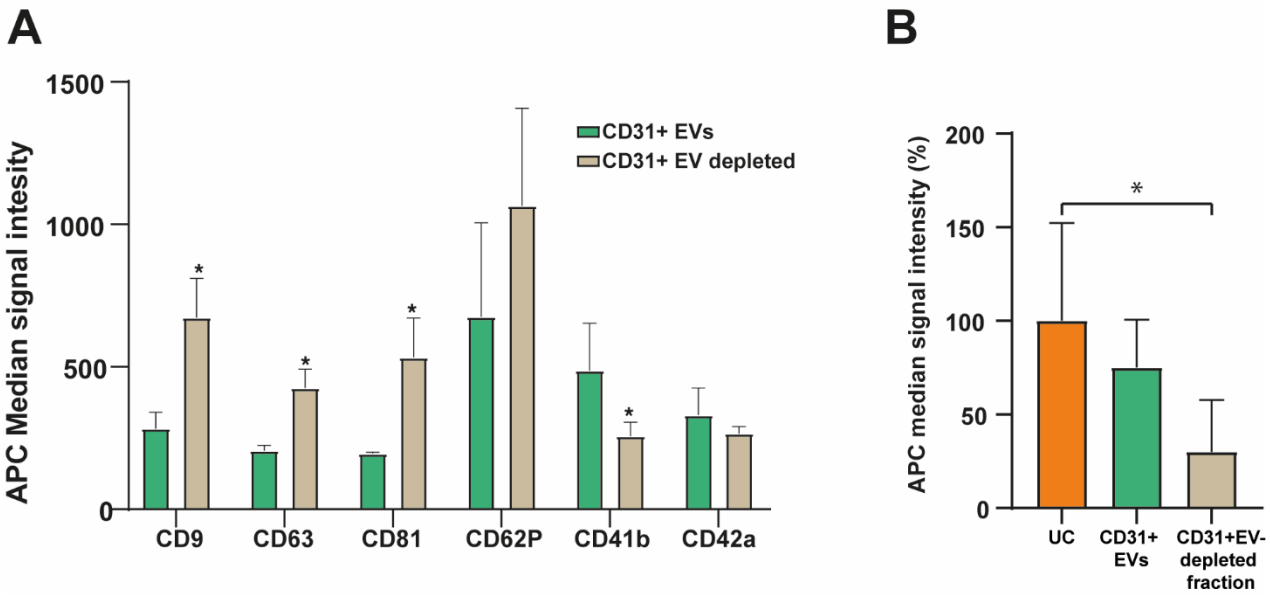
Supplementary Figure 1



A) Comparative cytofluorimetric detection of multiple markers in CD31+EVs vs CD31+ EV-depleted (n=3, from the same control plasma samples). * t test $p<0.05$. **B)** Estimation of the yield of the isolation technique. Comparative cytofluorimetric detection of CD31 in EVs isolated with UC, in CD31+EVs, and the CD31+ depleted EVs (n=3, from the same control plasma samples). * ANOVA $p<0.05$.

Supplementary Table 1. Literature supporting the selection of the miRNA panel.

miRNA	References
miR-126-3p	(Al-Kafaji et al., 2017; Amr et al., 2018; Jansen et al., 2016; Jansen et al., 2013; Liu et al., 2014; Meng et al., 2012; Mocharla et al., 2013; Olivieri et al., 2014; Olivieri et al., 2015b; Ortega et al., 2014; Rawal et al., 2017; Seyhan et al., 2016; Wang et al., 2014; Zampetaki et al., 2010; Zhang et al., 2017; Zhang et al., 2015; Zhang et al., 2013)
miR-146a-5p	(Alipoor et al., 2017; Baldeon et al., 2014; Garcia-Jacobo et al., 2019; Kong et al., 2011; Mensa et al., 2019; Radovic et al., 2018; Rong et al., 2013)
miR-155	(Akhbari et al., 2019; Barutta et al., 2013; Beltrami et al., 2018; CorralFernandez et al., 2013; Huang et al., 2014; Liang et al., 2018a; Liang et al., 2018b; Mazloom et al., 2015; Moura et al., 2019; Tome-Carneiro et al., 2013; Wang et al., 2019; Wang et al., 2018; Yang et al., 2015)
miR-195-5p	(Marques et al., 2016)
miR-21-5p	(Chien et al., 2016; Ghorbani et al., 2018; Jansen et al., 2016; Jiang et al., 2017; La Sala et al., 2019; Liang et al., 2018b; Nunez Lopez et al., 2016; Olivieri et al., 2015a; Villard et al., 2015; Wang et al., 2014; Zampetaki et al., 2010; Zang et al., 2019)
miR-24-3p	(de Candia et al., 2017; Demirsoy et al., 2018; Kokkinopoulou et al., 2019; Prabu et al., 2019)
miR-320a	(Flowers et al., 2015; Villard et al., 2015)
miR-342-3p	(Assmann et al., 2018; Collares et al., 2013; de Candia et al., 2017)
miR-376a	(Joglekar et al., 2009)
miR-422a	(Latorre et al., 2017)
miR-451a	(Ding et al., 2016)

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Supplementary Table 2. Comparison of $CD31^{+}$EV-shuttled miRNA relative expression among CTRL, T2DM-NC, and T2DM-C subjects. Variables are expressed as median (interquartile range). P value from Mann-Whitney *U* test for CTR vs. T2DM and from Kruskal-Wallis test for CTR vs. T2DM-NC vs. T2DM-C.

miRNA	**CTR**	**T2DM-C**	**T2DM-NC**	**p value (CTR vs. T2DM)**	**p value (CTR vs. T2DM-NC vs. T2DM-C)**
miR-126-3p	36.5 (44.4)	18.5 (21.0)	22.9 (34.7)	<0.001	<0.001
miR-146a-5p	0.4 (0.7)	1.7 (8.2)	30.8 (206.9)	<0.001	<0.001
miR-155	739.8 (677.1)	1.1 (1.2)	0.1 (0.9)	<0.001	<0.001
miR-195-5p	89.2 (60.4)	7.8 (7.1)	1.1 (7.9)	<0.001	<0.001
miR-21-5p	62.9 (100.4)	138.2 (127.5)	249.6 (156.8)	<0.001	<0.001
miR-24-3p	71.3 (109.2)	10.3 (8.8)	0.9 (6.1)	<0.001	<0.001
miR-320a	53.2 (110.9)	49.5 (83.5)	22.7 (37.9)	<0.001	<0.001
miR-342-3p	0.2 (0.2)	0.4 (0.5)	1.4 (2.5)	<0.001	<0.001
miR-376a	23.9 (146.9)	20.4 (46.2)	22.5 (150.6)	0.212	0.362
miR-422a	0.3 (0.6)	4.0 (7.4)	10.7 (8.2)	<0.001	<0.001
miR-451a	0.3 (0.3)	0.6 (0.7)	1.6 (1.5)	<0.001	<0.001

Supplementary Table 3. Binary logistic regression analysis of miRNAs associated with the presence of complications in T2DM patients. Odds ratio (95% CI) are expressed per 0.5 SD increase of each miRNA.

miRNA	**B**	**SE**	**P value**	**OR (95% CI)**
miR-146a-5p	0.693	0.343	0.043	1.999 (1.021 – 3.914)
miR-320a	-0.446	0.130	0.001	0.640 (0.496 – 0.826)
miR-422a	0.292	0.141	0.038	1.339 (1.016 – 1.763)
miR-451a	0.401	0.142	0.005	1.493 (1.131 – 1.973)

Supplementary Table 4. Binary logistic regression analysis of miRNAs associated with the presence of complications in T2DM patients. BMI and LDL-C were included into the model as covariates. Odds ratio (95% CI) are expressed per 0.5 SD increase of each miRNA.

miRNA	**B**	**SE**	**P value**	**OR (95% CI)**
miR-146a-5p	1.208	0.632	0.056	3.348 (0.969 – 11.563)
miR-320a	-0.874	0.268	0.001	0.417 (0.247 – 0.705)
miR-422a	0.616	0.304	0.043	1.852 (1.021 – 3.359)
miR-451a	0.804	0.304	0.008	2.235 (1.232 – 4.053)
BMI	-0.040	0.045	0.371	0.961 (0.880 – 1.049)
LDL-C	-0.015	0.006	0.023	0.986 (0.973 – 0.998)

Supplementary Table 5. Comparison of $CD31^{+}$-EV miRNA levels in T2DM individuals according to the presence of specific complications after adjustment for age and gender. In the case of MACE, comparisons after adjustment also for HbA1c and the presence of any other T2DM complication are also reported. P values of the comparison of the estimated marginal means are reported. Differences of the adjusted mean relative expressions between complication present and absent are reported where $p<0.05$.

miRNAs	At least one complication (n=101)	Neuropathy (n=28)	Nephropathy (n=20)	Retinopathy (n=48)	Peripheral artery disease (n=22)	MACE adj. for age and gender (n=52)	MACE adj. for age, gender, HbA1c, other complications (n=52)
miR-126-3p	0.214	0.166	0.693	0.309	0.312	0.213	0.949
miR-146a-5p	0.002 (125.6)	0.107	0.318	0.205	0.020 (124.5)	<0.001 (201.2)	<0.001 (204.8)
miR-155	<0.001 (-0.6)	0.192	0.980	0.542	0.013 (-0.45)	<0.001 (-1.1)	<0.001 (-1.0)
miR-195-5p	<0.001 (-5.3)	0.372	0.606	0.713	0.016 (-4.0)	<0.001 (-7.4)	0.002 (-5.7)
miR-21-5p	<0.001 (103.6)	0.903	0.538	0.522	0.970	<0.001 (131.2)	<0.001 (124.0)
miR-24-3p	<0.001 (-7.7)	0.168	0.175	0.497	0.008 (-4.8)	<0.001 (-9.8)	<0.001 (-7.3)
miR-320a	0.057	0.364	0.258	0.735	0.042 (-38.1)	0.065	0.962
miR-342-3p	<0.001 (1.2)	0.656	0.834	0.302	0.111	<0.001 (1.6)	<0.001 (1.5)
miR-376a	0.056	0.900	0.519	0.707	0.745	<0.001 (97.0)	<0.001 (92.6)
miR-422a	<0.001 (5.2)	0.685	0.737	0.517	0.064	<0.001 (6.2)	<0.001 (5.6)
miR-451a	<0.001 (0.8)	0.686	0.321	0.466	0.337	<0.001 (1.2)	<0.001 (1.3)

Supplementary Table 6. Complete correlation matrix of Pearson's correlations between 11 $CD31^{+}$EV miRNAs and selected clinical and biochemical variables.

Variables		miR-126-3p	miR-146a-5p	miR-155	miR-195-5p	miR-21-5p	miR-24-3p	miR-320a	miR-342-3p	miR-376a	miR-422a	miR-451a
Age	**r**	-0.026	0.149	-0.318	-0.415	0.252	-0.270	-0.084	0.224	0.039	0.301	0.281
	p	0.706	0.028	<0.001	<0.001	<0.001	<0.001	0.217	<0.001	0.567	<0.001	<0.001
BMI	**r**	0.007	0.096	-0.151	-0.176	0.138	-0.147	0.035	0.105	0.023	0.209	0.146
	p	0.920	0.160	0.026	0.009	0.043	0.030	0.603	0.121	0.733	0.002	0.032
Waist/hip ratio	**r**	-0.084	0.340	-0.217	-0.288	0.252	-0.224	-0.016	0.290	0.015	0.346	0.308
	p	0.217	<0.001	0.001	<0.001	<0.001	<0.001	0.813	<0.001	0.827	<0.001	<0.001
Fasting glucose	**r**	-0.162	0.163	-0.445	-0.513	0.281	-0.423	-0.170	0.272	-0.001	0.403	0.269
	p	0.017	0.016	<0.001	<0.001	<0.001	<0.001	0.012	<0.001	0.988	<0.001	<0.001
HbA1C	**r**	-0.086	0.173	-0.398	-0.475	0.271	-0.386	-0.122	0.295	0.055	0.382	0.286
	p	0.208	0.010	<0.001	<0.001	<0.001	<0.001	0.073	<0.001	0.418	<0.001	<0.001
Fasting insulin	**r**	-0.082	-0.012	-0.100	-0.095	0.012	-0.082	0.006	0.002	-0.021	-0.012	0.001
	p	0.229	0.855	0.140	0.162	0.858	0.225	0.929	0.976	0.756	0.860	0.985
HOMA index	**r**	-0.107	0.014	-0.176	-0.182	0.053	-0.157	-0.046	0.053	-0.022	0.056	0.046
	p	0.116	0.841	0.009	0.007	0.433	0.020	0.495	0.434	0.748	0.411	0.502
Azotemia	**r**	0.095	0.106	-0.100	-0.107	0.241	-0.101	0.153	0.280	0.126	0.152	0.390
	p	0.163	0.118	0.141	0.114	<0.001	0.136	0.024	<0.001	0.063	0.025	<0.001
Creatinine	**r**	0.078	0.206	-0.133	-0.197	0.310	-0.176	0.129	0.344	0.077	0.219	0.384
	p	0.250	0.002	0.049	0.003	<0.001	0.009	0.057	<0.001	0.257	0.001	<0.001
eGFR	**r**	-0.075	-0.119	0.080	0.138	-0.148	0.088	-0.003	-0.184	-0.088	-0.145	-0.198
	p	0.273	0.078	0.242	0.042	0.029	0.195	0.969	0.006	0.193	0.032	0.003
Uric acid	**r**	0.045	0.143	-0.060	-0.100	0.119	-0.081	-0.028	0.171	-0.005	0.107	0.082
	p	0.509	0.035	0.382	0.143	0.079	0.233	0.681	0.011	0.947	0.115	0.230
ALT	**r**	-0.054	0.016	-0.069	-0.051	-0.044	-0.052	0.013	0.043	-0.089	0.150	-0.098
	p	0.429	0.816	0.310	0.452	0.522	0.448	0.851	0.527	0.190	0.027	0.148
AST	**r**	-0.105	0.011	-0.075	-0.067	-0.004	-0.096	-0.060	0.050	-0.053	0.152	-0.064
	p	0.124	0.873	0.273	0.326	0.957	0.160	0.378	0.460	0.439	0.025	0.347
Gamma GT	**r**	-0.114	-0.007	-0.143	-0.149	0.046	-0.125	-0.150	0.126	-0.114	0.144	0.019
	p	0.094	0.919	0.034	0.028	0.498	0.065	0.027	0.063	0.092	0.034	0.778
Total bilirubin	**r**	-0.019	-0.036	0.071	0.097	-0.026	0.009	-0.054	0.016	-0.021	0.030	-0.023
	p	0.782	0.595	0.294	0.152	0.705	0.893	0.428	0.813	0.754	0.657	0.734

Variables		miR-126-3p	miR-146a-5p	miR-155	miR-195-5p	miR-21-5p	miR-24-3p	miR-320a	miR-342-3p	miR-376a	miR-422a	miR-451a
WBC	**r**	0.037	0.138	-0.088	-0.162	0.127	-0.153	-0.114	0.205	0.001	0.165	0.155
	p	0.586	0.042	0.196	0.017	0.061	0.023	0.094	0.002	0.983	0.015	0.022
RBC	**r**	-0.066	0.056	-0.181	-0.169	0.053	-0.199	-0.163	0.019	0.032	0.117	0.048
	p	0.334	0.414	0.007	0.012	0.432	0.003	0.016	0.783	0.638	0.085	0.478
Hemoglobin	**r**	-0.103	0.034	-0.165	-0.167	0.078	-0.173	-0.123	0.026	-0.001	0.095	0.011
	p	0.129	0.619	0.015	0.013	0.254	0.010	0.070	0.704	0.989	0.162	0.869
Hematocrit	**r**	-0.082	0.064	-0.177	-0.191	0.063	-0.182	-0.117	0.040	0.014	0.106	0.032
	p	0.226	0.344	0.009	0.005	0.352	0.007	0.084	0.552	0.842	0.119	0.643
Serum iron	**r**	-0.086	-0.062	-0.025	-0.017	0.021	-0.029	-0.157	0.023	-0.030	0.022	-0.050
	p	0.206	0.363	0.714	0.803	0.753	0.667	0.020	0.736	0.661	0.750	0.467
Transferrin	**r**	-0.106	0.012	-0.134	-0.091	0.047	-0.007	0.011	0.089	-0.095	0.084	0.055
	p	0.119	0.862	0.048	0.182	0.490	0.915	0.875	0.192	0.163	0.218	0.419
Ferritin	**r**	-0.086	-0.025	-0.007	-0.014	0.039	-0.094	-0.080	0.115	-0.078	0.073	-0.031
	p	0.204	0.715	0.923	0.837	0.569	0.168	0.238	0.091	0.254	0.282	0.653
Platelets	**r**	0.028	-0.028	0.096	0.087	-0.146	0.121	0.021	-0.121	-0.077	-0.081	-0.065
	p	0.684	0.681	0.159	0.199	0.031	0.074	0.754	0.074	0.255	0.234	0.342
Total cholesterol	**r**	0.109	-0.197	0.109	0.159	-0.175	0.171	-0.005	-0.214	-0.115	-0.239	-0.210
	p	0.108	0.003	0.110	0.019	0.010	0.012	0.943	0.001	0.090	<0.001	0.002
HDL-cholesterol	**r**	0.036	-0.181	0.247	0.314	-0.273	0.299	0.052	-0.243	-0.058	-0.343	-0.250
	p	0.596	0.007	<0.001	<0.001	<0.001	<0.001	0.444	<0.001	0.395	<0.001	<0.001
LDL-cholesterol	**r**	0.066	-0.235	0.104	0.168	-0.162	0.169	-0.010	-0.269	-0.054	-0.247	-0.222
	p	0.334	<0.001	0.126	0.013	0.017	0.012	0.888	<0.001	0.432	<0.001	<0.001
ApoA1	**r**	0.056	-0.175	0.197	0.296	-0.234	0.293	0.033	-0.203	-0.014	-0.319	-0.202
	p	0.408	0.009	0.003	<0.001	<0.001	<0.001	0.626	0.003	0.832	<0.001	0.003
ApoB	**r**	0.119	-0.124	0.078	0.156	-0.074	0.131	0.015	-0.161	-0.016	-0.190	-0.108
	p	0.080	0.068	0.254	0.021	0.278	0.054	0.826	0.017	0.812	0.005	0.112
Triglycerides	**r**	-0.016	0.109	-0.112	-0.127	0.051	-0.114	-0.028	0.156	-0.096	0.162	0.049
	p	0.809	0.110	0.099	0.062	0.452	0.092	0.678	0.021	0.156	0.017	0.471
hs-CRP	**r**	-0.044	0.180	-0.085	-0.115	0.055	-0.094	-0.039	0.131	0.059	0.141	0.009
	p	0.515	0.688	0.213	0.089	0.422	0.165	0.567	0.054	0.383	0.038	0.895
Fibrinogen	**r**	0.152	0.070	-0.057	-0.086	0.129	-0.097	0.047	0.208	-0.032	0.206	0.228
	p	0.034	0.329	0.426	0.230	0.072	0.177	0.510	0.004	0.652	0.004	0.001

Variables		miR-126-3p	miR-146a-5p	miR-155	miR-195-5p	miR-21-5p	miR-24-3p	miR-320a	miR-342-3p	miR-376a	miR-422a	miR-451a
PAI-1	**r**	-0.057	0.022	-0.088	-0.138	-0.071	-0.086	-0.028	-0.010	-0.066	-0.008	-0.043
	p	0.404	0.744	0.194	0.041	0.299	0.207	0.681	0.889	0.334	0.901	0.532
Total proteins	**r**	-0.052	0.034	-0.130	-0.162	0.077	-0.167	-0.132	0.179	-0.048	0.273	0.107
	p	0.441	0.620	0.056	0.017	0.260	0.013	0.051	0.008	0.480	<0.001	0.115
Telomere length	**r**	-0.021	-0.221	0.123	0.154	-0.185	0.111	0.005	-0.295	-0.031	-0.216	-0.200
	p	0.755	0.001	0.073	0.025	0.007	0.106	0.948	<0.001	0.651	0.002	0.003
miR-126-3p	**r**	1.000	0.098	0.222	0.313	0.079	0.143	0.169	0.110	-0.053	-0.016	0.143
	p	NA	0.148	<0.001	<0.001	0.244	0.035	0.012	0.104	0.434	0.811	0.035
miR-146a-5p	**r**	0.098	1.000	-0.173	-0.221	0.330	-0.211	0.065	0.590	0.054	0.440	0.405
	p	0.148	NA	0.010	0.001	<0.001	0.002	0.342	<0.001	0.429	<0.001	<0.001
miR-155	**r**	0.222	-0.173	1.000	0.832	-0.437	0.792	0.153	-0.314	0.055	-0.439	-0.331
	p	<0.001	0.010	NA	<0.001	<0.001	<0.001	0.023	<0.001	0.417	<0.001	<0.001
miR-195-5p	**r**	0.313	-0.221	0.832	1.000	-0.488	0.752	0.253	-0.393	0.056	-0.539	-0.394
	p	<0.001	0.001	<0.001	NA	<0.001	<0.001	<0.001	<0.001	0.409	<0.001	<0.001
miR-21-5p	**r**	0.079	0.330	-0.437	-0.488	1.000	-0.419	-0.007	0.686	0.055	0.723	0.686
	p	0.244	<0.001	<0.001	<0.001	NA	<0.001	0.913	<0.001	0.417	<0.001	<0.001
miR-24-3p	**r**	0.143	-0.211	0.792	0.752	-0.419	1.000	0.232	-0.353	0.034	-0.479	-0.355
	p	0.035	0.002	<0.001	<0.001	<0.001	NA	<0.001	<0.001	0.615	<0.001	<0.001
miR-320a	**r**	0.169	0.065	0.153	0.253	-0.007	0.232	1.000	0.027	-0.056	-0.140	0.136
	p	0.012	0.342	0.023	<0.001	0.913	<0.001	NA	0.696	0.409	0.039	0.044
miR-342-3p	**r**	0.110	0.590	-0.314	-0.393	0.686	-0.353	0.027	1.000	0.015	0.741	0.720
	p	0.104	<0.001	<0.001	<0.001	<0.001	<0.001	0.696	NA	0.825	<0.001	<0.001
miR-376a	**r**	-0.053	0.054	0.055	0.056	0.055	0.034	-0.056	0.015	1.000	0.068	0.073
	p	0.434	0.429	0.417	0.409	0.417	0.615	0.409	0.825	NA	0.320	0.282
miR-422a	**r**	-0.016	0.440	-0.439	-0.539	0.723	-0.479	-0.140	0.741	0.068	1.000	0.632
	p	0.811	<0.001	<0.001	<0.001	<0.001	<0.001	0.039	<0.001	0.320	NA	<0.001
miR-451a	**r**	0.143	0.405	-0.331	-0.394	0.686	-0.355	0.136	0.720	0.073	0.632	1.000
	p	0.035	<0.001	<0.001	<0.001	<0.001	<0.001	0.044	<0.001	0.282	<0.001	NA