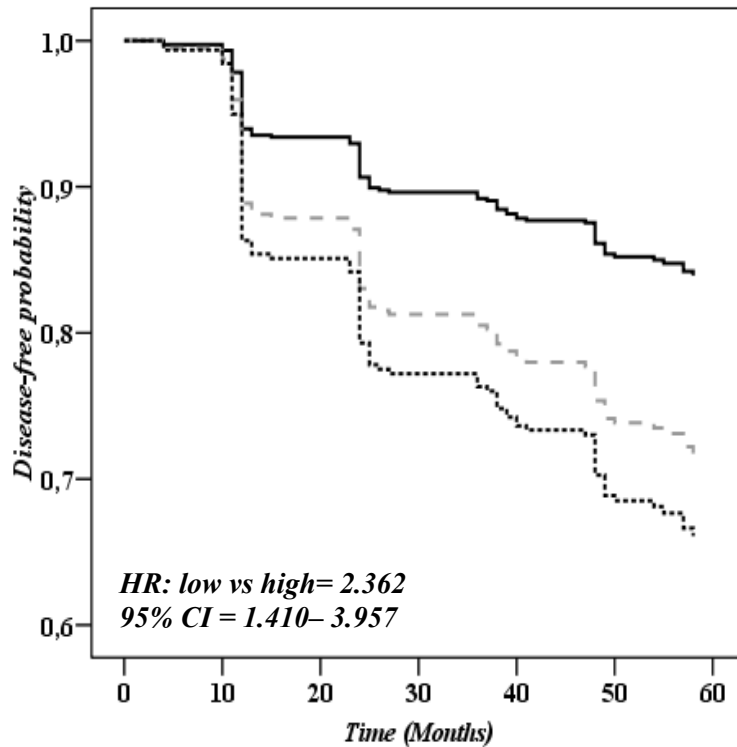


Supplemental Information

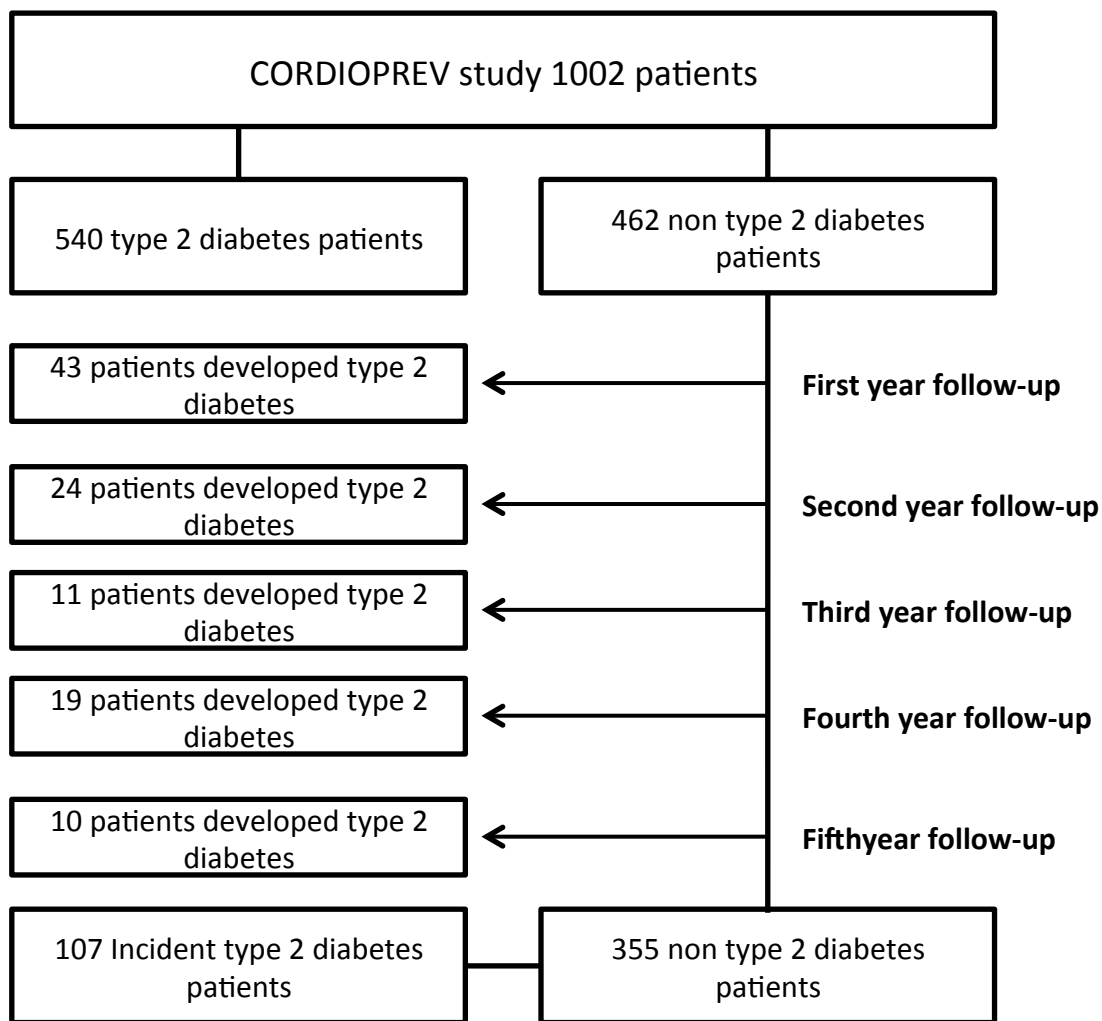
Circulating miRNAs as Predictive Biomarkers of Type 2 Diabetes Mellitus Development in Coronary Heart Disease Patients from the CORDIOPREV Study

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— Low FINDRISC - - - Medium FINDRISC High FINDRISC

Supplementary Figure 1. Disease-free analysis through a Cox regression model based on FINDRISC. Data represent subjects of our study categorized by tertiles of FINDRISC score, low risk (T1), medium risk (T2) and high risk (T3). The analysis was carried out through SPSS (now PASW Statistic for Windows (version 21.0)) (IBM, Chicago, Illinois).



Supplementary Figure 2. Flow chart of the study design.

<i>miRNA</i>	<i>amplified in plasma samples in our study</i>	<i>Fluid, tissue or cell type</i>	<i>Model</i>	<i>References</i>
<i>miR-103 and 107</i>	yes	Pancreatic cell line MIN6 Serum Liver C57BL/6J	Ob/ob mice and diet-induced obese (DIO) mouse human mouse	[1] Trajkovski, et al. [2] Foley, et al. [3] Xu, et al. [1] Trajkovski, et al.
	yes	Plasma	Human and hyperglycemic Lep(ob) mice	[4] Zampetaki, et al.
<i>miR-126</i>		Serum SK-Hep1 hepatocytes	Human Human Mouse ob/ob	[5] Liu, et al. [6] Ryu, et al. [7] Liang, et al.
<i>miR-143</i>	yes	C2C12 cells Muscle Liver	Human mice	[8] Gallagher, et al. [9] Jordan, et al.
<i>miR-144</i>	yes	Plasma C2C12 cells Muscle	Human, rat Human	[10] Karolina, et al [8] Gallagher, et al.
<i>miR-145</i>	yes	HepG2 cells Islets	mice	[11] Kang, et al.
<i>miR-150</i>	yes	Plasma b-cell Plasma C57BL/6J THP-1 cells Microvesicles	Human, rat mice Human mice Human Human	[10] Karolina, et al [12] Xiao, et al. [12, 13] Devaux, et al. [14] Li, et al.
	yes	Plasma	Human and hyperglycemic Lep(ob) mice	[4] Zampetaki, et al.
<i>miR-182</i>	yes	Plasma	Human, rat	[10] Karolina, et al
<i>miR-192</i>	< 80 % of samples	Plasma 3T3-L1 Adipocytes	human, rat. Rat	[10] Karolina, et al. [15] He, et al.
<i>miR-21</i>	< 80 % of samples	Wound tissues 3T3-L1 Adipocytes	KKAY mice (type-2 diabetic strain) mice	[16] Madhyastha, et al. [17] Ling, et al.
	yes	Plasma Macrophages Serum Cardiomyocytes	Human and hyperglycemic Lep(ob) mice Mice Human rat	[4] Zampetaki, et al. [18] Zhuang, et al. [19] Pescador, et al. [20] Lu, et al.
<i>miR-28-3p</i>	yes	Plasma	Human and hyperglycemic Lep(ob) mice	[4] Zampetaki, et al.
<i>miR-29a</i>	yes	Islets Myocytes and GLUT4myc myocytes Islets and plasma	Human; Db/db mice; NOD mice Rat db/m, db/db and DIO mice	[21, 15, 22-25] Bagge, et al.; Yang, et al.; Liang, et al.; Roggli, et al; He, et al.; Herrera, et al.
	yes	Adipocytes 3T3-L1 Plasma	mouse human, rat.	[10] Karolina, et al.
<i>miR-30a5-p</i>	yes	INS-1 cells	Rat.	[26] Kim, et al.
<i>miR-30d</i>	<80 % of samples	Plasma MIN6 cells Pancreatic b cells	human, rat. mouse mouse	[10, 4] Karolina, et al.; Zampetaki, et al. [27] Tang, et al.
<i>miR-320</i>	yes	Plasma	Human, rat	[10] Karolina, et al
<i>miR-33a</i>	no	HepG2 and Huh7 cells	human	[28] Dávalos, et al.
<i>miR-375</i>	yes	MIN6 and TC1 cells NIT1 cells INS-1E cells and primary rat islets	Goto-Kakizaki (GK) rats.	[29] Poy, et al. [30, 31] Li, et al.; Xia, et al. [32] El Ouaamari, et al.
		Pancreatic islets Serum	Human, mice. Human.	[33] Poy, et al. [34, 35] Kong, et al.; Higuchi, et al.
<i>miR-657</i>	no	Hep G2 cells	Human	[36] Lv, et al.
<i>miR-7</i>	yes	Pancreatic islets Islets	Human, mouse mouse	[37] Latreille, et al. [38] Wang, et al.
	yes	INS-1E and MIN6B1 beta-cell line MIN6B1	Rat, mouse mice	[39] Plaisance, et al. [40] Lovis, et al.
<i>miR-96</i>	no	beta-cell line MIN6B1	mice	[40] Lovis, et al.
<i>miR-let7</i>	< 80 % of samples		mice	[41] Frost and Olson.
		3T3-L1 Adipocytes	Human, mouse	[42, 43] Sun, et al.; Wei, et al.

Supplementary table 1. Bibliographic search of miRNAs related to T2DM.

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<i>Model</i>	<i>AUC</i>	<i>95% CI</i>	<i>Sensibility</i>	<i>Specificity</i>	<i>Accuracy %</i>
<i>15 miRNAs</i>	0.8487	0.808-0.889	0.796	0.774	76.9
<i>9 miRNAs target</i>	0.8178	0.771-0.864	0.758	0.779	77.4
<i>9 miRNAs target and HbA1c</i>	0.8342	0.790-0.878	0.776	0.809	80.0
<i>9 miRNAs target + HbA1c + body weight (without adjusting by covariables)</i>	0.8212	0.776-0.866	0.633	0.819	77.2
<i>9 miRNAs target + HbA1c + waist circumference (without adjusting by covariables)</i>	0.8234	0.778-0.868	0.610	0.814	77.9
<i>Clinical parameters</i>	0.7354	0.674-0.796	0.702	0.698	69.9
<i>Insulin sensitivity/resistance indexes and classical parameters</i>	0.7697	0.713-0.826	0.663	0.809	77.5
<i>9 target and FINDRISC</i>	0.8123	0.766-0.860	0.788	0.723	73.8
<i>9 target, FINDRISC and HbA1c</i>	0.8293	0.785-0.874	0.796	0.774	77.9
<i>Insulin sensitivity/resistance indexes, classical parameters and FINDRISC</i>	0.7647	0.709-0.820	0.663	0.755	73.3

Supplementary Table 2. Predictive models performed in our study by Operating Curve Analysis (ROC). We built models including all the miRNAs measured together with classical parameters (fasting glucose, 2-h glucose, HbA1c), beta cell function and insulin sensitivity/resistance indexes (IGI, ISI, DI, HIRI, MISI) and FINDRISC score. *AUC*, Area under curve; *CI*, Confidence interval; *HbA1c*, Glycosylated hemoglobin. All the models were adjusted for those covariables that were allowed avoiding over estimating information, the set of covariables included: diet, age, gender, BMI, HDL, TG, Hba1c and waist circumference.