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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.

Table 1
Unadjusted analysis for absolute counts, relative counts, and time to events for cardiac death (CD) or myocardial infarction (MI) according to maximal ischemia score (MIS), excluding patients undergoing revascularization as first event during follow-up.[a]

Event	Statistics	Total (*N* = 11,235)	No ischemia (*N* = 5340)	Any myocardial ischemia					*p*-value
				Subtotal (*N* = 5895)	Minimal (*N* = 2003)	Mild (*N* = 2601)	Moderate (*N* = 964)	Severe (*N* = 327)	
CD	Absolute count	91	16	75	6	26	20	23	<0.001
	% Relative to absolute counts	100%	17.6% (11.0–26.8%)	82.4% (73.2–89.0%)	6.6% (2.8–13.9%)	28.6% (20.3–38.6%)	22.0% (14.6–31.6%)	25.3% (17.4–35.1%)	
	% Relative to MIS	0.8% (0.7–1.0%)	0.3% (0.2–0.5%)	1.3% (1.0–1.6%)	0.3% (0.1–0.7%)	1.0% (0.7–1.5%)	2.1% (1.3–3.2%)	7.0 (4.7–10.4%)	
	Time to event (months)	19 (15–22)	21 (12–24)	10 (7–12)	13 (6–19)	10 (7–12)	10 (5–14)	7 (5–13)	<0.001
	Normalized absolute count[b]	118	16	102	6	31	37	59	<0.001
	Normalized % relative to absolute counts[b]	100%	13.6% (8.4–21.0%)	86.4% (79.0–91.6%)	5.1% (2.1–10.9%)	26.3% (19.1–34.9%)	31.3% (23.7–40.2%)	50.0% (41.1–58.9%)	
MI	Absolute count	133	52	81	21	25	25	10	<0.001
	% Relative to absolute counts	100%	39.1% (31.2–47.6%)	60.9% (52.4–68.8%)	15.8% (10.5–23.0%)	18.8% (13.0–26.3%)	18.8% (13.0–26.3%)	7.5% (4.0–13.4%)	
	% Relative to MIS	1.2% (1.0–1.4%)	1.0% (0.7–1.3%)	1.4% (1.1–1.7%)	1.0% (0.7–1.6%)	1.0% (0.7–1.4%)	2.6% (1.8–3.8%)	3.1% (1.6–5.6%)	
	Time to event (months)	18 (13–22)	25 (20–28)	13 (8–18)	21 (15–30)	7 (3–22)	10 (3–19)	12 (1–31)	0.023
	Normalized absolute count[b]	164	54	110	21	31	46	26	<0.001
	Normalized % relative to absolute counts[b]	100%	32.9% (26.2–40.5%)	67.1% (59.6–73.8%)	12.8% (8.5–18.9%)	18.9% (13.6–25.6%)	28.1% (21.7–35.4%)	15.9% (11.0–22.3%)	
CD or MI	Absolute count	224	68	156	27	51	45	33	<0.001
	% Relative to absolute counts	100%	30.4% (24.7–36.7%)	69.6% (63.3–75.3%)	12.1% (8.4–17.0%)	22.8% (17.7–28.7%)	20.1% (15.3–25.8%)	14.7% (10.7–20.0%)	
	% Relative to MIS	2.0% (1.8–2.3%)	1.3% (1.0–1.6%)	2.6% (2.3–3.1%)	1.3% (0.9–2.0%)	2.0% (1.5–2.6%)	4.7% (3.5–6.2%)	10.1% (7.2–13.9%)	
	Time to event (months)	14 (12–16)	22 (17–27)	11 (9–14)	17 (13–23)	9 (7–13)	10 (5–14)	10 (5–12)	<0.001
	Normalized absolute count[b]	274	71	258	27	62	84	85	<0.001
	Normalized % relative to absolute counts[b]	100%	21.6% (21.1–31.4%)	78.4% (90.7–96.4%)	8.2% (6.8–14.0%)	18.8% (18.1–28.0%)	25.5% (25.5–36.4%)	25.8% (25.8–36.7%)	

[a] Dichotomous variables are reported as point estimates (95% confidence interval according to the adjusted Wald method), and times to event are described as median with 95% bootstrapped confidence intervals (1000 samples), compared with log-rank test.
[b] According to distribution of patients at risk reported in Online supplement.

Discussion

Efforts aiming at minimizing the burden of cardiovascular disease have always been fraught by the difficulty in maximizing effectiveness while minimizing costs and hazards [5]. Accordingly, the identification of people at higher risk of adverse events has been the constant focus of patients, cardiovascular specialists, and policy makers alike [11,12]. In simplistic terms, there are two alternative perspectives pertinent to the concept of risk and burden. Specifically, risk may be dramatically higher in a subset of the population. Yet, if such a subset is tiny, the overall burden of disease attributable to this group of patients may be correspondingly small. Conversely, patients with a relatively low risk of adverse events may impact dramatically on burden estimates if they represent the vast majority of the overall population.

Two main hypotheses have prevailed so far on the estimate of coronary artery disease burden in developed countries [5,13]. The first paradigm, largely based on clinical series exploiting coronary angiography, states that most adverse cardiac events occur in patients without severe coronary lesions, and thus these people should be the main focus of preventive strategies [6,14,15]. The opposing paradigm, based largely on pathologic series, purports that most adverse cardiac events occur in patients with severe coronary artery disease, and thus they should be the main target of healthcare interventions aimed at reducing the burden of cardiovascular disease [7,16,17]. Attempts at reconciling these discrepancies have been to date limited in success. Our work provides interesting results suggesting that adverse events occur more frequently, in both relative and absolute terms, among patients with evidence of myocardial ischemia and supports previous findings by Hachamovitch et al. [4]. Furthermore, our study has several distinct strengths, including the large sample size, inclusion of patients more reflective of current cardiovascular treatment patterns, focus on several different outcomes, computation of normalized absolute and counts, assessment of warranty periods, and extensive risk-adjustment with standard Cox proportional hazard analysis and propensity score matching. Notably, the fact that adverse events occur more commonly in patients with ischemia, in absolute and relative terms, holds true for all cardiac events, both fatal and non-fatal, but is especially valid for CD. Similar findings were obtained for revascularization and the composite of CD, MI, and revascularization, or when focusing on counts relative to patients at risk or time to events. Analysis focusing on MI shows a similarly important but less progressive impact of severity of ischemia. At first, comparison of patients with vs without ischemia confirms that most MIs occurred in the first group. However, comparison of event counts relative to patients at risk suggests a less dramatic (irrespective of statistical significance) increase in risk, going from 1.0% in those without ischemia to 3.1% in those with ischemia. This does not translate

Table 2
Unadjusted analysis for absolute counts, relative counts, and time to events for coronary revascularization and the composite of cardiac death (CD), myocardial infarction (MI), or revascularization according to maximal ischemia score (MIS).[a]

Event	Statistics	Total (*N* = 13,254)	No ischemia (*N* = 5436)	Any myocardial ischemia					*p*-value
				Subtotal (*N* = 7818)	Minimal (*N* = 2095)	Mild (*N* = 3096)	Moderate (*N* = 1782)	Severe (*N* = 845)	
Revascularization	Absolute count	2498	256	2242	163	635	895	549	<0.001
	% Relative to absolute counts	100%	10.2% (9.1–11.5%)	89.8% (88.5–90.9%)	6.5% (5.6–7.6%)	25.4% (23.8–27.2%)	35.8% (34.0–37.7%)	22.0% (20.4–23.6%)	
	% Relative to MIS	18.8% (18.2–19.5%)	4.7% (4.2–5.3%)	28.7% (27.7–29.7%)	7.8% (6.7–9.0%)	20.5% (19.1–22.0%)	50.2% (47.9–52.5%)	65.0% (61.7–68.1%)	
	Time to event (months)	2 (2–3)	13 (11–17)	2 (2–2)	9 (7–11)	3 (3–4)	2 (2–2)	1 (1–1)	
CD, MI, or revascularizaton	Absolute count	2603	279	2324	171	661	919	573	<0.001
	% Relative to absolute counts	100%	10.7% (9.6–12.0%)	89.3% (88.0–90.4%)	6.6% (5.7–7.6%)	25.4% (23.8–27.1%)	35.3% (33.5–37.2%)	22.0% (20.5–23.7%)	
	% Relative to MIS	19.6% (19.0–20.3%)	5.1% (4.6–5.8%)	29.7% (28.7–30.8%)	8.2% (7.1–9.4%)	21.4% (19.9–22.8%)	51.6% (49.3–53.9%)	67.8% (64.6–70.9%)	
	Time to event (months)	3 (2–3)	14 (12–16)	2 (2–2)	9 (6–11)	3 (3–4)	2 (2–2)	1 (1–2)	<0.001
Revascularization occurring ≥3 months after MPS	Absolute count	1239	232	1007	137	373	337	160	<0.001
	% Relative to absolute counts	100%	18.7% (16.5–20.9%)	81.3% (79.1–83.4%)	11.1% (9.4–12.8%)	30.1% (27.6–32.7%)	27.2% (24.7–29.7%)	12.9% (11.0–14.8%)	
	% Relative to MIS	9.3% (8.8–9.8%)	4.3% (3.8–4.8%)	12.9% (12.1–13.6%)	6.5% (5.4–7.6%)	12.0% (10.9–13.1%)	18.9% (17.1–20.7%)	18.9% (16.3–21.5%)	
	Time to event (months)	8 (8–9)	17 (14–20)	7 (6–7)	11 (9–16)	8 (7–9)	5 (5–6)	5 (3–6)	<0.001
CD, MI, or revascularization occurring ≥3 months after MPS	Absolute count	1323	255	1.068	144	392	355	177	<0.001
	% Relative to absolute counts	100%	19.3% (17.2–21.4%)	80.7% (78.6–82.6%)	10.9% (9.2–12.6%)	29.6% (27.1–32.1%)	26.8% (24.4–29.2%)	13.4% (11.6–15.2%)	
	% Relative to MIS	10.0% (9.4–10.5%)	4.7% (4.1–5.3%)	13.7% (12.9–14.4%)	6.9% (5.8–8.0%)	12.7% (11.5–13.9%)	19.9% (18.0–21.8%)	20.9% (18.2–23.6%)	
	Time to event (months)	8 (8–9)	16 (13–20)	7 (6–7)	11 (9–14)	8 (7–9)	5 (5–6)	5 (5–6)	<0.001

MPS, myocardial perfusion scintigraphy.
[a] Dichotomous variables are reported as point estimate (95% confidence interval according to the adjusted Wald method), and times to event are described as median with 95% bootstrapped confidence intervals (1000 samples), compared with log-rank test.

however into a universal call for routine invasive management and aggressive revascularization strategy, especially in subjects without ischemia, as we can show, in keeping with others [4] that revascularization of non-ischemic coronary artery disease is associated with worse outcomes. Moreover, our work was not based on randomization and thus data on patients receiving revascularization cannot be considered a definitive scientific proof of its clinical validity in this setting.

Nonetheless, these findings have several implications. First, they may reconcile discrepancies in prior works [5–7,13–17]. Indeed, clinical studies by definition were excluding fatal cardiac events, and thus were usually focusing on non-fatal MIs. Conversely, pathologic studies were, per se, limited to fatal cardiac events, and thus were not truly representative of the overall population of patients at risk [5,7,16,17]. Moreover, both types of studies were limited by an anatomic approach at quantifying coronary artery disease severity which disregards the prognostically crucial role of myocardial ischemic burden. More pragmatically, our work may also be useful in the risk stratification of individual patients and in decision-making at large, as well as in supporting ongoing efforts at improving appropriate care, with MPS appearing as a key component of appropriate decision-making and management of patients with or at risk of coronary artery disease.

This study has several drawbacks, including the retrospective, observational, and single-center design, as well as the absence of details on coronary anatomy on all included subjects. Accordingly, prospective studies are required to confirm or disprove our findings, using standard or automated image analyses [18,19]. In addition, our population is fraught by an inherent bias due to convenience sampling, and thus may not be considered representative per se of the typical subjects in primary or secondary prevention settings, but rather more truthfully corresponding to the stable patients with or at risk of coronary artery disease undergoing MPS. While our study builds upon several others in the field [4,8,9,19,20], it adds incremental scholarly value mainly because of three important features. First, it represents a recent rather than remote series of patients more similar to those physicians treat in current clinical practice. Second, its sample size enables rather precise event estimates and accurate as well as robust analyses. Third, and most importantly, it exploits an altogether novel approach at appraising the severity of myocardial ischemia at MPS, which was originally described only recently [9]. Accordingly, it reinforces the importance of looking at MPS as a diagnostic and prognostic imaging modality with still significant room for improvements and refinements.

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Conflicts of interest

None declared.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jjcc.2014.11.007.

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