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Time to and risk of cardiac events after myocardial perfusion scintigraphy

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ABSTRACT

Background: The burden of cardiovascular disease is increasing, yet it remains difficult to focus preventive strategies on populations at highest absolute and relative risks. We compared absolute and relative cardiovascular event counts, plus time to first event, among patients undergoing myocardial perfusion scintigraphy (MPS).

Methods and results: Our database was queried to identify subjects without myocardial necrosis or recent revascularization, focusing on cardiac death (CD) or myocardial infarction (MI). A total of 13,254 patients were included, 5436 (41%) without, and 7818 (59%) with ischemia. After 32 ± 21 months, subjects without ischemia, compared to those with ischemia, had lower absolute (16 vs 75 events, 18% vs 82%, $p < 0.001$) and relative (0.3% vs 1.3%, $p < 0.001$) risk of CD. Similar findings were obtained for MI (52 vs 81 events, 39% vs 61%, $p < 0.001$, with corresponding rates of 1.0% vs 1.4%, $p < 0.001$, respectively). Medical therapy appeared associated with fewer outcomes in those without ischemia, with the opposite occurring for subjects with ischemia ($p < 0.001$). Median times to event ranged between 13 and 25 months in patients without ischemia vs 2 and 14 months in those with ischemia ($p < 0.001$ for all comparisons). Multivariable-adjusted and propensity matched analyses confirmed the independent prognostic role of myocardial ischemia and, apparently, revascularization.

Conclusion: Most fatal and non-fatal cardiac events appear to occur in patients with evidence of myocardial ischemia at MPS, especially those with moderate or severe ischemia not receiving revascularization during follow-up.

Introduction

The global burden of cardiovascular disease continues to increase, despite substantial improvements in prognostic, diagnostic, and management strategies in several countries [1]. Accordingly, it is paramount to improve and maximize preventive means of proven efficacy and safety in specific subpopulations. There is however uncertainty on which population subset should be targeted most aggressively [2–4]. This issue is further complicated by discrepancies between clinical and pathologic series appraising the association between coronary artery disease severity and clinical events. Specifically, most clinical series have reported that the majority of cardiovascular events occur, in absolute terms, in patients without severe coronary artery disease [5,6]. Conversely, pathologic series have typically concluded that most fatal cardiovascular events occur in subjects with severe coronary lesions [5,7].

Myocardial perfusion scintigraphy (MPS) offers an accurate and robust tool to appraise the ischemic (i.e. clinical) impact of

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suspected coronary artery disease [8,9]. Accordingly, we hypothesized that patient stratification according to MPS results could clarify the association between ischemic burden and event rates in patients with or at risk for coronary artery disease. We thus analyzed our institutional database to precisely quantify time to and risk of cardiac events after MPS.

Methods

This was a retrospective observational study exploiting prospectively collected data entered into a dedicated administrative database (OPCCardioPro, ETISAN, Rome, Italy) [9]. All patients provided written informed consent for imaging test and data collection and the competent institutional authority was notified.

Patients undergoing MPS for the diagnostic or prognostic work-up of coronary artery disease since April 2004 at our center were identified, excluding those aged <18 years, ineligible for 1-year clinical follow-up, having a history of coronary revascularization within the last 6 months before MPS, or evidence of myocardial necrosis at MPS. The test and imaging protocol has been described in detail elsewhere [9]. Briefly, semiquantitative interpretation of stress/rest images was performed based on the above 7-region model by consensus of 2 experienced observers using both visual assessment of the color-coded tomographic images for the 3 axes and the standard deviation (SD) polar map of detectable tracer uptake, finally obtaining for each region a 5-point scoring system (0 – normal uptake; 1 – minimally reduced uptake; 2 – mildly reduced uptake; 3 – moderately reduced uptake; and 4 – severely reduced or absent uptake). This score directly yielded the 5 classes of maximal ischemia score (MIS; 0 – no ischemia; 1 – minimal ischemia; 2 – mild ischemia; 3 – moderate ischemia; 4 – severe ischemia), with the final MIS strictly depending on the worst region of perfusion.

Clinical follow-up was systematically collected after the index MPS, by direct patient visit or telephone contact. In case an adverse event was elicited, hard copies of the source documents (e.g. hospitalization records) were retrieved to enable event adjudication and minimize information bias. Outcomes of interest were the long-term rates of cardiac death (CD), myocardial infarction (MI), revascularization, or their composite.

Continuous variables are reported as mean ± standard deviation. Categorical variables are reported as *n* (%), with 95% confidence intervals built according to the adjusted Wald method. Bivariate analyses were performed using ANOVA for continuous variables, chi-squared test for categorical variables, and Kaplan–Meier method for survival analysis, whereas times to event were computed with bootstrapped 95% confidence intervals of median values (based on 1000 samples), and compared with the log-rank test. Multivariable adjusted analysis was performed with Cox proportional hazard analysis entering as covariates all variables associated at bivariate $p < 0.10$ with MIS [reporting results as hazard ratios (HR) with 95% confidence intervals], with backward selection. Propensity scores were also generated to appraise the prognostic impact of revascularization vs medical therapy with a non-parsimonious logistic regression analysis, and then used to identify propensity matched pairs (1:1 ratio) using a 0.001 caliper [10]. Significance was set at the 2-tailed 0.05 level, and *p*-values unadjusted for multiplicity are reported throughout. Computations were performed with SPSS 20 (IBM, Armonk, NY, USA) and Stata 13 (StataCorp, College Station, TX, USA).

Results

A total of 13,254 patients were included, 5436 (41%) without ischemia, 2095 (16%) with minimal ischemia, 3096 (23%) with mild ischemia, 1782 (13%) with moderate ischemia, and 845 (6%) with severe ischemia. Several differences were found, as expected, in baseline and procedural features when comparing such groups (Online Tables 1 and 2).

After 32 ± 21 months of follow-up, patients without ischemia were at significantly lower absolute and relative risks of CD than subjects with ischemia, with corresponding differences in warranty periods (Table 1). Specifically, CD occurred in 16 vs 75, thus representing 18% vs 82% of all such events, with corresponding rates of 0.3% vs 1.3% ($p < 0.001$). Similar findings were obtained for MI, as patients without ischemia had lower absolute and relative risks of this event in comparison to subjects with ischemia, despite the fact that in absolute terms several still occurred in these patients: 52 vs 81, representing 39% vs 61% of all MIs, with corresponding rates of 1.0% vs 1.4% ($p < 0.001$).

Notably, in patients without ischemia, medical therapy appeared associated with a significantly lower risk of MI, as well as CD or their composite, than revascularization (respectively 1.0% vs 6.3%, $p < 0.001$, 0.3% vs 1.0%, $p < 0.001$, and 1.3% vs 7.3%, $p < 0.001$). Conversely, revascularization was apparently associated with markedly lower risks of MI, CD, or their composite in comparison to medical therapy in patients with moderate or severe ischemia.

Similar results to those obtained for CD or MI occurred when focusing on revascularizations or the composite of CD or MI, or revascularization (Table 2). Warranty periods, estimated from median time to events, were also significantly different according to the degree of ischemia. Specifically, CD occurred a median of 21 (95% confidence interval 12–24) months after the index MPS among subjects without ischemia vs 10 (7–12) months among those with ischemia. Corresponding figures for MI, revascularization, and their composite, were, respectively, 25 (21–29) vs 14 (8–22), 13 (11–17) vs 2 (2–2), and 14 (12–16) vs 2 (2–2).

Several sensitivity analyses were performed, including those excluding events occurring less than 3 months after MPS, as well as those based on the inclusion of all patients and normalizing event burdens according to crude event rates stemming from the cohort of subjects not receiving revascularization during follow-up, further confirming the above findings (Online Tables 3–5). Notably, analysis stratified according to the findings of coronary angiography (any catheterization, 1 – vessel disease, 2 – vessel disease, and 3 – vessel disease) confirmed our findings in terms of statistical magnitude and direction. We also performed multivariable-adjusted Cox proportional hazard analysis to identify independent predictors of CD or MI (Online Table 6), confirming that MIS was a significant independent predictor [HR = 1.23 (1.07–1.41, $p = 0.003$)], together with age [HR = 1.05 (1.03–1.07), $p < 0.001$], body mass index [HR = 1.04 (1.00–1.07), $p = 0.048$], maximum ST-segment deviation [HR = 1.22 (1.01–1.48), $p = 0.043$], ejection fraction [HR = 0.97 (0.95–0.98), $p < 0.001$], and revascularization as first follow-up event [HR = 0.65 (0.44–0.96)]. Risk-adjusted estimates of the prognostic impact of myocardial ischemia on CD or MI, as well as on the other endpoints, were also similar to unadjusted estimates, with the majority of CD or MI events occurring in patients with objective evidence of myocardial ischemia.

Propensity score matched pairs were also obtained to compare revascularization vs medical therapy, aiming at minimizing the role of confounders. Analysis based on such propensity matched pairs showed that revascularization was apparently associated with a significantly lower risk of CD or MI than medical therapy in patients with objective evidence of myocardial ischemia [HR for CD or MI = 0.35 (0.16–0.74); HR for MI = 0.21 (0.06–0.75)], as well as a trend toward fewer CDs [HR = 0.50 (0.19–1.33)]. Finally, analyses limited to patients with adverse events showed that MIS, ejection fraction, and ST-segment deviation were independent predictors of shorter time to event.