UNIVERSITÀ DEGLI STUDI DI NAPOLI

"FEDERICO II"

SCUOLA DI MEDICINA E CHIRURGIA

Dipartimento di Scienze Biomediche Avanzate

Direttore: Prof. Alberto Cuocolo

Dottorato di Ricerca in Scienze Biomorfologiche e Chirurgiche

XXXVI ciclo

Coordinatore: Prof. Alberto Cuocolo

Tesi di Dottorato

Prognostic value of modified coronary flow capacity by rubidium-82 PET/CT in patients with suspected CAD and normal myocardial perfusion imaging

Relatore
Ch.ma Prof.ssa Wanda Acampa

Candidata
Dott.ssa Adriana D'Antonio

ABSTRACT

Background. The purpose of this study was to assess the prognostic value of modified coronary flow capacity (mCFC) in patients with suspected CAD and normal myocardial perfusion imaging (MPI) at cardiac ^{82}Rb positron emission tomography (PET)/computed tomography (CT) imaging.

Methods. We evaluated 4560 patients without previous history of CAD who underwent stress/rest Rubidium-82 cardiac PET/CT. Patients without previous history of CAD and normal MPI (n=2053) were included. Six CFC categories were obtained according to myocardial blood flow (MBF) and myocardial flow reserve (MFR) results. The mCFC was defined as impaired in patients "mildly reduced" or worse coronary flow in at least one coronary territory. End- points were defined as cardiovascular death, nonfatal myocardial infarction, unplanned hospitalization for any cardiac reasons, and unplanned coronary revascularization.

Results. Follow-up was available in 1967 (96%) patients (median age 59±13 years). During a median time of 41 months (range 3-365), 72 events occurred (4% cumulative event rate, AER of 0.7% person-year). At multivariable COX analysis, age, diabetes, MFR < 2 and impaired mCFC ($p < .001$) resulted as independent predictors of events. In patients with reduced MFR, as well as in patients with normal MFR, the AER was significantly higher in patients with impaired mCFC as compared to those without (both $p < .05$). At Kaplan-Meier analysis the worse prognosis was observed in patients with impaired mCFC in both MFR groups.

Conclusions. In patients with suspected CAD and normal MPI, impaired mCFC is associated with a higher risk of cardiac events. The mCFC may be useful to identify patients' candidates to additional therapies in order to prevent future events.

INDEX

INTRODUCTION

Coronary artery disease (CAD) is a multifactorial process that may affect coronary vascular bed at different levels, involving both epicardial and microvascular compartments [1]. Cardiovascular events may occur after a latent phase of clinically unapparent disease in which patients may have normal functional tests [2]. Myocardial perfusion imaging (MPI) by positron emission tomography/computed tomography (PET/CT) is able to provide an accurate evaluation of vascular function, through absolute quantification of myocardial blood flow (MBF) and myocardial flow reserve (MFR) [3]. The MFR is the most validated index of coronary vasodilator function, able to provide an accurate evaluation of both epicardial and microvascular compartment [4-5]. The prognostic value of MFR has been previously demonstrated in several population, also in absence of other perfusion and structural abnormalities [6-10]. In the vast majority of patients hyperemic MBF and MFR provide concordant findings. However, MFR derives from the ratio between hyperemic and resting MFR and its estimation may be affected also under physiological conditions, resulting in discrepant findings compared with hyperemic MBF. Consequently, it has been suggested that both parameters should be considered in the interpretation of MPI results [11].

Coronary flow capacity (CFC) has been proposed as a comprehensive measure of the entire coronary vascular status, integrating both hyperemic MBF and MFR results into color-coded scatterplot [12-13]. The CFC evaluation provided an objective, regional, artery-specific, size–severity physiologic quantification of CAD severity associated with high risk of events [14, 15]. Recently, the concept of modified CFC (mCFC) has been introduced by integrating the regional CFC category within each coronary territory into the entire CFC category for each patient [16]. The prognostic value of this approach has been tested in a cohort of patients with and without evidence of CAD derived from [^{15}O] H2O-PET imaging [17]. We aimed to assess the prognostic value of modified CFC categories in predicting cardiac outcome in patients with no evidence of CAD and normal perfusion at cardiac PET/CT imaging.

MATERIAL AND METHODS

Study population

We studied 4560 consecutive patients who underwent stress/rest Rubidium-82 (^{82}Rb) cardiac PET/CT imaging. A total of 2026 patients have been excluded for: (1) documented history of CAD defined as luminal stenosis >50% at coronary angiography, previous percutaneous coronary intervention, coronary artery bypass graft surgery or myocardial infarction; (2) uncontrolled atrial fibrillation, pacemaker, or prosthetic valve. A total of 481 patients were also excluded for the presence of abnormal MPI, leaving 2053 subjects for the analysis. For each patient, the presence of coronary risk factors was noted. This study complies with the declaration of Helsinki. The review committee of our institution approved this study, and all patients gave informed consent ("Comitato Etico, Università Federico II", protocol number 110/17).

PET/CT Imaging

The patients were asked to discontinue nitrates for 6 h, calcium channel blockers and caffeine-containing beverages for 24 h, and beta-blockers for 48 h before PET/CT imaging. Rest and stress cardiac PET/CT images were acquired using Biograph mCT 64-slice scanners (Siemens Healthcare) After a CT scout to check patient position, a low-dose CT (0.4 mSv; 120 kVp; effective tube current, 26 mA [11-mAs quality reference]; 3.3 s) was performed for attenuation correction during normal breathing before and after PET acquisitions. For both rest and stress imaging, a 6-min list-mode PET acquisition was acquired after 1110 MBq of ^{82}Rb was injected. For stress images, pharmacologic stress test was performed by adenosine administration (140 μg × kg−1 × min−1 for 4.5 min, with tracer injection between 2 and 2.5 min). Both rest and stress dynamic images were reconstructed into 26-time frames (12 × 5 s, 6 × 10 s, 4 × 20 s and 4 × 40 s) using the vendor standard ordered-subsets expectation maximization 3D reconstruction (2 iterations, 24 subsets) with 6.5-mm Gaussian postprocessing filter. The images were corrected for attenuation using the low-dose CT. Hemodynamic parameters and 12-lead ECG were recorded at baseline and throughout the infusion

of adenosine. The rate-pressure product (RPP) was calculated as heart rate × systolic arterial blood pressure.

Imaging analysis

Trans-axial PET perfusion images were automatically reoriented into short-axis and vertical and horizontal long-axis slices. Myocardial perfusion was assessed using standardized segmentation of 17 myocardial regions using automated software (Cedars-Sinai Medical Center, Los Angeles, California) [18]. The total perfusion defect (TPD) was considered abnormal when ≥ 5% [19]. Myocardial blood flow (MBF) was calculated (mL/ min/g) for globally and for each vascular territory from the dynamic rest and stress imaging series with commercially available software (FlowQuant, University of Ottawa Heart Institute) [20] From the ratio of hyperemic to baseline MBF, corrected for rate-pressure product, MFR was calculated and considered reduced when < 2.

According to regional MBF and MFR thresholds previously proposed [13, 14], the 3 vascular territories of each patient were classified as follows: normal flow, minimal reduced flow, mildly reduced flow, moderately reduced flow, severe reduced flow, myocardial steal (Figure 1). The mCFC was defined as *preserved* in patients with normal flow or minimal reduced flow in every vascular territory, or *impaired* in patients with "mildly reduced" or worse coronary flow in at least one coronary territory [16].

Outcomes

Follow-up was prospectively obtained by using a questionnaire that was assessed by a phone call to all patients or referring physicians and by review of hospital or physicians' records. The outcome end points were cardiac death, myocardial infarction, or late coronary revascularization, whichever occurred first. The cause of death was confirmed by review of death certificate, hospital chart, or physician's records. Death was considered related to cardiac origin if the primary cause was defined as acute myocardial infarction, congestive heart failure, valvular heart disease, sudden cardiac death,

cardiac interventional/surgical procedure related. Myocardial infarction was defined when >2 of the following 3 criteria were met: chest pain or equivalent symptom complex, positive cardiac biomarkers, or typical electrocardiographic changes [21]. The date of the last examination or consultation was used to determine the length of follow-up.

Statistical Analysis

Continuous data are expressed as mean ± standard deviation and categorical data as percentage. A student two-sample *t* test and χ^2 test were used to compare the differences in continuous and categorical variables, respectively. A *P* value < .05 (two-sided) was considered statistically significant. Annualized event rate, expressed as % person-years, was calculated as the cumulative number of events divided by person-time. Hazard ratios with 95% confidence intervals were calculated by univariable and multivariable Cox regression analysis. Variables showing a *P* value < .05 at univariable analysis were considered for multivariable analysis. Event-free survival curves were obtained by the Kaplan-Meier method and compared using the log-rank test. Statistical analysis was performed with Stata 18 software (StataCorp, College Station, Texas USA).

RESULTS

Follow-up was available in 1967 (96%) patients. During a median time of 41 months (range 3-365), 72 events occurred (4% cumulative event rate, with an annual event rate of 0.7% person-years). The events were cardiac death in 16 (22%) patients, nonfatal myocardial infarction in 33 (46%), and coronary revascularization in 23 (32%) subjects.

Patients with events were older and showed higher prevalence of male gender, diabetes and hypertension as compared to those without (all $P < .01$) (Table 1). The imaging findings according to events are reported in Table 2. Lower hyperemic MBF and MFR values and a higher prevalence of MFR < 2, were observed in patients with events as compared to those without (all $P < .001$).

Moreover, the prevalence of impaired mCFC was significantly higher in patients with events as compared to those without ($P < .001$). Figure 1 shows the mean PET perfusion indices stratified by the occurrence of the end points.

Predictors of outcome

At univariable analysis age ($P < .001$), male gender ($P < .01$), diabetes ($P < .001$), hypertension ($P < .05$), MFR < 2 ($P < .001$), and impaired mCFC ($P < .001$) were predictors of adverse cardiac events. At multivariable analysis, age ($P < .05$), diabetes ($P < .05$), MFR < 2 ($P < .01$) and mCFC ($P < .001$) resulted as independent predictors (Table 3).

The AER according to MFR and mCFC groups is depicted in Figure 2. The patients with impaired MFR showed a higher AER as compared to those with preserved MFR (1.9% vs 0.5%, $P < .001$). Similarly, the AER was significantly higher in patients with impaired mCFC as compared to those without (2.6% vs 0.4%, $P < .001$).

At Kaplan-Meier analysis the overall event-free survival was significantly lower in patients with impaired mCFC as compared to those with preserved mCFC ($P < .001$) (Figure 3).

Among 1597 patients with preserved MFR, mCFC was concordant normal in 1458 (91%) patients and abnormal in 139 (9%) subjects. Moreover, among 370 patients with reduced MFR, mCFC was

normal in 189 (51%) and concordant abnormal in 181 (49%) subjects. In both MFR categories, the AER was significantly higher in patients with impaired mCFC as compared to those without (both $P < .01$) (Figure 4). At Kaplan-Meier analysis the worse prognosis was observed in patients with impaired mCFC in both MFR groups ($P < .001$) (Figure 5).

DISCUSSION

To our knowledge, this is the first study exploring the prognostic value of modified CFC in predicting outcome in patients with suspected CAD and normal myocardial perfusion. From our data, it emerged that in patients with normal MPI the presence of impaired mCFC increases the risk of future cardiac events as compared to patients with normal mCFC. Moreover, mCFC provides a more accurate risk stratification as compared to MFR alone.

An accurate risk stratification has become increasingly important in patients with suspected CAD, in order to adopt appropriate treatment strategies and improve outcome. However, CAD is a heterogeneous process that may involve myocardial vascular bed at different levels and its dynamic nature may lead to a long latent phase, evolving over a long time without significant evidence of disease. During this time, patients can be still asymptomatic or showing normal functional tests [2]. Radionuclide MPI is widely performed in patients with suspected CAD, and it is able to accurately identify patients at higher risk of future cardiac events [22]. Cardiac imaging by PET/CT has the main advantage of providing accurate measurements of coronary vascular function, in addition to the evaluation of myocardial ischemia [3]. This is particular useful in patients with normal perfusion, where the absence of perfusion abnormalities may not exclude the presence of underlying disease. Nowadays, MFR is considered the most validated index of coronary vascular function and a reduced MFR can be related to the presence of epicardial stenoses or microvascular impairment [4, 5]. The prognostic value of MFR has been extensively investigated and the presence of impaired MFR is strongly associated with adverse outcome also in absence of other perfusion and structural abnormalities [6-10]. It should be considered that MFR is a ratio between hyperemic and resting MBF and for most patients MFR findings are concordant normal or abnormal with hyperemic MBF results. However, in a minority of patient's physiological conditions may affect MFR quantification, producing discordances with hyperemic MBF that should be carefully interpreted. Therefore, both parameters should be considered in reporting test results. In a large cohort of 4029 patients, Gupta et al [23] tested the ability of hyperemic MBF and MFR in predicting cardiovascular mortality alone or

combined. The authors produced four patients' categories according to concordant or discordant findings. The authors confirmed that, despite MFR remains a strong predictor of outcome, the integrated evaluation with hyperemic MBF and MFR was helpful in identifying different phenotypes of disease. Fukushima et al. [24] found similar results in 224 patients during a short-term follow-up. The concept of CFC has been introduced a comprehensive framework for coronary physiology evaluation, in order to overcome some limitations related to using hyperemic MBF and MFR alone [12, 13]. Johnson and Gould [13, 14] first identified MFR and MBF thresholds under physiological and pathological conditions and integrated these measures in a color-coded scatterplot. The role of CFC has been previously tested for diagnostic and prognostic purposes, in particular according to revascularization status. Gould et al. [14] demonstrated that CFC was able to provide an accurate artery-specific quantification of CAD severity and it was a strong predictor of outcome in 3774 patients. More recently, Gould et al [15] CFC found a size-dependent highest mortality risk by integrating MFR and hyperemic MBF, that was significantly reduced after revascularization. Dietz et al. [25] compared hyperemic MBF, global MFR, and regional CFC, obtained by cardiac PET, in predicting outcome in 234 patients. They found that, despite all these measurements were powerful predictors of cardiovascular events, only reduced hyperemic MBF was independently associated with outcome [25]. Recently, Miura et al [16] proposed a more practical approach, introducing the concept of modified CFC that integrates regional MFR and hyperemic MBF values into the entire CFC category. This approach has been tested in 137 patients without evidence of obstructive CAD at coronary angiography, to identify the presence of microvascular dysfunction and its prognostic implications. The authors found that of the overall population, 25% had impaired mCFC and it as associated with an increased risk of cardiovascular mortality.

In our study, we aimed to test the prognostic value of modified CFC in 1967 patients with normal MPI and without evidence of previous CAD. From our data it emerged that both mCFC and MFR were independent predictors of events at survival analysis. Moreover, despite AER was significantly higher in patients with impaired mCFC, as well as in patients with reduced MFR, the mCFC seems

to provide a better risk prediction as compared to MFR alone. Interestingly, among 1597 patients with normal MFR, 1458 (91%) had also concordant normal mCFC. On the contrary, of 370 patients with reduced MFR only 181 (49%) had concordant abnormal mCFC. This percentage of concordant abnormal patients is lower as compared to the results observed by Miura et al [17], were 74% of the overall population had both impaired MFR and mCFC. It should be considered that for the present study we included a higher number of patients with normal perfusion irrespective to angiographic results. The risk of cardiac events resulted to be significantly higher in concordant abnormal MFR and mCFC patients as compared to those with impaired MFR but normal mCFC. In particular, this last group showed similar outcome as compared to patients with both preserved MFR and mCFC, suggesting that the evaluation of mCFC may have an additional prognostic power as compared to MFR alone. Moreover, we observed a significant reduction in event-free survival in patients with impaired mCFC as compared to those without, in both MFR categories. These data suggest that both MFR and MBF should be carefully interpreted as complementary indicators of coronary vascular function. Despite the presence of normal MFR is associated with a good outcome, the additional evaluation of mCFC may be required in order to identify high patients.

CONCLUSION

In patients with suspected CAD and normal MPI, mCFC is able to identify patients at higher risk of cardiovascular events. In particular, both in patients with normal and reduced MFR the presence of impaired mCFC help to better identify patients at risk of event. The evaluation of mCFC shows a higher prognostic impact compared to the quantification of MFR alone

REFERENCES

1. Taqueti VR, Di Carli MF. Coronary Microvascular Disease Pathogenic Mechanisms and Therapeutic Options: JACC State-of-the-Art Review. J Am Coll Cardiol. 2018 Nov 27;72(21):2625-2641. doi: 10.1016/j.jacc.2018.09.042. PMID: 30466521; PMCID: PMC6296779.
2. Ahmadi A, Argulian E, Leipsic J, Newby DE, Narula J. From Subclinical Atherosclerosis to Plaque Progression and Acute Coronary Events: JACC State-of-the-Art Review. J Am Coll Cardiol. 2019 Sep 24;74(12):1608-1617. doi: 10.1016/j.jacc.2019.08.012. PMID: 31537271.
3. Assante R, Zampella E, Arumugam P, Acampa W, Imbriaco M, Tout D, Petretta M, Tonge C, Cuocolo A. Quantitative relationship between coronary artery calcium and myocardial blood flow by hybrid rubidium-82 PET/CT imaging in patients with suspected coronary artery disease. J Nucl Cardiol. 2017 Apr;24(2):494-501. doi: 10.1007/s12350-015-0359-1. Epub 2016 Jan 15. PMID: 26780529.
4. Naya M, Murthy VL, Taqueti VR, Foster CR, Klein J, Garber M, Dorbala S, Hainer J, Blankstein R, Resnic F, Di Carli MF. Preserved coronary flow reserve effectively excludes high-risk coronary artery disease on angiography. J Nucl Med. 2014 Feb;55(2):248-55. doi: 10.2967/jnumed.113.121442. Epub 2014 Jan 9. PMID: 24408896; PMCID: PMC3962818.
5. Gould KL, Johnson NP, Bateman TM, Beanlands RS, Bengel FM, Bober R, Camici PG, Cerqueira MD, Chow BJW, Di Carli MF, Dorbala S, Gewirtz H, Gropler RJ, Kaufmann PA, Knaapen P, Knuuti J, Merhige ME, Rentrop KP, Ruddy TD, Schelbert HR, Schindler TH, Schwaiger M, Sdringola S, Vitarello J, Williams KA Sr, Gordon D, Dilsizian V, Narula J. Anatomic versus physiologic assessment of coronary artery disease. Role of coronary flow reserve, fractional flow reserve, and positron emission tomography imaging in revascularization decision-making. J Am Coll Cardiol. 2013 Oct 29;62(18):1639-1653. doi: 10.1016/j.jacc.2013.07.076. Epub 2013 Aug 28. PMID: 23954338.

6. Murthy VL, Naya M, Foster CR, Hainer J, Gaber M, Di Carli G, Blankstein R, Dorbala S, Sitek A, Pencina MJ, Di Carli MF. Improved cardiac risk assessment with noninvasive measures of coronary flow reserve. Circulation. 2011 Nov 15;124(20):2215-24. doi: 10.1161/CIRCULATIONAHA.111.050427. Epub 2011 Oct 17. PMID: 22007073; PMCID: PMC3495106.
7. Herzog BA, Husmann L, Valenta I, Gaemperli O, Siegrist PT, Tay FM, Burkhard N, Wyss CA, Kaufmann PA. Long-term prognostic value of 13N-ammonia myocardial perfusion positron emission tomography added value of coronary flow reserve. J Am Coll Cardiol. 2009 Jul 7;54(2):150-6. doi: 10.1016/j.jacc.2009.02.069. PMID: 19573732.
8. Assante R, Acampa W, Zampella E, Arumugam P, Nappi C, Gaudieri V, Mainolfi CG, Panico M, Magliulo M, Tonge CM, Petretta M, Cuocolo A. Prognostic value of atherosclerotic burden and coronary vascular function in patients with suspected coronary artery disease. Eur J Nucl Med Mol Imaging. 2017 Dec;44(13):2290-2298. doi: 10.1007/s00259-017-3800-7. Epub 2017 Aug 16. PMID: 28815291.
9. Zampella E, Acampa W, Assante R, Gaudieri V, Nappi C, Mannarino T, Mainolfi CG, Arumugam P, Petretta M, Cuocolo A. Combined evaluation of regional coronary artery calcium and myocardial perfusion by 82Rb PET/CT in predicting lesion-related outcome. Eur J Nucl Med Mol Imaging. 2020 Jul;47(7):1698-1704. doi: 10.1007/s00259-019-04534-x. Epub 2019 Dec 14. PMID: 31836909.
10. Gaudieri V, Mannarino T, Zampella E, Assante R, D'Antonio A, Nappi C, Cantoni V, Green R, Petretta M, Arumugam P, Cuocolo A, Acampa W. Prognostic value of coronary vascular dysfunction assessed by rubidium-82 PET/CT imaging in patients with resistant hypertension without overt coronary artery disease. Eur J Nucl Med Mol Imaging. 2021 Sep;48(10):3162-3171. doi: 10.1007/s00259-021-05239-w. Epub 2021 Feb 16. PMID: 33594472; PMCID: PMC8426234.

11. Murthy VL, Bateman TM, Beanlands RS, Berman DS, Borges-Neto S, Chareonthaitawee P, Cerqueira MD, deKemp RA, DePuey EG, Dilsizian V, Dorbala S, Ficaro EP, Garcia EV, Gewirtz H, Heller GV, Lewin HC, Malhotra S, Mann A, Ruddy TD, Schindler TH, Schwartz RG, Slomka PJ, Soman P, Di Carli MF; SNMMI Cardiovascular Council Board of Directors; ASNC Board of Directors. Clinical Quantification of Myocardial Blood Flow Using PET: Joint Position Paper of the SNMMI Cardiovascular Council and the ASNC. J Nucl Med. 2018 Feb;59(2):273-293. doi: 10.2967/jnumed.117.201368. Epub 2017 Dec 14. PMID: 29242396.
12. van de Hoef TP, Echavarría-Pinto M, van Lavieren MA, Meuwissen M, Serruys PW, Tijssen JG, Pocock SJ, Escaned J, Piek JJ. Diagnostic and Prognostic Implications of Coronary Flow Capacity: A Comprehensive Cross-Modality Physiological Concept in Ischemic Heart Disease. JACC Cardiovasc Interv. 2015 Nov;8(13):1670-80. doi: 10.1016/j.jcin.2015.05.032. PMID: 26585617.
13. Johnson NP, Gould KL. Integrating noninvasive absolute flow, coronary flow reserve, and ischemic thresholds into a comprehensive map of physiological severity. JACC Cardiovasc Imaging. 2012 Apr;5(4):430-40. doi: 10.1016/j.jcmg.2011.12.014. PMID: 22498334.
14. Gould KL, Johnson NP, Roby AE, Nguyen T, Kirkeeide R, Haynie M, Lai D, Zhu H, Patel MB, Smalling R, Arain S, Balan P, Nguyen T, Estrera A, Sdringola S, Madjid M, Nascimbene A, Loyalka P, Kar B, Gregoric I, Safi H, McPherson D. Regional, Artery-Specific Thresholds of Quantitative Myocardial Perfusion by PET Associated with Reduced Myocardial Infarction and Death After Revascularization in Stable Coronary Artery Disease. J Nucl Med. 2019 Mar;60(3):410-417. doi: 10.2967/jnumed.118.211953. Epub 2018 Aug 16. PMID: 30115688; PMCID: PMC6424226.
15. Gould KL, Kitkungvan D, Johnson NP, Nguyen T, Kirkeeide R, Bui L, Patel MB, Roby AE, Madjid M, Zhu H, Lai D. Mortality prediction by quantitative PET perfusion expressed as coronary fow capacity with and without revascularization. JACC Cardiovasc Imaging. 2021;14(5):1020–1034. https://doi.org/ 10.1016/j.jcmg.2020.08.040

16. Miura S, Naya M, Kumamaru H, Ando A, Miyazaki C, Yamashita T. Prognostic value of modified coronary flow capacity by 13N-ammonia myocardial perfusion positron emission tomography in patients without obstructive coronary arteries. J Cardiol. 2022 Feb;79(2):247-256. doi: 10.1016/j.jjcc.2021.09.001. Epub 2021 Sep 15. PMID: 34538532.
17. de Winter RW, Jukema RA, van Diemen PA, Schumacher SP, Somsen YBO, van de Hoef TP, van Rossum AC, Twisk JWR, Maaniitty T, Knuuti J, Saraste A, Nap A, Raijmakers PG, Danad I, Knaapen P. Prognostic Value of Modified Coronary Flow Capacity Derived From [^{15}O]H2O Positron Emission Tomography Perfusion Imaging. Circ Cardiovasc Imaging. 2023 Sep;16(9):e014845. doi: 10.1161/CIRCIMAGING.122.014845. Epub 2023 Sep 19. PMID: 37725672; PMCID: PMC10510823.
18. Cerqueira MD, Weissman NJ, Dilsizian V, Jacobs AK, Kaul S, Laskey WK, Pennell DJ, Rumberger JA, Ryan T, Verani MS; American Heart Association Writing Group on Myocardial Segmentation and Registration for Cardiac Imaging. Standardized myocardial segmentation and nomenclature for tomographic imaging of the heart. A statement for healthcare professionals from the Cardiac Imaging Committee of the Council on Clinical Cardiology of the American Heart Association. Int J Cardiovasc Imaging. 2002 Feb;18(1):539-42. PMID: 12135124.
19. Nakazato R, Dey D, Alexánderson E, Meave A, Jiménez M, Romero E, Jácome R, Peña M, Berman DS, Slomka PJ. Automatic alignment of myocardial perfusion PET and 64-slice coronary CT angiography on hybrid PET/CT. J Nucl Cardiol. 2012 Jun;19(3):482-91. doi: 10.1007/s12350-012-9528-7. Epub 2012 Mar 15. PMID: 22419224; PMCID: PMC3527130.
20. Klein R, Renaud JM, Ziadi MC, Thorn SL, Adler A, Beanlands RS, deKemp RA. Intra- and inter-operator repeatability of myocardial blood flow and myocardial flow reserve measurements using rubidium-82 pet and a highly automated analysis program. J Nucl Cardiol. 2010 Aug;17(4):600-16. doi: 10.1007/s12350-010-9225-3. Epub 2010 Apr 13. PMID: 20387135.

21. Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, White HD; ESC Scientific Document Group. Fourth universal definition of myocardial infarction (2018). Eur Heart J. 2019 Jan 14;40(3):237-269. doi: 10.1093/eurheartj/ehy462. PMID: 30165617.
22. Knuuti J, Wijns W, Saraste A, Capodanno D, Barbato E, Funck-Brentano C, Prescott E, Storey RF, Deaton C, Cuisset T, Agewall S, Dickstein K, Edvardsen T, Escaned J, Gersh BJ, Svitil P, Gilard M, Hasdai D, Hatala R, Mahfoud F, Masip J, Muneretto C, Valgimigli M, Achenbach S, Bax JJ; ESC Scientific Document Group. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. Eur Heart J. 2020 Jan 14;41(3):407-477. doi: 10.1093/eurheartj/ehz425. Erratum in: Eur Heart J. 2020 Nov 21;41(44):4242. PMID: 31504439.
23. Gupta A, Taqueti VR, van de Hoef TP, Bajaj NS, Bravo PE, Murthy VL, Osborne MT, Seidelmann SB, Vita T, Bibbo CF, Harrington M, Hainer J, Rimoldi O, Dorbala S, Bhatt DL, Blankstein R, Camici PG, Di Carli MF. Integrated Noninvasive Physiological Assessment of Coronary Circulatory Function and Impact on Cardiovascular Mortality in Patients With Stable Coronary Artery Disease. Circulation. 2017 Dec 12;136(24):2325-2336. doi: 10.1161/CIRCULATIONAHA.117.029992. Epub 2017 Sep 1. PMID: 28864442; PMCID: PMC5726898.
24. Fukushima K, Javadi MS, Higuchi T, Lautamäki R, Merrill J, Nekolla SG, Bengel FM. Prediction of short-term cardiovascular events using quantification of global myocardial flow reserve in patients referred for clinical 82Rb PET perfusion imaging. J Nucl Med. 2011 May;52(5):726-32. doi: 10.2967/jnumed.110.081828. Epub 2011 Apr 15. PMID: 21498538.
25. Dietz M, Kamani CH, Allenbach G, Rubimbura V, Fournier S, Dunet V, Treglia G, Nicod Lalonde M, Schaefer N, Eeckhout E, Muller O, Prior JO. Comparison of the prognostic value of impaired stress myocardial blood flow, myocardial flow reserve, and myocardial flow capacity on low-dose Rubidium-82 SiPM PET/CT. J Nucl Cardiol. 2023 Aug;30(4):1385-

1395. doi: 10.1007/s12350-022-03155-6. Epub 2022 Dec 27. PMID: 36574175; PMCID: PMC10371877.

FIGURES

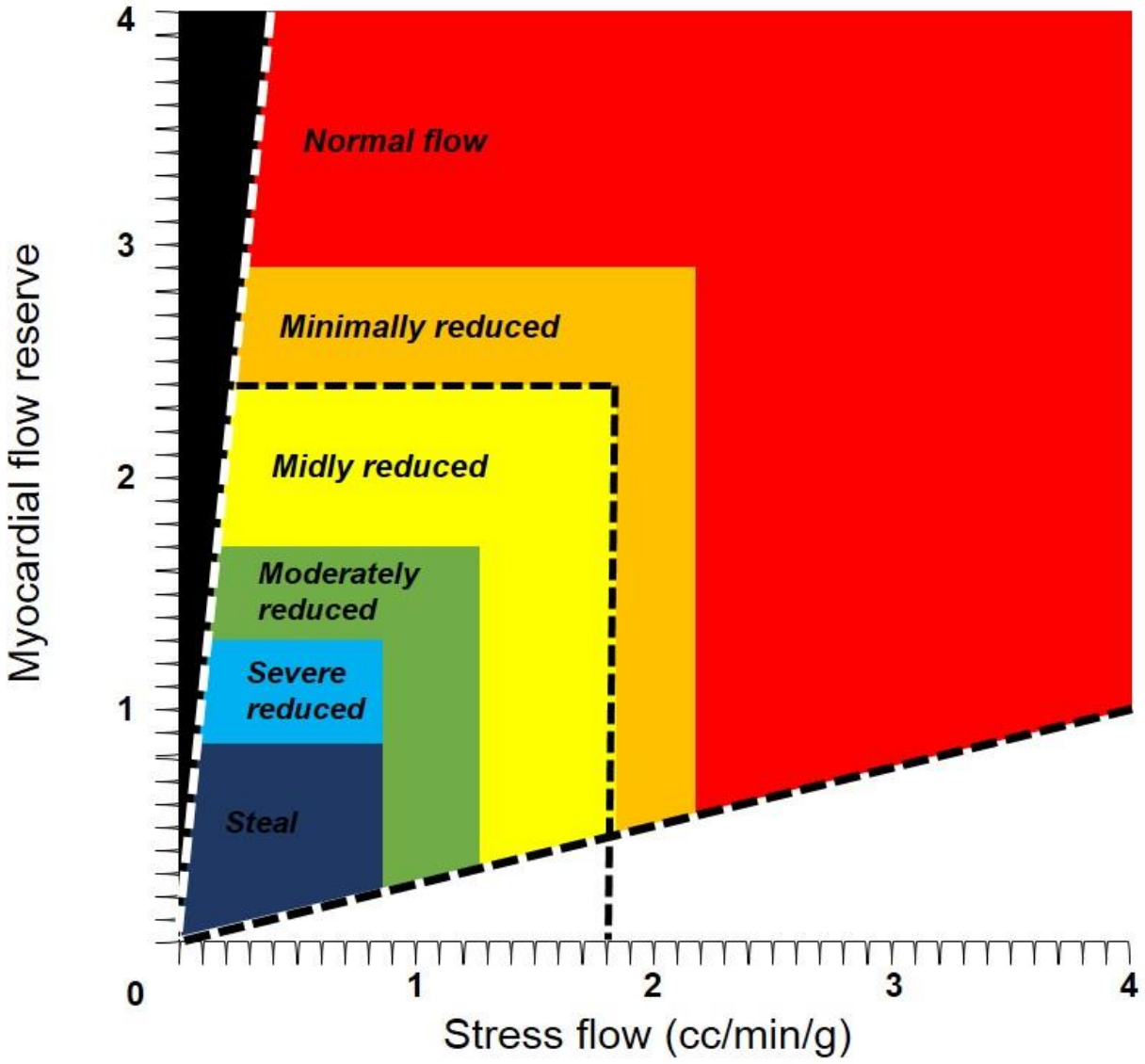

Figure 1. Modified coronary flow capacity map. The modified coronary flow capacity was defined as *preserved* in patients with normal flow or minimal reduced flow in every vascular territory, or *impaired* in patients with "mildly reduced" or worse coronary flow in at least one coronary territory.

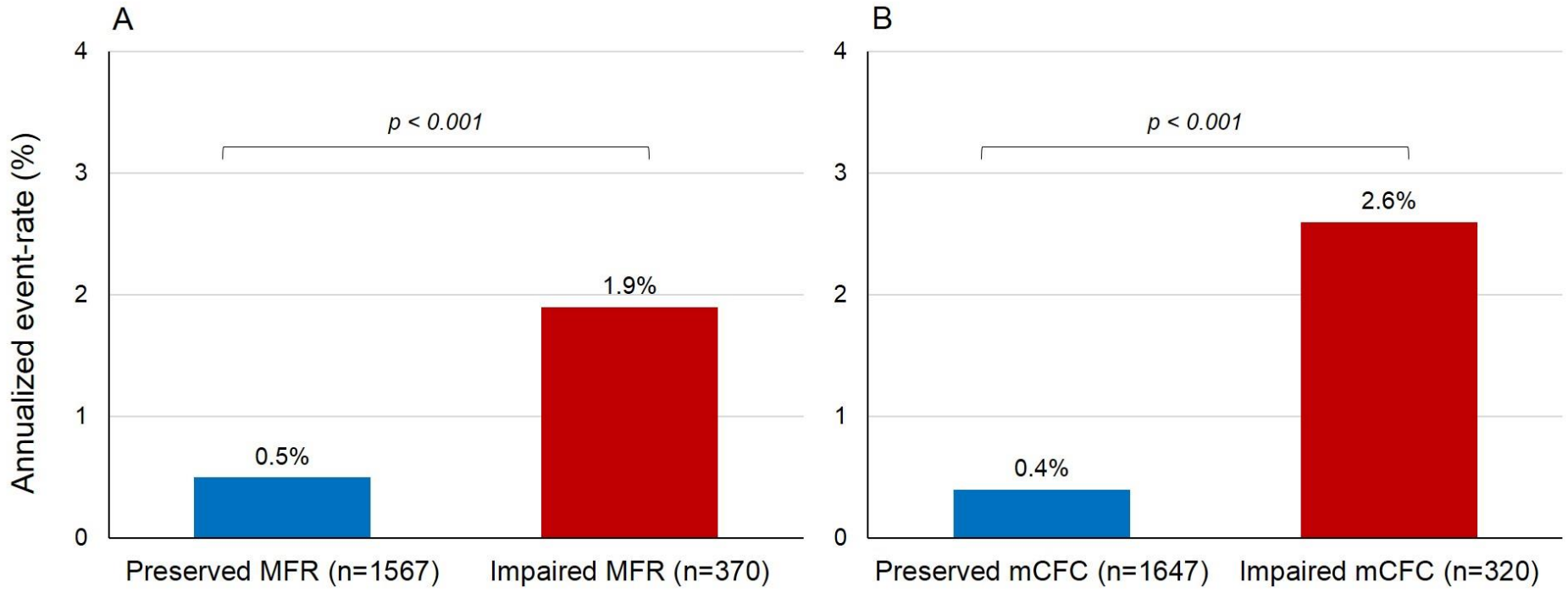

Figure 2. Annualized event rate by myocardial flow reserve (A) and modified coronary flow capacity (B). *MFR*, myocardial flow reserve; *mCFC*, modified coronary flow capacity.

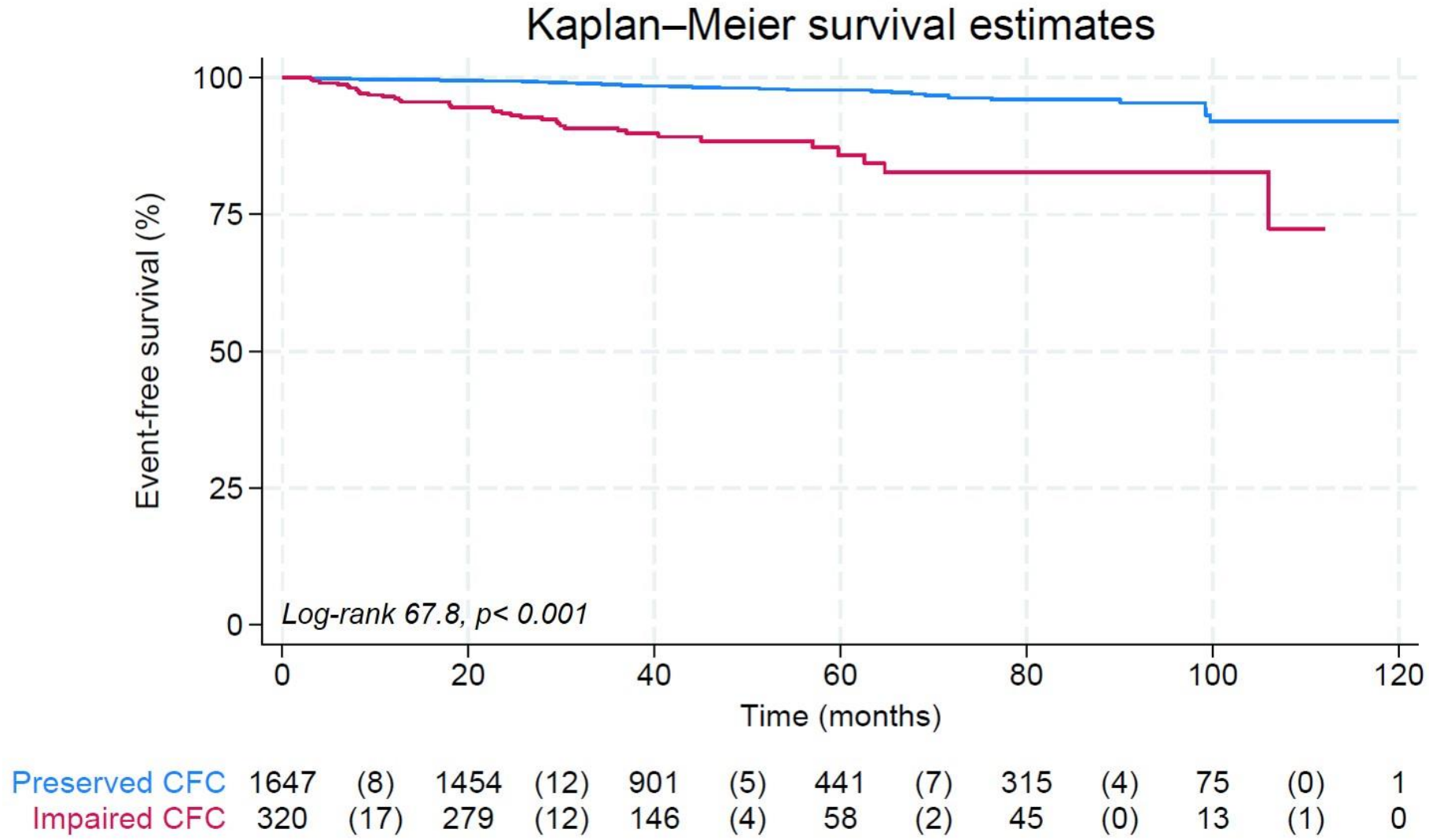

Figure 3. Event-free survival curves by Kaplan-Meier analysis according to modified coronary flow capacity. *CFC*, modified coronary flow capacity.

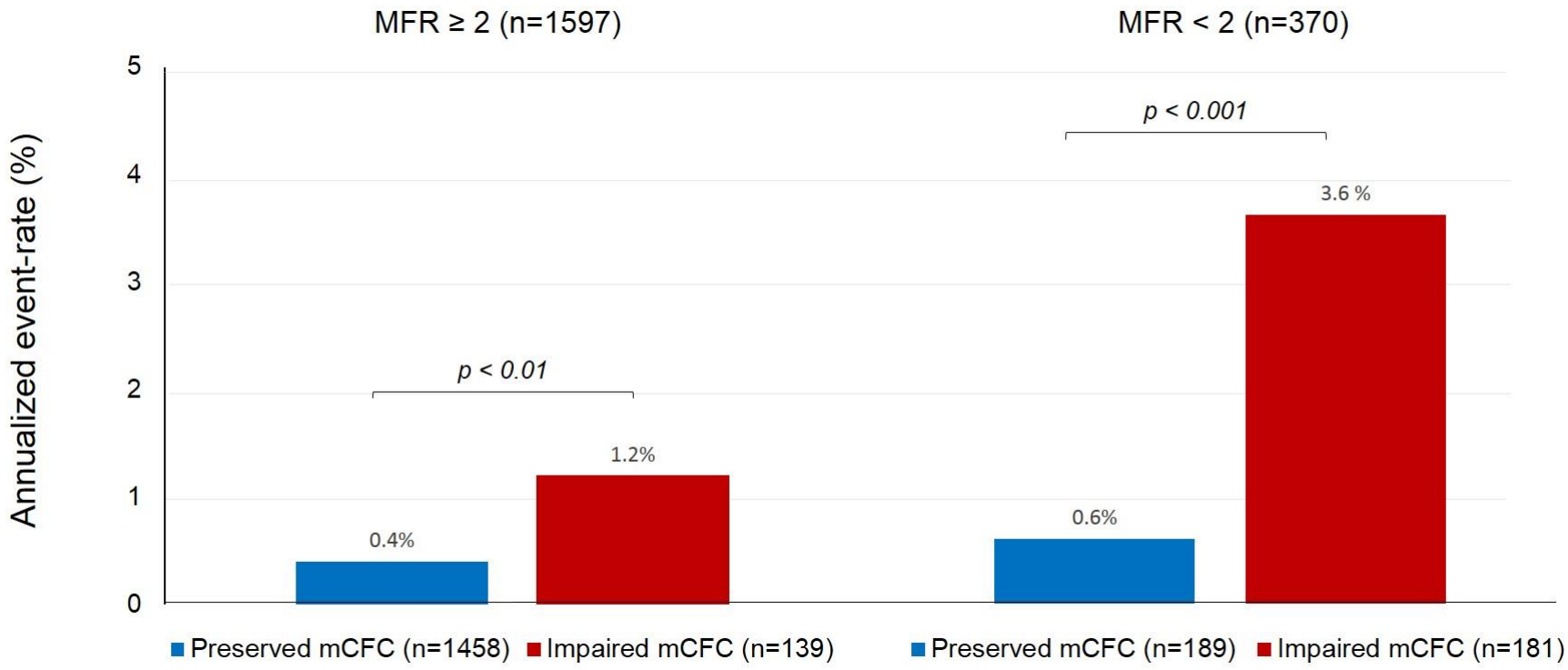

Figure 4. Annualized event rate by modified coronary flow capacity in patients with normal and impaired myocardial flow reserve. *MFR*, myocardial flow reserve; *mCFC*, modified coronary flow capacity.

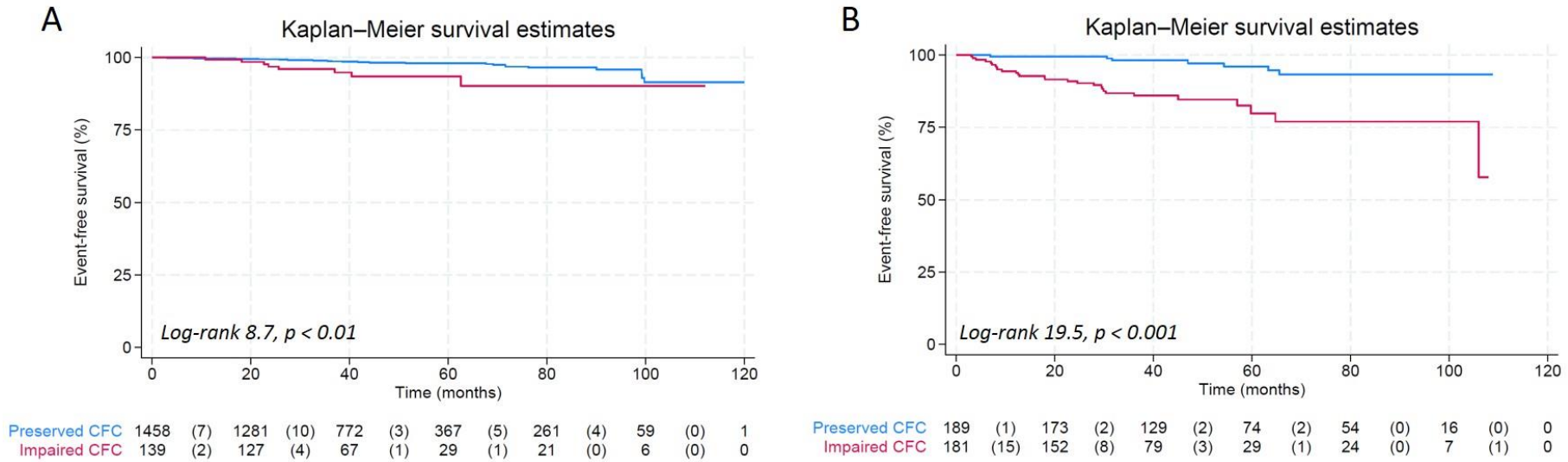

Figure 5. Event-free survival curves by Kaplan-Meier analysis according to modified coronary flow capacity in patients with normal (A) and impaired (B) myocardial flow reserve. *MFR*, myocardial flow reserve; *CFC*, modified coronary flow capacity.

TABLES

Table 1. Baseline clinical characteristics of overall patient population according to events

	All patients (n = 1967)	**With events (n = 72)**	**Without events (n = 1895)**	***P*-value**
Age (years)	29 ± 13	66 ± 11	58 ± 13	< .001
Male gender, *n* (%)	888 (45%)	43 (60%)	845 (46%)	< .05
Diabetes, *n* (%)	476 (24%)	32 (44%)	444 (23%)	< .001
Angina, *n (%)*	893 (45%)	19 (26%)	874 (46%)	< .01
Hypertension, *n* (%)	1355 (69%)	59 (82%)	1296 (68%)	< .05
Dyslipidemia, *n* (%)	1193 (61%)	50 (69%)	1143 (60%)	0.12
Smoking history, *n* (%)	576 (29%)	19 (26%)	557 (29%)	0.58
Family history of CAD, *n* (%)	940 (48%)	27 (37%)	913 (48%)	0.08

Values are expressed as mean value ± standard deviation or as number (percentage) of subjects. *CAD*, coronary artery disease;

Table 2. Imaging findings of overall patient population according to events

	All patients (n = 1967)	**With events (n = 72)**	**Without events (n = 1895)**	***P*-value**
Baseline MBF (mL/min/g)	1.2 ± 0.4	1.1 ±0.4	1.2 ± 0.5	0.37
Hyperemic MBF (mL/min/g)	2.8 ± 0.8	2.2 ± 0.7	2.8 ± 0.8	< .001
MFR	2.7 ± 0.8	2.1 ± 0.6	2.7 ± 0.8	< .001
MFR < 2, *n* (%)	370 (19%)	33 (46%)	337 (18%)	< .001
Preserved mCFC, *n* (%)	1647 (84%)	36 (50%)	1611 (85%)	< .001
Normal flow, *n* (%)	1319 (66%)	28 (39%)	1291 (68%)	< .001
Minimally reduced, *n* (%)	328 (17%)	8 (11%)	320 (17%)	0.20
Impaired mCFC, *n* (%)	320 (16%)	36 (50%)	284 (15%)	< .001
Mildly reduced, *n* (%)	259 (13%)	27 (37%)	232 (12%)	< .001
Moderately reduced, *n* (%)	33 (2%)	6 (8%)	27 (1%)	< .001
Definite ischemia, *n* (%)	11 (1%)	3 (4%)	8 (0.5%)	< .001
Myocardial steal, *n* (%)	17 (1%)	0	17 (1%)	0.42

MBF, myocardial blood flow; *MFR*, myocardial blood flow reserve; *mCFC*, modified coronary flow capacity.

Table 3. Univariable and multivariable predictors of adverse cardiac events

	Univariable analysis		Multivariable analysis	
	HR (95% CI)	***P*-value**	**HR (95% CI)**	***P*-value**
Age	1.06 (1.03 – 1.08)	< .001	1.02 (1.00 – 1.04)	< .05
Male gender	1.98 (1.23 – 3.18)	< .01	1.51 (0.92 – 2.48)	0.10
Diabetes	2.63 (1.69 – 4.29)	< .001	1.99 (1.23 – 3.22)	< .05
Hypertension	2.26 (1.24 – 4.13)	< .05	1.20 (0.64 – 2.27)	0.57
Dyslipidemia	1.54 (0.94 – 2.56)	0.09		
Smoking history	0.99 (0.58 – 1.68)	0.99		
Family history of CAD	0.66 (0.39 – 1.02)	0.06		
MFR <2	3.81 (2.39 – 6.05)	< .001	2.04 (1.21 – 3.45)	< .01
Impaired mCFC	5.66 (3.55 – 9.01)	< .001	2.80 (1.59 – 4.91)	< .001

HR, hazard ratio; *CI*, confidence interval; *CAD*, coronary artery disease; *MBF*, myocardial blood flow; *MFR*, myocardial blood flow reserve; *mCFC*, modified coronary flow capacity.