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Reclassification of cardiovascular risk by myocardial perfusion imaging in diabetic patients with abnormal resting electrocardiogram

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Abstract *Background and aims:* Despite an extensive use of stress myocardial perfusion single-photon emission computed tomography (MPS), no study addressed the role of perfusion imaging in diabetic patients with abnormal resting electrocardiogram (ECG). We compared analytical approaches to assess the added value of stress MPS variables in estimating coronary heart disease outcomes in diabetic patients with abnormal resting ECG.
Methods and results: A total of 416 patients with diabetes and abnormal resting ECG who underwent stress MPS were prospectively followed up after the index study. The end point was the occurrence of a major cardiac event, including cardiac death and nonfatal myocardial infarction. At the end of follow-up (median 58 months), 42 patients experienced events. MPS data increased the predictive value of a model including traditional cardiovascular risk factors and left ventricular (LV) ejection fraction (likelihood ratio χ^2 from 17.54 to 24.15, $p < 0.05$, with a C statistic of 0.72, 95% confidence interval: 0.65–0.79). The addition of MPS data resulted in reclassification of 25% of the sample with a net reclassification improvement of 0.20 (95% confidence interval: 0.05–0.36). Overall, 63 patients were reclassified to a lower risk category, with a 5-year event rate of 3.5%, and 40 patients were reclassified to a higher risk category, with a 5-year event rate of 20%.
Conclusion: The addition of MPS findings to a model based on traditional cardiovascular risk factors and LV ejection fraction improves risk classification for incident cardiac events in diabetic patients with abnormal resting ECG.

Introduction

Coronary artery disease (CAD) is the leading cause of morbidity and mortality in patients with diabetes mellitus [1]. In these patients, the prognostic value of stress myocardial perfusion single-photon emission computed tomography (MPS) has been largely investigated [2–5]. Yet, how to correctly identify diabetic patients in need of testing remains to be defined [6–8]. In a recent position statement on standards of medical care in diabetes [9], the American Diabetes Association (ADA) does not recommend screening for CAD in asymptomatic patients because it does not improve outcomes as long as cardiovascular risk factors are treated. Net reclassification improvement (NRI) has been adopted in diabetic patients with suspected or known CAD to evaluate the extent to which adding

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stress MPS imaging data to a model based on traditional risk factors and stress electrocardiogram (ECG) data correctly reclassifies the risk of subsequent cardiac events during a long-term follow-up [10–12]. In patients with diabetes mellitus, a variety of resting ECG abnormalities has been described, not only resulting from ischemia [13]. These abnormalities are predictive for adverse outcome independently of multiple risk factor adjustment [14,15]. So far no study addressed the prognostic role of stress MPS in a population of diabetic patients without known CAD and an abnormal resting ECG. The aim of this study was to compare analytical approaches to assess the added value of stress MPS variables in estimating CAD outcomes in diabetic patients with abnormal resting ECG.

Methods

Study population

The study population included consecutive patients ($n = 433$) with at least a 5-year history of type 2 diabetes presenting with an abnormal resting ECG, referred for stress MPS for the detection of inducible myocardial ischemia. Of these patients, 212 were part of the Impact of inDucible Ischemia by Stress MPS (IDIS) investigation [16]. Abnormal resting ECG was defined as ST-segment elevation $\geq$2 mm in 2 or more contiguous leads ($n = 59$), T-wave inversion of at least 1 mm ($n = 124$), presence of Q-wave $\geq$1 mm in depth ($n = 149$), ST-depression $\geq$1 mm ($n = 12$), left ($n = 57$) or right ($n = 36$) bundle branch block [17]. Patients have been excluded for: 1) clinical history of prior myocardial infarction; 2) recent acute coronary syndrome, recent stroke or transient ischemic attack (last 3 months); 3) uncompensated congestive heart failure or recent admission for congestive heart failure; 4) atrial fibrillation/flutter; 5) prior myocardial revascularization procedures; or 6) a concomitant noncardiac illness that would limit follow-up for at least 1 year. As part of the baseline examination, beside diabetes and its complications (including neuropathy, nephropathy, peripheral vascular disease, and retinopathy), clinical teams collected information on traditional cardiovascular risk factors (including age, sex, body mass index, dyslipidemia, smoking, hypertension, family history of CAD), and chest pain symptoms. From these variables the Morise clinical risk score was calculated for each patient [18]. The study was approved by the local Ethics Advisory Committee and carried out according to the Helsinki declaration. Participants gave written informed consent prior to the study.

MPS

All patients underwent same-day Tc-99m sestamibi rest and stress gated MPS by exercise or dipyridamole stress test, according to the recommendations of the European Association of Nuclear Medicine and European Society of Cardiology [19], as previously described in details [16]. An automated software program (e-soft, 2.5, QGS/QPS, Cedars-Sinai Medical Center, Los Angeles, California) was used to calculate left ventricular (LV) ejection fraction and the scores incorporating both the extent and severity of perfusion defects [20], using standardized segmentation of 17 myocardial regions. Each segment was scored from normal (score = 0) to absent perfusion (score = 4). The summed stress score is obtained by adding the scores of the 17 segments of the stress images. A similar procedure is applied to the resting images to calculate the summed rest score. The summed difference score represents the difference between the stress and rest scores and is taken to be an index of ischemic burden. Patients were considered to have an abnormal MPS with a summed stress score >3. Significant ischemia was defined by a summed difference score $\geq$2, and classified as mild (2–6) and moderate-severe (>6) [21].

Follow-up

Patient follow-up was prospectively obtained by use of a questionnaire administered by phone call to all patients, general practitioners or cardiologists and by review of hospital or physicians' records by individuals blinded to the patient's test results. The end point was the occurrence of a major adverse cardiac event (MACE) whichever occurred first, including cardiac death and nonfatal myocardial infarction. Cardiac death, defined as due to acute myocardial infarction, ventricular arrhythmias, refractory heart failure or cardiogenic shock, was confirmed by review of death certificate, hospital chart or physician's records. Nonfatal myocardial infarction was defined based on the criteria of typical chest pain, elevated cardiac enzyme levels and typical alterations of the ECG. The interval to an event was defined as the duration from the baseline MPS study to MACE, or the end of follow-up.

Statistical analysis

Continuous variables were expressed as mean $\pm$ standard deviation and categorical data as percentages. Differences between groups were analyzed by t test and χ^2 analysis, as appropriate. A two-tailed p value <0.05 was considered statistically significant. Cumulative event rates as function of time were calculated with the Kaplan–Meier method. Univariable associations with MACE were determined by Cox proportional hazards regression, and hazard ratios (HR) and 95% confidence intervals (CI) were calculated. To assess the added value of LV ejection fraction and MPS data in risk prediction, we considered a series of Cox models. Model 1 was based on clinical risk factors: age, sex, body mass index, dyslipidemia, smoking, hypertension, family history of CAD, and chest pain symptoms. In model 2, we added LV ejection fraction to the aforementioned risk factors. Model 3 added MPS data to model 2. The statistical significance of the contribution of the added variables was assessed with the likelihood ratio test [22]. In addition, we assessed for significant incremental changes in model C statistic [23]. The incremental value of LV ejection fraction and MPS data for predicting MACE was also evaluated using the NRI. The goal was to determine

whether reclassification would assign patients who developed events to a higher risk category and those who did not to a lower risk category. For this purpose, the estimated 5-year risk of MACE was calculated for each subject using the Cox models. We defined 5-year risk categories as follows: 0% to <5%; 5% to <15%; ≥15%. To take in account the issue of censored observations, the NRI was calculated using the prospective formula proposed by Pencina et al. [24]. Bootstrap technique (1000 replications) was used to calculate 95% CI of NRI. To assess whether the value of MPS in risk reclassification differs in patients with or without resting ECG abnormalities, we also calculated NRI in 416 age and sex-matched diabetic patients with normal resting ECG. Statistical analyses were performed with Stata 13 software (StataCorp, College Station, Texas USA) and with the R software (version 2.12.1), including the package nricens (version 1.2) [25].

Results

Patient characteristics and outcome

The median follow-up was 58 months (interquartile range, 52–67). Follow-up was 96% complete and the final cohort consisted of 416 patients (78% men) with a mean age of 62 ± 9 years and a LV ejection fraction of 52 ± 14%. At the end of follow-up, 42 patients experienced MACE (cardiac death in 20 and nonfatal myocardial infarction in 22). The baseline characteristics of patients with or without cardiac events are presented in Table 1. Patients with events were more likely to have hypertension ($p < 0.05$) and an abnormal stress MPS ($p < 0.01$) and exhibited lower LV ejection fraction ($p < 0.005$).

Table 1 Characteristics of patients with and without cardiac events.

	Events ($n = 42$)	No events ($n = 374$)	*P* Value
Age (years)	62 ± 8	63 ± 9	0.64
Male, *n* (%)	33 (79%)	290 (78%)	0.88
Body mass index (kg/m^2)	27 ± 3	26 ± 5	0.84
Dyslipidemia, *n* (%)	25 (60%)	234 (63%)	0.70
Smoking, *n* (%)	20 (48%)	177 (47%)	0.97
Hypertension, *n* (%)	35 (83%)	250 (67%)	<0.05
Family history of CAD, *n* (%)	9 (21%)	144 (39%)	<0.05
Chest pain symptoms, *n* (%)	16 (38%)	136 (36%)	0.82
Morise score	15 ± 3	14 ± 3	0.60
Low risk (<9), *n* (%)	1 (2%)	7 (2%)	
Intermediate risk (9–15), *n* (%)	24 (57%)	228 (61%)	
High risk (>15), *n* (%)	17 (41%)	139 (37%)	
LV ejection fraction (%)	47 ± 14	53 ± 13	<0.005
Dipyridamole stress test, *n* (%)	20 (48%)	129 (55%)	0.09
Abnormal MPS, *n* (%)	38 (90%)	251 (67%)	<0.001
Summed stress score	12.0 ± 8	9.2 ± 8	<0.05
Summed rest score	7.1 ± 7	6.2 ± 7	0.44
Summed difference score	4.7 ± 3	3.0 ± 3	<0.005

Values are expressed as mean ± SD or percentage.
CAD = coronary heart disease; LV = left ventricular; MPS = myocardial perfusion single-photon emission computed tomography.

Predictors of MACE

Univariable associations of age, sex, body mass index, traditional cardiovascular risk factors, LV ejection fraction, and stress MPS indices with MACE were measured (Table 2). Stress-induced myocardial ischemia was a strong predictor of cardiac events. The annual event rate (% person-year) was 0.82% in patients without ischemia ($n = 172$), 3.1% in those with mild ischemia ($n = 178$), and 4.0% in those with moderate to severe ischemia ($n = 66$) (p for trend <0.005). The occurrence of MACE was comparable in patients with or without chest pain symptoms ($p = 0.69$). The annualized event rate was 2.0% (95% CI: 1.3–3.0) in patients undergoing exercise and 3.3% (95% CI: 2.1–5.1) in those undergoing pharmacological stress testing ($p = 0.12$). The results of multivariable analysis for prediction of MACE for the 3 survival models are reported in Table 3. The addition of MPS data increased the predictive value of the model including traditional cardiovascular risk factors and LV ejection fraction (Fig. 1).

Risk reclassification

In patients with abnormal ECG, the 5-year event rate was 12.9%. The addition of LV ejection fraction to model 1 resulted in reclassification of 44% of the sample. The reclassification was correct in 163 patients and incorrect in 20 patients, with a NRI of 0.07 (95% CI: −0.09–0.44). Cross-tabulations of the 5-year risk of MACE comparing the model without and with MPS data are shown in Table 4. In patients with abnormal resting ECG, the addition of MPS data resulted in reclassification of 25% of the sample. The reclassification was correct in 69 and incorrect in 34

Table 2 Univariable Cox association with cardiac events.

	Hazard ratio (95% CI)	χ^2	*P* Value	C Statistic
Age	1.0 (0.96–1.02)	0.24	0.62	0.53
Male	1.1 (0.52–2.3)	0.06	0.81	0.51
Body mass index	1.0 (0.91–1.1)	0.01	0.94	0.49
Dyslipidemia	0.87 (0.47–1.6)	0.19	0.66	0.48
Smoking	0.98 (0.53–1.8)	0.01	0.94	0.52
Hypertension	2.4 (1.1–5.4)	5.26	<0.05	0.59
Family history of CAD	0.58 (0.21–0.96)	4.10	<0.05	0.53
Chest pain symptoms	1.1 (0.61–2.1)	0.15	0.69	0.51
Morise score	1.1 (0.91–1.2)	0.24	0.63	0.51
LV ejection fraction	0.97 (0.95–0.99)	0.73	<0.01	0.59
Dipyridamole stress test	1.6 (0.88–2.9)	2.39	0.12	0.56
Summed stress score	1.1 (0.99–1.1)	3.16	0.07	0.58
Summed rest score	1.0 (0.97–1.1)	0.31	0.58	0.53
Summed difference score	1.1 (1.0–1.2)	0.82	<0.005	0.67

CI = confidence interval; CAD = coronary artery disease; LV = left ventricular.

Table 3 Multivariable Cox regression analysis of different survival models for prediction of cardiac events.

	Model 1		Model 2		Model 3	
	Hazard ratio (95% CI)	*P* Value	Hazard ratio (95% CI)	*P* Value	Hazard ratio (95% CI)	*P* Value
Age	0.98 (0.95–1.1)	0.63	0.99 (0.95–1.1)	0.75	0.98 (0.94–1.1)	0.52
Male	1.1 (0.43–2.9)	0.82	0.96 (0.36–2.6)	0.94	0.81 (0.30–2.2)	0.68
Body mass index	1.0 (0.78–1.9)	0.77	1.0 (0.56–2.2)	0.97	0.99 (0.58–1.3)	0.99
Dyslipidemia	0.86 (0.46–1.6)	0.63	0.85 (0.45–1.6)	0.63	0.81 (0.42–1.6)	0.54
Smoking	1.1 (0.57–2.0)	0.84	1.1 (0.56–2.0)	0.85	1.1 (0.56–2.1)	0.83
Hypertension	2.7 (1.2–6.2)	<0.05	2.7 (1.2–6.2)	<0.05	2.6 (1.1–6.1)	<0.05
Family history of CAD	0.62 (0.34–1.1)	0.09	0.68 (0.37–1.1)	0.10	0.69 (0.33–1.1)	0.18
Chest pain symptoms	1.2 (0.56–2.6)	0.64	1.2 (0.54–2.5)	0.68	1.2 (0.56–2.6)	0.64
LV ejection fraction			0.97 (0.94–0.99)	<0.05	0.97 (0.95–0.99)	<0.05
Summed difference score					1.1 (1.0–1.2)	<0.01

Model 1 represents the multivariable Cox regression model based on clinical risk factors; model 2 represents addition of LV ejection fraction to model 1; and model 3 represents addition of and MPS data to model 2. CI = confidence interval; LV = left ventricular.

patients with a NRI of 0.20 (95% CI: 0.05–0.36). Overall, 63 patients were reclassified to a lower risk category, with a 5-year event rate of 3.5%, and 40 patients were reclassified to a higher risk category, with a 5-year event rate of 20%. In patients with normal resting ECG, the NRI was 0.21 (95% CI: 0.05–0.39), similar to those with abnormal resting ECG.

Discussion

This study shows that in diabetic patients with an abnormal resting ECG referred for MPS the addition of perfusion data to traditional cardiovascular risk factors and LV ejection fraction results in a significant improvement in the classification of risk for the prediction of cardiac events at long-term follow-up.

It is well known that diabetic patients are predisposed to a more aggressive form of vascular disease with diffuse coronary atherosclerosis and significantly higher incidence of heart failure, myocardial infarction, and cardiac death, as compared to non-diabetic patients [26–28]. Diabetic patients also have a greater number of cardiovascular risk factors as compared to patients without diabetes [9,29]. We recently demonstrated that the addition of MPS results to a prediction model based on traditional risk factors and ECG stress test data significantly improves the classification of risk in a large cohort of diabetic patients with suspected or known CAD [11]. Similar findings have been reported in asymptomatic diabetic patients without resting ECG abnormalities, in whom analytical approaches that establish the reclassification of events may serve for estimation of improved outcomes for stress MPS [12]. In particular, post-stress LV ejection fraction and stress-induced ischemia by gated MPS influence the temporal characteristic of the patient's risk at long-term follow-up. In the present investigation we focused on diabetic patients with abnormal resting ECG. The argument to study these subjects is based on the observations that in patients with diabetes, a variety of resting ECG abnormalities have been described, not only resulting from ischemia [13]. Easily assessable resting ECG abnormalities were

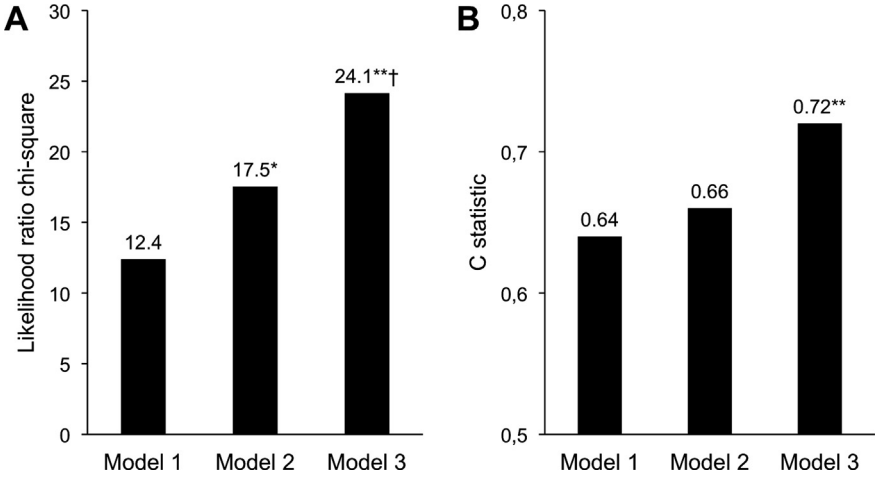

Figure 1 Likelihood ratio χ^2 (A) and C statistic (B) for prediction of cardiac events using different survival models. Model 1 is based on clinical risk factors; model 2 adds left ventricular ejection fraction to model 1; and model 3 adds MPS data to model 2. For C statistic the 95% confidence intervals of were 0.55–0.72 for model 1, 0.58–0.74 for model 2, and 0.65–0.79 for model 3. *$p < 0.05$ vs. model 1; **$p < 0.01$ vs. model 1; †$p < 0.05$ vs. model 2.

Table 4 Calculations of the net reclassification improvement by the addition of MPS data to clinical risk factors and LV ejection fraction.

Model without MPS	Model with MPS			
Abnormal resting ECG	<5%	5%–15%	≥15%	Total
Patients with events				
<5%	0	2	0	2
5%–15%	0	15	6	21
≥15%	0	2	17	19
Total	0	19	23	42
Patients without events				
<5%	23	3	0	26
5%–15%	22	182	29	233
≥15%	0	39	76	115
Total	45	224	105	374
Normal resting ECG	<5%	5%–15%	≥15%	Total
Patients with events				
<5%	5	1	0	6
5%–15%	5	5	3	13
≥15%	0	0	2	2
Total	10	6	5	21
Patients without events				
<5%	101	22	3	126
5%–15%	93	140	15	248
≥15%	0	12	9	21
Total	194	174	27	395

The 5-year event rate was 12.9% in patients with abnormal ECG (20% in those reclassified at higher risk, and 3.5% in those reclassified at lower risk) with a net reclassification improvement of 0.20 (95% confidence interval 0.05–0.36) and 6.1% in patients with normal resting ECG (10.9% in those reclassified at higher risk, and 3.2% in those reclassified at lower risk) with a net reclassification improvement of 0.21 (95% confidence interval 0.05–0.39).

predictive for adverse outcome in diabetic patients independently of multiple risk factor adjustment and should be considered in clinical care [14]. More recent results suggest that ECG Q waves in asymptomatic patients with type 2 diabetes are of some prognostic significance, especially in relation to death [15]. Thus, the presence of abnormalities on routine ECG screening should be taken into account for risk stratification of diabetic patients.

In the present study, diabetic patients with abnormal resting ECG were classified according to the 5-year risk of MACE, estimated by a model including clinical risk factors only (model 1), a model based on clinical risk factors and LV ejection fraction (model 2), and a model based on clinical risk factors, LV ejection fraction, and MPS data (model 3). The addition of LV ejection fraction to clinical variables added only a weak improvement in classification. On the other hand, the addition of MPS data to the model including clinical variables and LV ejection fraction resulted in reclassification of 25% of the sample with a NRI of 0.20. In particular, the 5-year event rate was 20% in patients reclassified to a higher risk category and 3.5% in those reclassified to a lower risk category. It should be considered that a favorable NRI does not necessary imply that the reclassification is correct for both patients with and without events [30]. In our study, for patients with events, 18% were correctly reclassified as higher risk, whereas only 5% were incorrectly reclassified as lower risk, resulting in a net 13% of the population being correctly reclassified. Conversely, for patients without events, the addition of MPS data resulted in 16% being correctly reclassified and 9% being incorrectly reclassified, yielding a net of 7% correctly reclassified. Thus, when shifts between risk categories (low, moderate, and high) determined by the 2 models are considered it appears that the major effect of applying NRI is correctly reclassifying low-risk patients, primarily by shifting patients who experience events from the low- and moderate-risk category to a higher risk category, rather than correctly identifying more low-risk patients. Our results also indicate that the value of MPS in risk reclassification is similar in patients with or without resting ECG abnormalities, suggesting that this approach can be broadly applied to all diabetic patients. However, although the risk classification suggests that patient management would be potentially altered based on the results of MPS, larger prospective clinical trials are necessary to demonstrate the real changes in clinical outcome.

Conclusion

The results of this study indicate that stress MPS provides incremental prognostic information for the prediction of MACE in patients with type-2 diabetes and an abnormal resting ECG. In these patients, the addition of MPS data to a prediction model based on traditional cardiovascular risk factors and LV ejection fraction provides an improvement in risk classification for incident cardiac events similar to that observed in diabetics with normal resting ECG.

References

[1] American Diabetes Association. Consensus development conference on the diagnosis of coronary heart disease in people with diabetes. Diabetes Care 1998;21:1551–9.
[2] Kang X, Berman DS, Lewin H, Miranda R, Erel J, Friedman JD, et al. Comparative ability of myocardial perfusion single-photon emission computed tomography to detect coronary artery disease in patients with and without diabetes mellitus. Am Heart J 1999;137:949–57.
[3] Giri S, Shaw LJ, Murthy DR, Travin MI, Miller DD, Hachamovitch R, et al. Impact of diabetes on the risk stratification using stress single-photon emission computed tomography myocardial perfusion imaging in patients with symptoms suggestive of coronary artery disease. Circulation 2002;105:32–40.
[4] Shaw LJ, Berman DS, Hendel RC, Alazraki N, Krawczynska E, Borges-Neto S, et al. Cardiovascular disease risk stratification with stress single-photon emission computed tomography technetium-99m tetrofosmin imaging in patients with the metabolic syndrome and diabetes mellitus. Am J Cardiol 2006;97:1538–44.
[5] Miller TD, Rajagopalan N, Hodge DO, Frye RL, Gibbons RJ. Yield of stress single-photon emission computed tomography in asymptomatic patients with diabetes. Am Heart J 2004;147:890–6.
[6] Wackers FJ, Young LH, Inzucchi SE, Chyun DA, Davey JA, Barrett EJ, et al., Detection of Ischemia in Asymptomatic Diabetics Investigators. Detection of silent myocardial ischemia in asymptomatic diabetic subjects: the DIAD study. Diabetes Care 2004;27:1954–61.
[7] Anand DV, Lim E, Hopkins D, Corder R, Shaw LJ, Sharp P, et al. Risk stratification in uncomplicated type 2 diabetes: prospective evaluation of the combined use of coronary artery calcium imaging and selective myocardial perfusion scintigraphy. Eur Heart J 2006;27:713–21.
[8] Valensi P, Pariès J, Brulport-Cerisier V, Torremocha F, Sachs RN, Vanzetto G, et al. Predictive value of silent myocardial ischemia for

cardiac events in diabetic patients: influence of age in a French multicenter study. Diabetes Care 2005;28:2722–7.
[9] American Diabetes Association. Standards of medical care in diabetes–2013. Diabetes Care 2013;36(Suppl. 1):S11–66.
[10] Petretta M, Cuocolo A. Prediction models for risk classification in cardiovascular disease. Eur J Nucl Med Mol Imaging 2012;39: 1959–69.
[11] Acampa W, Petretta M, Evangelista L, Daniele S, Xhoxhi E, De Rimini ML, et al. Myocardial perfusion imaging and risk classification for coronary heart disease in diabetic patients. The IDIS study: a prospective, multicentre trial. Eur J Nucl Med Mol Imaging 2012;39:387–95.
[12] Acampa W, Petretta M, Daniele S, Del Prete G, Assante R, Zampella E, et al. Incremental prognostic value of stress myocardial perfusion imaging in asymptomatic diabetic patients. Atherosclerosis 2013;227:307–12.
[13] Stern S, Sclarowsky S. The ECG in diabetes mellitus. Circulation 2009;120:1633–6.
[14] Pfister R, Cairns R, Erdmann E, Schneider CA, PROactive Investigators. Prognostic impact of electrocardiographic signs in patients with Type 2 diabetes and cardiovascular disease: results from the PROactive study. Diabet Med 2011;28:1206–12.
[15] Davis TM, Coleman RL, Holman RR, UKPDS Group. Prognostic significance of silent myocardial infarction in newly diagnosed type 2 diabetes mellitus: United Kingdom Prospective Diabetes Study (UKPDS) 79. Circulation 2013;127:980–7.
[16] Petretta M, Acampa W, Evangelista L, Daniele S, Ferro A, Cuocolo A, Impact of Inducible Ischemia by Stress SPECT (IDIS) Investigators. Impact of inducible ischemia by stress SPECT in cardiac risk assessment in diabetic patients: rationale and design of a prospective, multicenter trial. J Nucl Cardiol 2008;15:100–4.
[17] Cannon CP, Battler A, Brindis RG, Cox JL, Ellis SG, Every NR, et al. American College of Cardiology key data elements and definitions for measuring the clinical management and outcomes of patients with acute coronary syndromes. A report of the American College of Cardiology Task Force on Clinical Data Standards (Acute Coronary Syndromes Writing Committee). J Am Coll Cardiol 2001;38: 2114–30.
[18] Morise AP, Jalisi F. Evaluation of pretest and exercise test scores to assess all-cause mortality in unselected patients presenting for exercise testing with symptoms of suspected coronary artery disease. J Am Coll Cardiol 2003;42:842–50.
[19] Hesse B, Tägil K, Cuocolo A, Anagnostopoulos C, Bardiés M, Bax J, et al., EANM/ESC Group. EANM/ESC procedural guidelines for myocardial perfusion imaging in nuclear cardiology. Eur J Nucl Med Mol Imaging 2005;32:855–97.
[20] Germano G, Kavanagh PB, Waechter P, Areeda J, Van Kriekinge S, Sharir T, et al. A new algorithm for the quantitation of myocardial perfusion SPECT. I: technical principles and reproducibility. J Nucl Med 2000;41:712–9.
[21] Acampa W, Evangelista L, Petretta M, Liuzzi R, Cuocolo A. Usefulness of stress cardiac single-photon emission computed tomographic imaging late after percutaneous coronary intervention for assessing cardiac events and time to such events. Am J Cardiol 2007;100:436–41.
[22] Vickers AJ, Cronin AM, Begg CB. One statistical test is sufficient for assessing new predictive markers. BMC Med Res Methodol 2011; 11:13.
[23] Harrell Jr FE, Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. Stat Med 1996;15: 361–87.
[24] Pencina MJ, D'Agostino Sr RB, Steyerberg EW. Extensions of net reclassification improvement calculations to measure usefulness of new biomarkers. Stat Med 2011;30:11–21.
[25] Inoue E. NRI for risk prediction models with time to event and binary response data. Available at: http://cran.r-project.org/web/packages/nricens/index.html. [accessed September 2013].
[26] Pellegrini E, Maurantonio M, Giannico IM, Simonini MS, Ganazzi D, Carulli L, et al. Risk for cardiovascular events in an Italian population of patients with type 2 diabetes. Nutr Metab Cardiovasc Dis 2011;21:885–92.
[27] Stranges S, Guallar E. Cardiovascular disease prevention in women: a rapidly evolving scenario. Nutr Metab Cardiovasc Dis 2012;22:1013–8.
[28] De Berardis G, D'Ettorre A, Graziano G, Lucisano G, Pellegrini F, Cammarota S, et al., DADA (Diabetes Administrative Data Analysis) Study Group. The burden of hospitalization related to diabetes mellitus: a population-based study. Nutr Metab Cardiovasc Dis 2012;22:605–12.
[29] Hammoud T, Tanguay JF, Bourassa MG. Management of coronary artery disease: therapeutic options in patients with diabetes. J Am Coll Cardiol 2000;36:355–65.
[30] Miller TD, Askew JW. Net reclassification improvement and integrated discrimination improvement: new standards for evaluating the incremental value of stress imaging for risk assessment. Circ Cardiovasc Imaging 2013;6:496–8.