2. Jobic Y, Provost K, Larlet JM, et al. Intermittent left coronary occlusion caused by native aortic valve thrombosis in a patient with protein S deficiency. *J Am Soc Echocardiogr.* 1999;12:1114–1116.
3. Rachwan RJ, Daher GE, Fares J, et al. Complete resolution of a large bicuspid aortic valve thrombus with anticoagulation in primary antiphospholipid syndrome. *Front Cardiovasc Med.* 2017;4:59.
4. Jin Cho S, Hoon Yang J, Uk Shin J, et al. A case of spontaneous native aortic valvular thrombosis that caused aortic stenoinsufficiency in the bicuspid aortic valve. *Korean Circulation J.* 2006;36:666–668.
5. Patnaik M, Moll M. Inherited antithrombin deficiency: a review. *Haemophilia.* 2008;14:1229–1239.
6. Stein PD, Sabbah HN, Pitha JV. Continuing disease process of calcific aortic stenosis. Role of microthrombi and turbulent flow. *Am J Cardiol.* 1977;39:159–163.

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Prospective validation and comparison of new indexes for the assessment of coronary stenosis: resting full-cycle and quantitative flow ratio

Validación prospectiva y comparación de los nuevos índices de evaluación de las estenosis coronarias: resting full-cycle *y* quantitative flow ratio

To the Editor,

Coronary physiological indices are not widely used, despite evidence supporting their utilization.[1] This is largely because of confidence in the adequacy of angiographic assessment and because measurement of these indices requires coronary guidewire manipulation[2] or, in the case of fractional flow reserve (FFR), induction of hyperemia.[3]

A number of simplified indices have been developed to increase the use of functional assessment. These include instantaneous wave-free ratio [iFR], diastolic resting pressure ratio [dPR], resting full-cycle ratio [RFR], and quantitative flow ratio (QFR).[4] The success of iFR spawned the development of other indices not requiring hyperemia induction, such as RFR, which has been shown to have good correlation and agreement with iFR and FFR in retrospective analyses.[5] In addition, QFR does not require the use of a guidewires as it is based on 3-dimensional analysis of the coronary anatomy. It has also been found to have good correlation and agreement with FFR.[6] No prospective studies, however, have compared RFR or QFR with FFR. The aims of this study were to evaluate and compare the ability of RFR and QFR to predict FFR in a prospective sample and, based on our results, to propose a combined algorithm for minimally invasive functional assessment.

Following approval of the study by the research committee, we consecutively included patients scheduled for functional assessment in 3 high-volume hospitals. The physiological parameters requiring an invasive approach were measured using the Abbott Vascular guidewire (Abbott Vascular, USA). RFR was calculated using the dedicated Coroventis AB (Sweden) software program. Hyperemia was then induced to calculate FFR. Angiographic images captured using recommended procedures[6] were reconstructed to calculate QFR (Medis, Netherlands).

Pearson correlation analysis was used to assess correlations between QFR, RFR, and FFR. The level of agreement between the 3 indices was analyzed using the Bland-Altman method and the intraclass correlation coefficient. The ability of each index to predict significant stenosis was analyzed using receiver operating characteristic curves with a predefined cutoff value of ≤ 0.80 for FFR and QFR and ≤ 0.89 for RFR.

A total of 101 vessels (77 patients) were studied. The mean ± SD age of the patients was 69.3 ± 10 years and 70.1% were male. The most common diagnosis was stable angina (40.3%).

The mean percent diameter stenosis based on visual estimation was 54% ± 14%. Mean FFR was 0.84 ± 0.09 and, based on this index, 30.7% of the vessels had significant stenosis. RFR identified significant stenosis in 51.5% of the vessels and the mean value was 0.88 ± 0.09. Assessment of stenosis by QFR was possible in 89 vessels (88.1%). The mean value was 0.86 ± 0.08 and 27% of the vessels had significant stenosis.

The intraclass correlation coefficients between QFR and FFR and RFR and FFR were 0.92 (95% confidence interval [95%CI], 0.88-0.95) and 0.76 (95%CI, 0.67-0.84), respectively. The mean differences between the indices were 0.04 ± 0.006 for RFR and FFR and 0.01 ± 0.03 for QFR and FFR (figure 1A,B). RFR produced 20 false positive (30.3%) and 1 false negative (3%). By contrast, just 1 of the vessels (1.6%) identified as significant by QFR did not have significant stenosis and 5 (17.9%) of the vessels considered nonsignificant by QFR had an FFR ≤ 0.80 (figure 1C,D).

Assessment of the diagnostic accuracy of visual estimation to detect FFR with a cutoff of ≤ 0.80 (stenosis > 70% of diameter) showed a sensitivity of 34.4% and a specificity of 87.5%. The respective results for RFR and QFR were 96.7% and 82.15% for sensitivity and 67.7% and 98.36% for specificity (figure 1E). Although QFR and RFR had extreme diagnostic accuracy values of 100% and 84.4%, respectively, for values close to the cutoff point (FFR of between 0.75 and 0.85), their accuracy for values at or below the cutoff point was lower: 80% for QFR and 68.6% for RFR.

Our proposed combined algorithm-based approach is shown in figure 2. The accuracy of QFR at extreme values would have eliminated the need for a coronary guidewire in 61 lesions (42 patients, 54.5%). RFR should be used for values near the cutoff point and for cases where QFR cannot be measured. The diagnostic accuracy of this combined approach to detect FFR ≤ 0.80 was 97.03%.

This is the first prospective study to compare RFR and QFR with FFR. Our combined approach showed excellent diagnostic accuracy compared with FFR. Apart from overconfidence in the adequacy of visual estimation, the main reasons for not using coronary physiological indices are the need to induce hyperemia[1] and difficulties with guidewire manipulation.[2] Use of the algorithm shown in figure 2 would have avoided hyperemia induction in 100% of patients and use of a coronary guidewire in more than 50%.

Although our study has significant limitations, such as a lack of comparison with other resting coronary physiological indices and not knowing how consistent these data would be if measured by clinicians with less training in QFR analysis, our approach could be useful for increasing the use of functional assessment of coronary lesions. Further studies are needed to confirm our proposed strategy.

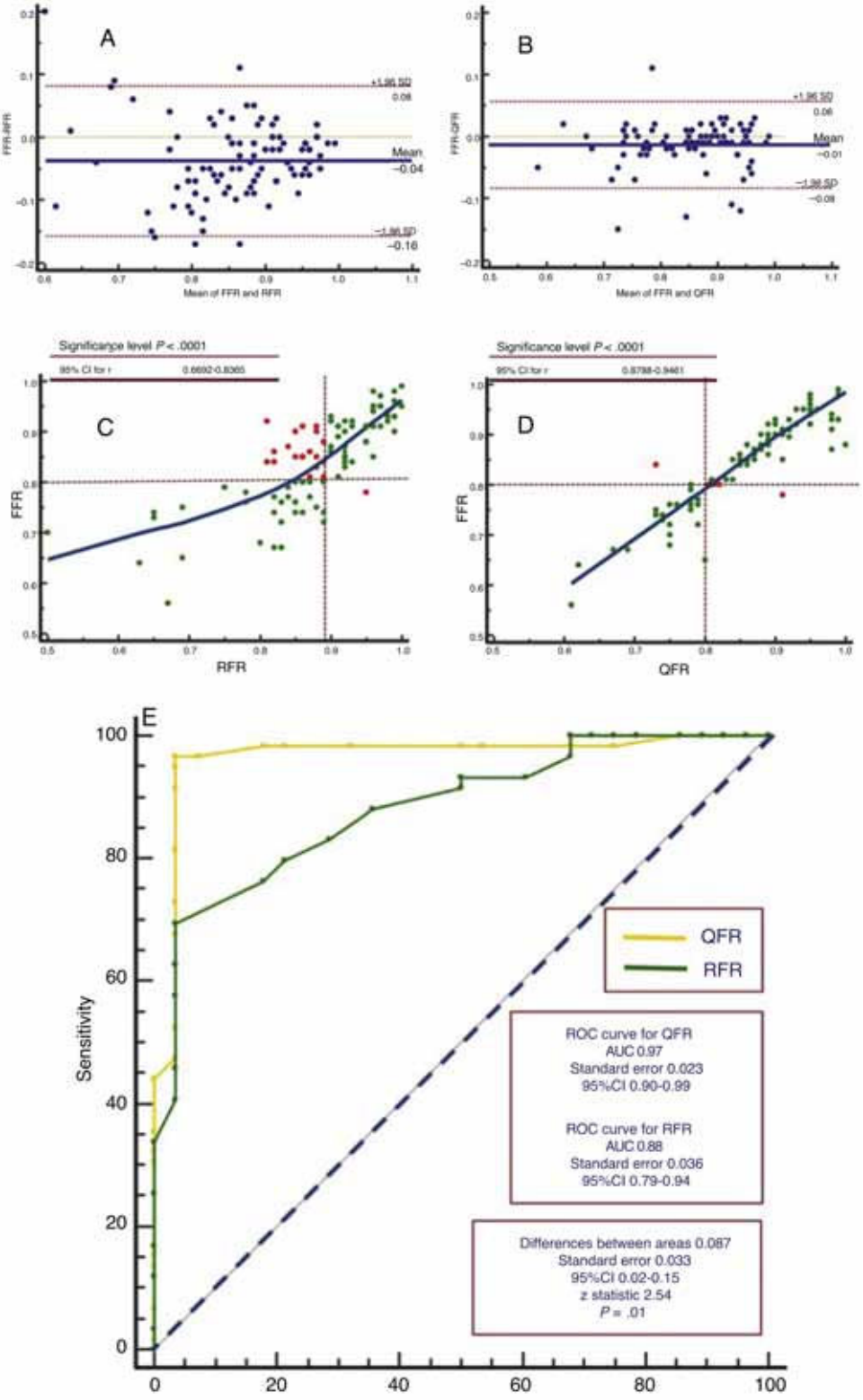
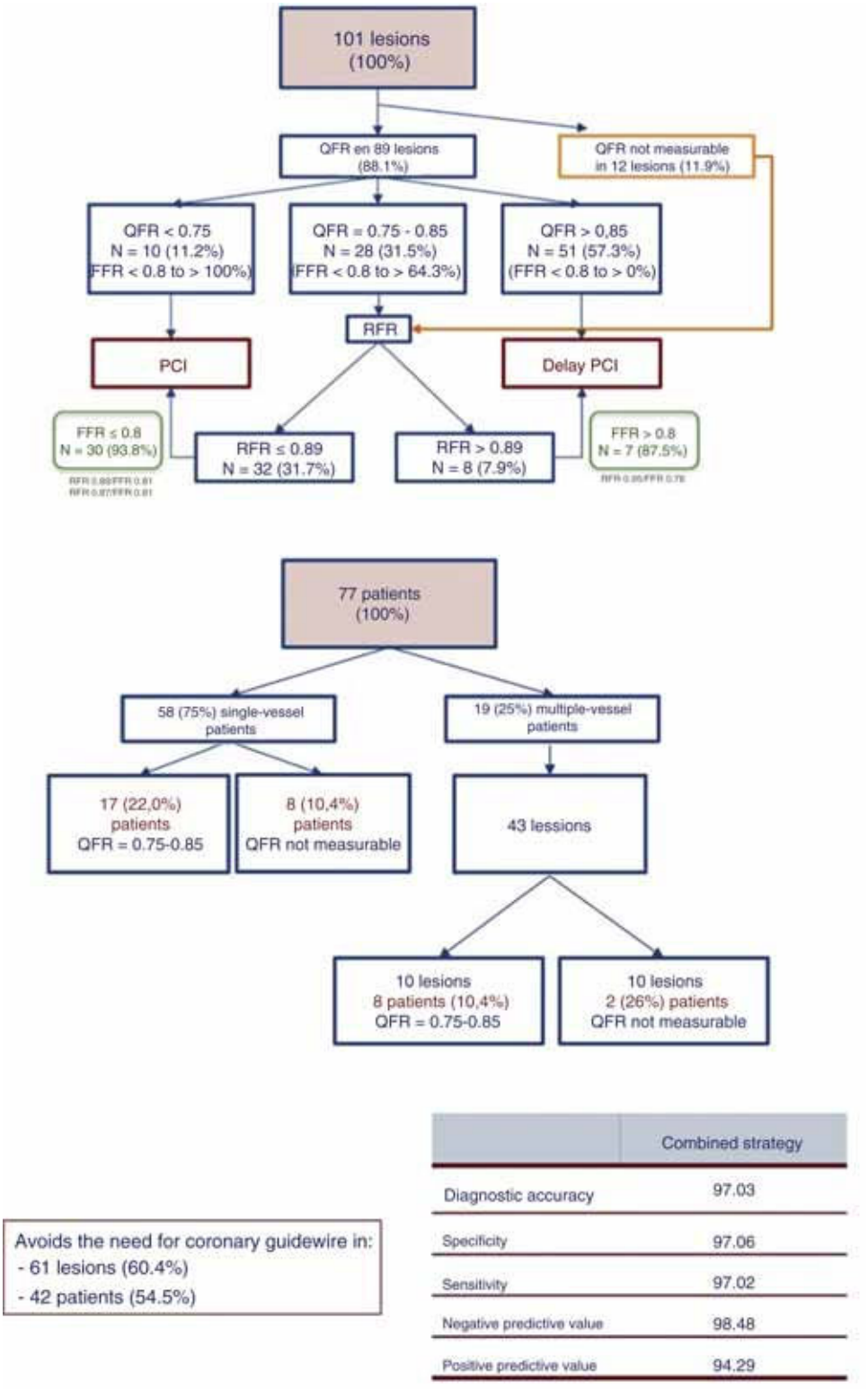


Figure 1. Agreement, correlation, and ROC curves for QFR and RFR compared with FFR. 95%CI, 95% confidence interval; AUC, area under the curve; FFR: fractional flow reserve; QFR, quantitative flow ratio; RFR, resting full-cycle ratio; ROC, receiver operating characteristic; SD, standard deviation.



	Combined strategy
Diagnostic accuracy	97.03
Specificity	97.06
Sensitivity	97.02
Negative predictive value	98.48
Positive predictive value	94.29

Figure 2. Combined approach for the physiological assessment of coronary stenosis and results for the study population. FFR: fractional flow reserve; PCI, percutaneous coronary intervention; QFR, quantitative flow ratio; RFR, resting full-cycle ratio.

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REFERENCES

1. Götberg M, Cook CM, Sen S, et al. The evolving future of instantaneous wave-free ratio and fractional flow reserve. *J Am Coll Cardiol.* 2017;70:1379–1402.
2. Tebaldi M, Biscaglia S, Fineschi M, et al. Evolving routine standards in invasive hemodynamic assessment of coronary stenosis. *JACC Cardiovasc Interv.* 2018;11:1482–1491.
3. Pijls NH, De Bruyne B, Peels K, et al. Measurement of fractional flow reserve to assess the functional severity of coronary-artery stenoses. *N Engl J Med.* 1996;334:1703–1708.
4. Sen S, Escaned J, Malik IS, et al. Development and validation of a new adenosine-independent index of stenosis severity from coronary wave-intensity analysis. *J Am Coll Cardiol.* 2012;59:1392–1402.
5. Svanerud J, Ahn J-M, Jeremias A, et al. Validation of a novel non-hyperaemic index of coronary artery stenosis severity: the Resting Full-cycle Ratio (VALIDATE RFR) study. *EuroIntervention.* 2018;14:806–814.
6. Cortés C, Carrasco-Moraleja M, Aparisi A, et al. Quantitative flow ratio — meta-analysis and systematic review. *Catheter Cardiovasc Interv.* 2020. http://dx.doi.org/10.1002/ccd.28857.

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High use of direct oral anticoagulants in elderly patients with atrial fibrillation: data from the REFLEJA registry

Uso amplio de anticoagulantes de acción directa en pacientes ancianos con fibrilación auricular: datos del registro REFLEJA

To the Editor,

The prevalence of atrial fibrillation (AF) increases with age and peaks at the age of ≥ 80 years (17.7%).[1] Decisions on oral anticoagulation (OAC) therapy are challenging in patients of this age due to a higher stroke and bleeding risk. Although direct oral anticoagulants (DOACs) have been shown to be an attractive option for elderly patients—they are at least as effective as vitamin K antagonists and substantially reduce intracranial hemorrhage—they are clearly underused.[2]

The aim of this study was to assess the use of DOACs in a contemporary clinical series of patients aged ≥ 80 years and to analyze predictors of DOAC use and the influence of age on choice of doses.

The REFLEJA AF study is a prospective registry of 1039 consecutive outpatients with nonvalvular AF (NVAF) evaluated between October 2017 and June 2018 at a single hospital in Jaen, Spain. The registry includes all patients aged ≥ 18 years with NVAF evaluated by the cardiology unit. We compared the baseline characteristics of patients aged < 80 years and ≥ 80 years by bivariate analysis, using the chi-square test for qualitative variables and the *t* test for quantitative variables. We then performed binary logistic regression to identify independent predictors of DOAC use in these populations and calculated their respective odds ratios (ORs).

The characteristics of the population are summarized in table 1. Compared with younger patients, the group of patients aged ≥ 80 years (n = 376) comprised significantly more women (57.7% vs 41.5%, $P < .001$) and patients with heart failure (29.8% vs 20.2%, $P < .001$) or vascular disease (19.7 vs 12.8%, $P = .003$). Although the differences were not significant, older patients were also more likely to have a history of bleeding (5.9% vs 3.8%, $P = .12$) or stroke (9.3% vs 7.1%, $P = .20$).

Despite their less favorable profile, patients aged ≥ 80 years were more likely to be on AOCs (94.9% vs. 90% for those aged < 80 years, $P = .005$). The difference for the prescription of DOACs, however, was not significant (64.1% v. 69.3%; $P = .08$), although a higher proportion of older patients were on low doses (29.9% vs 7.6%, $P < .001$). The only significant difference observed in terms of the use of specific DOACs was for dabigatran, which was prescribed less often to patients aged ≥ 80 years (figure 1).

On multivariate analysis, an age ≥ 80 years was not associated with a lower use of DOACs (OR = 1.16; 95% confidence interval [95%CI], 0.58-2.31; $P < 0.67$). By contrast, both heart failure (OR = 0.60; 95%CI, 0.40-0.90; $P = .013$) and chronic kidney failure (CKF) (OR = 0.55; 95%CI, 0.41-0.76; $P < .001$) were independent predictors of lower DOAC use.

Generally speaking, there is sufficient evidence to recommend AOC therapy to elderly patients as it produces a net benefit in terms of a reduced risk of death, ischemic stroke, and intracranial hemorrhage (in this last case even in patients with a HAS-BLED score ≥ 3).[3] There is also evidence that AOCs result in an absolute reduction of stroke risk in elderly patients and that the reduction in this population is even higher than in younger patients.[4]

One notable finding of our study was that over 90% of patients with NVAF were on AOC therapy, and there were no differences between patients aged < 80 years and ≥ 80 years. This rate is even higher than that reported in a quality US clinical practice registry, where less than 80% of patients with NFAF were on AOCs and use was higher in younger patients.[5]

Appropriate choice of anticoagulant dose is necessary to ensure effective protection against stroke and to prevent an increased risk of bleeding. Subjective judgements based on age could erroneously lead to the prescription of low DOAC doses in elderly patients if other factors such as low body weight (<60 kg) or CKF are not taken into account. It is noteworthy that underdosing (18.5%) and overdosing (38%) were common in our series, even though almost 35% of patients had a glomerular filtration rate < 50 mL/min, which is a criterion for using lower doses for certain DOACs. After adjusting for sex, bleeding risk, CKF,