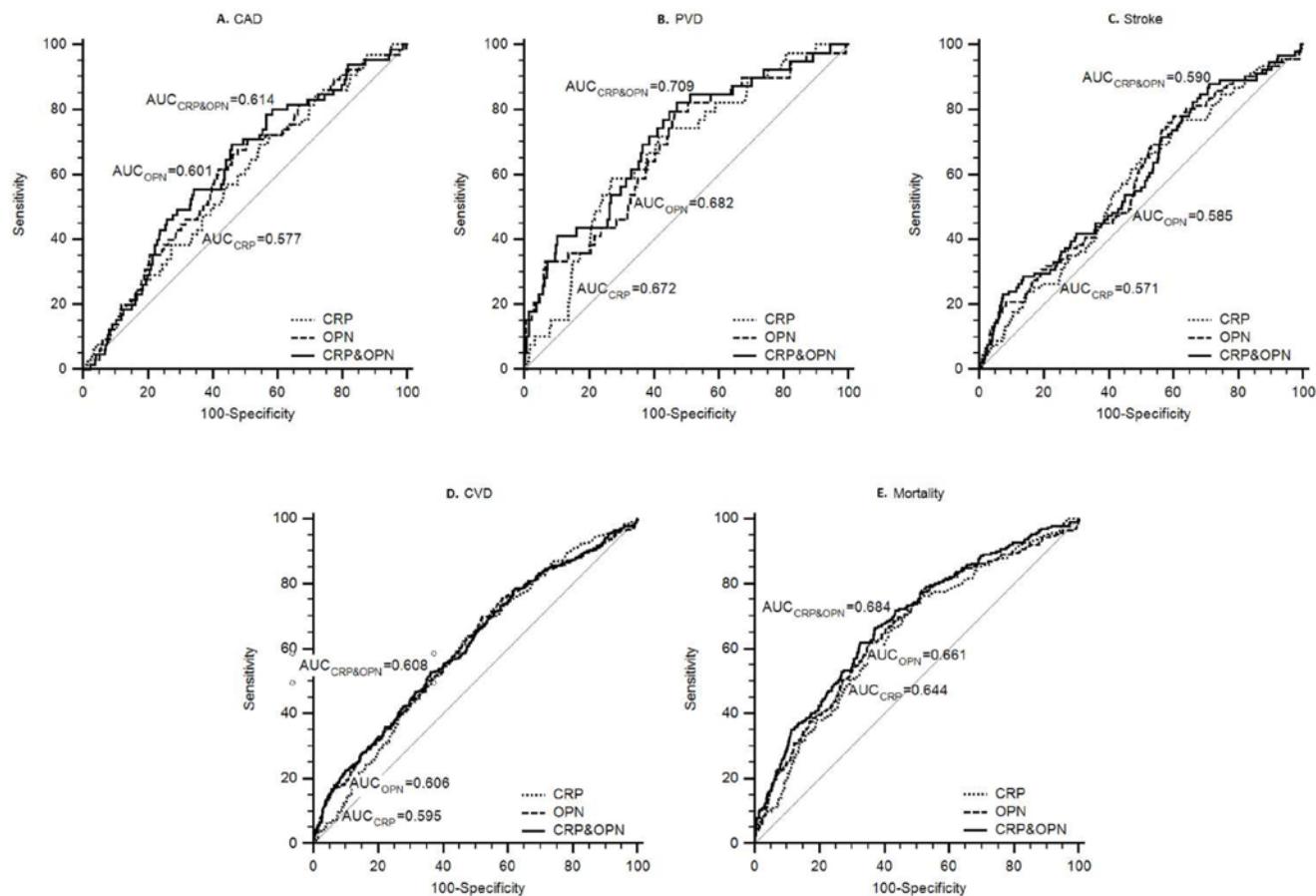


## SUPPLEMENTARY DATA

**Supplementary Figure 1.** ROC curve analysis for OPN and CRP for the prediction of (A) incident coronary artery disease (CAD), (B) incident peripheral vascular disease (PWD), (C) incident stroke, (D) incident cardiovascular disease (CVD), (E) all-cause mortality.

OPN – osteopontin; CRP – high sensitive C reactive protein;  $AUC_{OPN}$  – area under curve for OPN without adjustments;  $AUC_{CRP}$  – area under curve for CRP without adjustments;  $AUC_{OPN\&CRP}$  – area under curve for OPN and CRP used together in the same model, without any other correction.



## SUPPLEMENTARY DATA

### Supplementary Table 1. List of the FinnDiane Centers

#### The Finnish Diabetic Nephropathy Study Centers

Anjalankoski Health Center

S.Koivula, T.Uggeldorf

Central Finland Central Hospital, Jyväskylä

T.Forslund, A.Halonen, A.Koistinen, P.Koskiaho, M.Laukanen, J.Saltevo, M.Tiihonen

Central Hospital of Åland Islands, Mariehamn

M.Forsen, H.Granlund, A.-C.Jonsson, B.Nyroos

Central Hospital of Kanta-Häme, Hämeenlinna

P.Kinnunen, A.Orvola, T.Salonen, A.Vähänen

Central Hospital of Kymenlaakso, Kotka

R.Paldanius, M.Riihelä, L.Ryysy

Central Hospital of Länsi-Pohja, Kemi

H.Laukanen, P.Nyländen, A.Sademies

Central Ostrobothnian Hospital District, Kokkola

S.Anderson, B.Asplund, U.Byskata, P.Liedes,

M.Kuusela, T.Virkkala

City of Espoo Health Center: Espoonlahti

A.Nikkola, E.Ritola Tapiola M.Niska, H.Saarinen Samaria E.Oukko-Ruponen, T.Virtanen Viherlaakso

A.Lyytinen

City of Helsinki Health Center:

Puistola H.Kari, T.Simonen Suutarila A.Kaprio, J.Kärkkäinen, B.Rantaeskola Töölö P.Kääriäinen,

J.Haaga, A-L.Pietiläinen

City of Hyvinkää Health Center

S.Klemetti, T.Nyandoto, E.Rontu, S.Satuli-Autere

City of Vantaa Health Center:

Korso R.Toivonen, H.Virtanen

Länsimäki R.Ahonen, M.Ivaska-Suomela, A.Jauhainen

Martinlaakso M.Laine, T.Pellonpää, R.Puranen

Myyrmäki A.Airas, J.Laakso, K.Rautavaara

Rekola M.Erola, E.Jatkola

Tikkurila R.Lönnblad, A.Malm, J.Mäkelä, E.Rautamo

Heinola Health Center P.Hentunen, J.Lagerstam

Helsinki University Central Hospital, Department of

Medicine, Division of Nephrology A.Ahola, M.Feodoroff, D.Gordin, O.Heikkilä,

K.Hietala,L.Salovaara, J.Kytö, S.Lindh, K.Pettersson-Fernholm, A.Sandelin, L.Thorn, J.Tuomikangas,

T.Vesisenaho, J.Wadén

Herttoniemi Hospital, Helsinki V.Sipilä

Hospital of Lounais-Häme, Forssa

T.Kalliomäki, J.Koskelainen, R.Nikkanen, N.Savolainen, H.Sulonen, E.Valtonen

Iisalmi Hospital

E.Toivanen

Jokilaakso Hospital, Jämsä

A.Parta, I.Pirttiniemi

Jorvi Hospital, Helsinki University Central Hospital

S.Aranko, S.Ervasti, R.Kauppinen-Mäkelin, A.Kuusisto, T.Leppälä, K.Nikkilä, L.Pekkonen

## SUPPLEMENTARY DATA

Jyväskylä Health Center, Kyllö  
K.Nuorva, M.Tiihonen  
Kainuu Central Hospital, Kajaani  
S.Jokelainen, P.Kemppainen, A-M.Mankinen, M.Sankari  
Kerava Health Center  
H.Stuckey, P.Suominen  
Kirkkonummi Health Center  
A.Lappalainen, M.Liimatainen, J.Santaholma  
Kivelä Hospital, Helsinki  
A.Aimolahti, E.Huovinen  
Koskela Hospital, Helsinki  
V.Ilkka, M.Lehtimäki  
Kotka Health Center  
E.Pälikkö-Kontinen, A.Vanhanen  
Kouvola Health Center  
E.Koskinen, T.Siitonen  
Kuopio University Hospital  
E.Huttunen, R.Ikäheimo, P.Karhapää, P.Kekäläinen, M.Laakso, T.Lakka, E.Lampainen, L.Moilanen, L.Niskanen, U.Tuovinen, I.Vauhkonen, E.Voutilainen  
Kuusamo Health Center  
T.Kääriäinen, E.Isopoussu  
Kuusankoski Hospital  
E.Kilkki, I.Koskinen, L.Riihelä  
Laakso Hospital, Helsinki  
T.Meriläinen, P.Poukka, R.Savolainen, N.Uhlenius  
Lahti City Hospital  
A.Mäkelä, M.Tanner  
Lapland Central Hospital, Rovaniemi  
L.Hyvärinen, S.Severinkangas, T.Tulokas  
Lappeenranta Health Center  
P.Linkola, I.Pulli  
Lohja Hospital  
T.Granlund, M.Saari, T.Salonen  
Länsi-Uusimaa Hospital, Tammisaari  
I.-M.Jousmaa, J.Rinne  
Loimaa Health Center  
A.Mäkelä, P.Eloranta  
Malmi Hospital, Helsinki  
H.Lanki, S.Moilanen, M.Tilly-Kiesi  
Mikkeli Central Hospital  
A.Gynther, R.Manninen, P.Nironen, M.Salminen, T.Vänttinen  
Mänttä Regional Hospital  
I.Pirttiniemi, A-M.Hänninen  
North Karelian Hospital, Joensuu  
U-M.Henttula, P.Kekäläinen, M.Pietarinen, A.Rissanen, M.Voutilainen  
Nurmijärvi Health Center  
A.Burgos, K.Urtamo  
Oulaskangas Hospital, Oulainen

## SUPPLEMENTARY DATA

E.Jokelainen, P.-L.Jylkkä, E.Kaarlela, J.Vuolaspuro  
Oulu Health Center  
L.Hiltunen, R.Häkkinen, S.Keinänen-Kiukaanniemi  
Oulu University Hospital  
R.Ikäheimo  
Päijät-Häme Central Hospital  
H.Haapamäki, A.Helanterä, S.Hämäläinen, V.Ilvesmäki, H.Miettinen  
Palokka Health Center  
P.Sopanen, L.Welling  
Pieksämäki Hospital  
V.Javtsenko, M.Tamminen  
Pietarsaari Hospital  
M-L.Holmbäck, B.Isomaa, L.Sarelin  
Pori City Hospital  
P.Ahonen, P.Merensalo, K.Sävelä  
Porvoo Hospital  
M.Kallio, B.Rask, S.Rämö  
Raahe Hospital  
A.Holma, M.Honkala, A.Tuomivaara, R.Vainionpää  
Rauma Hospital  
K.Laine, K.Saarinen, T.Salminen  
Riihimäki Hospital  
P.Aalto, E.Immonen, L.Juurinen  
Salo Hospital  
A.Alanko, J.Lapinleimu, P.Rautio, M.Virtanen  
Satakunta Central Hospital, Pori  
M.Asola, M.Juhola, P.Kunelius, M.-L.Lahdenmäki, P.Pääkkönen, M.Rautavirta  
Savonlinna Central Hospital  
T.Pulli, P.Sallinen, M.Taskinen, E.Tolvanen, H.Valtonen, A.Vartia  
Seinäjoki Central Hospital  
E.Korpi-Hyövälti, T.Latvala, E.Leijala  
South Karelia Central Hospital, Lappeenranta  
T.Ensala, E.Hussi, R.Härkönen, U.Nyholm, J.Toivanen  
Tampere Health Center  
A.Vaden, P.Alarotu, E.Kujansuu, H.Kirkkopelto-Jokinen, M.Helin, S.Gummerus, L.Calonius,  
T.Niskanen, T.Kaitala,  
T.Vatanen  
Tampere University Hospital  
I.Ala-Houhala, T.Kuningas, P.Lampinen, M.Määttä, H.Oksala, T.Oksanen, K.Salonen, H.Tauriainen,  
S.Tulokas  
Tiirismaa Health Center, Hollola  
T.Kivelä, L.Petlin, L.Savolainen  
Turku Health Center  
I.Hämäläinen, H.Virtamo, M.Vähätilo  
Turku University Central Hospital  
K.Breitholz, R.Eskola, K.Metsärinne, U.Pietilä, P.Saarinen, R.Tuominen, S.Äyräpää,  
Vaajakoski Health Center  
K.Mäkinen, P.Sopanen

## SUPPLEMENTARY DATA

Valkeakoski Regional Hospital  
 S.Ojanen, E.Valtonen, H.Ylönen, M.Rautiainen,T.Immonen  
 Vammala Regional Hospital  
 I.Isomäki, R.Kroneld, M.Tapiolinna-Mäkelä  
 Vasa Central Hospital  
 S.Bergkulla, U.Hautamäki, V.-A.Myllyniemi, I.Rusk

**Supplementary Table 2.** ROC curve analysis for the main comparisons between osteopontin and high sensitive C reactive protein.

Receiver operating characteristic (ROC)	AUC	SE	95%CI	Differences between AUCs			
				Osteopontin		CRP	
				Difference	p	Difference	p
Incident CAD							
CRP	0.577	0.034	0.552 – 0.601	0.025	0.60	-	-
OPN	0.601	0.034	0.577 – 0.626	-	-	0.025	0.60
CRP&OPN	0.614	0.033	0.590 – 0.638	0.013	0.35	0.037	0.39
Incident PVD							
CRP	0.672	0.040	0.651 – 0.692	0.011	0.86	-	-
OPN	0.682	0.044	0.661 – 0.702	-	-	0.011	0.86
CRP&OPN	0.709	0.043	0.689 – 0.729	0.027	0.21	0.038	0.44
Incident Stroke							
CRP	0.571	0.030	0.550 - 0.593	0.013	0.75	-	-
OPN	0.585	0.031	0.563 - 0.606	-	-	0.013	0.75
CRP&OPN	0.590	0.031	0.568 - 0.611	0.005	0.71	0.019	0.59
Incident CVD							
CRP	0.595	0.017	0.574 - 0.617	0.011	0.64	-	-
OPN	0.606	0.018	0.585 - 0.628	-	-	0.011	0.64
CRP&OPN	0.608	0.018	0.587 - 0.629	0.002	0.77	0.013	0.54
Mortality							
CRP	0.644	0.021	0.623 – 0.665	0.017	0.57	-	-
OPN	0.661	0.021	0.640 – 0.681	-	-	0.017	0.57
CRP&OPN	0.684	0.021	0.663 – 0.703	0.023	0.06	0.039	0.09

OPN - univariate analysis for osteopontin; CRP – univariate analysis for high sensitive C reactive protein; L-CRP&OPN – Cox regression model with CRP plus OPN in the same model without adjustments; CAD – Coronary artery disease; CVD – Cardiovascular disease; ESRD – End stage renal disease; PVD – Peripheral vascular disease; ROC - Receiver operating characteristic; AUC – area under the curve; SE – standard error of AUC; 95% CI – 95% Confidence Interval for AUC; P – probability of no difference between the AUCs (considered significant when < 0.05).

## SUPPLEMENTARY DATA

**Supplementary Table 3.** Reclassification measures (net reclassification improvement – NRI and the integrated discrimination improvement – IDI) for OPN used on top of other prediction models.

A	Incident microalbuminuria				Progression to macroalbuminuria				Progression to ESRD			
	NRI	P	IDI	P	NRI	P	IDI	P	NRI	P	IDI	P
Backward selection	-1.44	0.62	0.07	0.73	5.33	0.32	0.14	0.78	2.73	0.94	1.95	0.10
Model 1	7.47	0.03	0.27	0.47	N/A*	N/A*	0.02	0.97	4.50	0.17	1.56	0.16
Model 2	7.14	0.07	0.41	0.38	-0.52	0.65	-0.02	0.93	3.15	0.33	0.61	0.49
Model 3	0.12	0.03	0.57	0.06	0.00 <sup>#</sup>	1.00 <sup>#</sup>	0.01	0.89	18.05 <sup>#</sup>	0.007 <sup>#</sup>	9.27	<0.0001

B	CVD				Death			
	NRI	p	IDI	p	NRI	p	IDI	p
Backward selection	3.51	0.02	0.53	0.11	6.37	0.01	0.79	0.19
Model 1	1.79	0.26	0.43	0.16	6.63	0.04	0.72	0.21
Model 2	3.30	0.02	0.43	0.18	4.71	0.09	0.66	0.25
Model 3	10.76	<0.001	2.11	<0.001	13.87	<0.001	2.92	<0.001
Model 3 + hsCRP	7.13	0.003	1.85	<0.001	12.58	0.001	2.15	0.008

C	Incident CAD				Incident stroke				Incident PVD			
	NRI	p	IDI	p	NRI	p	IDI	p	NRI	p	IDI	p
Backward selection	4.58	0.10	0.19	0.54	-3.99	0.31	0.13	0.49	6.44	0.52	2.97	0.26
Model 1	0.12	0.56	0.03	0.75	5.10	0.13	0.03	0.80	0.42	0.95	1.99	0.47
Model 2	0.25	0.16	0.03	0.72	0.19	0.92	-0.02	0.75	8.77	0.29	2.58	0.42
Model 3	8.74	0.01	0.47	0.37	2.80	0.41	0.11	0.62	2.93	0.80	4.50	0.15
Model 3 + hsCRP	6.76	0.03	0.40	0.42	0.33	0.92	0.05	0.80	9.36	0.43	4.41	0.16

\* No patient in the risk class 0-5% within the group of progressors according to this model. <sup>#</sup>Calculated only with two risk thresholds 10% and 20%.NRI is the difference in percent moving up and down risk strata among cases versus controls after the addition of a new biomarker to a known model. With regards to CAD prevention, the 5%, 10% and 20% cut-off points have been proposed as relevant for clinical decision making. The same cut-off points were also used for renal end points in this study. NRI is presented as a percent (%) of patients reclassified. IDI is presented as percent and should be interpreted as the increase of the difference in average predicted probabilities between cases and controls when OPN was added to the model.

ESRD; end-stage renal disease, CVD; established cardiovascular disease; hsCRP; high sensitivity C-reactive protein, OPN; osteopontin, CAD; coronary artery disease, PVD; peripheral vascular disease.

Model 1 was adjusted for sex, age, waist to hip-ratio, current smoking, A1C, triglycerides, antihypertensive medication, eGFR, AER, hsCRP.

Model 2 was adjusted for sex, age, duration of diabetes, BMI, waist to hip-ratio, current smoking, A1C, triglycerides, LDL cholesterol, systolic blood pressure, antihypertensive medication, eGFR, AER, hsCRP.

Model 3 was adjusted for the covariates in the Framingham risk score (sex, age LDL cholesterol, HDL cholesterol, systolic blood pressure, diabetes, smoking).

## SUPPLEMENTARY DATA

**Supplementary Table 4.** Cox regression analysis for the predictive value of OPN for incident CVD-events.

	<b>Incident CAD</b>		<b>Incident stroke</b>		<b>Incident PVD</b>	
	<b>HR (95% CI)</b>	<b>p-value</b>	<b>HR (95% CI)</b>	<b>p-value</b>	<b>HR (95% CI)</b>	<b>p-value</b>
Model 1	-	NS	1.02 (1.00-1.03)	0.01	1.03 (1.01-1.04)	<0.001
Model 2	-	NS	1.02 (1.00-1.03)	0.03	1.03 (1.01-1.05)	0.001
Model 3	1.03 (1.02-1.05)	<0.001	1.02 (1.01-1.04)	<0.001	1.04 (1.03-1.05)	<0.001

Results are presented as HR (95% CI); Hazard ratio (95% confidence interval).

Model 1 adjusted for sex, age, Waist to hip-ratio, current smoking, A1C, total cholesterol, antihypertensive medication, eGFR, microalbuminuria, macroalbuminuria, hsCRP.

Model 2 adjusted for sex, age, duration of diabetes, BMI, waist to hip-ratio, current smoking, A1C, LDL cholesterol, systolic blood pressure, antihypertensive medication, eGFR, microalbuminuria, macroalbuminuria, hsCRP.

Model 3 adjusted for the covariates in the Framingham risk score (sex, age, LDL cholesterol, HDL cholesterol, systolic blood pressure, diabetes, smoking).