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Revascularization decisions in patients with chronic coronary syndromes: Results of the second International Survey on Interventional Strategy (ISIS-2)

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ABSTRACT

Background: In chronic coronary syndromes, guidelines mandate invasive functional guidance of revascularization whenever non-invasive proof of ischemia is missing. ISIS-2 survey aimed to evaluate how the adoption of guideline recommendation on ischemia-guided revascularization has evolved over the last 5–7 years.
Methods: In ISIS-2 participants assessed five complete angiograms, presenting only intermediate stenoses without information on non-invasive pre-testing. Fractional flow reserve was known for each stenosis, but remained undisclosed. Participants could determine stenosis significance either by angiography or by requesting an adjunctive invasive diagnostic method (intravascular imaging or functional tests). Primary endpoint was the rate of requesting adjunctive functional assessment. Secondary endpoints were the rate of concordance between angiography-based decisions and know functional severity. ISIS-2 utilized the same web-based platform as ISIS-1 in 2013. (NCT04001452).
Results: 334 participants performed 2059 lesion evaluations: 1202 (59%) decisions were based solely on angiography without expressed need for further evaluation. These decisions were discordant with known functional significance in 39%, mainly with potential of overtreatment. Participants requested invasive functional assessment in 643 (31%) and intravascular imaging in 214 (10%) cases. Compared to ISIS-1 the rate of purely angiography-based decisions has decreased (59% vs 66%; $p < 0.001$), while invasive functional tests were more frequently requested (31% vs 25%; $p < 0.001$).
Conclusions: ISIS-2 suggests an evolving pattern in the intention to integrate invasive coronary physiology into the revascularization decisions. However, the disconnect between recommendations and current thinking is still dominant.

1. Introduction

While the anatomic definition of significant coronary artery disease derives from a physiological explanation, its clinical applicability suffers from an approximate 40% discrepancy between angiographic severity and functional significance. In practice, one out of three angiography-based decisions results in either overtreatment (i.e. revascularizing a stenosis not causing myocardial ischemia) or undertreatment (i.e. leaving a relevant stenosis untreated). Not surprisingly, angiography-guided coronary revascularization has failed to demonstrate clinical benefit as compared to conservative therapy [1–4], unlike the case when percutaneous coronary intervention is targeted exclusively to coronary stenoses identified as causing extensive myocardial ischemia [5–7]. Current European guidelines and American recommendations suggest limiting revascularization in chronic coronary syndromes (CCS) strictly to coronary stenoses with functional significance, proven either non-invasively or invasively [8,9]. Considering that non-invasive functional tests are often either not performed or correlate

Abbreviations: CCS, chronic coronary syndrome; FFR, fractional flow reserve; IVUS, intravascular ultrasound; NHPR, non-hyperemic pressure ratios; OCT, optical coherence tomography; PCI, percutaneous coronary intervention; QCA, quantitative coronary angiography.

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Table 1
Characteristics of the survey participants ($n = 334$).

Age	42 ± 10 years
Experience in interventional cardiology	
Less than 2 years	13%
Between 2 and 5 years	25%
Between 5 and 10 years	23%
More than 10 years	38%
Number of yearly PCI	
Less than 75	23%
Between 76 and 150	24%
Between 151 and 250	24%
More than 250	29%
Experience with FFR	
No experience	19%
Less than 1 year	12%
Between 1 and 3 years	24%
More than 3 years	45%
Experience with NHPR	
No experience	43%
Less than 1 year	21%
Between 1 and 3 years	23%
More than 3 years	12%
Experience with IVUS	
No experience	25%
Less than 1 year	19%
Between 1 and 3 years	19%
More than 3 years	36%
Experience with OCT	
No experience	47%
Less than 1 year	17%
Between 1 and 3 years	17%
More than 3 years	19%

Characteristics of the participants with focus on overall and specific experience. (FFR – fractional flow reserve, NHPR – non-hyperemic pressure ratios, IVUS – intravascular ultrasound, OCT – optical coherence tomography, PCI – percutaneous coronary intervention).

inconclusively with coronary anatomy, commonly revascularization decisions rely purely on information obtained in the catheterization laboratory. Still, the wide adoption of invasive functional assessment is limited, with financial restrictions or logistic issues like adenosine claimed as the main obstacles. The aim of the present study was to challenge this statement by eliminating all extrinsic burdens and evaluating behavior within the interventional cardiology community via a hypothetical 'ideal world scenario' where financial and logistical constraints would not play a role and decisions about additional diagnostic assessment on top of coronary angiography would be 'just a matter of a mouse click'.

2. Methods

2.1. Survey

ISIS-2 utilized the same web-based platform as ISIS-1 [10]. It was continuously available and promoted between June and December 2019 through PCRonline.com, the official PCR website, with a potential outreach to 60.000 members of the interventional community worldwide. In its *first part* the survey queried the general characteristics of participants regarding their experience in interventional cardiology, as well as specific experience with invasive functional and imaging diagnostic tools. Its *second part* investigated best clinical practice for assessing CCS in the catheterization laboratory. Here five cases were shown with complete coronary angiograms, presenting exclusively focal stenoses of intermediate angiographic severity ($n = 12$). According to the operators, cases had lesions exclusively in range of 50 to 90% visually estimated diameter stenosis. Importantly, it was declared for each case that patients had stable angina with severity of Canadian Cardiovascular Society Class II despite optimal medical therapy, while non-invasive proof of myocardial ischemia was not available. Accordingly each stenosis qualified for invasive functional assessment by guideline recommendation (class I, level of evidence A) [8,9]. Participants were asked to: (1) localize all stenoses; (2) visually estimate percent diameter stenosis; and (3) determine significance either based on angiographic appearance or by asking for the most appropriate adjunctive diagnostic tool, including invasive functional tests or invasive imaging. Note, to avoid any decision bias, the survey offered all the diagnostic tools potentially available in the catheterization laboratory. Importantly participants were asked *not* to make their decisions based on their local practice *but* to make their decisions following optimal clinical practice, assuming "ideal world conditions" with neither financial restrictions nor limitations in equipment availability. The survey included the same background questions and five clinical cases, including their order, similar to its previous edition except that non-hyperemic pressure indices were added as a diagnostic option. The survey was only accessible to professionals. Coronary

Table 2
Lesion characteristics and decisions for the 5 cases and 12 stenoses.

Case	Vessel	Segment	Lesion severity		Evaluation*	Decision (%)			
			FFR	DS_{QCA} (%)	DS_{visual} (%)	Significant†	Non-sign.†	Functional	Imaging
#1	LAD	6	0.85	32	60 (60; 70)	27%	4%	63%	5%
	LCx	11	0.91	42	40 (30; 50)	3%	65%	30%	3%
	RCA	2	0.83	62	90 (80; 90)	90%	0%	10%	1%
#2	LAD	6	0.76	46	50 (40; 60)	9%	21%	64%	6%
	LCx		Free from stenosis						
	RCA		Free from stenosis						
#3	LAD	6	0.82	69	60 (50; 70)	24%	9%	60%	7%
	LCx		Free from stenosis						
	RCA	2	0.76	57	80 (70; 90)	82%	1%	12%	5%
#4	LAD	7	0.39	72	80 (70; 90)	62%	2%	19%	17%
	LCx	12a	0.62	71	90 (90; 95)	99%	0%	1%	0%
	RCA	2	0.87	53	80 (75; 85)	77%	2%	20%	2%
#5	LAD	6	0.64	46	60 (50; 70)	21%	7%	40%	32%
	LCx	11	0.79	32	50 (40; 70)	17%	18%	29%	36%
	RCA	3	0.89	38	50 (40; 60)	13%	43%	36%	8%

Lesion characteristics, including quantitatively measured %DS and the values of FFR and the participants' evaluation, including visually estimated %DS values and the rate of different decisions regarding all twelve individual stenoses in the five individual cases. (LAD – left anterior descending coronary artery, LCx – left circumflex coronary artery, RCA – right coronary artery, %DS – percent diameter stenosis).

* Evaluation refers to the visual severity provided by the survey responses, summarized as median (1st; 3rd quartiles).

† Significant and non-significant decisions refer to clinical treatment, not statistical significance.

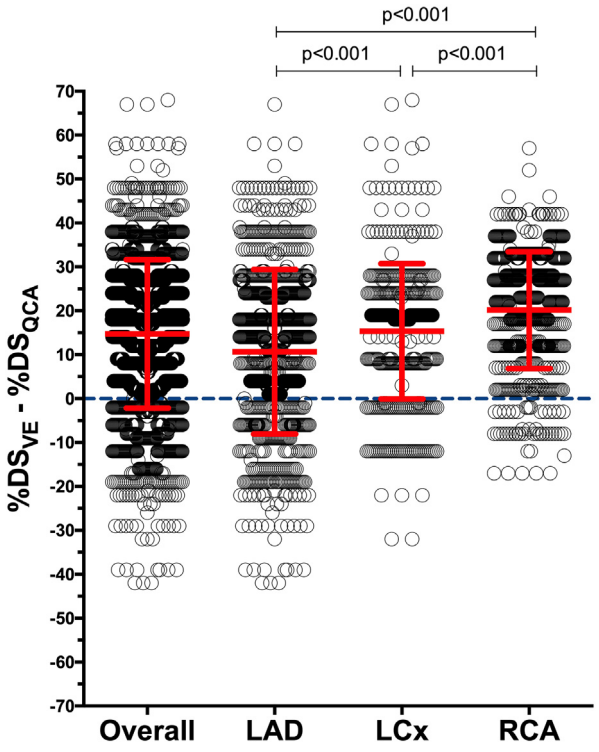

Fig. 1. Discrepancy between visual estimation and quantitatively assessed stenosis severity.

angiograms were anonymized and had been acquired in the context of trials. Participants were informed about the survey objectives and gave agreement by responding positively to the invitation. Primary endpoint was the rate of requesting adjunctive functional assessment. Secondary endpoint was the rate of concordance between angiography-based decisions and functional severity that was hidden to the survey participants. The project has been registered at clinicaltrials.gov (NCT04001452). Ethical approval and informed consenting was not applicable for the present project.

2.2. Statistical analysis

Descriptive statistics are reported as median [interquartile range, IQR], mean ± standard deviation, or counts (%), as appropriate. Variables were compared using ANOVA when continuous. Chi-squared compared categorical survey responses such as experience and PCI volume. Variances for differences between visual percent diameter stenosis (%DS) and quantitative coronary angiography (QCA)-derived %DS were compared using a Bartlett test for unequal variances. Multiple imputations were necessary for <1% of 6 demographic variables [age, annual PCI volume, experience in interventional cardiology, and duration of experience with fractional flow reserve (FFR) or non-hyperemic pressure ratios (NHPR), intravascular ultrasound (IVUS), and optical coherence tomography (OCT)] given missing survey responses. Univariate and multivariable regression models were used to predict treatment decisions (multinomial) or concordance with FFR/NHPR (logistic). To account for correlation among survey responses from the same participant, mixed logistic models used random effects among participants. The Cochran-Armitage test assessed the association between levels of experience and decision patterns. All applicable tests were two-tailed, and a probability value of $p < 0.05$ was considered statistically significant. Analysis was performed using Prism GraphPad 5.0 (GraphPad Software Inc., California, USA), SPSS 27.0 (IBM Inc., New York, USA), and R version 4.0.0 (R Foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1. Characteristics of participants

A total of 334 unique participants filled in the questionnaire. Their characteristics in terms of age and experience in interventional cardiology are detailed in Table 1. More detailed analysis can be found in the appendix. Table S1. In total 978 case assessments with 2059 lesion evaluations were obtained. Table 2. Unless stated otherwise, summary results regarding experience and decisions are presented on a per-lesion level.

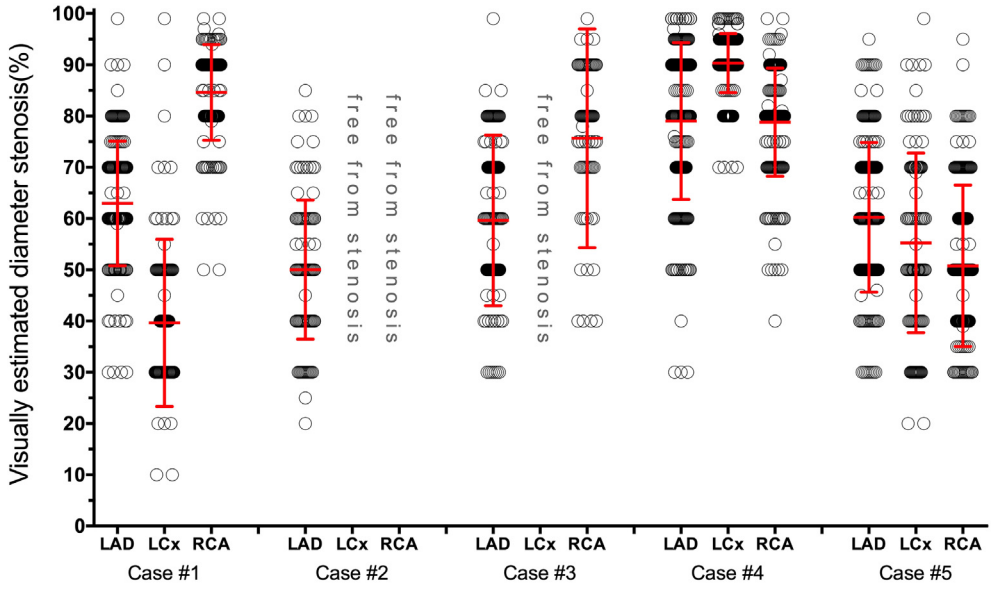

Fig. 2. Variance of visually assessed stenosis severity for the 5 cases with 12 stenoses.

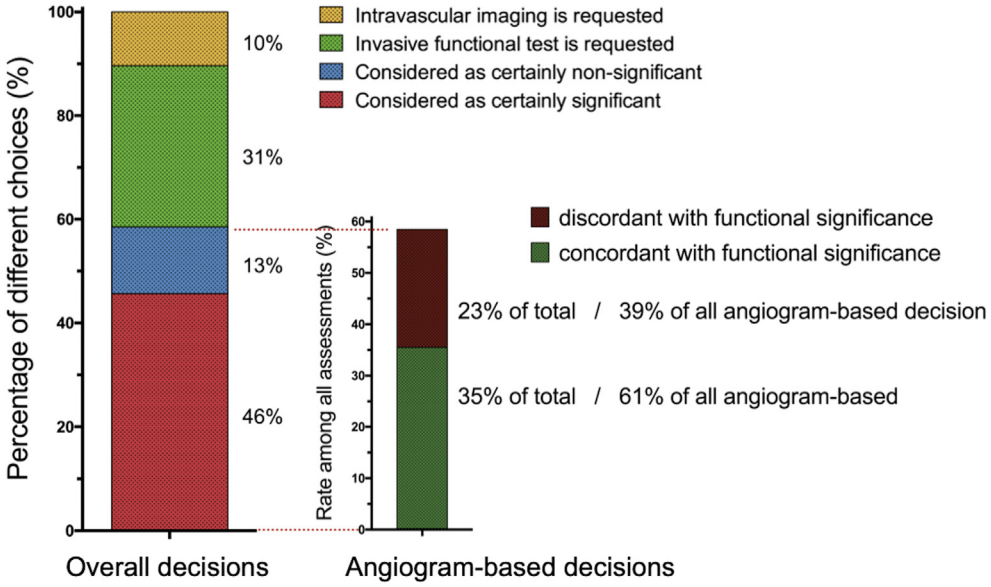

Fig. 3. Distribution of different decisions and the appropriateness of purely angiogram-based decisions.

3.2. Visually estimated diameter stenosis

The visually estimated %DS showed an absolute overestimation of +18% [IQR +4% to +27%] compared to the corresponding QCA-derived %DS values. The overestimation of stenosis severity, as compared to QCA-derived %DS was significantly more pronounced in the right coronary artery (+22% [+12% to +28%]) compared to the left circumflex (+19% [+8% to +24%]; $p < 0.001$) and compared to the left anterior descending (+13% [−2% to +24%]; $p < 0.001$). Fig. 1. Variances differed significantly among vessels, being largest for the left anterior descending (SD of 19%), intermediate for the left circumflex (SD of 15%), and smallest for the right coronary artery (SD of 13%; $p < 0.001$ across groups and for every paired comparison). Fig. 2.

3.3. Decisions and requested diagnostic tools

Most decisions were taken based on visual estimation alone (59%), resulting in discordance with undisclosed FFR in 39% (23% of all lesion assessments). In the remaining cases, angiographic appearance was considered to be insufficient for a treatment decision and additional

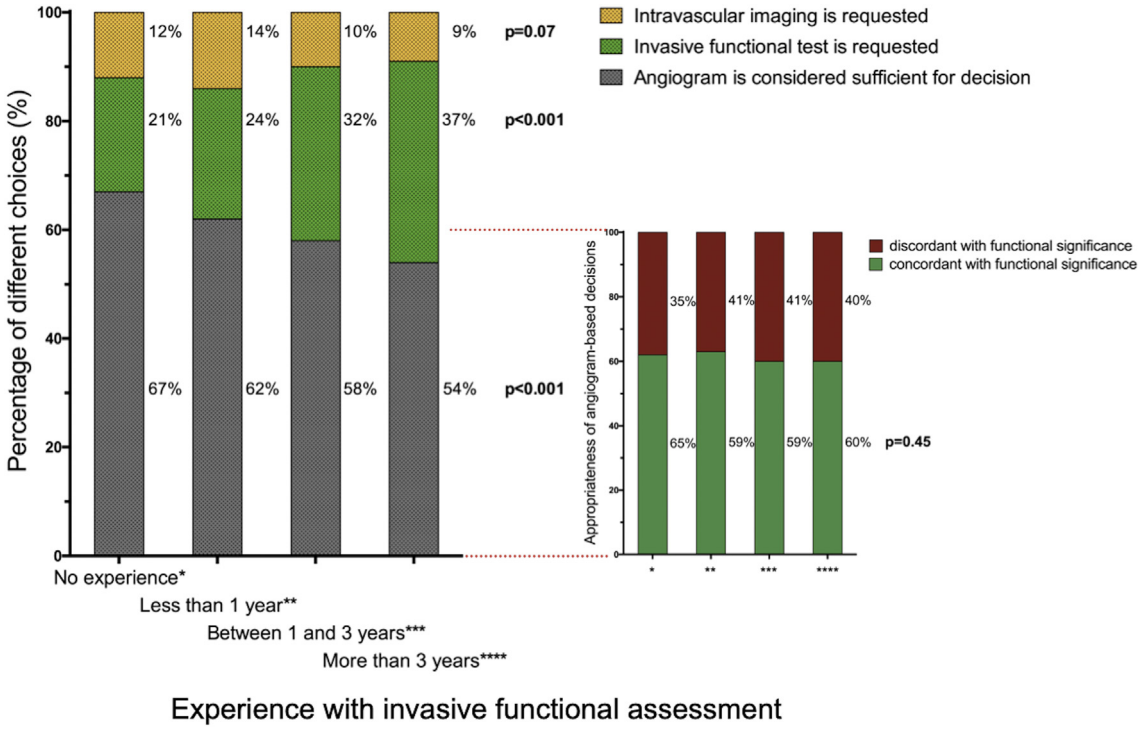

Fig. 4. Relation between experience with invasive functional assessment and different decision patterns in overall (Panel A) and in the subgroup of solely angiogram-based decisions (Panel B).

Table 3
Interaction between decision patterns and participant characteristics.

Level	Level of experience*	Age†	Experience	PCI volume	IVUS	FFR/NHPR	OCT
Concordant decisions, as % of total angiogram-based decisions							
	#1	61%	61%	60%	65%	62%	61%
	#2	59%	62%	64%	59%	63%	61%
	#3	61%	59%	58%	59%	60%	NA
	#4	61%	61%	62%	60%	60%	
Test for trend; *p* value		0.88	0.95	0.86	0.16	0.45	0.96
Concordant decisions, as % of total decisions							
	#1	37%	36%	36%	45%	42%	38%
	#2	34%	36%	36%	33%	39%	33%
	#3	34%	37%	32%	34%	35%	NA
	#4	37%	34%	37%	32%	32%	
Test for trend; p value		0.96	0.51	0.87	<0.001	<0.001	0.025
Discordant decisions, as % of total decisions							
	#1	23%	23%	24%	24%	25%	25%
	#2	24%	22%	21%	24%	23%	21%
	#3	22%	25%	24%	24%	23%	NA
	#4	23%	22%	23%	21%	22%	
Test for trend; p value		0.79	0.69	0.90	0.35	0.15	0.09
Requesting functional test, as % of total decisions							
	#1	32%	31%	28%	22%	21%	26%
	#2	32%	30%	32%	31%	23%	35%
	#3	31%	28%	36%	32%	32%	NA
	#4	30%	34%	29%	37%	37%	
Test for trend; p value		0.39	0.29	0.78	<0.001	<0.001	<0.001
Requesting imaging modality, as % of total decisions							
	#1	7%	10%	11%	10%	12%	11%
	#2	11%	12%	11%	12%	14%	10%
	#3	14%	9%	9%	10%	10%	NA
	#4	10%	11%	11%	10%	9%	NA
Test for trend; p value		0.08	0.98	0.62	0.58	0.07	0.65

* Levels #1 to #4 categorize overall experience ('Less, than 2 years'/'Between 2 and 5 years'/'Between 5 and 10 years'/'More, than 10 years'); PCI volume ('Less, than 75 per year'/'Between 75 and 150 per year'/'Between 151 and 250 per year'/'More, than 250 per year'); experience with IVUS ('No experience'/'Less, than 1 year of experience'/'Between 1 and 3 years of experience'/'More, than 3 years of experience'); experience with invasive physiology ('No experience'/'Less, than 1 year of experience'/'Between 1 and 3 years of experience'/'More, than 3 years of experience'); and experience with OCT ('No experience'/'Any experience'), respectively; †Grouped according to quartiles of participants' age.
Evaluation of the interaction between various decision patterns and characteristics of Participants. (FFR – fractional flow reserve, IVUS – intravascular ultrasound, NHPR – non-hyperemic pressure ratios, OCT – optical coherence tomography, PCI – percutaneous coronary intervention, QCA – quantitative coronary angiography).

diagnostic tools were requested: predominantly invasive functional evaluation with FFR or NHPR (31%), with imaging modalities like QCA, IVUS, or OCT markedly less often (10%). Fig. 3. Age, overall experience in interventional cardiology, and yearly PCI volume did not significantly impact the decision pattern. However, the more participants were experienced with invasive functional tests, the more frequently their use was requested. Fig. 4, Table 3. Conversely, increasing experience with IVUS or OCT did not translate into significantly more requests for imaging. Because of the significant, direct correlations between characteristics of the participants and the above described multiple significant trends, a multivariable analysis using a multinomial model was performed, showing that no participant characteristic remained a significant predictor of the decision pattern after adjustment. Details are shown in Table S2.

3.4. Angiogram-based decisions

Among the purely angiography-based decisions the rate of concordance with the undisclosed FFR was 61% considering FFR of 0.80 as valid cut-off value. Considering all lesion evaluations and decisions as denominator, this metric indicates a discordance rate of 23%. As detailed in Table 3, no participant characteristic was significantly associated with concordance between angiography-based decisions and functional metrics. Importantly, when comparing participants categorized according to their experience with functional assessment, increasing experience was not associated with improved concordance of angiography-based decisions (60% vs. 59% vs. 59% vs. 60% concordance over the four groups; $p = 0.45$). However, as the rate of requesting invasive physiology increased (21% vs. 24% vs. 32% vs. 37%, respectively; $p < 0.001$), the rate of purely angiography-based decisions decreased significantly over the four groups (67% vs. 62% vs. 58% vs. 54%, respectively; $p < 0.001$) with no significant change in requests for invasive imaging (12% vs. 14% vs. 10% vs. 9%, respectively; $p = 0.07$). The decreasing rate of angiography-based decisions was due to a decreasing proportion of proposed revascularization (59% vs. 49% vs. 44% vs. 42%, respectively; $p = 0.006$) with no difference in the rate of selecting medical therapy (15% vs. 13% vs. 14% vs. 12%, respectively; $p = 0.33$). The multinomial model also showed that no participant characteristic remained a significant predictor of *concordant decisions* after adjusting for the others. Details shown in Tables S3 and S4.

3.5. Cut-off value for visual estimation

A total of 235 participants provided an angiographic cut-off value used when determining lesion significance, while only 14 (6%) stated that they do not apply any well-defined cut-off value for decisions. The provided values varied between 30% and 95% DS for visually assessed severity, with the vast majority at 70%DS (56.6%), followed by 75%DS (12.3%), 80%DS (10.9%), 50%DS (9.0%), and 90%DS (5.7%).

3.6. Evolution of attitude in the interventional community

ISIS-2 was essentially the exact repetition of a survey conducted in 2013, with the same cases in the same order and the same possible decision choices, except for adding NHPR as a diagnostic option. Comparing the decision patterns between the two periods demonstrated a significant reduction in angiography-based decisions (66% vs. 59%, respectively; $p < 0.001$). While there was no change in requests for invasive imaging modalities (9% vs 10%, respectively; $p = 0.09$), requests for invasive functional assessment increased significantly (25% vs 31%, respectively; $p < 0.001$). Importantly, the rate of FFR requests was unchanged between 2013 and 2019 (25% vs. 23%, respectively; $p = 0.09$), indicating that the increase in requests for invasive functional testing was driven by the introduction of NHPR (not available vs. 8%, respectively). Table 4.; Fig. 5.

4. Discussion

ISIS-2 was performed to understand how far guideline recommendations for diagnosis and treatment of intermediate stenosis in CCS have been adopted in the current thinking process of the interventional community. Results indicate that, although marked improvement can be seen over the last 7 years, despite the increasing body of evidence in support of physiological guidance, and the introduction of resting indexes, which facilitate physiological assessment, a relevant disconnect still persists between evidence-based recommendations and the attitude of interventional cardiologists.

Table 4
Evolution of attitude in the community between 2013 and 2019.

Decision	ISIS-1	ISIS-2	Adjusted odds ratio	Adjusted *p*-value
Angiogram-based	65.9%	58.5%	reference	N/A
Invasive physiology	25.2%	31.1%	1.26	0.002
Intracoronary imaging	8.9%	10.4%	1.13	0.26

Using a multinomial model, ISIS-2 respondents have requested invasive physiology significantly more often, while there was no difference in requesting intravascular imaging modality.

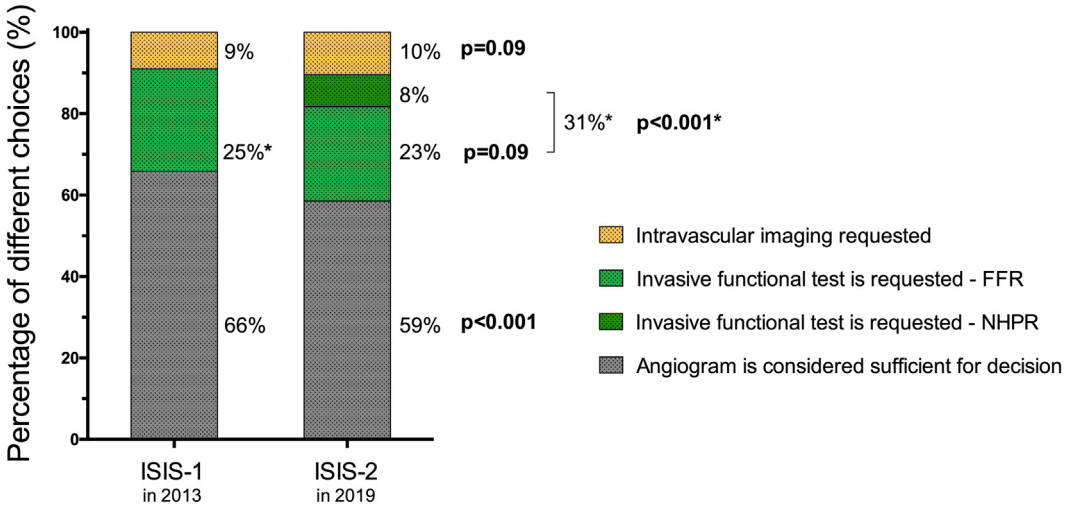

Fig. 5. Evolution of decision patterns between the two periods (ISIS-1 and ISIS2).

The present study found that even in an ideal world scenario, where financial constrains do not play a role and additional diagnostic steps do not have any logistic disadvantages (i.e. prolonged procedure, higher cost, or extra nursing or technician effort), interventional cardiologists still base their decisions purely on stenosis appearance by angiographic in almost 60% of all cases. Such decisions were concordant with the true, ischemia-based indications in less than two thirds of cases. Remainder represented predominantly overtreatment (19% of *all* cases), but also undertreatment (3% of *all* cases). Importantly, ISIS-2 has been conducted prior the publication of the ISCHEMIA [4] trial. Therefore its potential impact on changing decision-making processes cannot be assessed by present results. However, assuming an ISCHEMIA-like primarily conservative approach, patients are presented in the catheterization laboratory only when medical therapy has failed and therefore decisions about revascularization still need to be taken. While on the other hand, a large proportion of patients in real life practice do not even have an ISCHEMIA-like extensive non-invasive diagnostic work-up prior to coronary angiography [11].

Interestingly, with increasing experience operators selected revascularization less frequently purely based on the angiogram, while no tendency was observed in the rate of deferrals. This might suggest a deeper understanding that the indication for revascularization cannot be justified by angiography alone but requires detailed evaluation of the coronary artery disease first.

When an additional tool was requested for further assessment, it was predominantly an invasive functional test while the 'virtual intention' to use invasive imaging for this specific purpose remained a minority. Remarkably, while guidelines would recommend invasive function assessment for all lesions, the 334 interventional cardiologists provided in total 286 different diagnostic and treatment strategies for the same five patients. (Fig. 6 – Graphical abstract) Similarly, assessment of a single patient with intermediate stenoses in all three major coronary arteries ended with 44 different approaches, out of which only one, with 6.8% of all decisions, represents current guideline recommendation and an approach validated in a randomized controlled trial [5]. This demonstrated a marked disconnect between recommendations of the Practice Guidelines and the way operators think about treating or deferring revascularization in chronic coronary syndromes. While the rate of requesting FFR remained unchanged over the years, the increase in requests for invasive functional testing has to be attributed to the introduction of NHPR alone. This finding might suggest that colleagues who are recently adopting invasive functional testing are more prone to use NHPR. At the same time, prior FFR users are not likely to convert to NHPR.

The goal of coronary revascularization is to restore normal blood supply to viable myocardium and to eliminate the epicardial sources of ischemia. Even though animal studies have established a link between angiographic stenosis severity and functional relevance, [12] considering the multifactorial characteristic of the balance between myocardial blood supply and demand in a real-life population, it is illusory that a two-dimensional luminal silhouette of the macrovasculature is the proper diagnostic gatekeeper [13]. Accordingly, in CCS any benefit from revascularization can be expected if it is limited to ischemia-inducing stenoses, regardless of angiographic stenosis severity [3,14]. In addition, not even revascularization of patients with non-invasively proven myocardial ischemia is associated per se with improved long-term outcome [4], unless it is targeted exclusively to the individual ischemia-inducing lesions [5]. Thus when non-invasive proof of ischemia is missing or it cannot be directly linked to angiographic findings, the use of invasive functional assessment has recommendation Level I with evidence Level A in the most recent guidelines, which should have been applied to all five cases and all twelve stenoses in our survey. Still, only 26% of all stenosis were assessed by an invasive functional test, as would be indicated, while in 61% no functional test-based decision was taken at all. Note, while there were only 7% of participants who indicated the need for functional assessment for at least one stenosis in each assessed case, 20% did not select that option at all in any of the scenarios.

Results of present survey shed new light on the common beliefs behind barriers to evidence-based revascularization strategies: while common arguments regarding catheter laboratory logistics, cost and reimbursement might play a role in many practices, the human factor dominates. The driving force of 'willingness to use' becomes overruled by the belief that one can accurately assess angiographic coronary stenoses in a purely visual manner. Therefore, remaining humble in face of the gross discrepancies between angiographically-justified decisions and true functional needs regardless of experience and years of activity in the field of interventional cardiology and raising reservation and critical thinking about technical and personal capability of making angiogram-based assessments appears to be key in improving practices and resource allocation. Another opportunity for increased adoption of physiological guidance may result from the implementation of image-based computational techniques that can offer on-line functional assessment co-registered with coronary anatomy "by default" and without the need for hyperemia or dedicated pressure wires [15]. Making the functional information available to the heart team along with the anatomy "ex officio" is likely to release the main rate-limiting step to

adoption of physiological guidance, namely the "no need" perception by the interventional cardiologist.

4.1. Limitations

ISIS-2 shares the common limitations of all anonymous surveys. It was considered to offer a larger number of cases for scoring during the design of the survey. However, this option was eventually not considered, knowing that response rates decline quickly as the survey becomes more extensive and the time required for contribution increases. Missing data in the survey might have affected our results and we used multiple imputations as detailed above to examine the sensitivity of our findings to this criticism. Being aware of the results of ISIS-1 might have introduced a bias in decisions; however, a post-hoc query showed that only a minority of the current participants had joined the previous project.

5. Summary

ISIS-2 provides an update on how the interventional cardiology community thinks about invasive evaluation strategies in CCS, and its evolution over the last several years. Our findings confirm that even though there has been a significant increase in the rate of invasive functional assessment, there remains a disconnect between clinical decisions and current guideline recommendations, despite our virtual elimination of all 'non-human' factors. Solely 'eye-balling' is still the primer gatekeeper for most physicians, resulting in a worrisomely high rate of discordant decisions with respect to true functional importance. In our survey such behavior is associated with unnecessary stenting or inappropriate deferral in almost a quarter of lesions.

Author statement

GT, NJ, WW and EB contributed in Conceptualization; Methodology; Writing - original draft. BT was responsible for the Software. GT, NJ, AA and SF contributed in Data curation; Formal analysis; All co-authors were involved in Writing - review & editing submission.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2021.05.005.

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