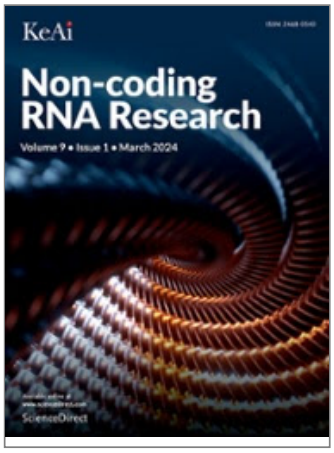

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