

# Pilot Phase of the SPECTRUM Trial. Fractional Flow Reserve vs. Angiography for Evaluation and Management of Patients with Intermediate Coronary Stenosis: Rationale and Study Design

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## ABSTRACT

**Background:** Despite its well-known limitations, invasive coronary angiography remains the most used, and often times the only method used to define treatment strategies in patients undergoing diagnostic cardiac catheterization. Measurement of coronary fractional flow reserve (FFR) has been used in several studies in patients for whom an interventional strategy was determined based on angiography. However, this method has not been tested in the opposite scenario, in which the angiographic evaluation does not indicate the need for interventions. The purpose of this pilot study, to be performed in two sites, is to test the hypothesis that for intermediate injuries, in which angiography does not indicate the need for coronary intervention, measurement of FFR might change the therapeutic approach based on angiography. **Methods:** Consecutive clinically stable patients, with coronary disease in the proximal or middle segment of one or more epicardial vessels (diameter > 2.5 mm), with injuries between 40 and 70% by visual estimation will be enrolled in this trial. The treatment approach (clinical or interventional) based on angiography will be defined independently and by consensus of two observers. Thereafter, patients in both groups will be randomized into two subgroups: (1) maintenance of the angiography-based therapeutic strategy; and (2) use of FFR to define therapeutic strategy. Patients with FFR < 0.80 will be treated by percutaneous or surgical revascularization, whereas patients with FFR ≥ 0.80 will be treated clinically. **Conclusions:** The present study is aimed at evaluating whether FFR measurement in intermediate lesions in which an interventional therapy is not indicated by angiography results in change of conduct.

**Descriptors:** Coronary artery disease. Cardiac catheterization. Fractional flow reserve, myocardial. Coronary angiography. Percutaneous coronary intervention.

## RESUMO

**Fase Piloto do Estudo SPECTRUM. Reserva de Fluxo Fracionada Versus Angiografia para Avaliação e Conduta em Pacientes com Lesões Obstrutivas Coronárias de Grau Moderado: Racional e Desenho do Estudo**

**Introdução:** A despeito de suas reconhecidas limitações, a angiografia coronária invasiva é o método mais usado (muitas vezes único) para a adoção de estratégias terapêuticas em pacientes submetidos a cateterismo cardíaco diagnóstico. A mensuração de reserva de fluxo fracionada (FFR) tem sido empregada em diversos estudos, fundamentalmente no contexto de pacientes em que a avaliação angiográfica per se indica a necessidade de intervenção sobre as lesões coronárias. No entanto, o método praticamente não foi ainda testado, em condições opostas, no cenário clínico em que as obstruções, angiograficamente, não indicariam intervenções. O propósito deste trabalho, a ser realizado de forma piloto em dois centros, é testar a hipótese de que também para lesões intermediárias, nas quais a angiografia não demonstra necessidade de intervenção coronária, a medida de FFR resultaria em alteração da conduta terapêutica baseada em angiografia. **Métodos:** Serão incluídos pacientes consecutivos e clinicamente estáveis, com doença coronária em segmento proximal e/ou médio de um ou mais vasos epicárdicos (diâmetro > 2,5 mm), apresentando obstruções entre 40 e 70%, por estimativa visual. Em seguida, a conduta terapêutica (clínica ou intervencionista) baseada em angiografia, relativamente a essas lesões, será definida de maneira independente por consenso de dois observadores. A partir daí, os pacientes, em ambos os grupos, serão randomizados para dois subgrupos: (1) manutenção de conduta baseada na angiografia; e (2) realização de FFR para decisão terapêutica. Os pacientes com lesões em que se obtiver FFR < 0,80 serão tratados com revascularização percutânea ou cirúrgica, enquanto os portadores de lesões com FFR ≥ 0,80 serão tratados clinicamente. **Conclusões:** O presente estudo visa avaliar se a medida de FFR em lesões intermediárias não consideradas necessárias de tratamento intervencionista pela angiografia resulta em mudança de conduta.

**Descritores:** Doença da artéria coronariana. Cateterismo cardíaco. Reserva fracionada de fluxo miocárdico. Angiografia coronária. Intervenção coronária percutânea.

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The determination of the severity of intermediate lesions – stenoses that reduce the lumen diameter by 40 to 70% – by angiographic methods potentially incurs several limitations.<sup>1,2</sup> Correlations between histopathological and angiographic results show many discrepancies between these analyzes.<sup>3</sup> A wide variability of visual estimates of gravity also occurs, usually documented by different examiners, as demonstrated by comparative studies of quantitative angiography.<sup>4,5</sup> Recently, studies correlating angiographic estimates of severity of coronary stenoses with intravascular ultrasonography performed during cardiac catheterization also showed difficulties in those angiographic evaluations, including on the elucidation of discrepant aspects regarding function assessment methods, such as myocardial perfusion scintigraphy.<sup>6</sup>

Despite these limitations, angiography remains not only the gold-standard method, but also the most used and preferred method in determining approaches related to revascularization resulting from coronary lesions.<sup>7</sup>

In other words, in most interventional cardiology laboratories and in most circumstances in which coronary lesions are diagnosed, normally the angiographic criterion has an absolute value and is the sole option for the adoption of a percutaneous interventional treatment, referral to coronary artery bypass grafting (CABG), or, alternatively, for the maintenance of the patient in an exclusively clinical treatment.<sup>8</sup> In less frequent conditions, after angiography, cardiologists resort to complementary methods of assessing functional consequences of a coronary lesion of intermediate severity, to define the therapeutic approach. In such cases, after a diagnostic cardiac catheterization, performing examinations, such as myocardial perfusion scintigraphy or stress echocardiography, is important.<sup>9</sup> At the end of this process, the angiographic information, mainly anatomical, is combined with functional diagnostic elements, for the therapeutic conduct that, if resulting in an interventional cardiology procedure, necessarily will require another cardiac catheterization – now with therapeutic purposes.

Thus, this rationale for forwarding solutions to the problems faced by patients with coronary artery disease suffers from two key limitations: first, in the sense that various coronary revascularization procedures by percutaneous intervention or cardiac surgery will eventually be performed without proven necessity, due to an overestimation of the severity, only assessed by the anatomical method (angiography); second, by occasionally causing an excessive loss of an opportune time for intervention, requiring a functional assessment by another method and, finally, making it necessary to perform two cardiac catheterization procedures – that which allowed for the anatomical evaluation, and that which will result in the percutaneous therapeutic intervention. Besides these limitations, there is also the consequent increase in costs and the cost-effective commitment of the process.

## METHOD OF FRACTIONAL FLOW RESERVE MEASUREMENT

Fractional flow reserve (FFR) is defined as the maximum blood flow towards myocardium in the presence of a particular stenosis (or stenoses), divided by the maximum achievable flow, if there were no stenosis. This index represents the normal maximum myocardial flow fraction that can be achieved, despite the presence of stenosis. Based on theoretical concepts validated in experimental models, FFR can be directly determined by dividing the average pressure distal to the coronary lesion, by the average aortic pressure during maximal coronary vasodilation (induced by papaverine, or by intracoronary or intravenous adenosine). A FFR of 0.60 means that the maximum flow of blood (and oxygen) which supplies that particular myocardial area reaches only 60% of what it would achieve if the culprit artery was completely normal. If, after a percutaneous intervention, FFR increases to 0.90, this indicates that the maximum achievable flow to the myocardial area supplied by that artery (and hence, the oxygen supply) will have increased by 50%, and now accounts for 90% of the total achievable value if the artery was completely normal.<sup>10-13</sup>

## USE OF THE METHOD OF FRACTIONAL FLOW RESERVE MEASUREMENT IN CLINICAL PRACTICE

The method of FFR measurement, applied while performing the diagnostic cardiac catheterization, allows for an immediate, quick, and objective intravascular evaluation of functional significance of angiographically detected coronary lesions.<sup>14</sup> A meta-analysis of several correlative studies using FFR determination, quantitative angiography, and/or non-invasive functional tests proved that this FFR estimate was able to assess the conditions of regional myocardial blood supply, regardless of the prevailing conditions of heart rate, blood pressure, and cardiac contractility.<sup>15</sup>

FFR determination is particularly suitable for an analysis of functional significance of moderately severe coronary lesions (40 to 70% reduction in luminal diameter, as detected by angiography).<sup>16,17</sup> Based on the results of multiple studies, it was demonstrated that patients with coronary lesions associated with a FFR value > 0.80 can be treated conservatively (i.e., without an intervention for coronary revascularization), with an evolution, in medium and long term, equivalent or even superior to that observed when patients are treated with percutaneous coronary intervention (PCI) with the aim to treat such lesions.<sup>18-20</sup> It should be emphasized that the protocol of these studies focused only groups of patients in whom FFR was used exclusively to determine whether or not to maintain an interventionist conduct hither to considered as the preferred option, based on purely angiographic aspects.

However, no randomized studies were published on a broader population of patients with stable coronary disease who underwent coronary angiography without previous functional tests, in which intermediate lesions were observed, in order to permit the identification of a change of angiographic conduct based on FFR, and the prognostic clinical impact, compared to the usual approach solely based on angiographic studies. To such end, it is critical to evaluate the impact of the combined use of an angiographic evaluation and FFR measurement on the overall patient population essentially presenting with the problem of one or more intermediate severity lesions, but whose intervention conduct has been dictated exclusively by angiography. With that purpose, a group of such patients must be randomized to determine FFR vs. therapeutical conduct usually based only on coronary angiography.

## OBJECTIVES

The purpose of this work, to be conducted as a pilot study in two sites, but keeping in mind a future extension in a multicenter format (with broader and clinically more relevant goals), is to verify the impact of a combined angiographic and functional evaluation by means of cardiac catheterization in stable patients, and with lesions considered intermediate. To this end, the following primary and secondary goals have been defined.

### Primary goal

To assess whether, in this population, the strategy of measuring FFR in patients with intermediate coronary lesions would result in a significant change in the conduct usually adopted, based on angiography, with respect to revascularization procedures. The change of conduct eventually promoted by FFR measurement is then assessed not only in patients in whom there is an angiographic indication for coronary intervention, but also – and especially – in those patients who, after an angiographic evaluation, would be medically treated by a conservative approach, without coronary intervention.

### Secondary goal

To evaluate whether the strategy based on this immediate and direct functional approach at the cardiac catheterization laboratory itself results in clinical outcomes superior to those provided by a strategy solely based on angiographic studies. In the pilot phase of the study, using a limited sample population, this goal will be characterized as a merely exploratory hypothesis.

## METHODS

Consecutive, clinically stable patients will be included, referred for coronary angiography without functional evidence of ischemia by imaging methods.

In this pilot phase of the SPECTRUM trial, the study will be bicentrically developed; the initial criteria for patient enrollment are described below. Inclusion criteria: patients over 18 years old; with coronary heart disease in proximal and/or middle segments of one or more major epicardial vessels, with at least one lesion affecting 40-70% by angiographically-based visual estimation; and able to provide an informed consent. Exclusion criteria: patients with severe ventricular dysfunction (left-ventricle ejection fraction – LVEF < 30%); with multivessel coronary disease and left-ventricular dysfunction (EF < 40%); with left main coronary artery disease > 50% by visual estimation; presenting chronic vessel occlusions; presenting vessels with diameter < 2.5 mm; with unfavorable coronary anatomy for percutaneous intervention (e.g., excessive tortuosity) or CABG (e.g., coronary arteries without adequate surgical targets for implantation of arterial and/or venous grafts); with an intracoronary thrombus; with myocardial infarction with ST-segment elevation < 30 days; with functional evidence of ischemia with imaging studies prior to catheterization; with prior CABG; with heart-valve disease in need of percutaneous or surgical intervention; with contraindication to anticoagulation; with contraindication to use of antiplatelet agent; pregnancy; or with comorbid condition that limits life expectancy to less than two years.

After due clarification about the purposes of the study and having signed an informed consent, patients will undergo a coronary angiography procedure in the usual manner at the Interventional Cardiology Unit, Hospital das Clínicas, Faculdade de Medicina de Ribeirão Preto, Ribeirão Preto, SP, Brazil, and Instituto do Coração, São Paulo, SP, Brazil. The protocol was reviewed and approved on April 14, 2008 by the Research Ethics Committee, Hospital das Clínicas, Faculdade de Medicina de Ribeirão Preto, Universidade de São Paulo (protocol 2317/2008).

After enrollment in the study, the initial angiography-based therapeutic approach for these lesions will always be independently defined by consensus of two observers with angiographic and interventional experience. In case of disagreement between the two observers, a third observer will be independently responsible for the decision. After the definition of an angiography-based conduct, which may indicate a clinical or interventional (i.e., percutaneous or surgical) strategy for each intermediate coronary lesion, patients will be allocated by a central randomized algorithm, in a ratio of 1:1 between two groups: (1) a group of angiography-based conduct maintenance; (2) and a group in which an estimate of the FFR of the lesions in question will be performed.

Patients with lesions with FFR < 0.80 will be treated by conventional percutaneous revascularization or CABG, whereas patients with lesions with FFR ≥ 0.80 will be treated conservatively. Determining the modality of revascularization (percutaneous or CABG) will be

at the discretion of the investigator, and angiographic, clinical, and logistical aspects of the institution will be considered. These steps are illustrated in Figure 1.

The estimate of FFR will be performed with manometric analyzers, using intracoronary instrumentation with a guide wire (diameter of 0.014", 0.36 mm) which uses a specific sensor located at a distance of 3 cm from its tip (Radi Medical Systems, Uppsala, Sweden; or Volcano Smartwire II, Volcano Corporation, Rancho Cordova, United States), after induction of maximal hyperemia with intracoronary injections (bolus) of 80-450 µg of adenosine. Usually, for each evaluation of a coronary lesion, 2-3 intracoronary injections of adenosine are applied, and the lowest FFR value is computed. In the

case of serial lesions, revascularization only will be indicated if FFR < 0.80 after superseding all lesions; in the case of percutaneous revascularization, the investigator should intervene in the lesion which appears to be the most serious one. After the intervention in this lesion, FFR should be measured again, and if FFR remains < 0.80, residual lesions should be treated.

The patients will be followed for at least 12 months, with visits scheduled for 30, 90, 180, and 360 days after randomization. At visits of 30, 180, and 360 days, a 12-lead electrocardiogram is planned. The primary endpoint of this pilot phase of the SPECTRUM study is the rate of occurrence of change in the angiography-based approach usually adopted for revascularization

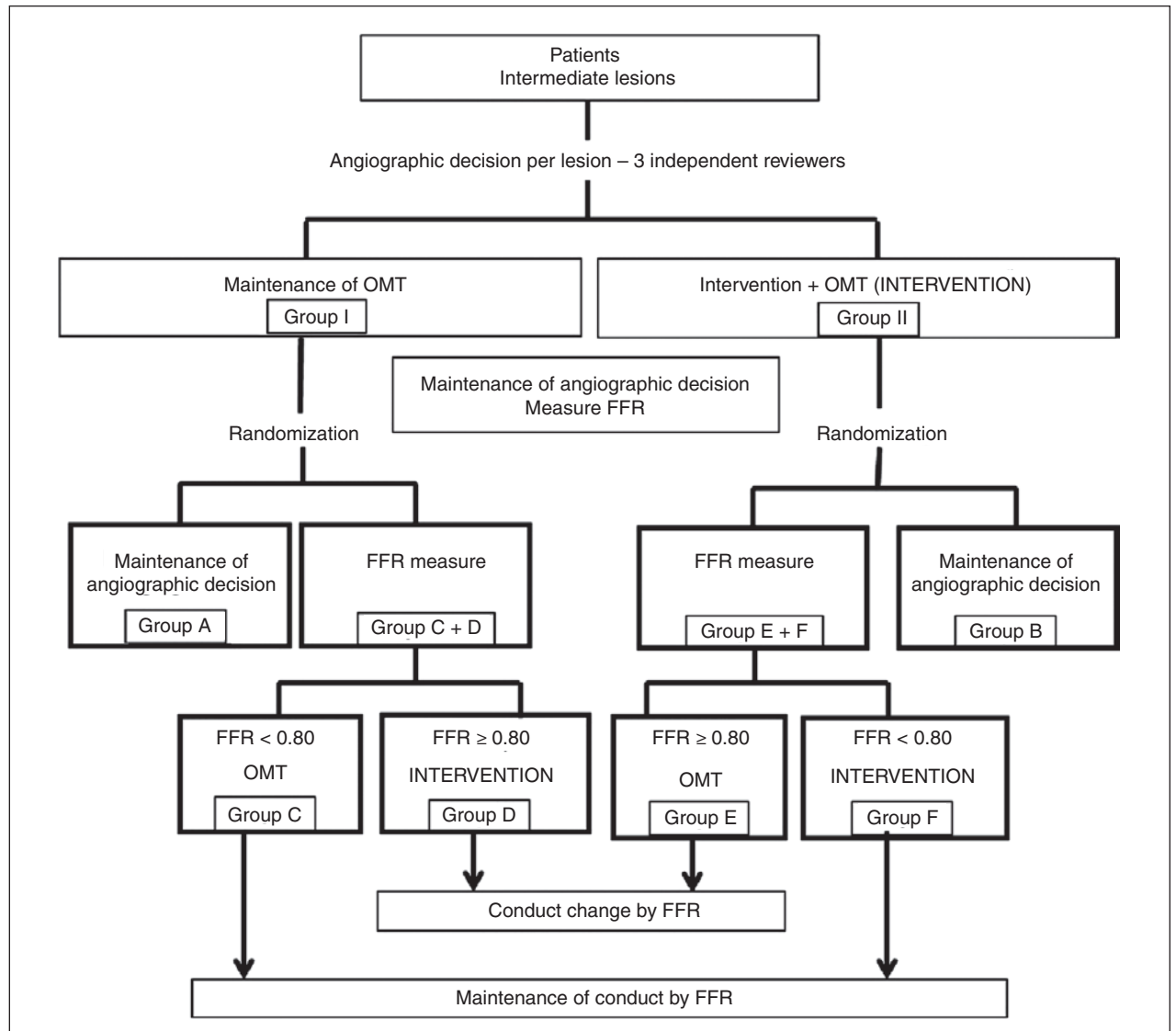


Figure 1 – Patients referred for coronary angiography without functional imaging tests. OMT: optimal medical treatment; FFR: fractional flow reserve.



procedures, with or without indication based on FFR results. The secondary endpoint is the cumulative rate of occurrence of a composite of major adverse cardiac events, including death, non-fatal myocardial infarction, and repeated revascularization, for those lesions initially considered as intermediate (object of study) during the first year of follow-up.

### Sample size calculation

In the sample size calculation, the rationale was based on the seven premises below, according to Poisson's formula.<sup>21</sup>

**Premise I:** intermediate lesions (40 to 70% luminal diameter reduction in at least two angiographic projections, defined by qualitative analysis). The patient must have one or more intermediate lesions, and all will be individually randomized.

**Premise II:** by consensus between two experienced examiners, or by deciding vote of a *tertius* (in case of disagreement between examiners) and also by angiographic qualitative evaluation, an initial decision shall: (a) proceed with an optimal medical treatment; (b) perform a revascularization procedure for the lesion-dependent myocardium, with percutaneous or surgical treatment, in combination with an optimal medical treatment. Thus, based on angiography:

- N = total final number of lesions.
- N1 = number of lesions allocated to an optimal medical treatment (M).
- N2 = number of lesions allocated to revascularization (R).

**Premise III:** sample size calculation based on the comparison of the proportion of lesions to be revascularized (R), and all of them, which constitute the M and R groups, will be randomized in a 1:1 ratio to evaluate whether there is (+F) or not (-F) functional significance of the lesion with FFR measurement.

**Premise IV:** alpha and beta errors for sample size calculation will have fixed values, respectively, at 5 and 20% (power of the study to detect differences in proportions, as noted below, of 80%).

### Randomization in group N1

Lesions allocated to optimal medical treatment (M) by angiography:

$N1 \times 0.5$ : randomized to (-F):  $N1' =$  number of lesions to be treated medically (M).

In the other 50% of this group:

$N1' = N1 \times 0.5$ : randomized to (+F).

**Premise V:** The FFR-based assessment will change in 20% the angiographic conduct.<sup>22</sup> Then:

$N \times 0.5 \times 0.8$ : the number of lesions that will remain in optimal medical treatment (M).

$N \times 0.5 \times 0.2$ : the number of lesions that will be treated with percutaneous revascularization or CABG (R).

Thus,

- P(0), if there was no FFR assessment: 100% of lesions that would be medically treated (M) and 0% by revascularization (R).

- P(1), after FFR assessment: 90% of lesions that will continue to be medically treated (M) and 10% by revascularization (R).

- $N1' = [(0 \times 100) + (90 \times 10)] \times 7.9 / (100-90)^2$ .
- $N1' = 71$  lesions (in each randomization arm).
- $N1 = 2 \times N1' = 142$  lesions.

### Randomization in group N2

Lesions allocated to revascularization (R) by angiography:

$N2 \times 0.5' = N2'$ : randomized to (-F): then all lesions will be treated with revascularization (R).

The other 50% of this group:  $N2' = N2 \times 0.5$ : randomized to (+F).

**Premise VI:** a FFR evaluation in this group will change the conduct in 35%.<sup>21</sup>

Thus:

$N \times 0.5 \times 0.35$ : the number of lesions that will have an optimal medical treatment (M).

$N \times 0.5 \times 0.65$ : the number of lesions that will continue with revascularization (R).

Then,

- P(0), if there was no FFR assessment: 0% would continue being medically treated (M) and 100% would be treated with revascularization (R).

- P(1), after FFR assessment: 17.5% of the lesions will be medically treated (M) and 82.5% will continue with revascularization (R).

- $N2' = [(0 \times 100) + (17.5 \times 82.5)] \times 7.9 / (100-82.5) 2$ .

- $N2' = 38$  lesions (in each randomization arm).
- $N2 = 2N2' = 76$  lesions.

Thus:  $N = 142 + 76 = 218$  lesions.

Therefore, in a proportion of 65% vs. 35% of intermediate lesions allocated by angiography, respectively in groups of optimal medical therapy and revascularization.

**Premise VII:** at a basis of 1.3 lesions per patient, 177 individuals in this phase of the SPECTRUM project must be included.

In summary, considering the hypotheses of the study, after completion of FFR measurement there will be a reduction of 20% in revascularizations and conduct change in 25% of lesions, according to the experimental protocol implemented in this phase. However, if FFR were implemented in all patients, the potential for change of conduct in the treatment of the lesions would be up to 60% (20% in those 60% of lesions allocated by angiography for clinical treatment and 40% in those 40% of lesions allocated by angiography for revascularization).

Also considering these hypotheses, the potential of change in the conduct of revascularization would reach up to:  $60\% / 5 = 12\%$  increase in group 1 (allocated to medical treatment, at first by angiography) and  $40\% / 3 = 16\%$  reduction in group 2 (allocated to revascularization, at first by angiography), with a net saving of 4%. Then, from the actual results of this study, in its pilot phase, these changes will be really measured and will determine the basis for further conduction of the multicentric phase of the project.

## CONCLUSIONS

This is the first investigation aiming to study groups of patients randomly allocated and, thus, with angiographic lesions of intermediate severity, and in whom an initial decision, based only on anatomic criteria (but not limited to those cases referred for intervention), will be compared to a fractional flow reserve measurement-based decision. Thus, the impact of functional assessment with use of fractional flow reserve will be also evaluated in the group of patients to whom the initial angiographic decision will indicate an exclusively medical treatment, without coronary intervention. This pilot phase of the SPECTRUM study will form the basis for the verification phase of the study, in a more comprehensive number of cases, on the impact of both decision strategies on the patients' outcome, focusing on clinically relevant endpoints.

## CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

## FUNDING SOURCES

None.

## REFERENCES

1. Fischer JJ, Samady H, McPherson JA, Sarembock IJ, Powers ER, Gimple LW, et al. Comparison between visual assessment and quantitative angiography versus fractional flow reserve for native coronary narrowings of moderate severity. *Am J Cardiol.* 2002;90(3):210-5.
2. Topol EJ, Nissen SE. Our preoccupation with coronary luminology: the dissociation between clinical and angiographic findings in ischemic heart disease. *Circulation.* 1995;92(8):2333-42.
3. Roberts WC, Virmani R. Quantification of coronary arterial narrowing in clinically-isolated unstable angina pectoris: an analysis of 22 necropsy patients. *Am J Med.* 1979;67(5):792-9.
4. Detre KM, Wright E, Murphy ML, Takaro T. Observer agreement in evaluating coronary angiograms. *Circulation.* 1975;52(6):979-86.
5. Zir LM, Miller SW, Dinsmore RE, Gilbert JP, Harthorne JW. Interobserver variability in coronary angiography. *Circulation.* 1976;53(4):627-32.
6. Rodes-Cabau J, Candell-Riera J, Angel J, de Leon G, Perezto O, Castell-Conesa J, et al. Relation of myocardial perfusion defects and nonsignificant coronary lesions by angiography with insights from intravascular ultrasound and coronary pressure measurements. *Am J Cardiol.* 2005;96(12):1621-6.
7. Marin-Neto JA, Ayres-Neto EM. Cinecoronariografia: quando não é e quando é preciso indicar? In: Timerman A CL, editor. *Manual de cardiologia.* São Paulo: Atheneu; 2000. p. 207-11.
8. Feres FM, Marin-Neto JA. Angiografia de contraste: ainda o método padrão para estratificação de risco em pacientes com síndrome isquêmica miocárdica instável em nosso meio? In: Nicolau JC M-NJ, editor. *Síndromes isquêmicas miocárdicas instáveis.* São Paulo: Atheneu; 2001. p. 189-201.
9. Simões MV, Salis FV, Marin-Neto JA. Exames com radionuclídeos nas síndromes isquêmicas miocárdicas instáveis: o que acrescentam à avaliação ergométrica e ecocardiográfica? In: Nicolau JC M-NJ, editor. *Síndromes isquêmicas miocárdicas instáveis.* São Paulo: Atheneu; 2001. p. 135-76.
10. van de Hoef TP, Meuwissen M, Escaned J, Davies JE, Siebes M, Spaan JA, et al. Fractional flow reserve as a surrogate for inducible myocardial ischaemia. *Nat Rev Cardiol.* 2013;10(8):439-52.
11. Kern MJ, Lerman A, Bech JW, De Bruyne B, Eeckhout E, Fearon WF, et al. Physiological assessment of coronary artery disease in the cardiac catheterization laboratory: a scientific statement from the American Heart Association Committee on Diagnostic and Interventional Cardiac Catheterization, Council on Clinical Cardiology. *Circulation.* 2006;114(12):1321-41.
12. Lim MJ, Kern MJ. Coronary pathophysiology in the cardiac catheterization laboratory. *Curr Probl Cardiol.* 2006;31(8):493-550.
13. Gould KL, Lipscomb K, Hamilton GW. Physiologic basis for assessing critical coronary stenosis. Instantaneous flow response and regional distribution during coronary hyperemia as measures of coronary flow reserve. *Am J Cardiol.* 1974;33(1):87-94.
14. Pijls NH, De Bruyne B, Peels K, Van Der Voort PH, Bonnier HJ, Bartunek JKJ, et al. Measurement of fractional flow reserve to assess the functional severity of coronary-artery stenoses. *N Engl J Med.* 1996;334(26):1703-8.
15. Christou MA, Siontis GC, Katritsis DG, Ioannidis JP. Meta-analysis of fractional flow reserve versus quantitative coronary angiography and noninvasive imaging for evaluation of myocardial ischemia. *Am J Cardiol.* 2007;99(4):450-6.
16. Chamuleau SA, Meuwissen M, Koch KT, van Eck-Smit BL, Tio RA, Tijssen JG, et al. Usefulness of fractional flow reserve for risk stratification of patients with multivessel coronary artery disease and an intermediate stenosis. *Am J Cardiol.* 2002;89(4):377-80.
17. Fearon WF, Takagi A, Jeremias A, Yeung AC, Joye JD, Cohen DJ, et al. Use of fractional myocardial flow reserve to assess the functional significance of intermediate coronary stenoses. *Am J Cardiol.* 2000;86(9):1013-4, A10.
18. Pijls NH, van Schaardenburgh P, Manoharan G, Boersma E, Bech JW, van't Veer M, et al. Percutaneous coronary intervention of functionally nonsignificant stenosis: 5-year follow-up

- of the DEFER Study. *J Am Coll Cardiol.* 2007;49(21):2105-11.
19. Berger A, Botman KJ, MacCarthy PA, Wijns W, Bartunek J, Heyndrickx GR, et al. Long-term clinical outcome after fractional flow reserve-guided percutaneous coronary intervention in patients with multivessel disease. *J Am Coll Cardiol.* 2005;46(3):438-42.
20. Wongpraparut N, Yalamanchili V, Pasnoori V, Satran A, Chandra M, Masden R, et al. Thirty-month outcome after fractional flow reserve-guided versus conventional multivessel percutaneous coronary intervention. *Am J Cardiol.* 2005;96(7):877-84.
21. Pocock SJ. The size of a clinical trial. *clinical trials: a practical approach.* Chichester: John Wiley & Sons; 1983. p. 123-38.
22. Sant'Anna FM, Silva EE, Batista LA, Ventura FM, Barrozo CA, Pijls NH. Influence of routine assessment of fractional flow reserve on decision making during coronary interventions. *Am J Cardiol.* 2007;99(4):504-8.