My warranty has expired: I need to be retested

Mario Petretta, MD,[a] Wanda Acampa, MD, PhD,[b,c] Roberta Assante, MD, PhD,[b] Emilia Zampella, MD, PhD,[b] Carmela Nappi, MD,[b] Andrea Petretta, MD, PhD,[d] and Alberto Cuocolo, MD[b]

[a] Department of Translational Medical Sciences, University Federico II, Naples, Italy
[b] Department of Advanced Biomedical Sciences, University Federico II, Naples, Italy
[c] Institute of Biostructure and Bioimaging, National Council of Research, Naples, Italy
[d] Department of Arrhythmology, Maria Cecilia Hospital, GVM Care and Research, Cotignola, Italy

Received Nov 29, 2017; accepted Nov 30, 2017
doi:10.1007/s12350-017-1154-y

The concept of warranty period, the duration of time during which the patient's risk remains low, is appealing. However, some points remain to be resolved before its translation in the clinical arena. Methodological issues should be standardized in order to compare the results of studies in different patient populations. Also, the definition of a ''normal'' study should always take into consideration the history of prior revascularization, the achieved level of exercise, and the stressor used. The promise of warranty can be questioned by the patient's baseline demographic and clinical characteristics and may also be influenced by life-style modification in the course of the follow-up. The ''warranty period'' concept should shift from data reflecting the time to a cardiac event to the development of ischemia, given an opportunity for intervention before a cardiac event occurs. In this context, clarify the role of serial imaging can be extremely useful, in particular to evaluate if and when retesting a patient after a normal scan.

Key Words: Myocardial perfusion imaging • SPECT • gated SPECT • ischemia • myocardial • outcomes research

THE CONCEPT OF WARRANTY PERIOD

A warranty is a contractual obligation of a manufacturer/dealer associated with sale of a product. Under such contractual agreement, a manufacturer/dealer takes the responsibility to rectify defects or failures of products due to design, manufacturing and quality assurance problems over a certain period of time after the sale.[1] Hachamovitch first introduced the concept of a warranty period after normal myocardial perfusion scans in 1995.[2] Stress myocardial perfusion imaging with single-photon emission computed tomography (MPS) is able to provide important clinical information for diagnosis and risk stratification of patients with suspected or known coronary artery disease (CAD). It is well known that a normal stress MPS implies a good clinical outcome with rates of hard cardiac events and all-cause death comparable to those of the general population.[3] Indeed, patients with normal myocardial perfusion are considered at low risk of cardiac events and the annualized event rate is generally $< 1\%$ during the first few years after testing.[4] However, knowledge of this event rate alone is potentially misleading.[5] In fact, an annualized event rate of $> 1\%$ after a normal MPS may be the result of a constant $> 1\%$ per year event rate over the follow-up interval, but it may also result from an event rate of $< 1\%$ during the first year and a markedly increased event rate later in the follow-up

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s12350-017-1154-y) contains supplementary material, which is available to authorized users.

The authors of this article have provided a PowerPoint file, available for download at SpringerLink, which summarises the contents of the paper and is free for re-use at meetings and presentations. Search for the article DOI on SpringerLink.com.

Reprint requests: Alberto Cuocolo, MD, Department of Advanced Biomedical Sciences, University Federico II, Naples, Italy; *cuocolo@unina.it*

J Nucl Cardiol 2019;26:998–1006.
1071-3581/$34.00

period. Similarly, even an annualized event rate < 1% over more than one year does not exclude the possibility that risk was exceedingly low initially, but increased with time, and risk was not < 1% later. These undefined temporal characteristics of risk (''how risk changes with time'') may be important in determining test performance as well the length of time that a patient remains at low risk after the index normal MPS, hence defining whether a ''warranty'' period exists. It has been demonstrated that duration of low-risk status after a normal stress MPS depends on several factors. In particular, expected event rate is driven not only by MPS findings but also by the underlying risk factors and comorbidity burden as well as the extent of atherosclerosis. Yet, the rates vary from a low of 0.2% to a high of nearly 2%, reflecting differences in underlying clinical risk and prior CAD.[6] Thus, in patients with normal stress MPS, CAD risk factors and the mode of testing can influence the trajectory of long-term outcomes. Ottenhof et al.[7] found that Kaplan-Meier survival analysis revealed wide heterogeneity in all-cause mortality rates when risk factors burden and performance of exercise vs pharmacologic testing were considered, ranging from only 0.8% per year in exercise patients without risk factors to 4.2% per year in pharmacologic patients with ≥ 2 risk factors; mortality rates in exercise patients with ≥ 2 risk factors were comparable to those in pharmacologic patients with no risk factors. It should be also considered that several clinical, stress, and MPS findings are associated with angiographically proven high-risk CAD among patients with normal MPS and that considering these factors may improve the overall assessment of the likelihood of high-risk CAD in patients undergoing stress MPS.[8]

THE EVOLVING PICTURE OF WARRANTY PERIOD

Studies reporting the warranty period for normal scan are listed in Table 1. In their first report introducing the concept of warranty period applied to a normal scan, Hachamovitch et al.[2] concluded that patients with normal scans have a common temporal component limited to about 600 days; thereafter, those at ''high risk'' (i.e., age ≥ 65 years or pre-test likelihood of CAD ≥0.15 or previous revascularization) should undergo to repeat testing. In 2003, two studies aimed to evaluate whether a ''warranty'' period exists after a normal scan.[5,9] Hachamovitch et al.[5] extended the 1995 preliminary report[2] on 7376 consecutive patients with normal exercise or adenosine MPS followed-up for 665 ± 200 days. The event rate was greater in patients with previous CAD than in those without. Pharmacologic stress test, known CAD, diabetes mellitus, male gender, and increasing age were independent predictors of events at multivariable Cox analysis. A significant interaction was also found between stress type and previous CAD (lower risk in patients without previous CAD undergoing exercise stress vs all others) and between diabetes and gender (higher risk in diabetes females vs all others). The highest risk subgroups had a maximal event rate of 1.4-1.8% per year. Parametric survival modeling (Weibull distribution) revealed that in patients without previous CAD, for each subgroup the level of predicted risk was uniform with time while in patients with known CAD predicted that risk increased with time showing a dynamic temporal component. In particular, in patients with known CAD, comparing the first to the fourth six-month interval, patient risk increased approximately 2-2.5 times, and event rates in the first year were lower than in the second year.

Thus, it is imperative not only to define the patient's risk within bounded time intervals after a normal MPS, but also the change in risk over time and the duration of time after the study that the risk remains low. The study of Hachamovitch et al.[5] demonstrated that clinical factors alter the time at which repeat testing after a normal scan might be appropriate, hence establishing the existence of differences in the ''warranty'' periods for normal MPS according to patient's characteristics. The study also indicates that, if risk change over the follow-up period, simply reporting the overall annualized event rate may misestimate the actual risk.

SUBSEQUENT STUDIES

The notion of ''warranty period'' was used later by Acampa et al.[10] in a study assessing predictors and temporal characteristics of cardiac risk in 336 patients undergoing stress MPS 12-18 months after successful percutaneous coronary intervention (PCI). At Cox univariate analysis, prescan likelihood of ischemia, ischemia at MPS, and summed difference score were found to be significant predictors of events. The parametric model used for prediction of time to events identified prescan likelihood of ischemia and presence of ischemia at MPS as univariate significant variables and including these variables in the survival model the authors have demonstrated that, for each level of prescan likelihood of ischemia, cardiac risk was greater for all intervals and accelerated more over time in patients with ischemia compared with those without. Indeed, patients with low prescan likelihood of ischemia and without ischemia at MPS stayed at < 2% estimated risk for the entire follow-up period. This study outlined the importance of knowledge of temporal characteristics of risk and how the risk changes over time as a function of patient characteristics and test imaging results after PCI,

Table 1. Studies reporting the warranty period for a normal scan

	Hachamovitch[5]	Acampa[10]	Carrier[11]	Schinkel[12]
Recruitment	1991-1997	2000-2002	2002	NA
Follow-up (mo)	20 ± 6	31 ± 10	60	185 ± 57
Warranty period	Low risk time after index MPS	Low risk time	Low risk time after index MPS	Low risk time after index MPS
Low risk definition	Event rate < 1% per year	Annualized event rate < 2%	Annualized risk of MI or death < 1%	Annualized event rate < 1%
Inclusion	Suspected or known CAD	Referred for MPS after PCI	Suspected or known CAD	Suspected or known CAD
Sample size (n)	7376 (6046 suspected, 1330 known CAD)	346 (17 event, 329 no event)	3010 (656 suspected, 2354 known CAD)	233 (176 suspected, 57 known CAD)
Age (years)	61 ± 13 suspected, 66 ± 12 known CAD	59 ± 9 event, 60 ± 8 no event	62 ± 12 suspected, 67 ± 11 known CAD	54 ± 12
Male gender (%)	51 suspected, 56% known CAD	83 event, 88 no event	54 suspected, 77 known CAD	52
Outcome	CD, MI	CD, MI	Worsening symptoms, MI, PCI, CABG	ACM, CD, MI, PCI, CABG
Events (n)	78 (45 CD, 33 MI)	17 (2 CD, 15 MI)	140 (127 worsening symptoms, 6 PCI, 2 CABG, 5 MI)	78 (13 CD, 18 MI, 47 PCI or CABG)
Statistical analysis	Cox proportional hazards Parametric survival/Weibull	Kaplan-Meier Cox proportional hazards Parametric survival/Weibull	Kaplan-Meier	Kaplan-Meier Cox proportional hazards

	Simonsen[13]	Nudi[15]	Acampa[14]	Romero[16]
Recruitment	2002-2007	From 2004	2006-2007	1997-2007
Follow-up (mo)	72	32 ± 21	53 (44-63)	60 ± 39
Warranty period	Low risk time after index MPS	Estimated time from median time to events	Low risk time after index MPS	Low risk time
Low risk definition	Annualized event rate < 1%	NA	Annual risk of MI or death < 1%	Event rate < 1% per year
Inclusion	Suspected or known CAD	Suspected or known CAD	Suspected or known CAD	Suspected or known CAD

Table 1. continued

	Simonsen[13]	Nudi[15]	Acampa[14]	Romero[16]
Sample size (n)	2157 (1327 normal, 830 abnormal MPS)	13254	828 (402 diabetic, 426 nondiabetic)	2992
Age (years)	61 ± 0.2	64 ± 10	62 ± 9 diabetic, 59 ± 10 nondiabetic	63 ± 13
Male gender (%)	53	69	53 diabetic 60 nondiabetic	47
Outcome	ACM, CD, MI	CD, MI, PCI, CABG	CD, MI	ACM, CD HF, MI, PCI, CABG
Events (n)	588 (85 CD, 227 ACM, 114 MI, 237 PCI or CABG)	2722 (91 CD, 133 MI, 2498 PCI or CABG)	24 (13 CD, 11 MI)	424 (269 ACM, 81 HF, 74 PCI or CABG)
Statistical analysis	Kaplan-Meier Cox proportional hazards	Kaplan-Meier Cox proportional hazards	Kaplan-Meier Cox proportional hazards Parametric survival/ Weibull	Kaplan-Meier Cox proportional hazards

MPS, myocardial perfusion imaging with single-photon emission computed tomography; *CAD*, coronary artery disease; *PCI*, percutaneous coronary intervention; *CD*, cardiac death; *MI*, myocardial infarction; *CABG*, coronary artery bypass grafting; *ACM*, alla cause mortality; *HF*, heart failure

for patient management and for retest planning during follow-up. Interesting, the authors proposed an algorithm of the times that might represent the ''warranty period'' before retesting patients with normal MPS results after PCI, based on prescan likelihood of ischemia and results of stress MPS.

Carryer et al.,[11] using the same definition of ''warranty period'' proposed by Hachamovitch et al.,[5] evaluated the time to reach 1% risk after a normal MPS in 3010 consecutive patients with and without prior CAD during a 5-year follow-up. The authors examined 708 patients who had follow-up studies at a median of 2 years, stratified by the clinical indications for follow-up scan, ''routine vs non-routine.'' For each patient ''warranty period,'' defined as time to 1% risk, was calculated by Kaplan-Meier method and compared with the interval between images. The results of this study indicate that only 19% of patients with normal initial MPS and no history of CAD performed retesting during the next 5 years. Moreover, two-thirds of the follow-up scan in these patients were performed as a routine scan and the majority of these follow-up scans were performed before the mid-point of the patient's warranty period. The timing of these scans may explain the low rate of highly abnormal scans and the absence of any subsequent revascularization. On the other hand, 39% of patients with known CAD were retested during follow-up. The presence of CAD at baseline increases the likelihood of conversion of a normal MPS to abnormal over a 2-year period. Because the warranty period in these patients is much shorter, most follow-up scans were performed after expiration of their warranty period and also after an additional 50% of the warranty period had passed. Nevertheless, of the patients with prior CAD and routine follow-up studies, only 7% referred to coronary angiography, and no revascularization procedure was performed after these scans.

Schinkel et al.[12] assessed the very long-term outcome after a normal exercise MPS in 233 patients with known or suspected CAD. The probability of survival was calculated using the Kaplan-Meier method. Annualized event rates were relatively low during the entire follow-up period and prognosis was favorable even at 15-year follow-up. Particularly, in the first 5 years after normal exercise MPS annualized event rates were very low. Multivariate Cox proportional hazard regression analysis demonstrated that several clinical and exercise testing parameters, as age, male gender, and diabetes or heart rate at rest, peak exercise heart rate, diastolic blood pressure at rest, rate pressure product at rest, and ST segment changes influence the very long-term outcome. The authors suggested that repeated testing should be considered in patients with a change in symptoms or worsening clinical status.

Simonsen et al.[13] demonstrated in a cohort of 1327 patients with suspected or known CAD and normal MPS that the risk was very low immediately after testing, increasing slowly during the first 3 years to reach a plateau, not surpassing 2% in the first 5 years. However, risk varied accordingly to gender, age, and presence of CAD. The authors according to their results advise a general warranty period following a normal MPS of 5 years. As a methodology, these authors used Kaplan-Meier plots and log-rank tests for the survival analyses and Cox proportional hazards modeling to describe the influence of covariates by calculation both unadjusted and adjusted hazard ratios. Finally, smoothed hazards functions were used to estimate mortality rates over time.

In a subsequent study, Acampa et al.[14] analyzed a propensity score-matched cohort of 828 diabetic and non-diabetic patients with normal stress MPS to evaluate the relationship between diabetes and the temporal characteristics of cardiac risk at long-term follow-up (median 53 months). During follow-up, 18 events (11 cardiac death and 7 non-fatal myocardial infarction) occurred in diabetic and 6 events (2 cardiac death and 4 non-fatal myocardial infarction) in non-diabetic subjects. Univariable associations with cardiac events were determined by Cox proportional hazards regression, and event-free survival stratified by diabetes was estimated by Kaplan-Meier method. In addition, the authors used a parametric survival model to identify how the variables influenced time to event and to estimate risk-adjusted event rates during the follow-up. The Cox proportional hazards model identified diabetes and post-stress left ventricular (LV) ejection fraction (EF) $\leq$ 45% as the model most predictive of cardiac events. Parametric survival analysis, including in the model diabetes and post-stress LVEF $\leq$ 45%, showed that the hazard rate increases with time with a shape parameter of 1.2. The highest probability of cardiac events and the major risk acceleration was observed in diabetic patients with post-stress LVEF $\leq$ 45%. Conversely, non-diabetic patients with normal post-stress LVEF had the lowest probability of events. The authors also estimated the time to achieve a cumulative cardiac risk level $>$ 3% in diabetic and non-diabetic patients according to post-stress LVEF. Non-diabetic patients with normal post-stress LVEF remained at low risk for the length of follow-up, while in diabetic patients with post-stress LVEF $\leq$ 45% the time to achieve a risk level of events $>$ 3% was 12 months. Of note, non-diabetic patients with post-LVEF $\leq$ 45% and diabetic patients with normal post-stress LVEF achieved a risk $>$ 3% after 40 months. Thus, Acampa et al.[14] demonstrated that warranty period of a normal stress MPS varies according to diabetic status and post-stress LVEF. In particular, in diabetic patients that are at

higher risk for cardiac death and non-fatal myocardial infarction, a normal stress MPS seems to be not reassuring. Indeed, the highest probability of cardiac death or non-fatal myocardial infarction and the major risk acceleration was observed in patients with diabetes and abnormal post-stress LVEF.

In a retrospective observational study, Nudi et al.[15] analyzed 13,254 patients referred to MPS for the diagnostic or prognostic workup of CAD. Only patients with normal MPS or with evidence of ischemia were included in the study. In particular, the authors analyzed the association between ischemic burden and event rates in these patients and quantify time to and risk of cardiac events after MPS. Cox proportional hazard analysis was performed to identify independent predictors of cardiac events and Kaplan-Meier method for survival analysis. Their results suggested that adverse events occur more frequently among patients with evidence of myocardial ischemia. Warranty periods, estimated as median time to events, were significantly different according to the degree of ischemia. Multivariable adjusted Cox proportional hazard analysis confirmed that maximal ischemia score was significant independent predictor of events together with age, body mass index, maximum ST-segment deviation, ejection fraction, and revascularization as first follow-up event. Moreover, propensity score matched pairs were also obtained to compare revascularization versus medical therapy, aiming at minimizing the role of confounders. Propensity analysis showed that revascularization was apparently associated with a significantly lower risk of cardiac events than medical therapy in patients with moderate or severe myocardial ischemia. Conversely in patients without ischemia, medical therapy appeared associated with a significantly lower risk of events than revascularization.

Romero-Farina et al.[16] estimated the different warranty periods of a normal MPS based on the different types of stress used, clinical patient characteristics, and LV systolic function. The longest warranty periods were observed in patients who underwent exercise MPS, followed by those who underwent exercise-dipyridamole MPS, and, finally, those undergoing dipyridamole MPS alone. The warranty periods for cardiac events were shorter in cases where there was a decrease both in metabolic equivalents (METs), and in peak heart rate achieved on exercise MPS. The warranty period for dipyridamole MPS was similar to the warranty period of patients who had been unable to achieve 5 METs or a peak heart rate below 80% of the predicted peak heart rate for the patient's age. Moreover, the warranty period is shorter in the case of abnormal LVEF on gated-MPS, even when perfusion imaging is normal. In conclusion, all these factors can reduce the warranty period of a normal MPS. The finding that rates of freedom from adverse cardiac events differ significantly for patients with normal exercise MPS as compared to patients with normal pharmacological MPS has been confirmed by a meta-analysis of 14,918 patients from 24 studies evaluating prognosis in patients undergoing pharmacologic or exercise stress[17].

METHODOLOGICAL ISSUE

Alternative to Cox Model for Survival Analysis

Cox proportional hazards regression model has become the statistician's mainstay in the analysis of survival data. Briefly, the Cox model evaluates the hazard (h) to have an event in the time $t + 1$ for those subjects that are still alive at time t.[18] The crucial assumption of the Cox model is that the covariate effects are not associated with time (proportional hazards). However, the Cox model makes no assumption about the distribution of survival times, and thus the baseline hazard, $h_0(t)$, is not estimated from the Cox model. This characteristic of Cox model is both an advantage and a disadvantage. The advantage is that it is possible to fit survival models without knowing or assuming the distribution of survival time. The disadvantage is that the Cox model only estimates the relative effect of a covariate on the hazard rate. Thus, direct quantification of the improvement in survival time is not possible, except in the case of truly exponentially distributed times, where the reciprocal of the hazard ratio estimates the ratio of median times (as well as other quantile times) to event.[19] However, lifetimes are seldom truly exponential in their distribution. Several alternatives to Cox model have been proposed and are under active investigation.[20] One approach is to built a probability model that fit the data reasonably well, to make inferences on event-free survival times. The advantages rely on the mathematical form of the model, which may be manipulated to become smoother than the observed data instead of a step function, as predicted by the counting-process theory embedded in the Cox model.[21] Thus, fitted values from a probabilistic model supply estimates of survival time and residuals between observed and predicted values of survival times, also in the presence of censoring. Statistical techniques used to make assumptions about the functional form of the probability distribution function of failure time and to assess how explanatory variables influence the risk of failure are called parametric techniques. Parametric models have advantages over Cox model for prediction, extrapolation and quantification of absolute risk as well as of relative differences in risk. Parametric models are also useful for modeling time-dependent effects,

understanding and communicating the results obtained. Complex models in large datasets with time-dependent effects and or multiple time-scales could be all cause could be handled and cause-specific or relative survival also analyzed.[22,23]

A parametric probability distribution often used in the analysis of survival data is the Weibull distribution, first described in 1951 as a distribution with truly wide applicability in several context, in particular industrial reliability testing.[24] In addition to hazard ratio, Weibull analysis provides means of directly estimating the relative improvement in survival time, namely the event time ratio. The quantification of this effect is of clinical relevance and is likely to be better understood than the conventional hazard ratio. Other parametric survival models used for survival analysis are the exponential (a special case of Weibull), Gompertz, log-logistic, log-normal, and generalized gamma models. Only the exponential and Weibull models work both in the accelerated failure-time and in the proportional hazard framework.[25] Disadvantages of parametric models are as follows: it is necessary to decide how the hazard function depends on time; it may be difficult to find a parametric model if the hazard function is believed to be non-monotonic; it is awkward to develop fully parametric models that include time-varying covariates, in particular for constructing predictions. The adequacy of the Weibull parameterization is suggested if the estimated coefficients (and hazard ratio) are very similar to that estimated by Cox model. However, Weibull model is inadequate if the proportional hazard assumption does not hold and with non-monotic hazard functions, i.e., that go up, peak, and decrease, changing direction with time. It should be outlined that the data distribution is often chosen on the shape of the model without covariates and this can change as covariates are added. Thus, dynamic prediction in clinical survival analysis is an active research field to overcome these limitations.[26]

Royston-Parmar Model

Royston and Parmar[27] expanded the idea of Efron[28] of spline-smoothing the distribution function and proposed extensions of the Weibull and log-logistic models in which natural cubic splines are used to smooth the baseline log cumulative hazard and log cumulative odds of failure functions. Further extensions to allow non-proportional effects of some or all of the covariates have been introduced. An important feature of flexible parametric models is the ability to model time-dependent effects, i.e., there are non-proportional hazards. Time-dependent effects are modeled using splines, but will generally require fewer knots than the baseline. This is because we are now modeling deviation from the baseline hazard rate. It is also possible to split time to estimate hazard ratio in different intervals.

Joint Modeling of Repeated Measurements and Time-to-Event Data

In the recent years, patients' prediction has changed from short-term to long-term outcome. Thus, it has been hypothesized that serial MPS testing may have a central role in cardiac risk stratification. In a pivotal study, El-Hajj et al.[29] evaluated 698 patients who underwent two regadenoson MPS studies within 16 ± 9 months for clinical indications. In 399 patients, both MPS studies were normal; however, the primary outcome occurred in 57 (14%) of them during 24 ± 16 months of follow-up after the second MPS. Of course, the prognosis was worse in the 37 patients with normal perfusion on MPS-1 and abnormal perfusion on MPS-2 (35% of patients having events). Thus serial MPS seems useful to confirm in the time the warranty period of a normal scan. However, with serial MPS testing several issues await an answer.[30] In particular, unresolved questions are: when serial testing is it indicated? How is it performed and analyzed? How reproducible are the results so that serial changes can be accurately assessed? Are results of serial testing able to cost-effectively alter outcome? It should be also considered that when a longitudinal studies include both repeated measurement and survival outcomes, instead of analyzing these data separately appropriate statistical methods are required, which use available tools for simultaneous analysis. In fact, repeated measurement sequences are intermittently collected and subject to measurement error; occurrence of the end-point terminates the measurement process, potentially in an informative manner; and the measurement process may affect the hazard for survival.[31,32]

Some statistical packages can fit shared parameter joint models for longitudinal and survival data using maximum likelihood.[33,34] A linear mixed effects model is used for the longitudinal submodel, which lets time be modeled using fixed and/or random polynomials or restricted cubic splines. Currently available distributions for the survival submodel include exponential, Weibull, Gompertz, 2-component proportional hazards mixture models. The flexible parametric survival model, modeled on the log cumulative hazard scale, is also available.

CONCLUSIONS

The concept of warranty period, the duration of time during which the patient's risk remains low, is appealing. However, some points remain to be resolved before its translation in the clinical arena. Methodological issues should be standardized in order to compare the

results of studies in different patient populations. Also, the definition of a ''normal'' study should always take into consideration the history of prior revascularization, the achieved level of exercise, and the stressor used. The promise of warranty can be questioned by the patient's baseline demographic and clinical characteristics and may also be influenced by life-style modification in the course of the follow-up. The ''warranty period'' concept should shift from data reflecting the time to a cardiac event to the development of ischemia, given an opportunity for intervention before a cardiac event occurs. In this context, clarify the role of serial imaging can be extremely useful, in particular to evaluate if and when retesting a patient after a normal scan. Finally, the nuclear cardiology laboratory is continuously and rapidly evolving and it is unknown in what degree it will include MPS and/or PET and how nuclear imaging will compete and/or integrate with other imaging modalities.

Disclosures

M. Petretta, W. Acampa, R. Assante, E. Zampella, C. Nappi, A. Petretta, A. Cuocolo declare that they have no conflict of interest.

References

1. Blischke WR, Karim MR, Murthy DNP. An overview. Warranty data collection and analysis. In: Springer series in reliability engineering. London: Springer; 2011. p. 1-15.
2. Hachamovitch R, Berman D, Kiat H, Cohen I, Cabico A, Diamond G. What is the warranty for normal exercise sestamibi SPECT? Circulation 1995;92(8):2491.
3. Schinkel AF, Elhendy A, Van Domburg RT, Bax JJ, Valkema R, Roelandt JR, et al. Long-term prognostic value of dobutamine stress 99mTc-sestamibi SPECT: single-center experience with 8-year follow-up. Radiology 2002;225:701-6.
4. Montalescot G, Sechtem U, Achenbach S, Andreotti F, Arden C, Budaj A, et al. 2013 ESC guidelines on the management of stable coronary artery disease: the Task Force on the management of stable coronary artery disease of the European Society of Cardiology. Eur Heart J 2013;34:2949-3003.
5. Hachamovitch R, Hayes S, Friedman JD, Cohen I, Shaw LJ, Germano G, et al. Determinants of risk and its temporal variation in patients with normal stress myocardial perfusion scans: what is the warranty period of a normal scan? J Am Coll Cardiol 2003;41:1329-40.
6. Rozanski A, Gransar H, Min JK, Hayes SW, Friedman JD, Thomson LE, et al. Long-term mortality following normal exercise myocardial perfusion SPECT according to coronary disease risk factors. J Nucl Cardiol 2014;21:341-50.
7. Ottenhof MJ, Wai MC, Boiten HJ, Korbee RS, Valkema R, van Domburg RT, et al. 12-Year outcome after normal myocardial perfusion SPECT in patients with known coronary artery disease. J Nucl Cardiol 2013;20:748-54.
8. Nakanishi R, Gransar H, Slomka P, Arsanjani R, Shalev A, Otaki Y, et al. Predictors of high-risk coronary artery disease in subjects with normal SPECT myocardial perfusion imaging. J Nucl Cardiol 2016;23:530-41.
9. Elhendy A, Schinkel A, Bax JJ, van Domburg RT, Poldermans D. Long-term prognosis after a normal exercise stress Tc-99m sestamibi SPECT study. J Nucl Cardiol 2003;10:261-6.
10. 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.
11. Carryer DJ, Askew JW, Hodge DO, Miller TD, Gibbons RJ. The timing and impact of follow-up studies after normal stress single-photon emission computed tomography sestamibi studies. Circ Cardiovasc Imaging 2010;3:520-6.
12. Schinkel AF, Boiten HJ, van der Sijde JN, Ruitinga PR, Sijbrands EJ, Valkema R, et al. 15-Year outcome after normal exercise Tc-99m sestamibi myocardial perfusion imaging: what is the duration of low risk after a normal scan? J Nucl Cardiol 2012;19:901-6.
13. Simonsen JA, Gerke O, Rask CK, Tamadoni M, Thomassen A, Hess S, et al. Prognosis in patients with suspected or known ischemic heart disease and normal myocardial perfusion: long-term outcome and temporal risk variations. J Nucl Cardiol 2013;20:347-57.
14. Acampa W, Petretta M, Cuocolo R, Daniele S, Cantoni V, Cuocolo A. Warranty period of normal stress myocardial perfusion imaging in diabetic patients: a propensity score analysis. J Nucl Cardiol 2014;21:50-6.
15. Nudi F, Neri G, Schillaci O, Pinto A, Procaccini E, Vetere M, et al. Time to and risk of cardiac events after myocardial perfusion scintigraphy. J Cardiol 2015;66:125-9.
16. Romero-Farina G, Candell-Riera J, Aguadé-Bruix S, Ferreira-González I, Cuberas-Borrós G, Pizzi N, et al. Warranty periods for normal myocardial perfusion stress SPECT. J Nucl Cardiol 2015;22:44-54.
17. Navare SM, Mather JF, Shaw LJ, Fowler MS, Heller GV. Comparison of risk stratification with pharmacologic and exercise stress myocardial perfusion imaging: a meta-analysis. J Nucl Cardiol 2004;11:551-6.
18. Cox DR. Regression models and life-tables. J R Stat Soc B 1972;34:187-220.
19. Barraclough H, Simms L, Govindan R. Biostatistics primer: what a clinician ought to know: hazard ratios. J Thorac Oncol 2011;6:978-82.
20. Hagar Y, Dignam JJ, Dukic V. Flexible modeling of the hazard rate and treatment effects in long-term survival studies. Stat Methods Med Res 2017;26:2455-80.
21. Andersen PK, Gill RD. Cox's regression model for counting processes: a large sample study. Ann Stat 1982;10:1100-20.
22. Reid M. A conversation with Sir David Cox. Stat Sci 1994;9:439-55.
23. George B, Seals S, Aban I. Survival analysis and regression models. J Nucl Cardiol 2014;21:686-94.
24. Weibull W. A Statistical Distribution Function of Wide Applicability. J Appl Mech 1951;18:293-7.
25. Prentice RL, Kalbfleisch JD. Hazard rate models with covariates. Biometrics 1979;35:25-39.
26. van Houwelingen HC, Putter H. Dynamic prediction in clinical survival analysis. Boca Raton: Chapman & Hall; 2011.
27. Royston P, Parmar MK. Flexible parametric proportional-hazards and proportional-odds models for censored survival data, with application to prognostic modeling and estimation of treatment effects. Stat Med 2002;21:2175-97.

28. Efron B. Logistic regression, survival analysis, and the Kaplan-Meier Curve. J Am Stat Assoc 1988;83:414-25.
29. El-Hajj S, AlJaroudi WA, Farag A, Bleich S, Manaoragada P, Iskandrian AE, et al. Effect of changes in perfusion defect size during serial regadenoson myocardial perfusion imaging on cardiovascular outcomes in high-risk patients. J Nucl Cardiol 2016;23:101-12.
30. Iskandrian AE, Dilsizian V, Garcia EV, Beanlands RS, Cerqueira M, Soman P, et al. Myocardial perfusion imaging: lessons learned and work to be done-update. J Nucl Cardiol. 2017. https://doi.org/10.1007/s12350-017-1093-7.
31. Asar Ö, Ritchie J, Kalra PA, Diggle PJ. Joint modeling of repeated measurement and time-to-event data: an introductory tutorial. Int J Epidemiol 2015;44:334-44.
32. Petretta M, Salvatore M, Cuocolo A. Immortality time and serial myocardial perfusion imaging: only those who do not die may repeat the exam. J Nucl Cardiol 2016;23:113-6.
33. Rizopoulos D. JM: an R package for the joint modeling of longitudinal and time-to-event data. J Stat Soft 2010;35:1-33.
34. Crowther MJ, Abrams KR, Lambert PC. Joint modeling of longitudinal and survival data. Stata J 2013;13:165-84.