

SUPPLEMENTARY REFERENCES

ONLINE ONLY REFERENCES FOR MAIN TEXT

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SUPPLEMENTARY TABLES

Table S1: Summary of microRNAs and their targets that have been associated with processes fundamental to the initiation and progression of atherosclerosis

miR	Target(s)	Ref(s)
<i>Cholesterol Metabolism & Homeostasis</i>		
miR-10b	ABCA1, ABCG1	[1]
miR-26	ABCA1, ARL7	[2]
miR-27a/b	ABCA1, ACAT1, ANGPTL3, CD36, GPAM, LPL	[3,4]
miR-30c	LPGAT1, MTP	[5]
miR-33a/b	ABCA1, ABCG1, AMPK α , CPT1A, CROT, HADHB, IRS2, NPC1, PRKAA1, SREBP-1	[6-14]
miR-106b	ABCA1	[15]
miR-144	ABCA1	[16,17]
miR-185	SREBP-2	[18]
miR-206	LXR α	[19]
miR-378	ABCG1	[20]
miR-467b	LPL	[21,22]
miR-613	ABCA1, LXR α	[23]
miR-758	ABCA1	[24]
<i>Endothelial Cell Dysfunction</i>		
miR-1	MLCK	[25]
miR-27a/b	SEMA6A	[26]
miR-34a	SIRT1	[27]
miR-92a	KLF2, KLF4, PTEN, SOCS5	[28-31]
miR-126-5p	DLK1	[32]
miR-144	IDH2	[33]
miR-146a	NOX4	[34]
miR-155	AT1R, ETS-1, MLCK	[35,36]
miR-216a	BECN1	[37]
miR-217	Sirt1	[38]
miR-221/222	c-Kit, eNOS, ETS-1, PAK1, p27, p57, STAT5A	[36,39-43]
miR-223	IGF-1R	[44]
miR-365	BCL-2	[45]
miR-492	Resistin	[46]
miR-513a-5p	XIAP	[47]
miR-663	-	[48]
miR-712	TIMP3	[49]
let-7c	BCL-XL	[50]
let-7g	CASP3, SMAD2, TGFBR1, THBS1	[51,52]
<i>Inflammation</i>		
miR-9	ACAT1, PPAR δ	[53,54]
miR-10a	MAP3K7, β TRC	[55]
miR-15a	CARM1	[56]
miR-17-3p	ICAM-1	[57]
miR-21	PPAR α , TLR4	[58,59]
miR-29a	LPL	[60]

miR	Target(s)	Ref(s)
<i>Inflammation (continued)</i>		
miR-31	E-selectin	[57]
miR-125a-5p	ORP9	[61]
miR-126-3p	VCAM-1	[62,63]
miR-145	JAM-A	[64]
miR-146a/b	CD40L, IRAK1, IRAK2, TLR4, TRAF6	[65-67]
miR-147	-	[68]
miR-155	BCL-2, ETS-1, FADD, HBP1, MAP3K10	[36,69-74]
miR-181a	c-Fos	[75]
miR-181b	IPOA3	[76]
miR-342-5p	AKT1	[77]
<i>VSMC Differentiation & Proliferation</i>		
miR-1	KLF4, MRTF-A, PIM-1	[78-80]
miR-21	BCL-2, PDCD4, PPAR α , PTEN, TPM1	[81-84]
miR-26a	SMAD1, SMAD4	[85]
miR-29b	DNMT3b	[86]
miR-125b	SP7	[87]
miR-126	BCL-2, FOXO3, IRS1	[88]
miR-132	LRRFIP1	[89]
miR-133	SP1	[90]
miR-133a	IGF-1R, RUNX2	[91,92]
miR-143/145	ELK1, fascin, KLF4, KLF5, PDGF-R α , PKC- ϵ	[93-99]
miR-181a	OPN	[100]
miR-195	CDC42	[101]
miR-208	p21	[102]
miR-221/222	c-Kit, p27, p57	[43,103-105]
miR-490-3p	PAPP-A	[106]
miR-638	NOR1	[107]
miR-663	JUNB, MYL9	[108]
let-7d	KRAS	[109]
let-7g	LOX-1	[110]

ABCA1 = ATP binding cassette transporter A1; ABCG1 = ATP binding cassette transporter G1; ACAT1 = acyl-CoA:cholesterol acyltransferase 1; AKT1 = v-akt murine thymoma viral oncogene homolog 1; AMPK α = AMP kinase subunit- α ; ANGPTL3 = angiopoietin-like 3; ARL7 = ADP-ribosylation factor-like 7; AT1R = angiotensin II type 1 receptor; BCL-XL = B-cell lymphoma-extra large; BCL-2 = B-cell lymphoma 2; BCL-6 = B-cell lymphoma 6; BECN1 = Beclin1; CARM1 = coactivator-associated arginine methyltransferase 1; CASP3 = caspase-3; CDC42 = cell division control protein 42; CD36 = scavenger receptor CD36; CPT1A = carnitine palmitoyltransferase 1A; CROT = carnitine O-octaniltransferase; DLK1 = delta-like 1 homolog; DNMT3b = DNA methyltransferase 3b; ELK1 = ELK1, member of ETS oncogene family; eNOS = endothelial nitric oxide synthase; ETS-1 = E26 transformation-specific sequence 1; FADD = Fas-associated death domain-containing protein; FOXO3 = forkhead box O3; GPAM = glycerol-3-phosphate acyltransferase 1; HADHB = hydroxyacyl-CoA-dehydrogenase; HBP1 = HMG box-transcription protein 1; ICAM-1 = intercellular adhesion molecule 1; IDH2 = isocitrate dehydrogenase 2; IGF-1R = insulin like growth factor 1 receptor; IPOA3 = importin- α 3; IRAK1 = interleukin-1 receptor-associated kinase 1; IRAK2 = interleukin-1 receptor-associated kinase 2;

IRS1 = insulin receptor substrate 1; IRS2 = insulin receptor substrate 2; JAM-A = junctional adhesion molecule-A; JUNB = transcription factor Jun-B; KLF2 = Krüppel-like factor 2; KLF4 = Krüppel-like factor 4; KRAS = Kirsten rat sarcoma viral oncogene homolog; LOX-1 = lectin-like oxidized LDL receptor-1; LPGAT1 = lysophosphatidylglycerol acyltransferase 1; LPL = lipoprotein lipase; LRRFIP1 = leucine-rich repeat (in Flightless 1) interacting protein-1; LXR α = liver X receptor α ; MAP3K7 = mitogen-activated kinase kinase kinase 7; MAP3K10 = mitogen-activated kinase kinase kinase 10; MLCK = myosin light chain kinase; MYL9 = myosin light chain 9; MRTF-A = myocardin-related transcription factor A; MTP = microsomal triglyceride transfer protein; NOR1 = neuron-derived orphan receptor 1; NOX4 = NADPH oxidase 4; NPC1 = Niemann-Pick C1; OPN = osteopontin; ORP9 = oxysterol binding protein-like 9; PAK1 = p21/Cdc42/Rac1-activated kinase 1; PAPP-A = pregnancy-associated plasma protein A; PDCD4 = programmed cell death 4; PDGF-R α = platelet-derived growth factor receptor α ; PKC- ϵ = protein kinase C- ϵ ; PIM-1 = serine/threonine-protein kinase PIM-1; PPAR α = peroxisome proliferators-activated receptor- α ; PPAR δ = peroxisome proliferators-activated receptor- δ ; PRKAA1 = protein kinase, AMP-activated, alpha 1 catalytic subunit; PTEN = phosphatase and tensin homolog; RUNX2 = Runt-related transcription factor 2; SEMA6A = semaphorin 6A; SIRT1 = sirtuin 1; SirT1 = silent information regulator 1; SMAD1 = SMAD family member 1; SMAD2 = SMAD family member 2; SMAD4 = SMAD family member 4; SOCS5 = suppressor of cytokine signalling 5; SP1 = SP1 transcription factor; SP7 = SP7 transcription factor; SREBP-1 = sterol regulatory element-binding protein 1; SREBP-2 = sterol regulatory element-binding protein 2; STAT5A = signal transducer and activator of transcription 5A; TGFBR1 = transforming growth factor beta receptor 1; THBS1 = thrombospondin 1; TIMP3 = tissue inhibitor of metalloproteinase 3; TLR4 = toll-like receptor 4; TPM1 = tropomyosin 1; TRAF6 = TNF receptor associated factor 6; VCAM-1 = vascular cell adhesion molecule 1; XIAP = X-linked inhibitor of apoptotic protein; β TRC = β -transducin repeat-containing

Table S2: Summary of papers assessing the role of circulating microRNAs as biomarkers in the diagnosis of acute coronary syndromes

Study Population	Source	Notable miRNAs	Ref
AMI = 348; CAD = 100; HC = 368	Plasma	↓ = miR-125b, miR320b	[111]
ACS = 89; CAD = 86; HC = 103	Serum	↑ = miR-146a, miR-186, miR-208b, miR-499	[112]
AMI = 224; Non-AMI CP = 931	Plasma	↑ = miR-208b, miR-320a, miR-499 ↔ = miR-133a, miR-223, miR-451	[113]
AMI = 17; CAD = 4; HC = 5	Plasma	↑ = miR-423-5p ↔ = miR-1, miR-208a	[114]
UA = 19; AP = 34; HC = 20	Plasma	↑ = miR-1, miR-122, miR-126, miR-133a, miR-133b, miR-145, miR-199, miR-433, miR-485-3p ↔ = miR-17-5p, miR-92a, miR-155, miR-208a, miR-375, miR-499-5p	[115]
AMI = 13; AP = 176; HC = 127	Plasma	↑ = miR-133a	[116]
AMI = 21; CAD = 17; HC = 30	Plasma	↑ = miR-499	[117]
AMI = 117; AP = 182; HC = 100	Serum	↑ = miR-1, miR-134, miR-186, miR-208, miR-223, miR-499	[118]
STEMI = 173; NSTEMI = 146; Non-AMI CP = 88	Plasma	↑ = miR-1, miR-208b, miR-499-5p	[119]
AMI = 15; HC = 15	Serum	↑ = miR-34a	[120]
AMI = 67; HC = 32	Plasma	↑ = miR-1, miR-133a, miR-208b, miR-499	[121]
AMI = 18; HC = 30	Plasma	↑ = miR-30a, miR-195 ↓ = let-7b	[122]
AMI = 30; AP = 35; Non-CAD = 22	Plasma	↑ = miR-146a, miR-155 ↔ = miR-9, miR-125a-5p ↓ = miR-29a	[72]
AMI = 17; HC = 25	Plasma	↑ = miR-1 ↓ = miR-126	[123]
NSTEMI = 92; HF = 81; HC = 99	Plasma	↑ = miR-1, miR-21, miR-133a, miR-423-5p, miR-499-5p ↔ = miR-208a	[124]
STEMI = 397; NSTEMI = 113; HC = 87	Plasma	↑ = miR-208b, miR-499	[125]
AMI = 51; HC = 28	Plasma & WB	↑ = miR-133, miR-328	[126]
AMI = 16; UA = 15; AP = 15; NCCP = 16	Plasma	↑ = miR-21, miR-146a ↔ = miR-31, miR-125a-5p, miR-125b ↓ = miR-155	[127]
AMI = 327; UA = 117	Plasma	↑ = miR-1, miR-133a, miR-208b ↔ = miR-133b, miR-208a, miR-499	[128]
STEMI = 25; HC = 11	Plasma	↑ = miR-1, miR-133a, miR-208b, miR-499-5p	[129]
ACS = 29; Non-ACS = 42	Serum	↑ = miR-1, miR-133a	[130]
AMI = 36; Non-AMI CP = 32	Plasma	↑ = miR-1 (NS), miR-133a, miR-208b, and miR-499 ↔ = miR-122 ↓ = miR-223	[131]
STEMI = 20; Stable CAD = 20; HC = 20	WB	↑ = miR-30c, miR-145 ↓ = miR-663b, miR-1291	[132]

Study Population	Source	Notable miRNAs	Ref
STEMI = 33; HC = 17	Plasma	↑ = miR-1, miR-133a, miR-133b, miR-499-5p ↔ = miR-208a ↓ = miR-122, miR-375	[133]
AMI = 31; HC = 20	Serum	↑ = miR-1	[134]
AMI = 9; UA = 5; HC = 10	Plasma	↑ = miR-499	[135]
UA = 25; AP = 25; HC = 20	PBMC	↑ = miR-134, miR-198 & miR-370	[136]
AMI = 26; UA = 25; AP = 22; NCCP = 18	PBMC	↑ = miR-146a	[137]
AMI = 33; Non-AMI CP = 33; HC = 30	Plasma	↑ = miR-1, miR-133a, miR-208a, miR-499	[138]
AMI = 93; HC = 66	Plasma	↑ = miR-1 ↔ = miR-133	[139]

ACS = Acute Coronary Syndrome; AMI = Acute Myocardial Infarction; AP = Angina Pectoris; CAD = Coronary Artery Disease; CP = Chest Pain; HC = Healthy Control; HF = Heart Failure; NCCP = Non-Cardiac Chest Pain; NSTEMI = Non-ST-Elevation Myocardial Infarction; PBMC = Peripheral Blood Mononuclear Cells; STEMI = ST-Elevation Myocardial Infarction; UA = Unstable Angina; WB = Whole Blood

Table S3: Summary of studies assessing the role of circulating microRNAs as biomarkers of prognosis following acute coronary syndromes

Study Population	Source	Notable miRNAs	Summary Results	Ref
NSTEMI = 142	Plasma	miR-21, miR-499-5p	Increased miR-499-5p levels at admission were associated with a significant increase in 12-month cardiovascular mortality in multivariate analyses; this association was not present for 24-month mortality The performance of the overall model to predict 12-month mortality was moderate at best	[140]
AMI = 224 Non-AMI CP = 931	Plasma	miR-133a, miR-208b, miR-223, miR-320a, miR-451	None of the studied miRNAs predicted long-term mortality or recurrent AMI miR-208b was a moderate predictor of 30 day mortality but not recurrent AMI	[113]
AMI = 150	Plasma	miR-16, miR-27a, miR-101, miR-150	Low levels of miR-101 & miR-150 and high levels of miR-16 & miR-27a were associated with increased risk of impaired LV contractility at 6-months A combination of the miR16, miR-27a, miR-101 & miR-150 improved the prediction of LV contractility based on clinical variables	[141]
AMI = 510	Plasma	miR-208b, miR-499	Increased miR-208b was associated with increased age & increased BMI miR-208b & miR-499 were not associated with diabetes, gender, hypercholesterolaemia or smoking miR-208b & miR-499 were not associated with mortality at any time-point	[142]
AMI = 86	Serum	miR-34a, miR-192, miR-194, miR-208, miR-499	miR-34a, miR-192 & miR-194 were upregulated in patients who developed HF within 1 year of AMI vs. those who did not miR-34a & miR-194 were positively correlated with LV diastolic dimension & negatively correlated with LVEF miR-208 & miR-499 were undetectable in either group	[143]
STEMI = 90	Plasma	miR-150	miR-150 was downregulated in patients with remodelling (Δ LV EDV >0) vs. those without miR-150 outperformed Nt-proBNP to predict remodelling	[144]
STEMI = 173 NSTEMI = 146 Non-AMI CP = 88	Plasma	miR-1, miR-208b, miR-499-5p	miR-208b & miR-499-5p were associated with death or heart failure in multivariate analyses These associations were lost after adjustment for hsTnT miR-1 was not associated with death or heart failure in any of the analyses All miRNAs were weakly negatively associated with LVEF in multivariate analyses	[119]
AMI = 246	Plasma	miR-133a, miR-423-5p	miR-133a & miR-423-5p were not associated with any markers of LV remodelling in univariate or multivariate analyses miR-133a & miR-423-5p were not associated with peak CK-MB or LVEF at baseline and did not differ between those who did or did not develop heart failure during hospitalisation miR-133a & miR-423-5p were not associated with BNP at any point during 12 month follow-up	[145]
STEMI = 216	Serum	miR-133a	miR-133a was significantly correlated with infarct size, MVO & MSI miR-133a was a univariate predictor of major adverse cardiovascular events but this association was lost upon multivariate adjustment for traditional clinical and CMR prognostic markers	[146]
AMI = 49	Plasma	miR-1	miR-1 levels negatively correlated with LVEF, LV fractional shortening & the ratio of peak early diastolic velocity of mitral flow to late diastolic velocity of mitral flow	[147]
AMI = 40 (Death = 19; Survival = 21)	Serum	miR-155, miR-380*	miR-155 & miR380* were significantly increased in the 'cardiac death within 1 year' group vs. survivors	[148]

Study Population	Source	Notable miRNAs	Summary Results	Ref
Prospective Study = 820; AMI = 47	Plasma	miR-126, miR-197, miR-223	Baseline levels of miR-126, miR-197 & miR-223 were associated with risk of AMI at 10 year follow-up Addition of these three miRNAs improved classification in the Framingham Risk Score for hard CAD	[149]
AMI = 12 HC = 12	Plasma	miR-1, miR-21, miR-29a, miR-133a, miR-208a	miR-29a on Day 5 post-AMI was significantly associated with LV EDV on Day 90 post-AMI	[150]
AMI = 327 UA = 117	Plasma	miR-1, miR-133a, miR-133b, miR-208a, miR-208b, miR-499	miR-133a & miR-208b significantly associated with death in multivariate analyses This association was lost after adjustment for hsTnT	[128]

AMI = Acute Myocardial Infarction; BMI = Body Mass Index; CAD = Coronary Artery Disease; CK-MB = Creatine Kinase-MB Isoenzyme; CMR = Cardiovascular Magnetic Resonance Imaging; CP = Chest Pain; EDV = End Diastolic Volume; HC = Healthy Control; HF = Heart Failure; hsTnT = High Sensitivity Troponin T; LV = Left Ventricle; LVEF = Left Ventricular Ejection Fraction; MSI = Myocardial Salvage Index; MVO = Microvascular Obstruction; NSTEMI = Non-ST-Elevation Myocardial Infarction; Nt-proBNP = N-terminal prohormone of Brain-type Natriuretic Peptide; STEMI = ST-Elevation Myocardial Infarction; UA = Unstable Angina

Table S4: Summary of papers assessing the role of circulating microRNAs as biomarkers in the diagnosis of stable coronary artery disease

Study Population	Source	Notable miRNAs	Ref
AMI = 348; CAD = 100; HC = 368	Plasma	↓ = miR-125b, miR320b	[111]
CAD with Calcified Plaque = 62; CAD with Non-calcified Plaque = 63; Non-CAD = 61	Serum	↓ = miR-21	[151]
CAD = 45; HC = 25	Plasma	↓ = miR-31	[152]
ACS = 89; Stable CAD = 86; Intermediate CV Risk = 40; Low CV Risk = 112; HC = 103	Serum	↑ = miR-146a, miR-186, miR-208b, miR-499	[112]
UA = 58; AP = 31; NCCP = 50	Plasma	↑ = miR-21, miR-25, miR-92a, miR-106b, miR-126*, miR-451, miR-590-5p	[153]
AMI = 17; CAD = 4; HC = 5	Plasma	↔ = miR-1, miR-208a, miR-423-5p	[114]
UA = 19; AP = 34; HC = 20	Plasma	↑ = miR-337-5p, miR-433, miR485-3p miR-1, miR-122, miR-126, miR133a, miR-133b, miR-199a ↔ = miR-17-5p, miR-92a, miR-145, miR-155, miR-208a, miR-375, miR-499-5p	[115]
AMI = 13; AP = 176; HC = 127	Plasma	↑ = miR-133a	[116]
AMI = 12; UA = 16; AP = 12; NCCP = 10; HC = 5	Plasma	↓ = miR-214	[154]
AMI = 30; AP = 35; Non-CAD = 22	Plasma	↑ = miR-146a, miR-155 ↔ = miR-9, miR-125a-5p ↓ = miR-29a	[72]
CAD ≥ 70% = 34; CAD < 70% = 49	Plasma	↑ = miR-490-3p, miR-494, miR-769-3p	[155]
CAD = 31; Non-CAD = 36	Plasma	↔ = miR-126	[156]
CAD = 155; Non-CAD = 100	Plasma	↑ = miR-122, miR-370 ↔ = miR-33a, and miR-33b	[157]
CAD = 81; Non-CAD = 44	CD14 ⁺ PBMC	↔ = miR-181b, miR-181d ↓ = miR-181a	[158]
CAD = 12; HC = 12	WB	↑ = miR-140-3p, miR-182	[159]
CAD = 67; HC = 31	Plasma	↔ = miR-133a, miR208a ↓ = miR-17, miR-92a, miR-126, miR-145, miR-155, miR-199a (NS)	[160]
UA = 25; AP = 25; HC = 20	PBMC	↑ = miR-135a ↓ = miR-147	[136]

ACS = Acute Coronary Syndrome; AMI = Acute Myocardial Infarction; AP = Angina Pectoris; CAD = Coronary Artery Disease; CV = Cardiovascular; HC = Healthy Control; NCCP = Non-Cardiac Chest Pain; PBMC = Peripheral Blood Mononuclear Cells; UA = Unstable Angina; WB = Whole Blood

Table S5: Summary of papers assessing the role of circulating microRNAs as biomarkers in the diagnosis of heart failure

Study Population	Source	Notable miRNAs	Ref
HF = 53; HC = 39	WB & Serum	↑ = miR-122, miR-200b, miR-519e*, miR-520d-5p, miR-622 ↓ = miR-558	[161]
HF = 76; COPD = 47; Other SOB = 59; HC = 29	Plasma	↓ = miR-103, miR-142-3p, miR-30b, miR-342-3p	[162]
HF = 22; HC = 18	Serum	↑ = miR-30a, miR-210	[163]
HF = 13; HC = 6	PBMC	↑ = miR-210	[164]
NSTEMI = 92; HF = 81; HC = 99	Plasma	↑ = miR-21, miR-133a, miR-423-5p, miR-499-5p ↔ = miR-1, miR-208a	[124]
HF = 30; HC = 30	Serum	↑ = miR-22, miR-92b, miR-320a, miR-423-5p	[165]
HF = 33; HC = 17	Plasma	↔ = miR-122, miR-499 ↓ = miR-126	[166]
HF = 33; HC = 34	Plasma	↑ = miR-122, miR-133a (NS), miR-208b (NS), miR-499 ↔ = miR-1, miR-122, miR-233	[131]
NIDCM = 26; ICM = 23; HC = 28	PBMC	↑ = miR-29b, miR-142-3p ↓ = miR-107, miR-125b, miR-139, miR-142-5p, miR-497	[167]
HF = 15; HC = 10	Plasma	↔ = miR-499	[135]
HF = 42; Non-HF SOB = 20; HC = 51	Plasma	↑ = miR-18b*, miR-129-5p, miR-423-5p, miR-622, miR-675, miR-1254, HS_202.1	[168]

COPD = Chronic Obstructive Pulmonary Disease; HC = Healthy Control; HF = Heart Failure; ICM = Ischaemic Cardiomyopathy; NIDCM = Non-Ischaemic Dilated Cardiomyopathy; NSTEMI = Non-ST-Elevation Myocardial Infarction; PBMC = Peripheral Blood Mononuclear Cells; SOB = Shortness of Breath; WB = Whole Blood

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