Coronary vascular age: An alternate means for predicting stress-induced myocardial ischemia in patients with suspected coronary artery disease

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Received Oct 13, 2017; accepted Jan 4, 2018
doi:10.1007/s12350-018-1191-1

Background. **Coronary artery calcium (CAC) can be used to estimate vascular age in adults, providing a convenient transformation of CAC from Agatston units into a year's scale. We investigated the role of coronary vascular age in predicting stress-induced myocardial ischemia in subjects with suspected coronary artery disease (CAD).**

Methods. **A total of 717 subjects referred to CAC scoring and ^{82}Rb PET/CT stress-rest myocardial perfusion imaging for suspected CAD were studied. CAC score was measured according to the Agatston method and coronary vascular age by equating estimated CAD risk for chronological age and CAC using the formula $39.1 + 7.25 \times \ln(\text{CAC} + 1)$.**

Results. **Stress-induced ischemia was present in 105 (15%) patients. Mean chronological age, CAC score, and coronary vascular age were higher (all $P < .001$) in patients with ischemia compared to those without. At incremental analysis, the global Chi square increased from 41.26 to 68.77 ($P < .001$) when chronological age was added to clinical variables. Including vascular age in the model, the global Chi square further increased from 68.77 to 106.38 ($P < .001$). Adding chronological age to clinical data, continuous net reclassification improvement (cNRI) was 0.57, while adding vascular age to clinical data and chronological age cNRI was 0.62. At decision curve analysis, the model including vascular age was associated with the highest net benefit compared to the model including only clinical data, to the model including chronological age and clinical data, and to a strategy considering that all patients had ischemia. The model including vascular age also showed the largest reduction in false-positive rate without missing any ischemic patients.**

Conclusions. **In subjects with suspected CAD, coronary vascular age is strongly associated with stress-induced ischemia. The communication of a given vascular age would have a superior emotive impact improving observance of therapies and healthier lifestyles. (J Nucl Cardiol 2019;26:1348–55.)**

Key Words: coronary artery disease • coronary artery calcium • coronary vascular age

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s12350-018-1191-1) contains supplementary material, which is available to authorized users.

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1071-3581/$34.00

Abbreviations	
CAC	Coronary artery calcium
CT	Computed tomography
CIMT	Carotid intima-media thickness
CAD	Coronary artery disease
PET	Positron emission tomography
ROC	Receiver-operating characteristic
RPART	Recursive partitioning and regression trees
cNRI	Continuous net reclassification improvement
IDI	Integrated discrimination improvement
CI	Confidence interval

See related editorial, pp. 1356–1357

INTRODUCTION

The majority of cardiovascular risk estimates are strongly influenced by chronological age and, starting from 50 years, age turns out to be the predominant cardiovascular risk factor.[1] The main explanation of this evidence is the progressive accumulation of atherosclerotic plaques over time and the use of chronological age in cardiovascular risk assessment is a surrogate for atherosclerotic burden. However, the atherosclerotic burden of individuals with the same chronological age can be considerably different, due to contribution of the other traditional risk factors.[1–3] Therefore, a technique that better measures atherosclerotic impairment could represent a helpful clinical tool.[4,5]

Two of the most promising procedures for the evaluation of subclinical atherosclerosis are coronary artery calcium (CAC) scanning by computed tomography (CT) and carotid intima-media thickness (CIMT) assessment by B-mode ultrasonography.[6,7] ''Vascular age'' is an emerging concept based on the assumption that the conversion of chronological age to an age derived from vascular imaging data would lead to a more accurate assessment of individual cardiovascular risk. Both CAC score and CIMT assessment have been used to define vascular age.[8] In particular, CIMT vascular age is determined by linear regression modeling using published nomograms of CIMT percentiles or the age at which the individual's measurement would represent the 50th percentile of a reference database. Conversely, the CT approach provides a convenient transformation of CAC score from Agatston units in years. It has been reported that CAC and CIMT provide similar information in the assessment of vascular age.[8] However, the rational to use these tools in cardiovascular risk prediction models is still debated. Vascular age may contribute to a superior understanding of long-term cardiovascular risk especially in young adults, but despite the growing interest in the clinical utility of this novel concept, only few data are available.[9] Yet, the impact of vascular age to predict myocardial ischemia in patients with suspected coronary artery disease (CAD) has not been evaluated. The purpose of this study was to investigate the potential role of coronary vascular age, estimated by transforming CAC score values, in the prediction of stress-induced myocardial ischemia in patients with suspected CAD.

METHODS

Patients

From July 2015 to December 2016, a total of 875 patients underwent concurrent CAC scanning and myocardial perfusion imaging by positron emission tomography (PET)/CT as part of their diagnostic program. For the purpose of the present study, only subjects with suspected CAD ($n = 717$) were considered. For each patient, the presence of coronary risk factors was noted. Hypertension was defined as a blood pressure $\geq$ 140/90 mmHg or the use of anti-hypertensive medication.[10] Hypercholesterolemia was defined as total cholesterol level $>$ 6.2 mmol/L or treatment with cholesterol lowering medication. Patients were classified as having diabetes if they were receiving treatment with oral hypoglycemic drugs or insulin. A positive family history of CAD was defined by the presence of disease in first-degree relatives younger than 55 years in men or 65 years in women. Exclusion criteria were documented history of CAD defined as previous percutaneous coronary intervention, coronary artery bypass graft surgery, or myocardial infarction. Patients with uncontrolled atrial fibrillation, pacemaker, or prosthetic valve were also excluded. The ethics committee of our institution approved the study and all patients gave informed consent.

PET Imaging

As a routine preparation for ^{82}Rb cardiac PET/CT, patients were asked to discontinue taking nitrates for 6 hours, calcium channel blockers and caffeine-containing beverages for 24 hours, and β-blockers for 48 hours before their appointment. Scans were acquired using a Biograph mCT 64-slice scanner (Siemens Healthcare), as previously described.[11] Rest and stress cardiac PET/CT images were acquired as follows: scout CT to check the patient position and low-dose CT (0.4 mSv; 120 kVp; effective tube current, 26 mA [11-mAs quality reference]; 3.3 seconds) were performed for attenuation correction, during normal breathing before and after PET acquisitions. For both rest and stress images, 1110 MBq of ^{82}Rb was injected intravenously and a 6-minute list-mode PET study was acquired. Pharmacologic stress was then administered using adenosine (140 $\mu g \times kg^{-1} \times min^{-1}$ for 4.5 minutes). Both rest and stress dynamic images were reconstructed into 26 time frames (12 $\times$ 5, 6 $\times$ 10, 4 $\times$ 20, and 4 $\times$ 40 seconds; total, 6 minutes) using the vendor standard ordered subsets expectation maximization 3D

reconstruction (2 iterations, 24 subsets) with 6.5-mm gaussian post-processing filter. Regional myocardial perfusion was visually assessed, using standardized segmentation of 17 myocardial regions.[12] Each myocardial segment was scored from normal (score = 0) to absent perfusion (score = 4). The summed stress score was obtained by adding the scores of the 17 segments of the stress images. A similar procedure was applied to the resting images to calculate the summed rest score and summed difference score was the difference between the stress and rest scores. Myocardial perfusion was considered abnormal when summed stress score was ≥ 3. Subjects with summed difference score ≥ 2 were defined as having stress-induced myocardial ischemia.

CT Imaging

All patients underwent a CT scan for CAC scoring. Those with heart rate > 75 bpm received prior intravenous betablockers (5-10 mg atenolol). A standard scanning protocol was applied, with 18-mm section collimation (30 × 0.6 mm), 0.24-ms gantry rotation time, 120-kVp tube voltage, and 60 quality reference mAs tube current. CAC scoring was obtained during a single breath hold and coronary calcification was defined as a plaque with an area of 1.03 mm^2 and a density $\geq$ 130 Hounsfield units. The CAC score was calculated according to the method described by Agatston.[13] Experienced nuclear medicine physicians analyzed the CT, blinded to the PET results (Siemens, Syngo Multimodality Workplace). CAC scores were calculated separately for left anterior descending, left circumflex, and right coronary arteries and summed to provide a total CAC score. Coronary vascular age was estimated by equating estimated CAD risk for chronological age and CAC using the formula $39.1 + 7.25 \times \ln(\text{CAC} + 1)$.[14]

Statistical Analysis

Continuous data are expressed as mean ± standard deviation and categorical data as percentage. Comparison between groups was performed with unpaired *t* test and Chi-square test as appropriate. Correlation between variables was assessed with Pearson's correlation coefficient. A P value < 0.05 was considered statistically significant. Univariable logistic regression analysis was performed to identify the variables associated with ischemia. The ln(CAC score + 1) transformation was used to adjust for the rightward skew of the data and to reduce heteroscedasticity.[15] The incremental value of chronological age vs vascular age over clinical data (age, gender, body mass index, diabetes, hypertension, hypercholesterolemia, smoking history, and family history of CAD) in predicting ischemia was assessed considering variables in hierarchical order. Receiver-operating characteristic (ROC) curve analysis was used to discriminate between patients with and those without ischemia. Recursive partitioning and regression trees (RPART) package (R software, version 3.3.1) was used to select the cut-off value that best classify patients with or without stress-induced myocardial ischemia. To evaluate whether vascular age is able to reclassify patients with ischemia, the continuous net reclassification improvement (cNRI) and the integrated discrimination improvement (IDI) with 95% bootstrap confidence interval (CI) were calculated as previously described.[16] The estimation of the additive value of vascular age was also assessed comparing the clinical net benefit curves obtained with decision curve analysis.[17] The net benefit was calculated as true-positive rate—false-positive rate × weighting factor. Specifically, the false-positive rate was multiplied by the ratio of the threshold probability divided by 1—the threshold probability. The usefulness of vascular age estimation in reducing the number of false positive at the same number of true-positive prediction was also evaluated and graphically represented. All the analyses were performed using STATA version 15.0 for Windows (StataCorp LP, College Station, TX).

RESULTS

Stress-induced myocardial ischemia was present in 105 (15%) patients. Clinical characteristics of patients with and without ischemia are reported in Table 1. Patients with ischemia were older and had higher prevalence of male gender, diabetes, and hypertension, as compared to patients without ischemia. Patients with ischemia also had higher CAC score and estimated vascular age compared to those without. In patients with ischemia, vascular age was higher than chronological age, while in patients without ischemia vascular age was lower than chronological age. In the whole patient population, summed difference score was 1.99 ± 4.15 and it significantly correlated to vascular age ($r = 0.33$, $P < .001$). Chronological age and vascular age in patients with and without ischemia according to gender are depicted in Figure 1. As shown, both chronological age and vascular age were significantly higher in patients with ischemia compared to those without regardless of gender. Chronological age of patients with ischemia did not differ among sex categories, while vascular age was significantly lower in females without ischemia compared to males.

Predictors of Ischemia

Univariable logistic regression analysis is reported in Table 2. Age, male gender, diabetes, hypertension, CAC score, and vascular age were significant predictors of ischemia. At incremental analysis, the global Chi square increased from 41.26 to 68.77 ($P < .001$) when chronological age was added to clinical variables. Including also vascular age in the model, the global Chi square further increased from 68.77 to 106.38 ($P < .001$). Accordingly, the Akaike's information criterion and Bayesian information criterion were smaller (indicating a better fit) for the model including vascular age (510.87 and 556.62) compared to the models

including only clinical variables (571.47 and 608.65) and clinical variables and chronological age (546.47 and 587.65).

Figure 2 illustrates the probability of stress-induced myocardial ischemia according to vascular age adjusted for clinical data and chronological age. RPART analysis showed that a value of vascular age of 88 was the cut-off that best classified patients with or without stress-induced myocardial ischemia. The incidence of ischemia was 11% for patients with a vascular age < 88 and 41% for those with a vascular age ≥ 88.

ROC curves for predicting myocardial ischemia based on clinical data, clinical data and chronological age, and clinical data, chronological age and vascular age are depicted in Figure 3. As shown, for the model based on clinical data alone the ROC area was 0.69 (95% CI 0.64-0.77) and it increased to 0.74 (95% CI 0.69-0.79, $P = .003$) including chronological age and to 0.80 (95% CI 0.76-0.84, $P = .001$) adding vascular age.

When only patients with CAC score of zero ($n = 319$) were considered, the addition of chronological age to clinical data increased the global Chi square from 12.99 to 18.02 ($P = .03$). Accordingly, the Akaike's information criterion and Bayesian information criterion were smaller (indicating a better fit) for the model including chronological age (120.98 and 154.87) as compared to the model including only clinical data (124.01 and 154.13).

Patient Reclassification

Adding chronological age to clinical data, cNRI was 0.57 (95% CI 0.28-0.73) and IDI 0.043 (95% CI 0.02-0.08). In particular, cNRI was 0.33 (95% CI 0.11-0.44) for patients with ischemia and 0.24 (95% CI 0.13-0.32) for those without and IDI was 0.037 (95% CI 0.017-0.071) for patients with ischemia and 0.006 (95% CI 0.003-0.012) for those without. Adding vascular age to clinical data and chronological age, cNRI was 0.62 (95% CI 0.43-0.83) and IDI 0.057 (95% CI 0.022-0.104). In particular, cNRI was 0.35 (95% CI 0.21-0.49) for patients with ischemia and 0.27 (95% CI 0.20-0.37) for those without and IDI was 0.049 (95% CI 0.018-0.089) for patients with ischemia and 0.008 (95% CI 0.003-0.016) for those without.

Clinical Benefit

At decision curve analysis, for a wide range of threshold probabilities the model including vascular age was associated with the highest net benefit compared to the model including only clinical data, to the model including chronological age and clinical data, and to a

Table 1. Baseline characteristics and CT imaging results according to stress myocardial perfusion imaging results

	All patients ($n = 717$)	With ischemia ($n = 105$)	Without ischemia ($n = 612$)	*P* value
Age (years)	61.8 ± 9.8	66.1 ± 8.8	60.9 ± 9.7	< .001
Male gender	367 (51)	78 (74)	289 (47)	< .001
Body mass index (kg/m^2)	31.4 ± 6.6	30.5 ± 5.1	31.5 ± 6.8	0.17
Diabetes	166 (23)	35 (33)	131 (21)	< .01
Hypertension	477 (66)	80 (80)	397 (65)	< .05
Hypercholesterolemia	402 (56)	61 (58)	341 (56)	0.65
Smoking history	209 (29)	28 (27)	181 (30)	0.54
Family history of CAD	381 (53)	48 (46)	333 (55)	0.09
LV ejection fraction (%)	55 ± 10	56 ± 9	54 ± 10	0.11
CAC score[a]	240 ± 545	719 ± 957	158 ± 382	< .0001
CAC categories				
0	319 (44)	15 (14)	304 (50)	
1-100	157 (22)	19 (18)	138 (23)	
101-400	113 (16)	24 (23)	89 (14)	
Coronary vascular age	58.8 ± 20.1	75.1 ± 18.6	56.1 ± 19.1	< .001

Values are expressed as mean value ± standard deviation or as number (percentage) of subjects
CAD, coronary artery disease; *CAC*, coronary artery calcium; *LV*, left ventricular

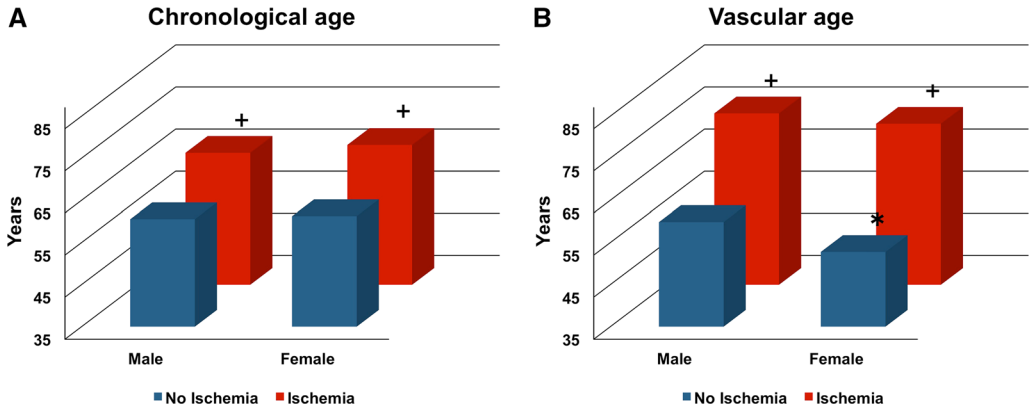

Figure 1. Chronological age (**A**) and coronary vascular age (**B**) in patients with and without stress-induced myocardial ischemia according to gender. +indicates $P < .001$ comparing patients with ischemia vs those without in the same sex category. *indicates $P < .001$ in females without ischemia compared to males.

Table 2. Predictors of stress-induced myocardial ischemia at univariable analysis

	β coefficient	SE	Odds ratio (95% CI)	*P* value
Age	0.062	0.011	1.07 (1.04-1.09)	< .001
Male gender	1.172	0.238	3.23 (2.02-5.14)	< .001
Body mass index	− 0.024	0.017	0.98 (0.94-1.01)	0.17
Diabetes	0.606	0.229	1.84 (1.17-2.88)	0.008
Hypertension	0.550	0.240	1.73 (1.07-2.80)	0.02
Hypercholesterolemia	0.097	0.214	1.10 (0.72-1.68)	0.65
Smoking history	− 0.144	0.238	0.87 (0.54-1.38)	0.55
Family history of CAD	− 0.349	0.212	0.70 (0.47-1.07)	0.10
CAC score	0.369	0.046	1.45 (1.32-1.58)	< .001
Coronary vascular age	0.051	0.006	1.07 (1.04-1.09)	< .001

CAD, coronary artery disease; *CAC*, coronary artery calcium

strategy considering that all patients had ischemia (Figure 4). The clinical model including vascular age also showed the largest reduction in false-positive rate without missing any ischemic patients (Figure 5). As an example, at a probability threshold of 30%, compared to a strategy assuming that all patients are ischemic, the net reduction in false-positive rate without missing any ischemic patients is about 51 per 100 patients for the model including only clinical data, 53 per 100 patients for the model including clinical data and chronological age, and 57 per 100 patients for the model including also vascular age.

DISCUSSION

To our knowledge, this is the first study investigating the potential role of estimated coronary vascular age in the prediction of stress-induced myocardial ischemia in patients with suspected CAD. We found that chronological age, male gender, CAC score, and coronary vascular age were associated with ischemia. These findings confirm the importance of CAC score evaluation in the assessment of cardiovascular impairment. Coronary calcium accumulation is the result of an active process related to atherosclerosis, and thus detection of coronary artery calcifications corresponds to an atherosclerosis advancement report. The strong predictive value of calcium deposit evaluation, regardless of the risk category estimated by traditional risk scores, has been widely demonstrated.[18–20]

The emerging idea to assign a vascular age, according to observed CAC, shoots for taking into account the relationship between calcium deposit process and actual obsolescence of vascular system, tailoring individual cardiovascular risk aside from chronological age.[21] Prognostic data from MESA[14]

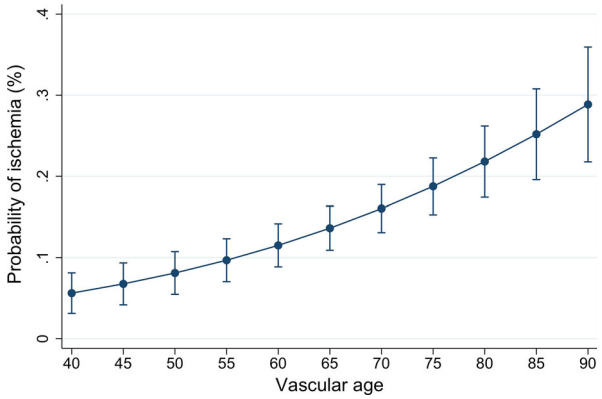

Figure 2. Probability of stress-induced myocardial ischemia according to vascular age adjusted for clinical data and chronological age.

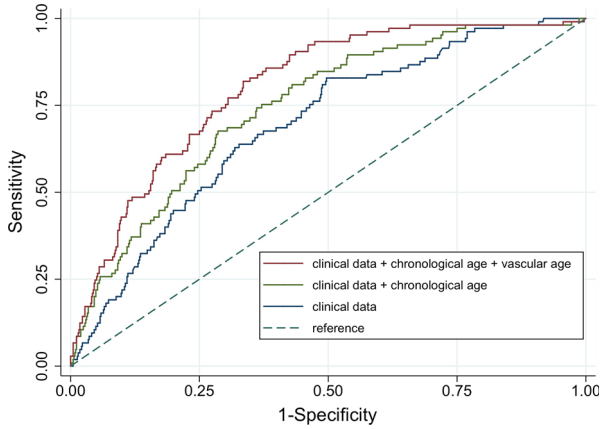

Figure 3. Receiver-operating characteristic (ROC) curve for stress-induced myocardial ischemia based on chronological age and on vascular age, in addition to the other clinical risk factors. The curve for the model including vascular age rather than chronological age is higher, indicating better discrimination between patients with and without ischemia (ROC area 0.79 vs 0.74, $P = .04$).

showed that the risk associated with vascular age was a much stronger predictor of cardiovascular events than predictions based on chronological age. Moreover, in the same cohort, chronological age did not provide additional information after controlling for vascular age. It has also been showed that there is a significant inverse relationship between telomere length and coronary artery calcifications in individuals with no clinical history of CAD suggesting a potential association of telomere length, a marker of biological aging, with cumulative lifelong burden of oxidative stress detected with coronary artery calcification increase.[22,23]

As expected, among patients with ischemia vascular age was significantly higher than chronological age, while in patients without ischemia vascular age was significantly lower compared to chronological age confirming a stronger potential of vascular age, than chronological age, in identifying patients at high risk of CAD. Moreover, chronological age of patients with ischemia did not differ among sex categories, while vascular age was significantly lower in females without ischemia compared to male subjects proposing a potential strong negative predictive value of vascular age in female individuals. All these findings are also supported by incremental analysis that showed a powerful additive value of vascular age over clinical variables and chronological age in predicting presence of ischemia. The probability of stress-induced myocardial ischemia progressively augmented with increase of vascular age also after adjustment for clinical data and chronological age. Of note, myocardial ischemia was unlikely when vascular age was below 88. This finding may have useful clinical implications by highlighting a group of subjects that may not need PET imaging. In patients with a CAC score of zero, chronological age remained a predictor of myocardial ischemia.

The NRI evaluation and decision curve analysis indicate that the incremental predictive value of coronary vascular age over clinical variables and chronological age translates into a clinically relevant benefit that could change clinical decision-making. Indeed, the model including vascular age resulted in a higher net benefit across a wide range of decision threshold probabilities over the model including chronological age.

Our results support the hypothesis that vascular age may be an alternate means of representing an individual's cardiovascular risk. A randomized clinical trial recently compared three strategies for improving cardiovascular risk profile: standard clinical care with no information on vascular risk or vascular age (control group), clinical care with information on the individual's absolute risk, and clinical care with information on the individual's vascular age.[24] This latter group gained the largest decrease in their cardiovascular risk factor. Thus, vascular age would be a useful tool to communicate test results to patients and to apply stricter therapeutic strategies to freeze cardiovascular disease progression in patients with a coronary vascular age higher than the respective chronological age.[9,25]

NEW KNOWLEDGE GAINED

This is the first study investigating the potential role of estimated coronary vascular age in the prediction of stress-induced myocardial ischemia in patients with suspected CAD. We found that the incremental

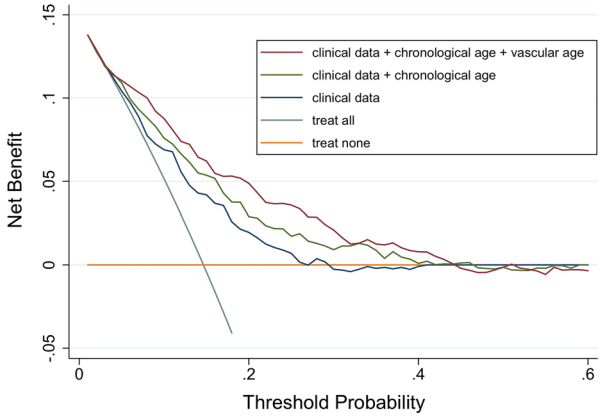

Figure 4. Decision curves analysis graphically representing net benefit (*y*-axis) for the prediction of myocardial ischemia with the model including vascular age (orange line) or chronological age (green line) beyond other clinical variables in a range of decision threshold probabilities (*x*-axis). The navy (*treat all*) and maroon (*treat none*) solid lines represent making the same decision in all patients assuming that all or none are ischemic.

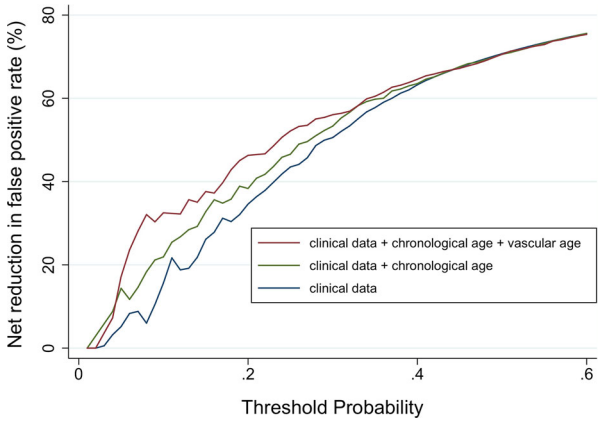

Figure 5. Net reduction in false-positive rate at different threshold probabilities with the model including vascular age (orange line) or chronological age (green line) beyond other clinical variables compared with the strategy of considering that all patients are ischemic.

predictive value of coronary vascular age over clinical variables and chronological age translates into a clinically relevant benefit that could change clinical decision-making.

CONCLUSION

Coronary vascular age estimated by CAC score is associated with stress-induced myocardial ischemia in patients with suspected CAD and this marker appears to be more accurate than chronological age in predicting ischemia. The communication of a given vascular age would have a superior emotive impact improving observance of therapies and healthier lifestyles.

Disclosure

Carmela Nappi, Valeria Gaudieri, Wanda Acampa, Parthiban Arumugam, Roberta Assante, Emilia Zampella, Teresa Mannarino, Ciro Gabriele Mainolfi, Massimo Imbriaco, Mario Petretta, and Alberto Cuocolo declare that they have no conflict of interest.

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