

SUPPLEMENTAL MATERIAL

Value of Progression of Coronary Artery Calcification for Risk Prediction of Coronary and Cardiovascular Events

- Result of the Heinz Nixdorf Recall (HNR) Study -

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Suppl. Table 1. **5-year Follow-up Characteristics of the Heinz Nixdorf Recall Cohort (N=3281) with two CT Scans, the second after a Time Interval without Events of 5 Years. According to Coronary (N=85), Hard Cardiovascular (N=161) and Total Cardiovascular events (N=241) during a Follow-up Time of 7.8 ± 2.2 years after the Last CT Scan**

	All subjects (n=3281)	Coronary event (n=85)	No coronary event (n=3196)	P-value*	Hard CV event (n=161)	No CV event (n=3120)	P-value*	Total CV event (n=241)	No CV event (n=3040)	P-value*
Age, yrs	63.9 ± 7.5	66.5 ± 7.7	63.8 ± 7.5	0.0011	68.2 ± 7.7	63.7 ± 7.4	<0.0001	67.6 ± 7.3	63.6 ± 7.5	<0.0001
Male sex, n(%)	1524 (46.4)	61 (71.8)	1463 (45.8)	<0.0001	105 (65.2)	1419 (45.5)	<0.0001	163 (67.6)	1361 (44.8)	<0.0001
Systolic BP, mmHg	133.7 ± 19.7	139.1 ± 18.2	133.6 ± 19.7	0.0011	142.2 ± 20.9	133.3 ± 19.5	<0.0001	141.9 ± 20.5	133.1 ± 19.4	<0.0001
Diastolic BP, mmHg	79.5 ± 10.4	80.2 ± 10.2	79.4 ± 10.4	0.48	81.3 ± 10.8	79.4 ± 10.4	0.021	81.4 ± 11.1	79.3 ± 10.3	0.0032
Total Cholesterol, mg/dL	228.7 ± 40.0	232.8 ± 58.6	228.6 ± 39.4	0.34	229.0 ± 50.8	228.7 ± 39.4	0.92	229.5 ± 48.4	228.7 ± 39.3	0.74
HDL-C, mg/dL	60.9 ± 16.1	53.2 ± 14.5	61.2 ± 16.1	<0.0001	55.4 ± 15.1	61.2 ± 16.1	<0.0001	55.5 ± 15.0	61.4 ± 16.2	<0.0001
LDL-C, mg/dL	133.4 ± 34.4	133.4 ± 38.1	133.4 ± 34.3	0.98	130.8 ± 34.9	133.5 ± 34.4	0.32	134.5 ± 36.2	133.3 ± 34.2	0.60
Never smoker, n(%)	1437 (43.8)	29 (34.1)	1408 (44.1)		65 (40.4)	1372 (44.0)		101 (41.9)	1336 (43.9)	
Former smoker, n(%)	1260 (38.4)	33 (38.8)	1227 (38.4)	0.048	62 (38.5)	1189 (38.4)	0.47	89 (36.9)	1171 (38.5)	0.37
Present smoker, n(%)	584 (17.8)	23 (27.1)	561 (17.6)		34 (21.1)	550 (17.6)		51 (21.2)	533 (17.5)	
Diabetes, n(%)	532 (16.2)	23 (27.1)	509 (15.9)	0.006	46 (28.6)	486 (15.6)	<0.0001	68 (28.2)	464 (15.3)	<0.0001
hsCRP median (Q1-Q3) mg/L	1.4 (0.8 - 2.9)	1.8 (1.1 - 4.2)	1.4 (0.8 - 2.8)	0.0084	1.7 (0.9 - 3.5)	1.4 (0.8 - 2.8)	0.021	1.6 (0.8 - 3.7)	1.4 (0.8 - 2.8)	0.011
eGFR, mL/min	65.6 ± 10.7	65.2 ± 11.6	65.6 ± 10.7	0.74	64.1 ± 11.9	65.6 ± 10.7	0.07	64.9 ± 11.2	65.6 ± 10.7	0.30
Antihypertensive medication, n(%)	1422 (43.3)	53 (62.4)	1369 (42.8)	0.0003	105 (65.2)	1317 (42.2)	<0.0001	150 (62.2)	1272 (41.8)	<0.0001
Lipid-lowering medication, n(%)	550 (16.9)	16 (18.8)	538 (16.8)	0.63	30 (18.6)	524 (16.8)	0.54	52 (21.6)	502 (16.5)	0.043
CAC median (Q1 - Q3)	24.0 (0 - 180.5)	282.9 (63.9 - 731.6)	21.5 (0 - 170.1)	<0.0001	183.3 (34.0 - 542.3)	19.6 (0 - 114.9)	<0.0001	269.0 (58.5 - 757.6)	16.8 (0 - 149.7)	<0.0001
CAC=0, n(%)	1179 (35.9)	11 (12.9)	1168 (36.5)		20 (12.4)	1159 (37.1)		22 (9.1)	1157 (38.1)	
CAC=1 - 99, n(%)	1022 (31.1)	15 (17.6)	1007 (31.5)		44 (27.3)	978 (31.3)		56 (23.2)	966 (31.8)	
CAC=100 - 399, n(%)	615 (18.7)	25 (29.4)	590 (18.5)	<0.0001	48 (29.8)	567 (18.2)	<0.0001	71 (29.5)	544 (17.9)	<0.0001
CAC≥400, n(%)	465 (14.2)	34 (40.0)	431 (13.5)		49 (30.4)	416 (13.3)		92 (38.2)	373 (12.3)	

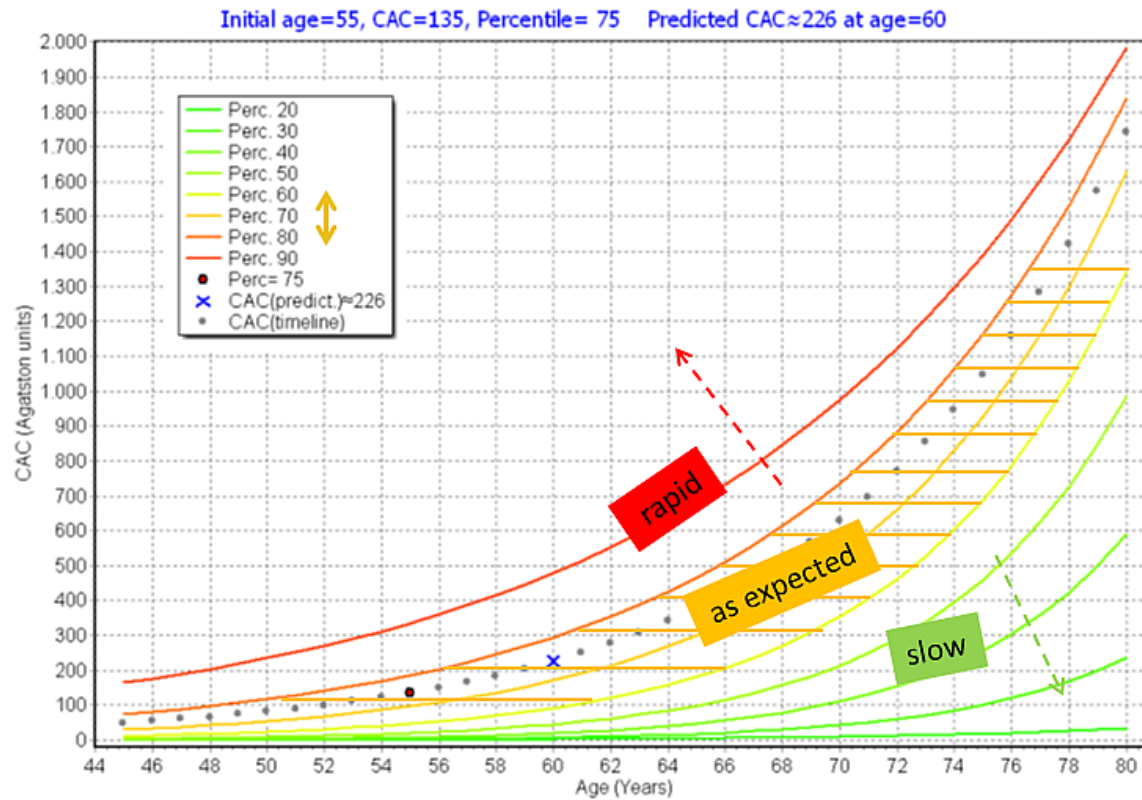
BP indicates blood pressure, CAC coronary artery calcification, eGFR glomerular filtration rate, HDL-C high density lipoprotein-cholesterol, hsCRP high sensitive C-reactive protein, LDL-C low-density lipoprotein-cholesterol, values are for frequency (%), median (interquartile range) or mean (± SD). CVD event: cardiovascular event without / including revascularizations. *P-values are for differences between groups using chi-square or Fisher's exact test or Cochran-Armitage trend test, t-test or Mann-Whitney U-test.

Suppl. Table 2. List of Criteria Used for Estimating Coronary Artery Calcification Progression Calculated from Baseline and 5-Year CT Scans

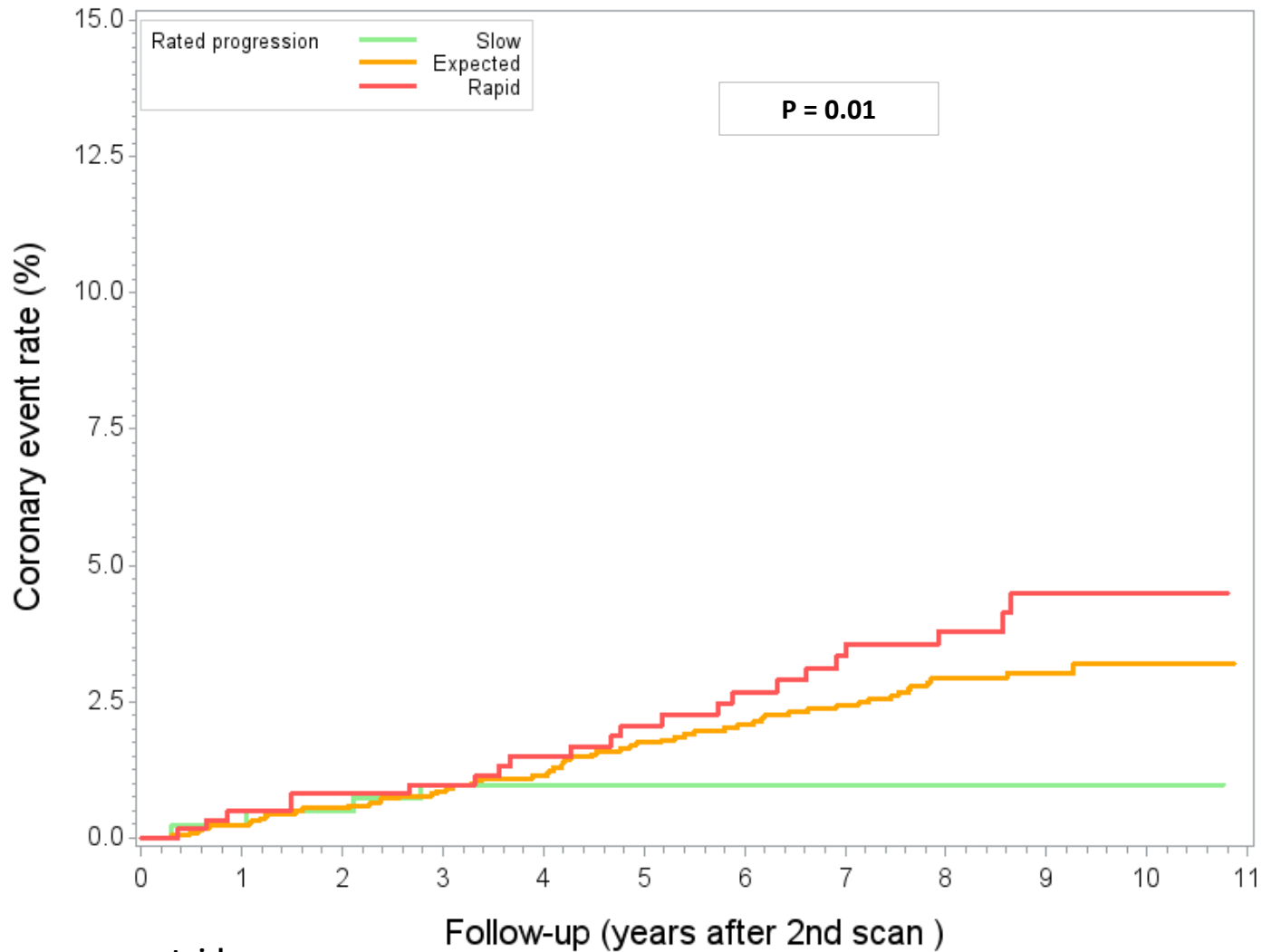
Criterion	Algorithm	Unit	Abbreviation
Berry criterion	CAC _b =0: CAC _{5y} >0 CAC _b =1-100: (CAC _{5y} -CAC _b) ≥10 per year - CAC _b >100: (CAC _{5y} -CAC _b)/CAC _b ≥10% per year	1 vs. 0	Berry
Hokanson criterion	($\sqrt{CAC_{5y}} - \sqrt{CAC_b}$) >2.5	1 vs. 0	Hokanson
Slow vs. expected CAC progression*) Rapid vs. expected CAC progression*)	Progression below / above acceptance band *)	1 vs. 0 1 vs. 0	Slow & Rapid
Annualized change of CAC	(CAC _{5y} -CAC _b) per year	Per SD, 40.4/year	Absolute
Annualized change of CAC, square root scale	($\sqrt{CAC_{5y}} - \sqrt{CAC_b}$) per year	Per SD, 0.76/year	Root
Annualized change of CAC , log scale	(log(CAC _{5y} +1)-log(CAC _b +1)) per year	Per SD, 0.22/year	Log
Expected CAC _{5y} calculated following individual CAC _b percentile for time between CT scans *)	Observed log(CAC _{5y} +1) minus expected log(CAC _{5y} +1)	Per SD, 1.20/year	Log obs – log exp
Model including observed CAC _{5y} and time between CT scans	log(CAC _{5y} +1) Time between CT scans	Per SD, 2.59 Per SD, 0.26 years	Log(CAC5y+1) & time
Raggi criterion	CAC _b >0: (CAC _{5y} -CAC _b)/CAC _b >15% per year	1 vs. 0	Raggi
Annualized percent change of CAC	CAC _b >0: (CAC _{5y} -CAC _b)/CAC _b (%/year)	Per SD, 149.3 %/year	Percent

CAC indicates coronary artery calcium, at baseline, CAC_b, and after a 5-year interval, CAC_{5y}. SD stands for standard deviation

*)The individual percentile of the CAC distribution remains stable over time and can be used for calculating the CAC_{5y} value (expected CAC progression) and compared to the observed CAC_{5y} (observed CAC progression). A higher than expected value was defined as rapid and a lower than expected value as slow CAC progression. For the observed CAC progression an interval of percentiles around the expected value was predefined (acceptance band).

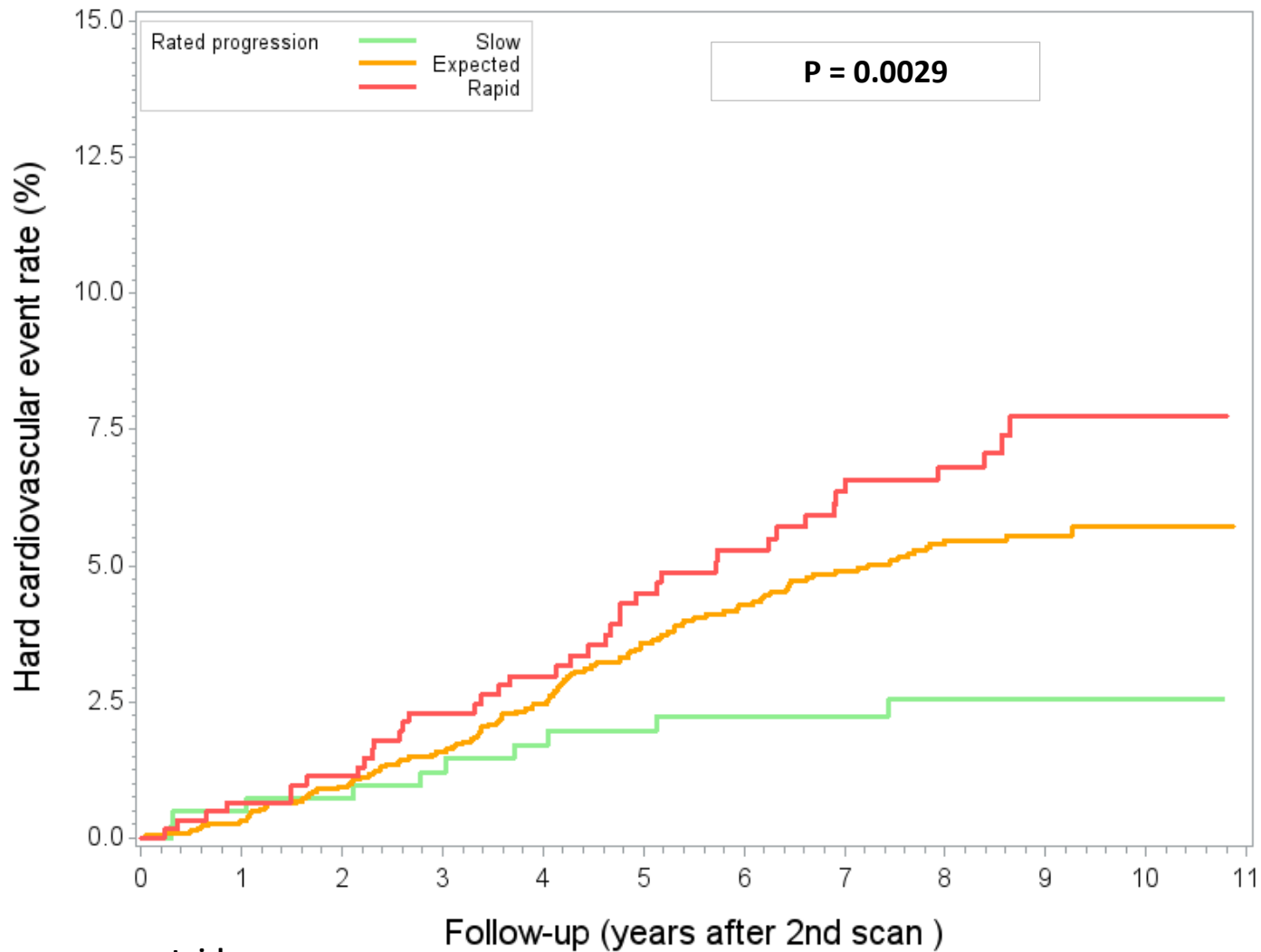


Suppl. Figure 1: The 20th, 30th ... 90th percentiles of the CAC (Agatston score) distribution as functions of age in men, calculated from the Heinz Nixdorf Recall study cohort at baseline.^{1, 2} For a man aged 55 on the 75th percentile (CAC=135, predicted CAC=226 after 5 years), the definition of rapid progression (red color, CAC_{5y} above the yellow hatched acceptance band), slow progression (green color, CAC_{5y} below the yellow hatched acceptance band), and progression as expected (within that acceptance band – yellow hatched range) is illustrated.



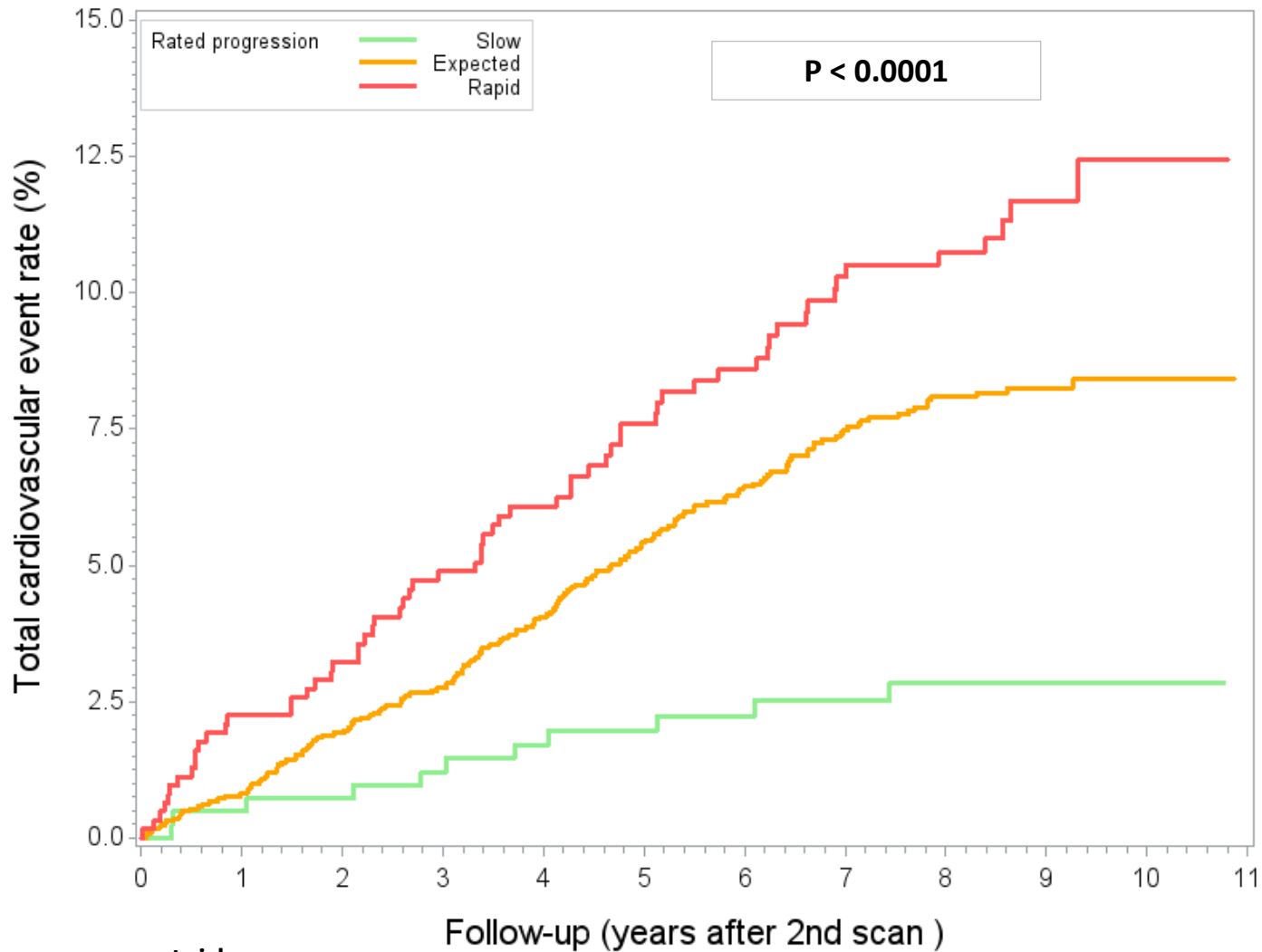
	n at risk					
Slow	415	409	397	339	296	14
Expected	2242	2207	2096	1718	1515	129
Rapid	624	603	573	464	415	34

Suppl. Figure 2 A. Kaplan-Meier curves for coronary events, stratified by rated progression. P-value from log-rank test of trend.



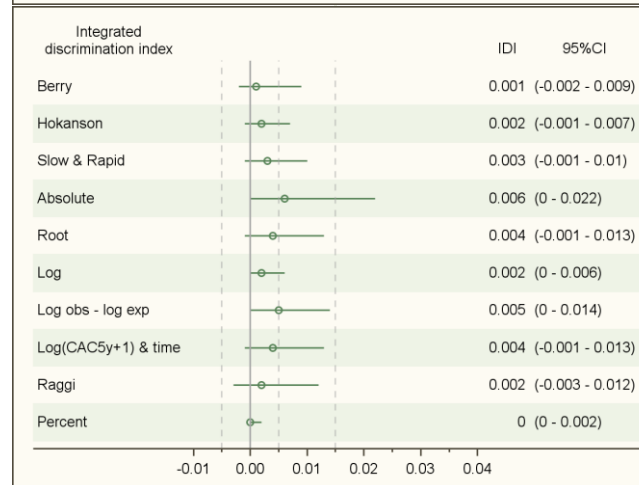
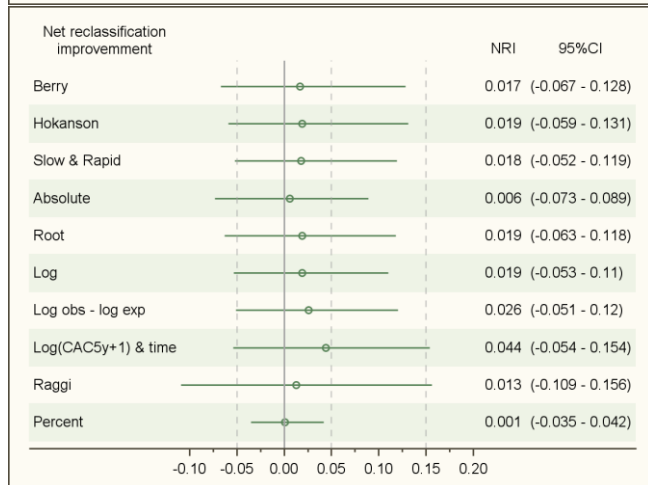
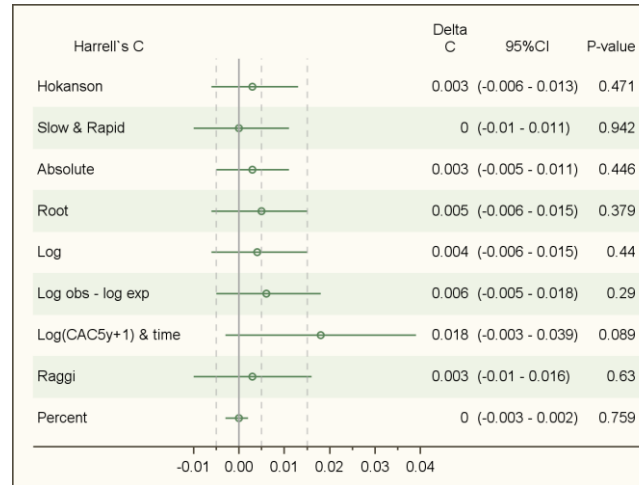
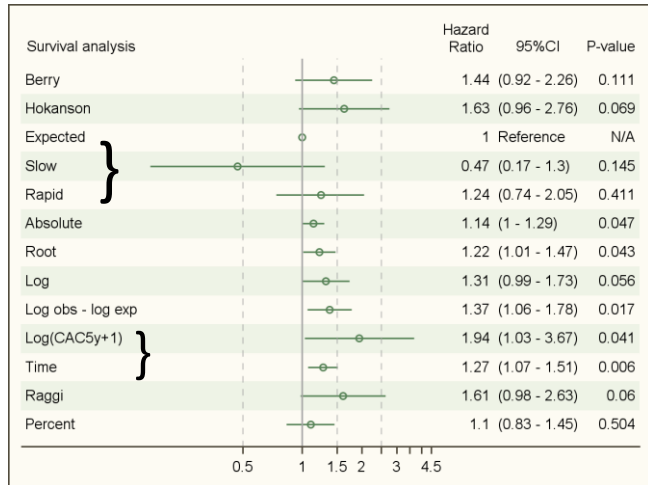
	n at risk					
Slow	415	409	395	338	294	14
Expected	2242	2202	2076	1699	1459	128
Rapid	624	601	576	458	410	34

Suppl. Figure 2 B. Kaplan-Meier curves for hard CV events, stratified by rated progression. P-value from log-rank test of trend.

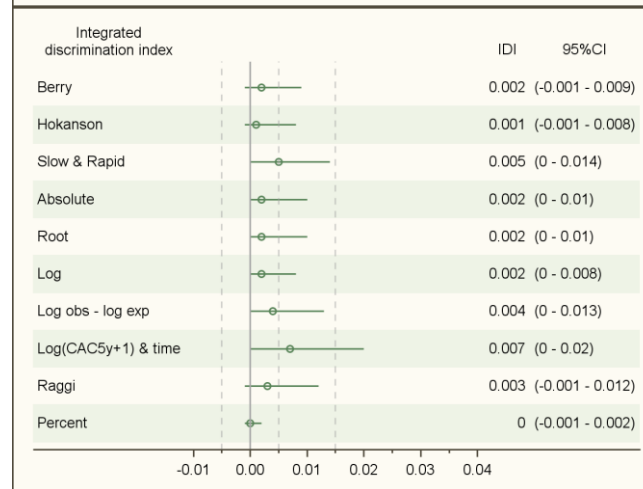
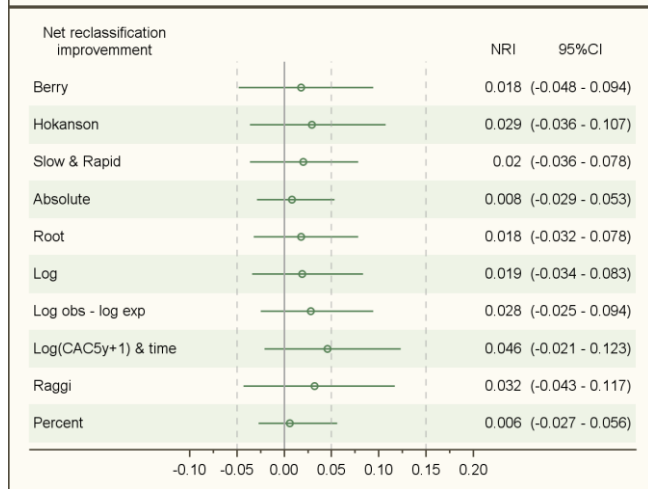
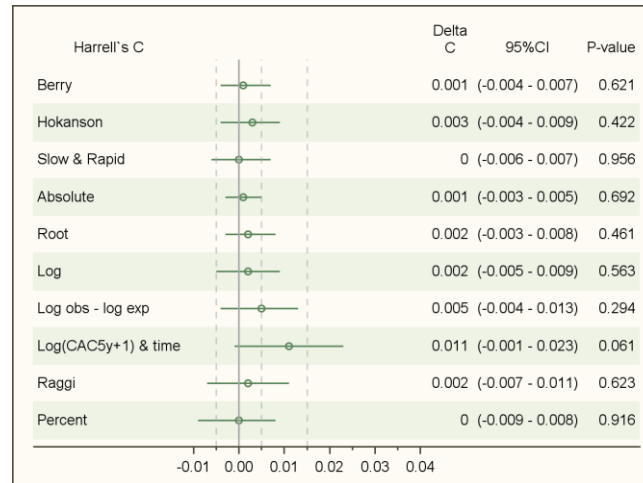
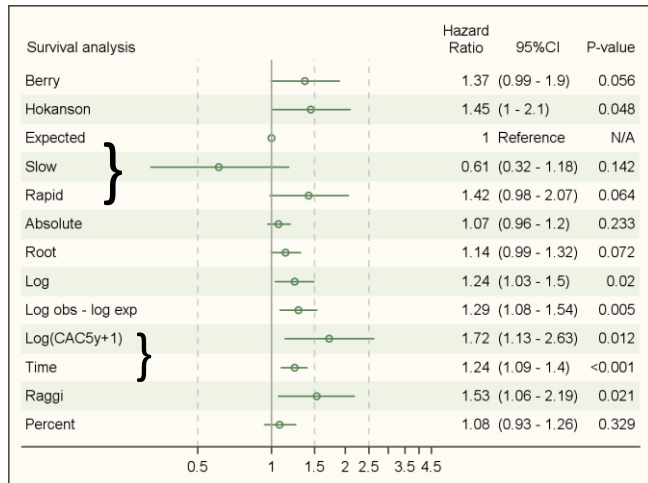


	n at risk					
Slow	415	409	395	338	293	14
Expected	2242	2180	2042	1664	1456	125
Rapid	624	588	549	440	391	32

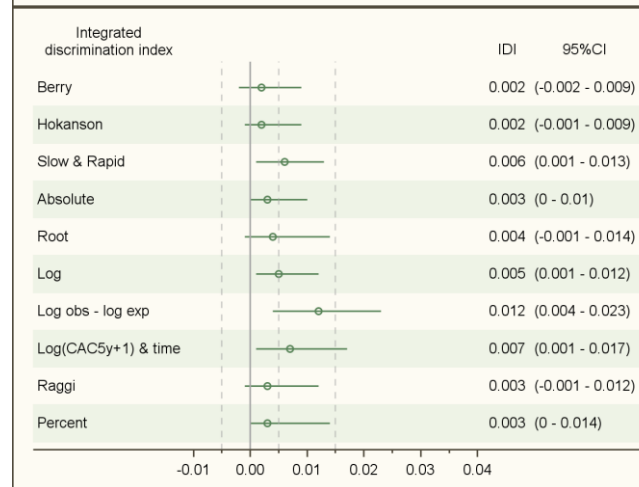
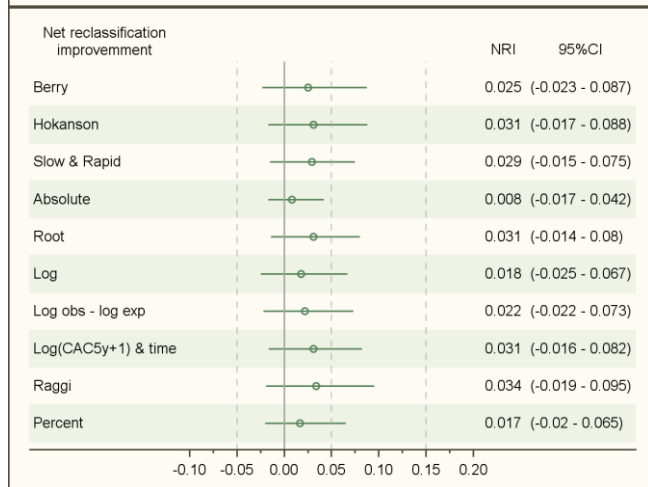
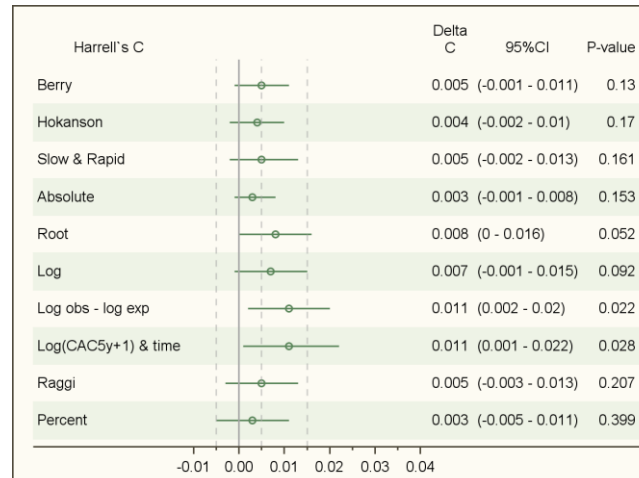
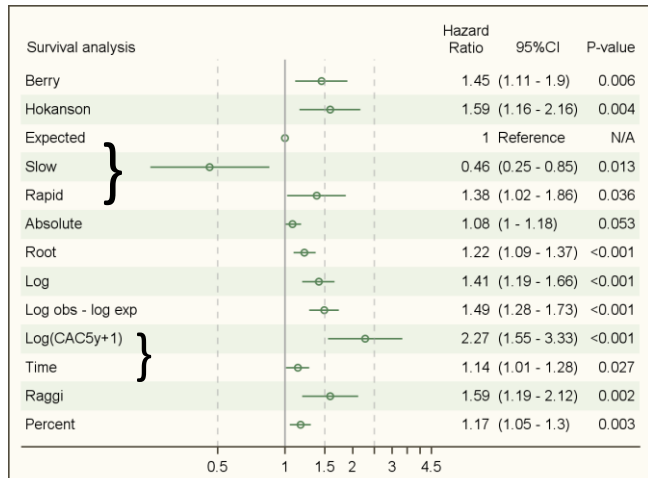
Suppl. Figure 2 C. Kaplan-Meier curves for total CV events, stratified by rated progression. P-value from log-rank test of trend.



Suppl. Figure 3 A. **Added predictive value analysis for coronary events (for different CAC progression algorithms, with respect to 5-year risk assessment and baseline CAC). Upper left, hazard ratios; upper right, change in c-statistics; lower left, NRI; lower right, IDI. Base model: log(CAC+1) at baseline and, evaluated at 5-year examination, age, sex, LDL, HDL, diabetes, present smoking, systolic blood pressure, intake of cholesterol lowering or antihypertensive medications. Base model C-statistics: for the cohort with baseline CAC >0 (Raggi and Percent) C=0.723, all other C=0.747. For definition of progression algorithms, see Suppl. Table 2. Hazard ratios for continuous measures are given per SD, see Suppl. Table 2.**



Suppl. Figure 3 B: As Suppl. Figure 3 A, for hard CV events. Base model C-statistics: for the cohort with baseline CAC >0 (Raggi and Percent) C=0.718, all other C=0.759. For definition of progression algorithms, see Suppl. Table 2. Hazard ratios for continuous measures are given per SD, see Suppl. Table 2.



Suppl. Figure 3 C: As Suppl. Figure 3 A, for total CV events. Base model C-statistics: for the cohort with baseline CAC >0 (Raggi and Percent) C=0.736, all other C=0.774. For definition of progression algorithms, see Suppl. Table 2. Hazard ratios for continuous measures are given per SD, see Suppl. Table 2.

Supplemental References

1. Erbel R, Lehmann N, Churzidse S, Rauwolf M, Mahabadi AA, Möhlenkamp S, Moebus S, Bauer M, Kälsch H, Budde T, Montag M, Schmermund A, Stang A, Führer-Sakel D, Weimar C, Roggenbuck U, Dragano N, Jöckel KH; Heinz Nixdorf Recall Study Investigators. Progression of coronary artery calcification seems to be inevitable, but predictable - results of the Heinz Nixdorf Recall (HNR) study. *Eur Heart J.* 2014; 35:2960-2971. doi: 10.1093/eurheartj/ehu288.
2. Lehmann N, Erbel R, Mahabadi AA, Kälsch H, Möhlenkamp S, Moebus S, Stang A, Roggenbuck U, Strucksberg KH, Führer-Sakel D, Dragano N, Budde T, Seibel R, Grönemeyer D, Jöckel KH; Heinz Nixdorf Recall Study Investigators. Accelerated progression of coronary artery calcification in hypertension but also prehypertension. *J Hypertens.* 2016; 4:2233-2242. doi: 10.1097/HJH.0000000000001080.