Meta-analysis of resting indices for functional stenosis assessment

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Disclosure Information

To discuss applied coronary physiology projects, I have signed a mutual non-disclosure agreement with Volcano Corporation, a company that makes FFR and CFR wires.

However, I have *never received any money* from Volcano or any other commercial company.

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Volume 301 JULY 12, 1979 Number 2

NONOPERATIVE DILATATION OF CORONARY-ARTERY STENOSIS

Percutaneous Transluminal Coronary Angioplasty

ANDREAS R. GRÜNTZIG, M.D., ÅKE SENNING, M.D., AND WALTER E. SIEGENTHALER, M.D.

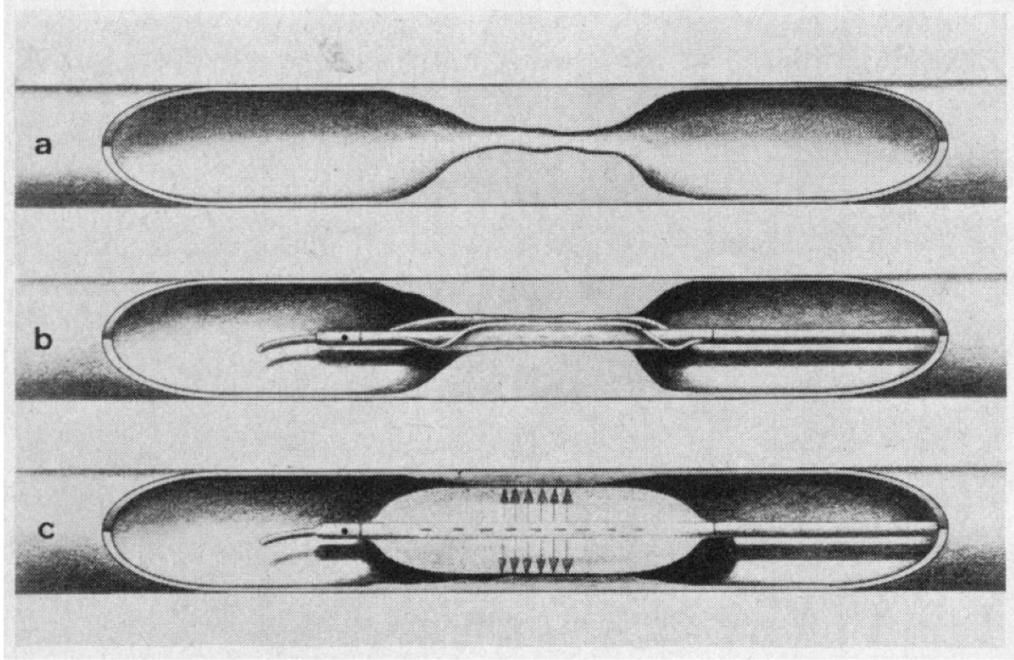
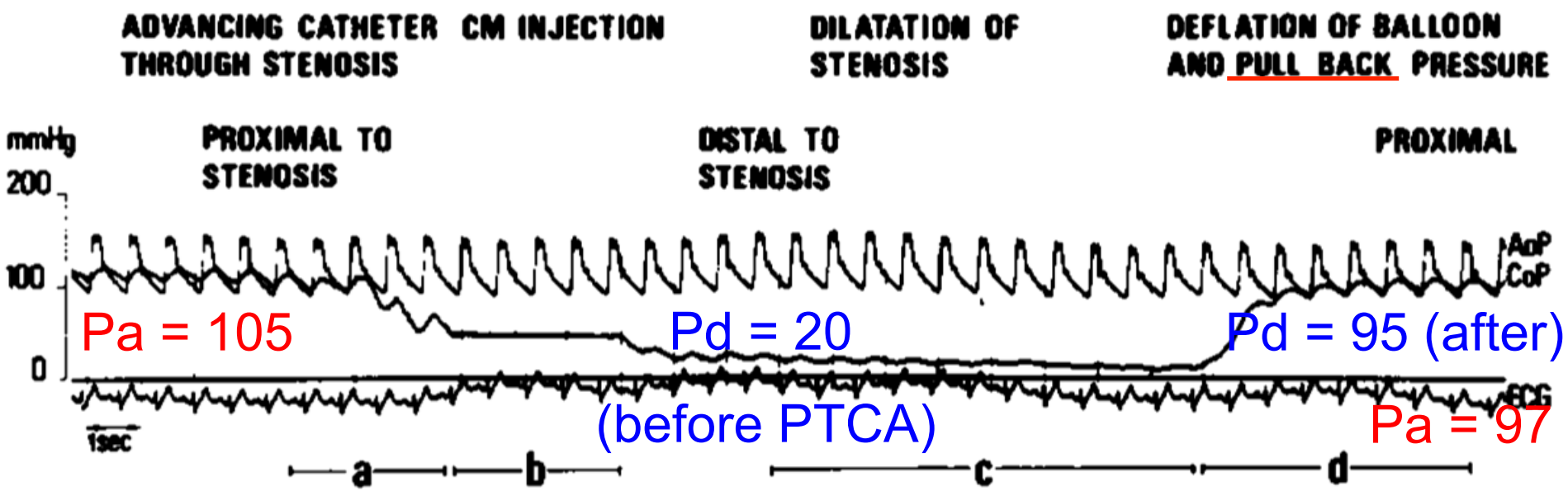


Figure 1. Percutaneous Transluminal Coronary Angioplasty and Catheters Used in the Procedure.



rest **Pd/Pa**	20/105 = **0.19**	95/97 = **0.98**
ΔP = Pd - Pa	105-20 = **85 mmHg**	97-95 = **2 mmHg**

"… the pressure gradient across the stenosis provides only an index of the severity of the lesion since *insertion of the dilation catheter … contributes to the stenosis*" (emphasis added)

1979 ≈35 years → 2013

- Absolute rest gradient (mmHg)
- Rest Pd/Pa (no units)
- Instantaneous wave-free ratio (iFR)
- Basal stenosis resistance

PRIMARY Results of ADVISE

ADenosine Vasodilation Independent Stenosis Evaluation

Dr Justin Davies MD, PhD

Imperial College London

on behalf of the ADVISE investigators

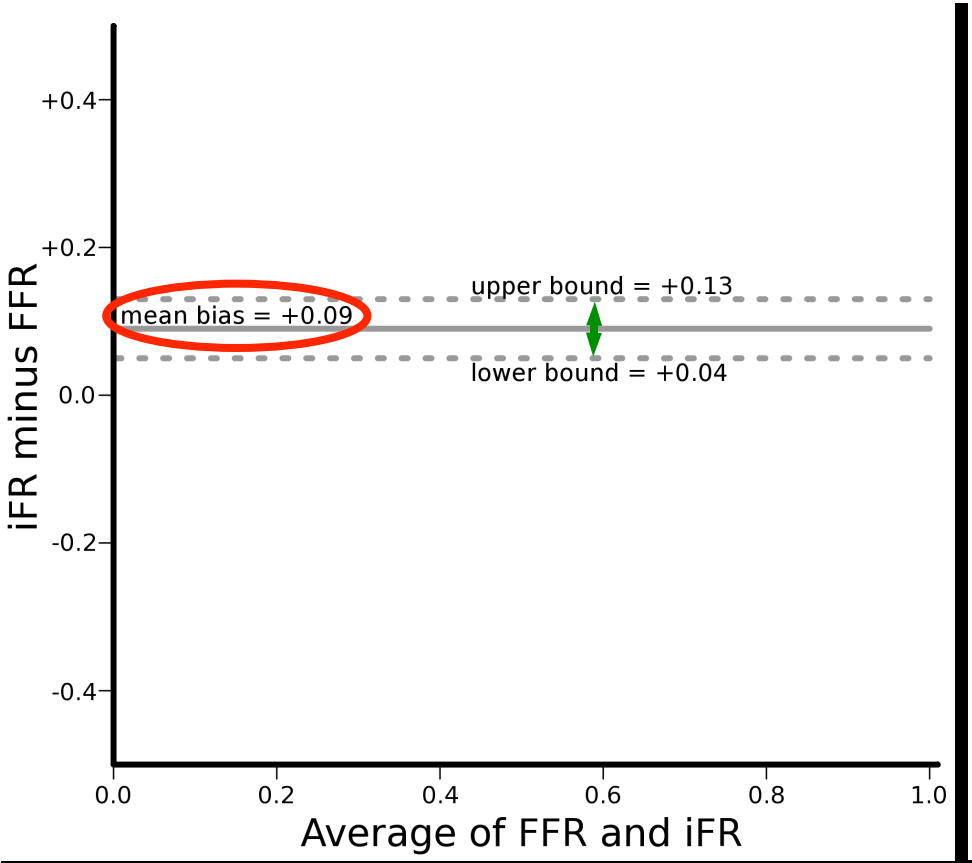
TCT2011

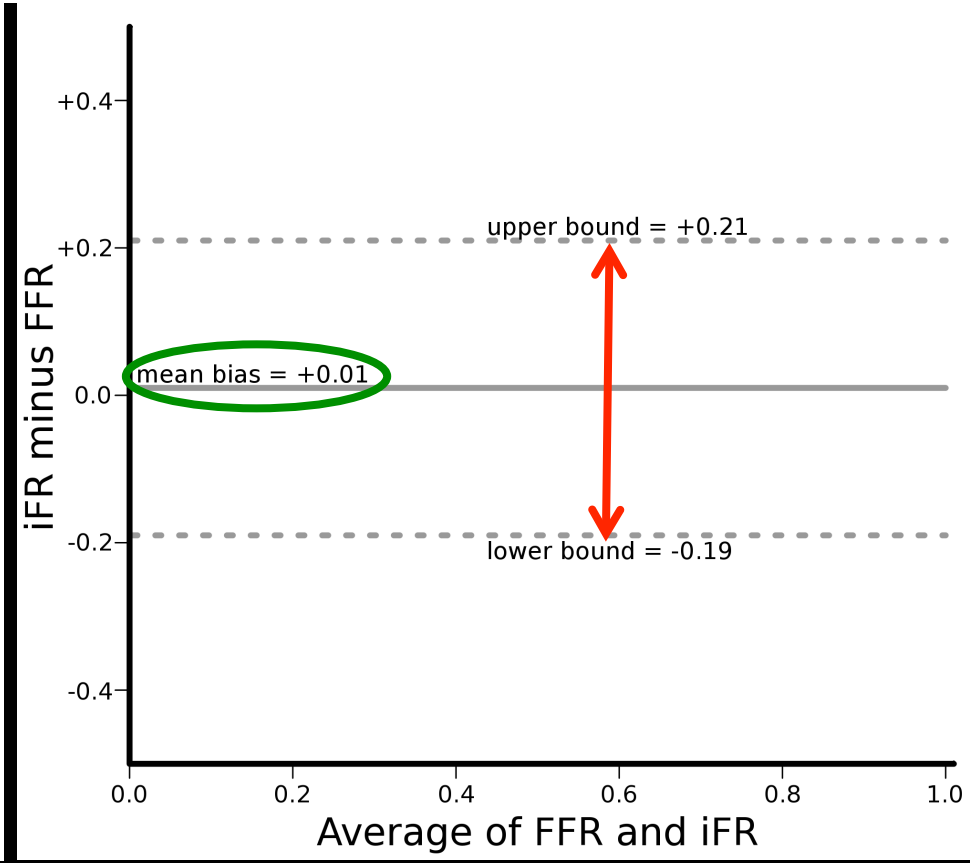
Hypothesis 2

Assess whether ***iFR*** was numerically similar to ***fractional flow reserve***.

Slides 1 and 23 of Davies J, TCT 2011, San Francisco, California (November 11, 2011).

iFR ≈? FFR





- ***POSITIVE BIAS***
- ***very precise***

- ***no bias***
- ***IMPRECISE***

conceptual Bland-Altman plots

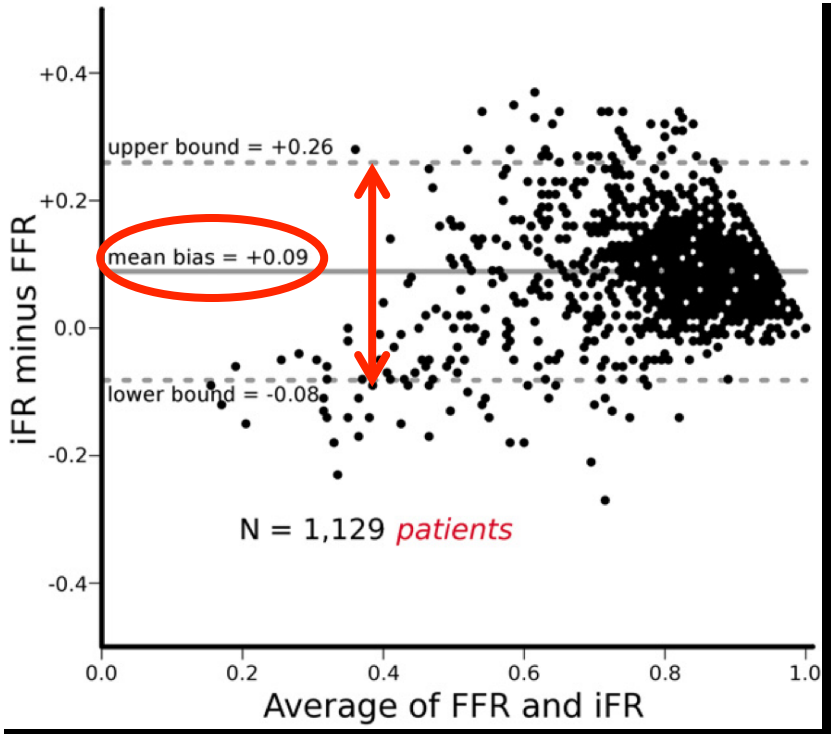
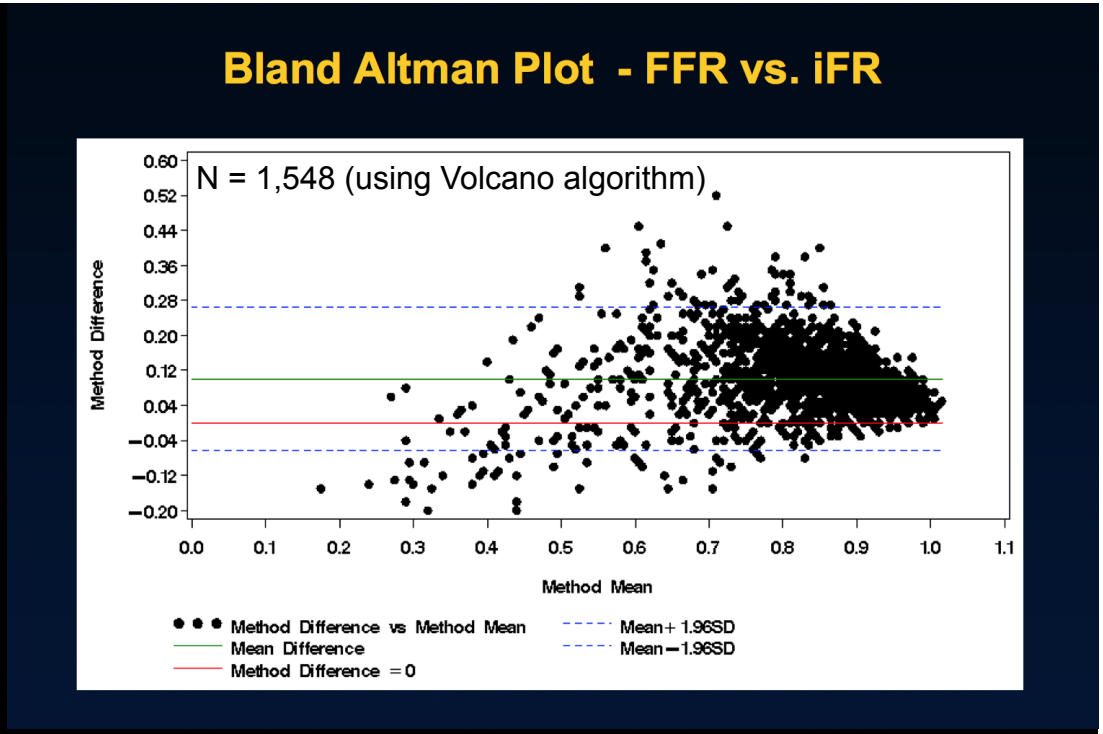


Figure 2 of Johnson NP, *JACC* 2013;61(13):1428-35.

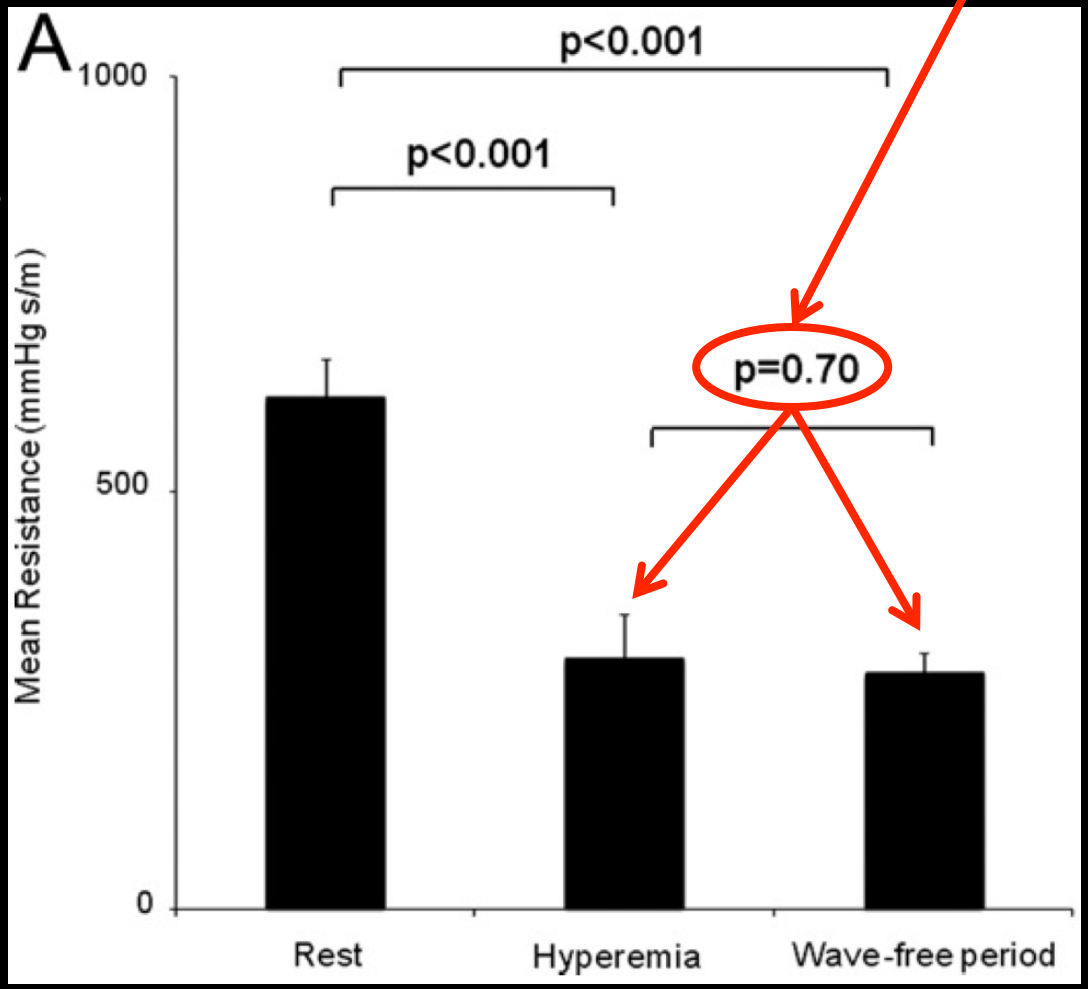


Slide 17 of Jeremias A, CPI 2013, Montréal, Québec (January 30, 2013).

- iFR ≠ FFR (*cannot* substitute values)
- Large imprecision (wide *scatter*) in iFR

In the first part of this study, we identified the existence of a diastolic interval in which intracoronary resistance at rest is equivalent to time-averaged resistance during FFR measurements.

N = 39 lesions



Text and Figure 5A of Sen S, *JACC* 2012;59(15):1392-402.

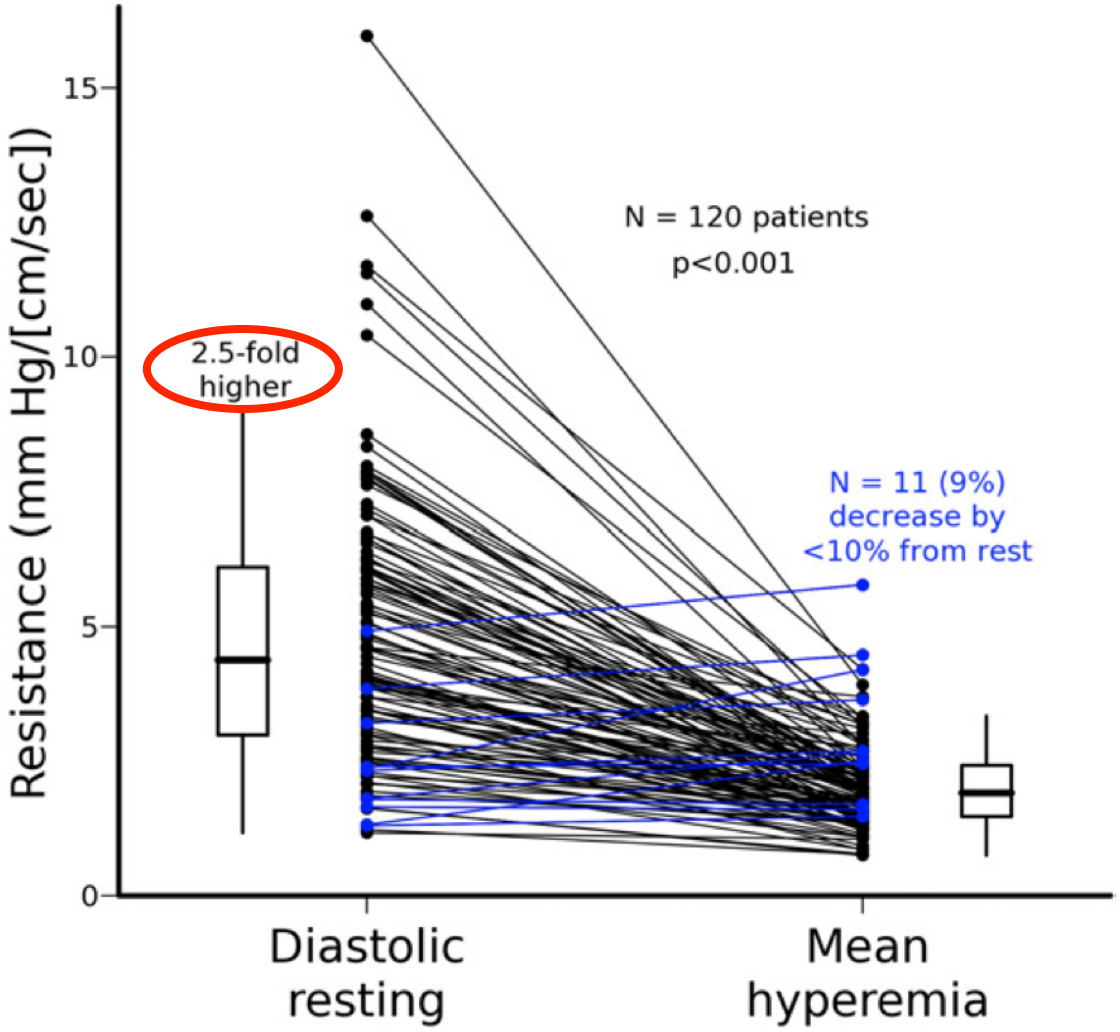


Figure 4 of Johnson NP, *JACC* 2013;61(13):1428-35.

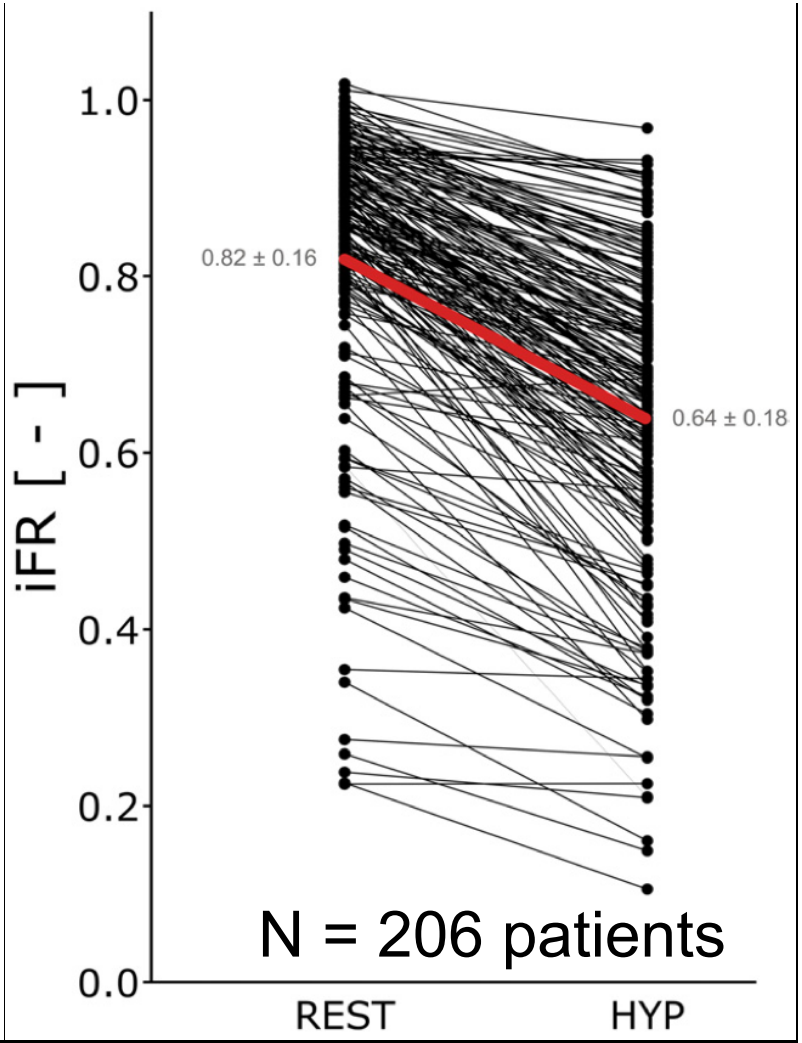


Figure 3 of Berry C, *JACC* 2013;61(13):1421-7.

Resistances *not* equal
(key *hypothesis* behind iFR)

Using *Volcano algorithm*

iFRa had significantly lower values than FFR and iFR (median iFRa 0.74 [0.58, 0.85] versus median FFR 0.84 [0.70, 0.89] and median iFR 0.93 [0.83, 0.98], $p < 0.001$ for both).

Text from Sen S, *JACC* 2013;61(13):1409-20.

iFR decreases with adenosine

- REST = 0.93
- HYP "iFRa" = 0.74
- Δ = 0.19 (CLARIFY)

Not Volcano algorithm

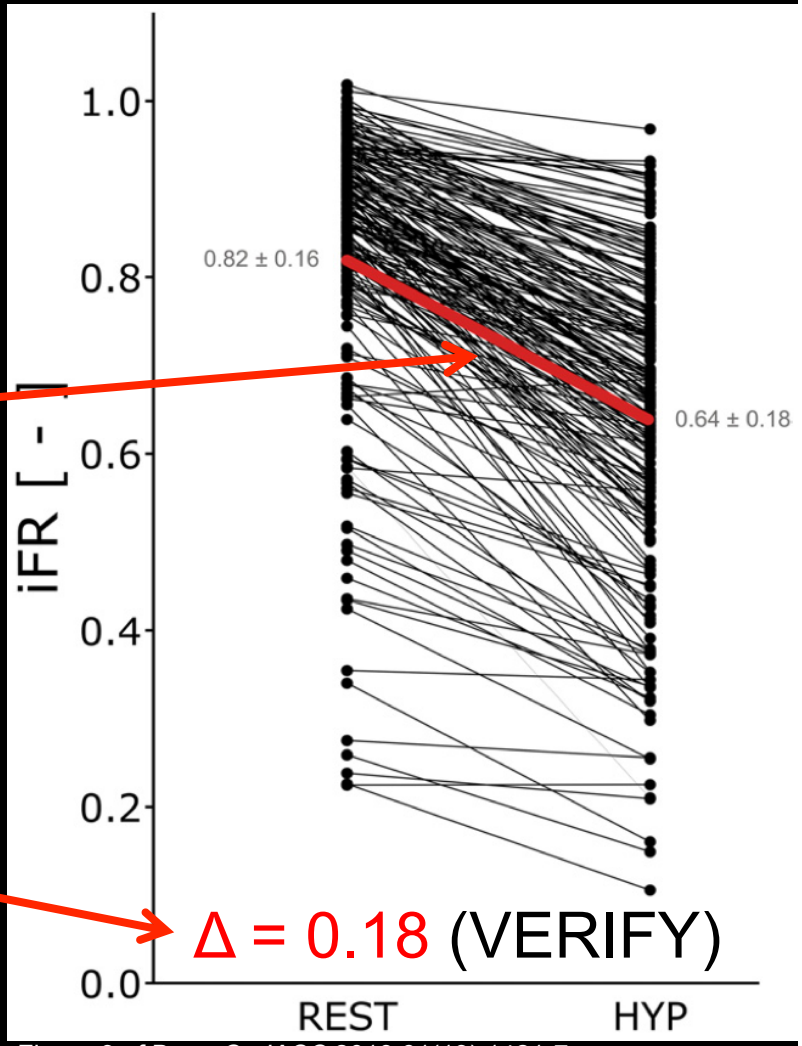
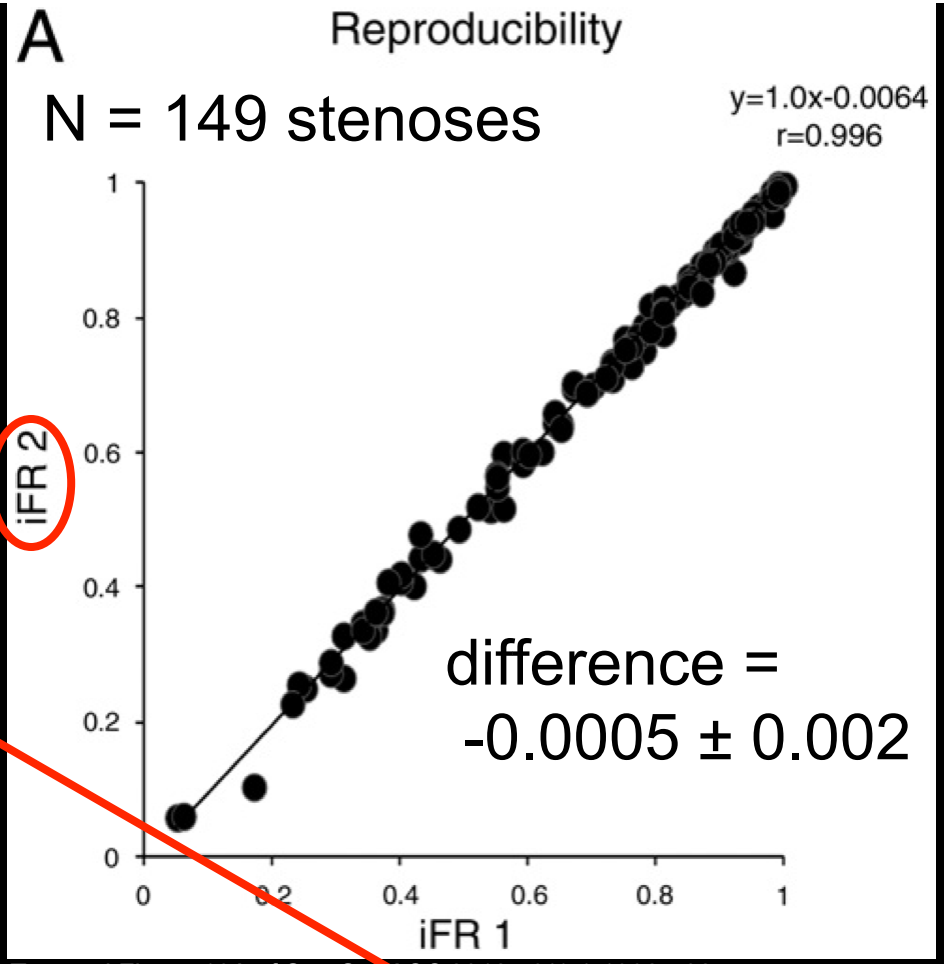


Figure 3 of Berry C, *JACC* 2013;61(13):1421-7.

Only data on iFR provided, not FFR



Text and Figure 10A of Sen S, *JACC* 2012;59(15):1392-402.

"Although the variability in FFR is small, that ***in the iFR is smaller***." (emphasis added)

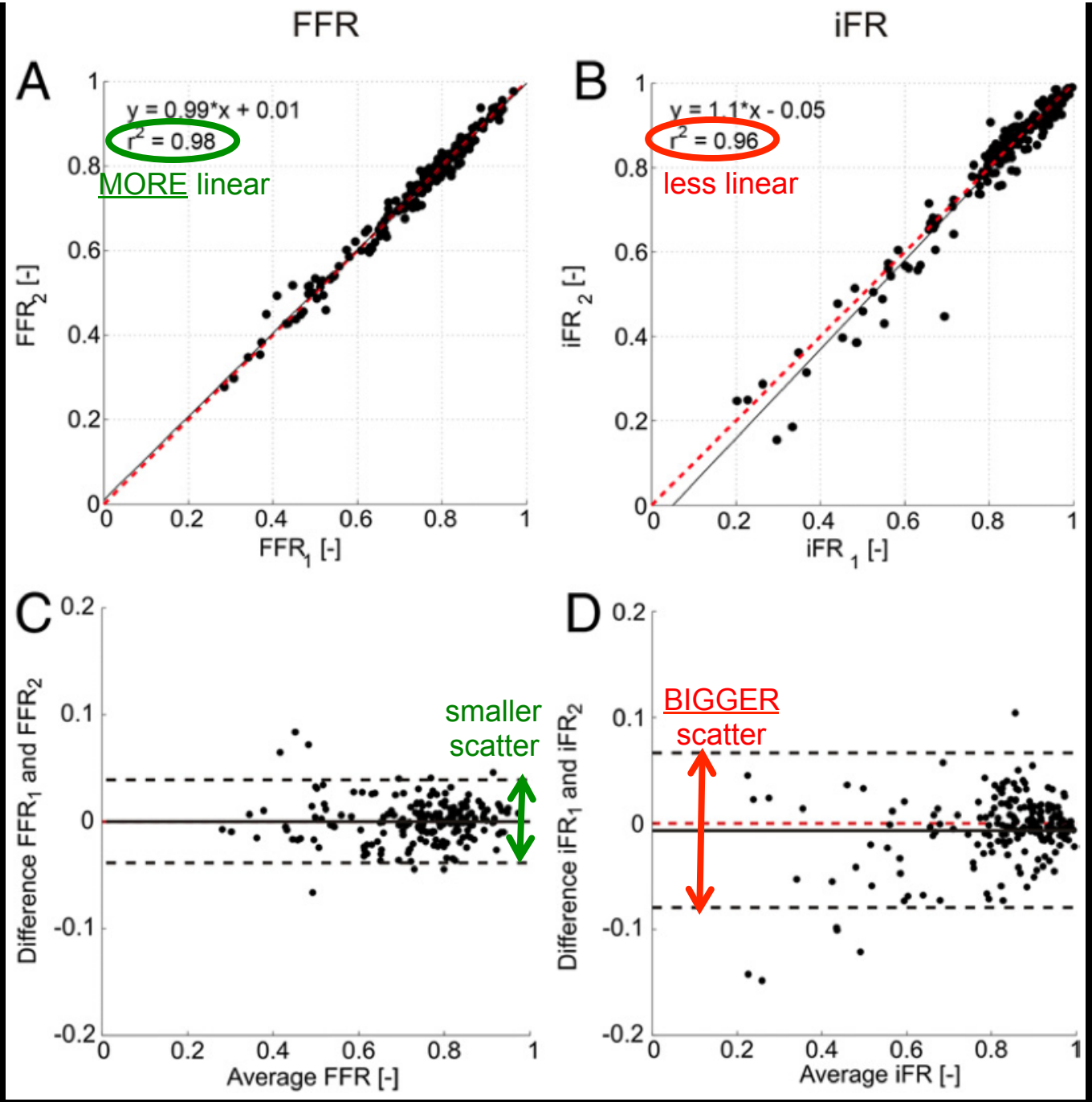


Figure 5 of Berry C, *JACC* 2013;61(13):1421-7.

ADVISE

- Only 1 measurement
- Compared first versus second half of single recording (*seconds apart*): "… performed by comparing the iFR from the *first half of the recording* with the value from the *second half of the recording*" (emphasis added to ADVISE quote)
- No FFR analysis (borrowed DEFER data)

VERIFY

- Two separate measurements
- 2 *minutes apart*
- Both iFR and FFR analysis
- Automated analysis by a core lab

Author	Citation	N	Bias	SD	Notes
Repeat measurements using adenosine					
Bech	Circulation 2001;103:2928	325	0.03	0.02	IC+IV (DEFER)
Berry	JACC 2013;6:1421	206	0.00	0.02	IV only (VERIFY)
Barbato	EHJ 2004;25:2034	20	0.00		IC only
De Bruyne	Circulation 1996;94:1842	15	0.01		IC only
Repeat measurements comparing adenosine to other drug					
van der Voort	CCD 1996;39:120	24	0.02	0.01	papaverine
Nair	JACC Interv 2011;4:1085	25	0.00	0.02	regadenoson
Arumugham	EuroIntervention 2013;8:1166	20	0.00	0.03	regadenoson

Literature on repeat FFR measurements

- standard deviation (SD) ±0.02
- 635 patients
- 7 papers from 1996 to 2013
- IC and/or IV adenosine, other drugs

iFR and hemodynamics

- "iFR was found to be independent of heart rate (range 46 to 120/min; r^2 = 0.016), systolic (r^2=0.001), and diastolic (r^2=0.005) pressure" (ADVISE)

- "relative error (iFR-FFR/FFR) for heart rate (p = 0.032) and pressure rate product (p = 0.032) indicated that iFR was susceptible to variations in heart rate and blood pressure during resting conditions" (VERIFY)

ADVISE quote from Sen S, *JACC* 2012;59(15):1392-402.
VERIFY quote from Berry C, *JACC* 2013;61(13):1421-7.

FFR and hemodynamics

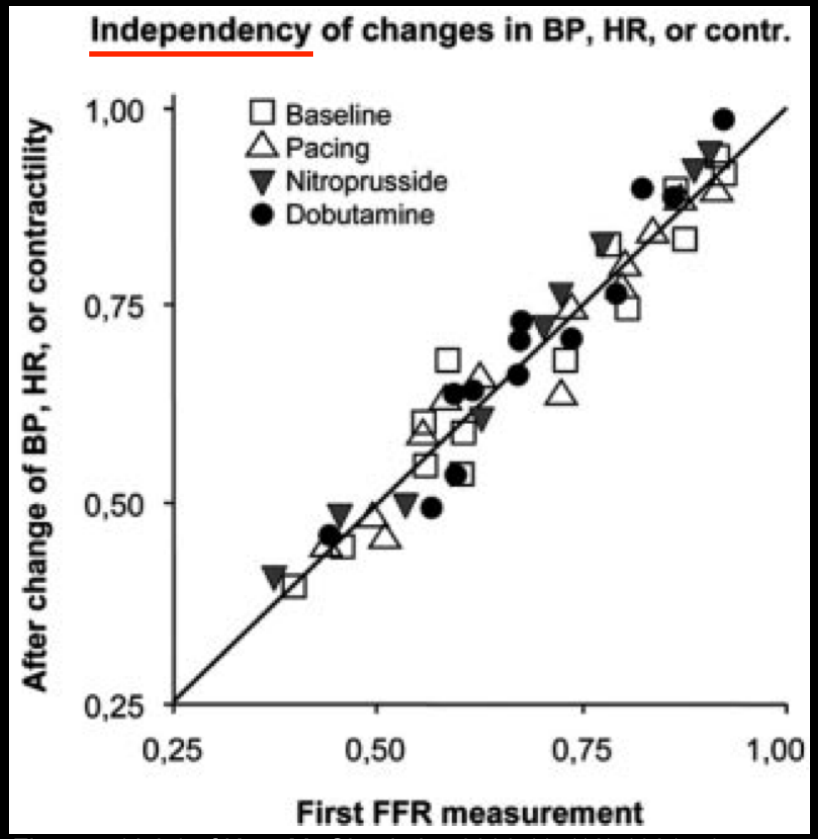


Figure 5 (right) of Kern M, *Circulation* 2006;114(12):1321-41.
Based on data from De Bruyne B, *Circulation* 1996;94(8):1842-9.

Hemodynamic dependence: iFR > FFR
Stability of repeated values: iFR < FFR

PRIMARY Results of ADVISE

ADenosine Vasodilation Independent Stenosis Evaluation

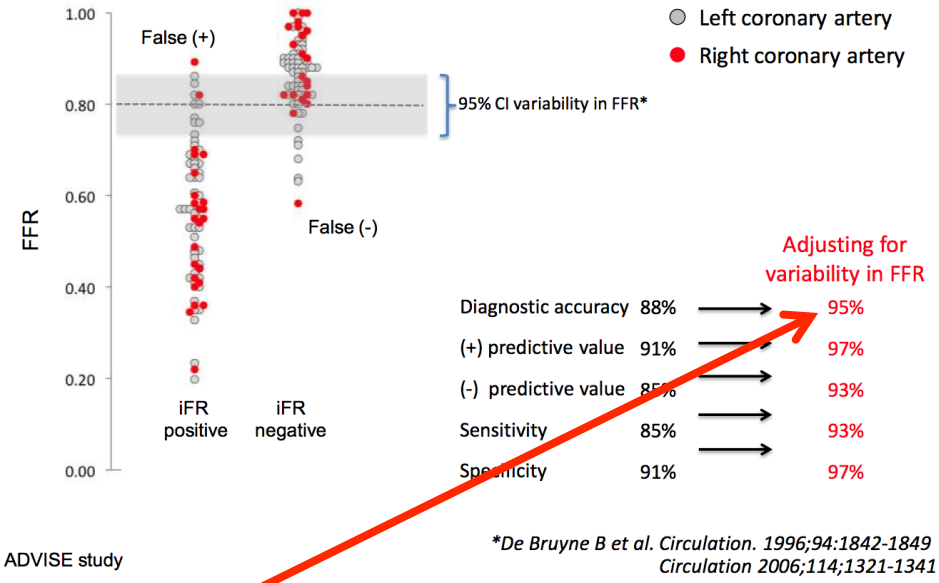
Dr Justin Davies MD, PhD

Imperial College London

on behalf of the ADVISE investigators

TCT2011

Assessment of diagnostic efficiency of iFR after ***adjustment for inherent variability*** in FFR



ADVISE study

*De Bruyne B et al. Circulation. 1996;94:1842-1849
Circulation 2006;114;1321-1341

Slides 1 and 31 of Davies J, TCT 2011, San Francisco, California (November 11, 2011).

"adjusted" accuracy ≈ 95%

Population from	Distribution of FFR values			Overall classification agreement between		iFR accuracy
	Mean FFR ±SD	FFR <0.7	FFR 0.7-0.9	Repeated FFR measurements	iFR and FFR (observed)	
ADVISE Registry	0.81±0.09	10%	71%	85%	80%	94% (80/85)
FFR reproducibility study (DEFER)	0.75±0.14	36%	46%	91%	86%	94% (86/91)
ADVISE study	0.72±0.2	41%	41%	93%	88%	94% (88/93)
FFR - PET study	0.63±0.19	73%	14%	100%	96%	96% (96/100)

SD: standard deviation of the mean

Table 2 from Petraco R, *EuroIntervention* 2012 Aug 25 [Epub ahead of print].

But these studies *never repeated FFR* measurements

And these studies *never measured iFR*

"Adjusts" by dividing *two hypothetical numbers* (neither is real)

When the intrinsic variability of FFR is taken into account, the overall level of classification agreement between iFR and FFR in this registry population is 94% (80% observed iFR-FFR agreement as a fraction of the 85% FFR repeatability agreement)

Text from Petraco R, *EuroIntervention* 2012 Aug 25 [Epub ahead of print].

but neglects the intrinsic variability of ***iFR***

validation cohort used *different cutoff* than derivation cohort (ADVISE)

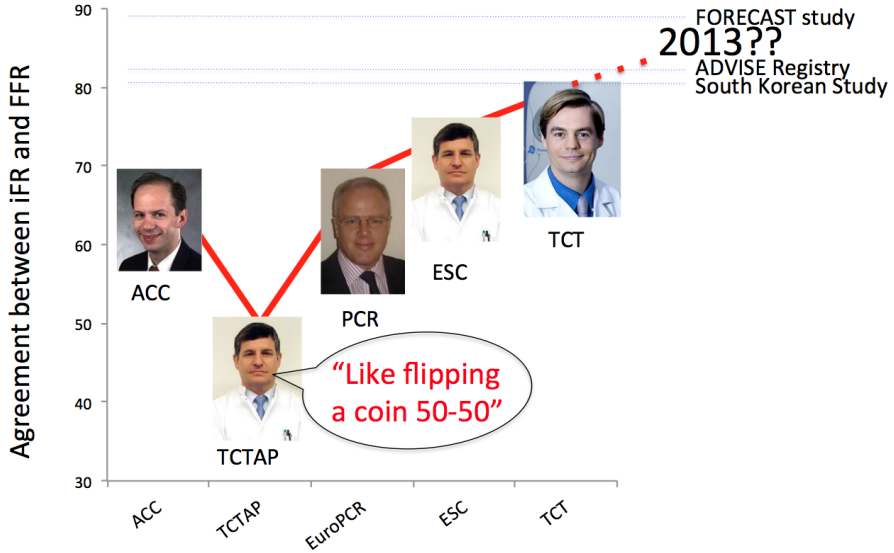
derived from *different* study in *separate* population performed *≈15 years* earlier

RESOLVE: The rebuttal

Dr Sayan Sen
Imperial College London
Hammersmith Hospital

Imperial College London

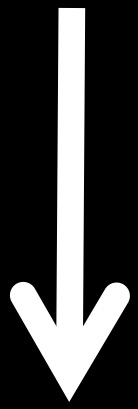
Fluctuating levels of agreement between ***iFR and FFR*** by VERIFY investigators in 2012



Slides 1 and 9 of Sen S, CPI 2013, Montréal, Québec (January 30, 2013).

Fluctuating accuracy?

iFR cutoff



accuracy

Author	Meeting or Citation	Date	N	iFR cutoff*
Davies	TCT	2011 November	157	none**
Sen	JACC 59:1392	2011 December		0.83
Park	EuroPCR	2012 May	238	0.89
Petraco	EuroIntervention^	2012 August	339	0.89
Jeremias	TCT	2012 October	1,548	0.90
Indolfi	TCT	2012 October	71	0.93
Johnson	JACC 61:1428	2013 February	1,129	0.89
Sen	JACC 61:1409	2013 April	51	0.86

* = all cutoffs used Volcano iFR algorithm *except* Indolfi and Johnson
** = stated iFR "numerically similar" to FFR
^ = posted to journal website on 2012 Aug 25 [Epub ahead of print]

iFR cutoffs: ≈0.80, 0.83, 0.86, 0.89, 0.90, 0.93

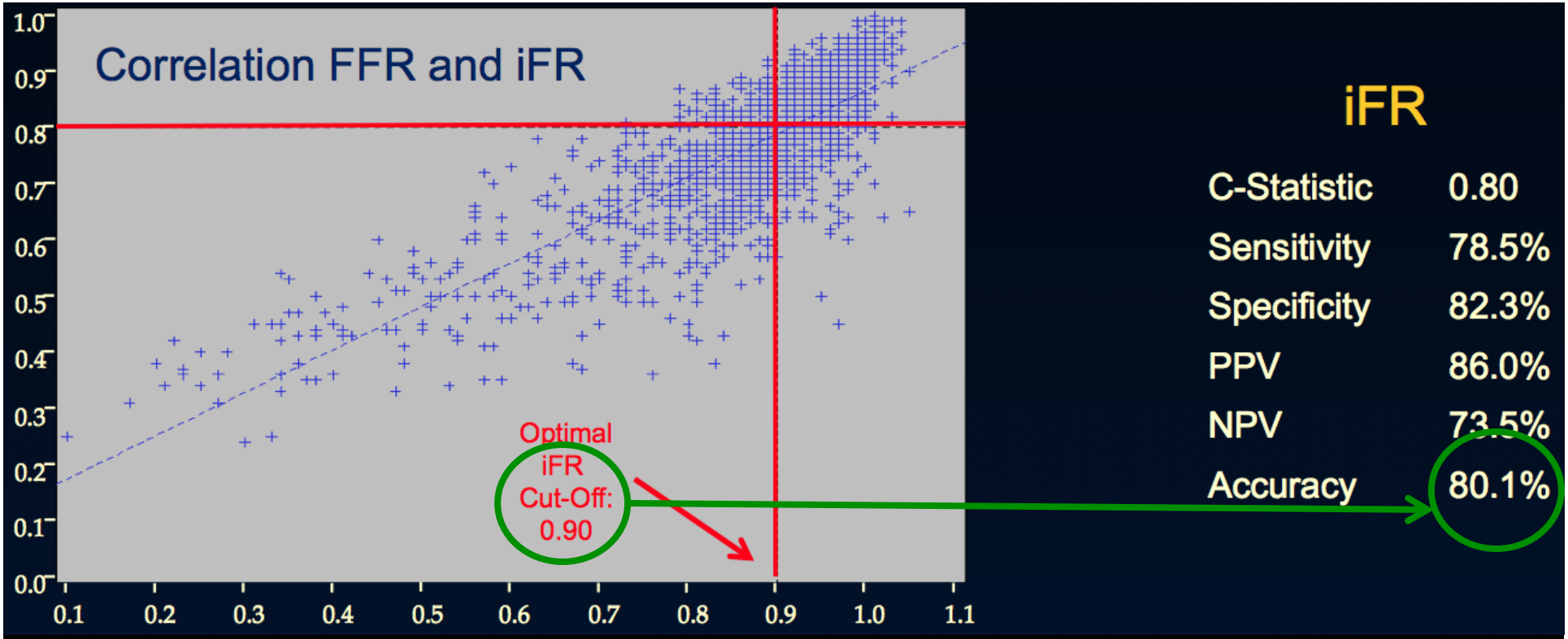
Table 2 Diagnostic Performance and Accuracy of iFR ≤0.80

Table 3 Diagnostic Performance and Accuracy of iFR ≤0.83

Data from Tables 2 and 3 (prospective cohort) of Berry C, *JACC* 2013;61(13):1421-7.

iFR cutoff	VERIFY accuracy (all lesions)	VERIFY accuracy (FFR=0.6-0.9 only)
0.80*	60%	51%
0.83^	68%	60%
0.89**	Not reported since this iFR cutoff had not yet been suggested***	

* = based on TCT "numerically similar", November 2011
^ = based on ADVISE cutoff in JACC, December 2011
** = suggested May 2012 at EuroPCR
*** = VERIFY study performed in January and February 2012



Slide 18 (top portion) of Jeremias A, CPI 2013, Montréal, Québec (January 30, 2013).

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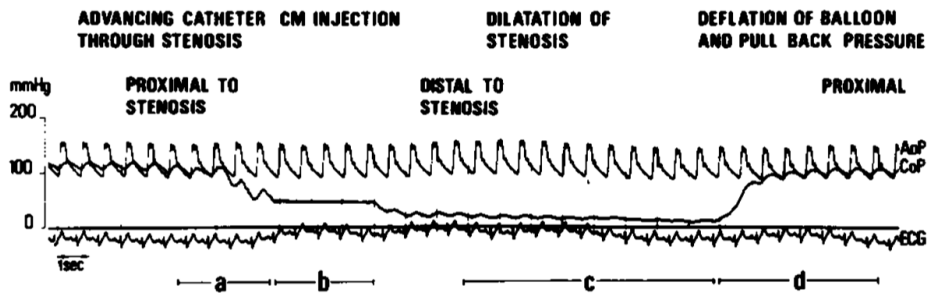

Figure 2. Original Tracing with Recording of Mean Pressure and Electrocardiogram during Dilatation, September 16, 1977, in a 39-Year-Old Man with Severe Angina and 85 Per Cent Stenosis of the Left Coronary Artery.

July 1979

↑ accuracy?

December 2011

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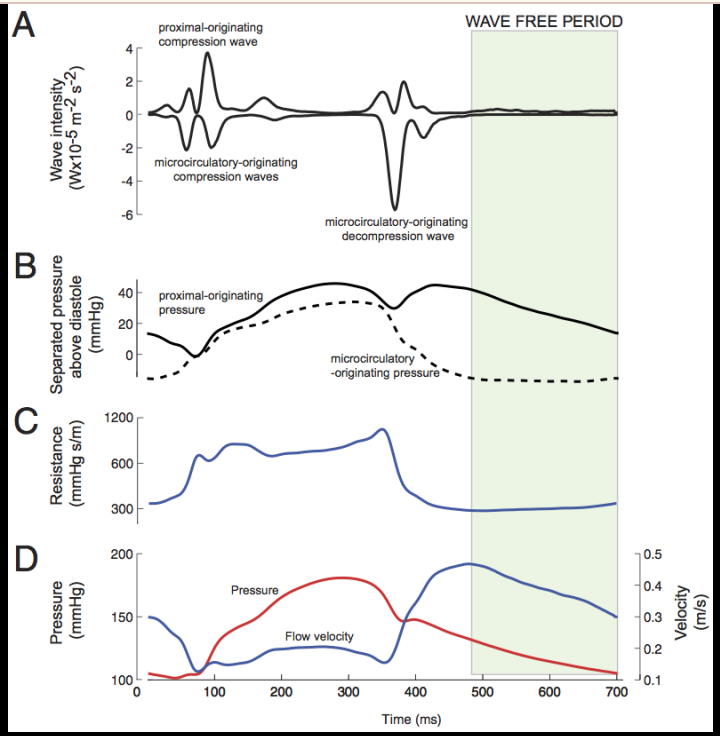
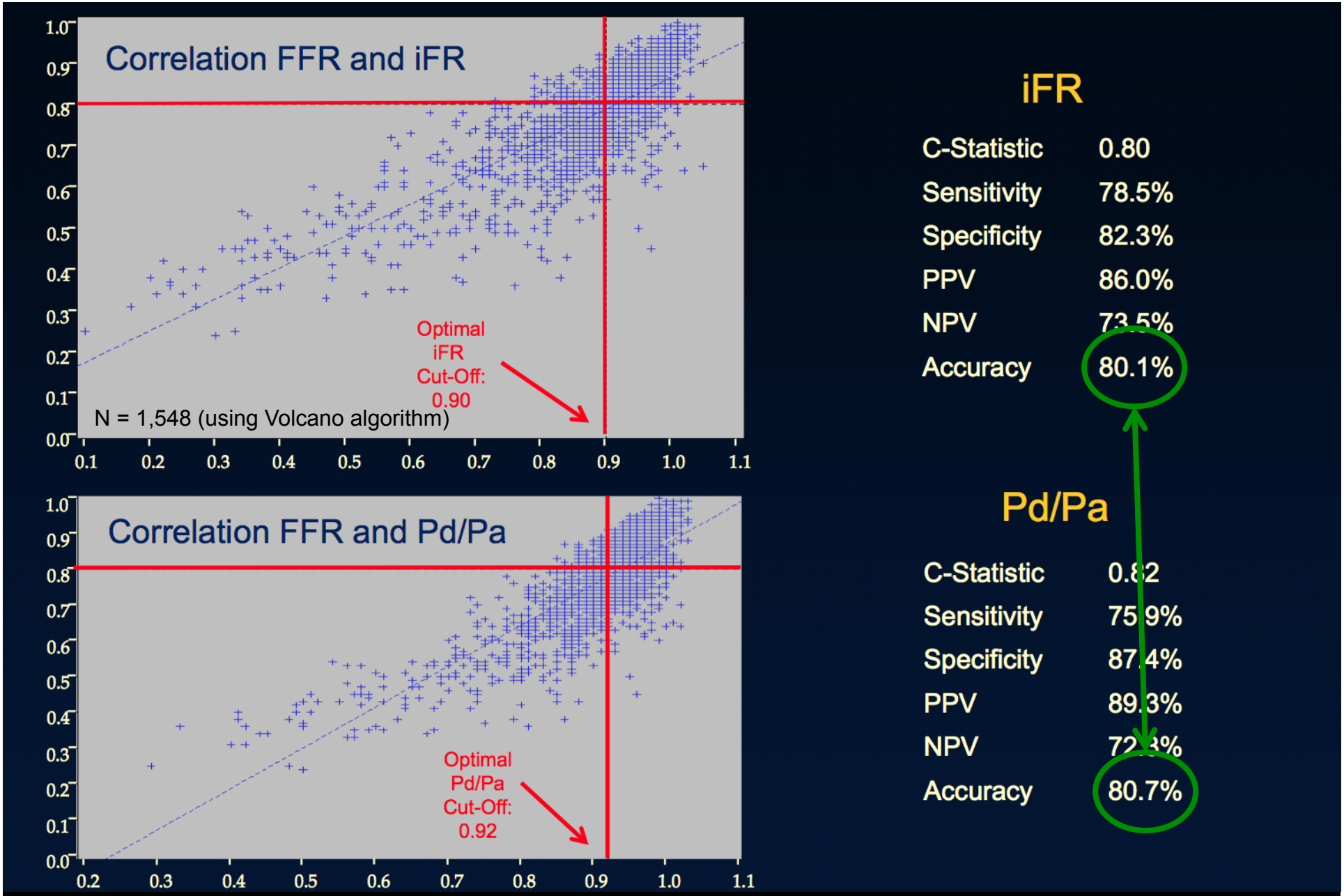
FOCUS ISSUE: TRANSCATHETER CARDIOVASCULAR THERAPEUTICS
Coronary Disease

Development and Validation of a New Adenosine-Independent Index of Stenosis Severity From Coronary Wave–Intensity Analysis

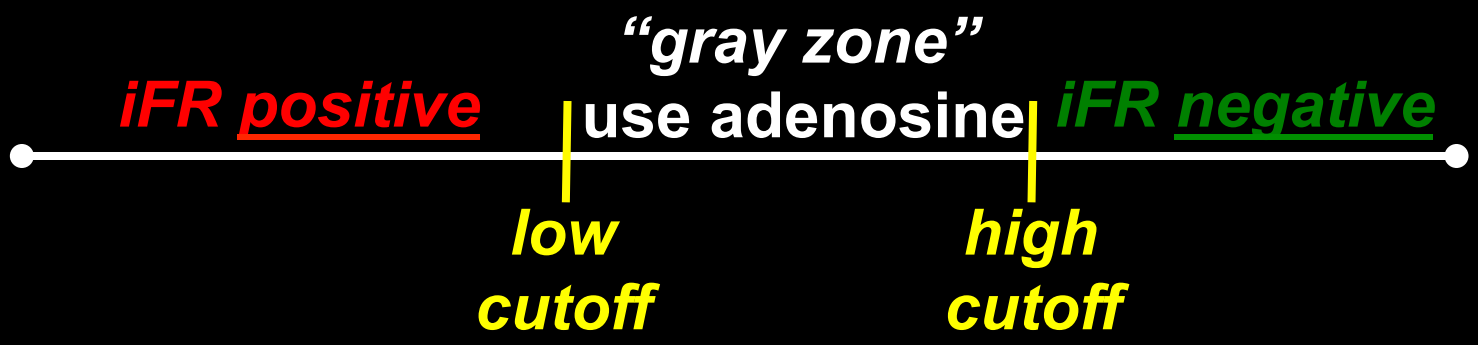
Results of the ADVISE (ADenosine Vasodilator Independent Stenosis Evaluation) Study

Sayan Sen, MBBS,* Javier Escaned, MD, PHD,† Iqbal S. Malik, MBBS, PHD,‡
Ghada W. Mikhail, MBBS, MD,‡ Rodney A. Foale, MD,* Rafael Mila, MD,† Jason Tarkin, MBBS,*
Ricardo Petraco, MD,* Christopher Broyd, MBBS,* Richard Jabbour, MBBS,*
Amarjit Sethi, MBBS, PHD,‡† Christopher S. Baker, MBBS, PHD,‡ Micheal Bellamy, MBBS, MD,‡
Mahmud Al-Bustami, MD,‡ David Hackett, MD,‡ Masood Khan, MB, BCHIR, MA,‡
David Lefroy, MB, BCHIR, MA,‡ Kim H. Parker, PHD,§ Alun D. Hughes, MBBS, PHD,*
Darrel P. Francis, MB, BCHIR, MA, MD,* Carlo Di Mario, MD, PHD,‖
Jamil Mayet, MBCHB, MD, MBA,* Justin E. Davies, MBBS, PHD*
London, United Kingdom; and Madrid, Spain



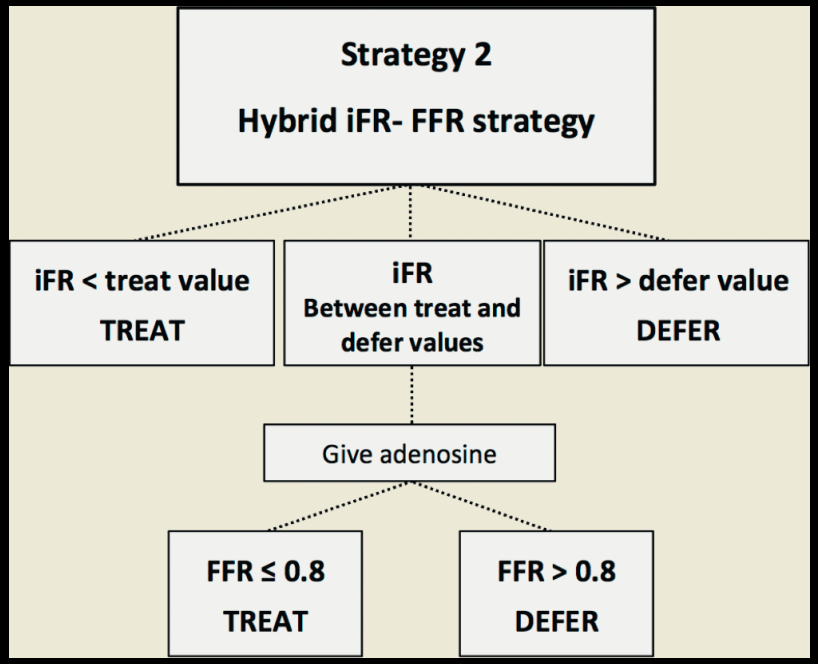


Slide 18 (entire) of Jeremias A, CPI 2013, Montréal, Québec (January 30, 2013).



Hybrid iFR-FFR decision-making strategy: implications for enhancing universal adoption of physiology-guided coronary revascularisation

Title and Figure 1 (right-hand side) of Petraco R, *EuroIntervention* 2013;8(10):1157-65.



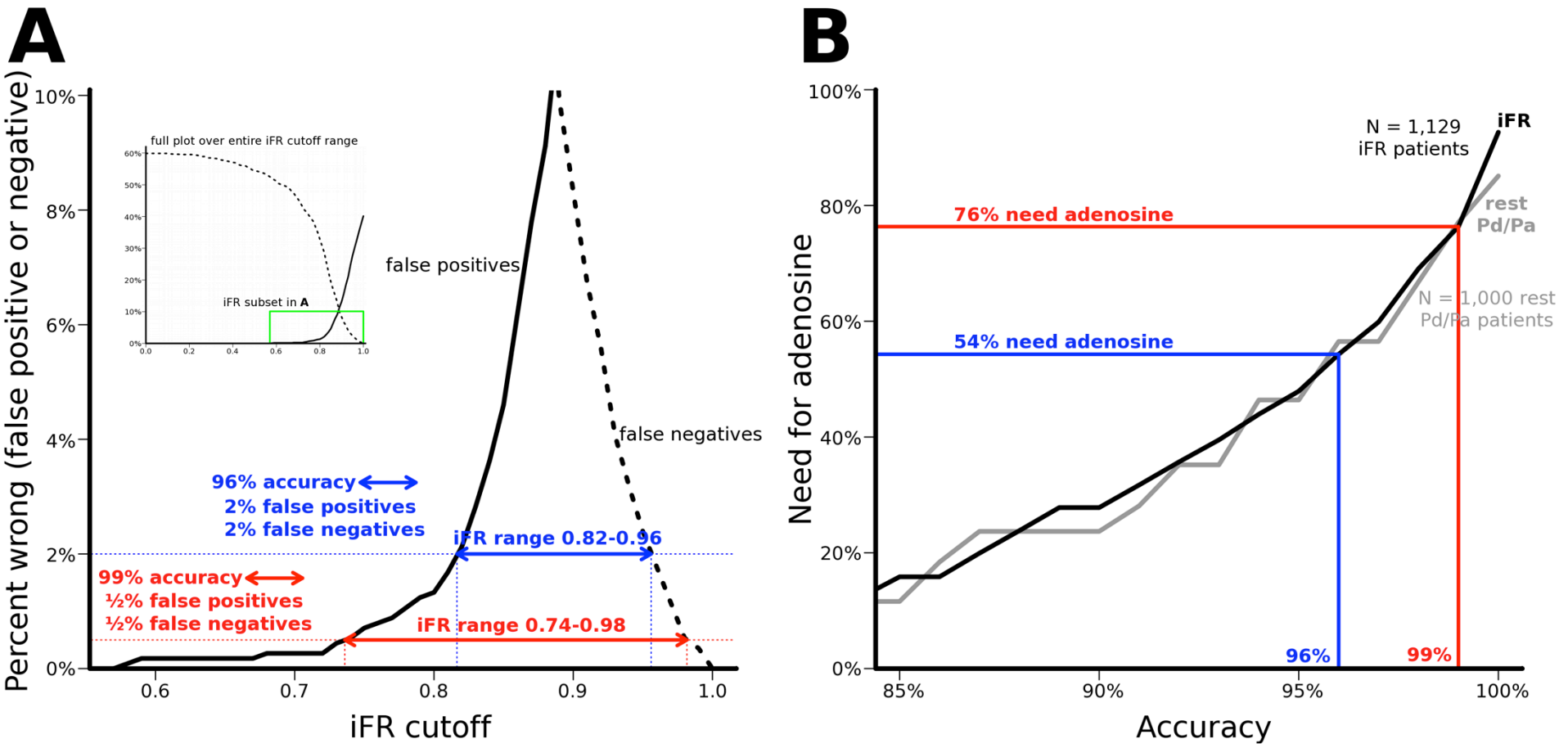
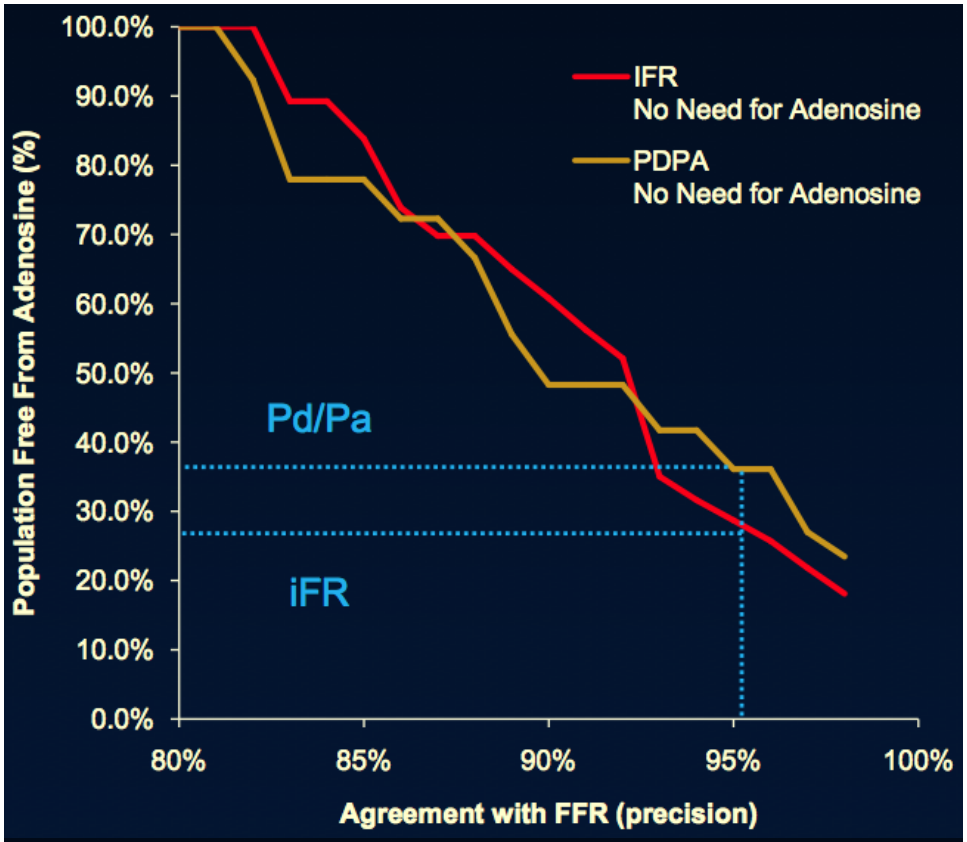


Figure 3 (entire) of Johnson NP, *JACC* 2013;61(13):1428-35.

Slide 24 (right) of Jeremias A, CPI 2013, Montréal, Québec (January 30, 2013).



Population Free From Adenosine

RESOLVE

B

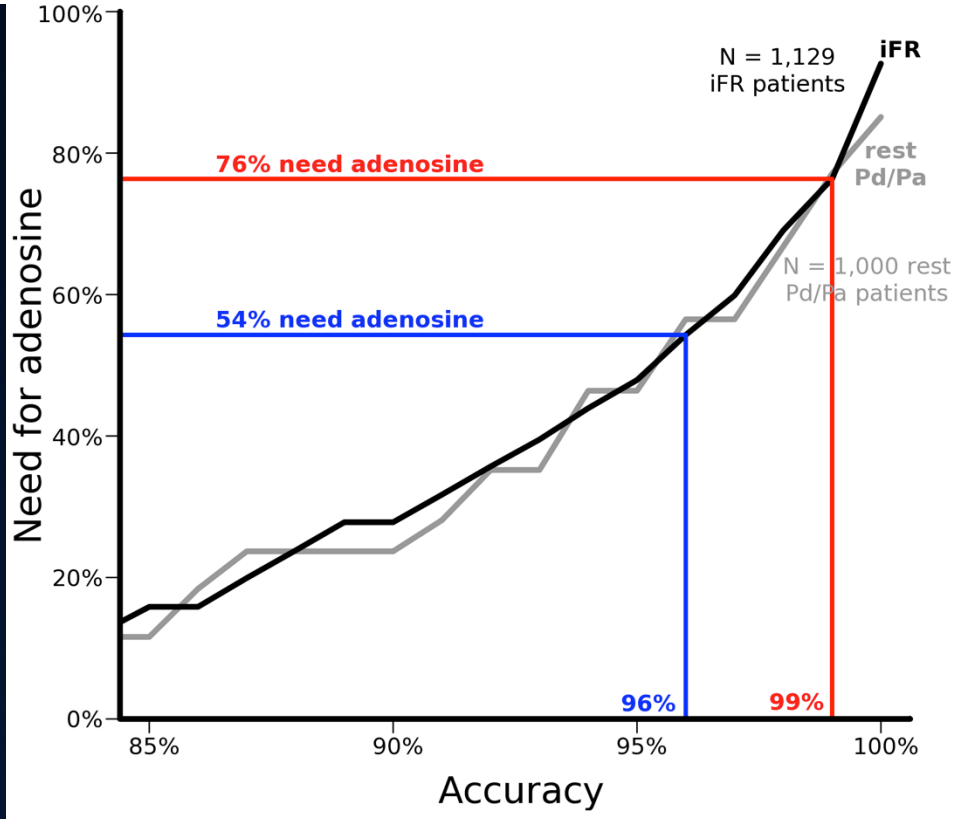
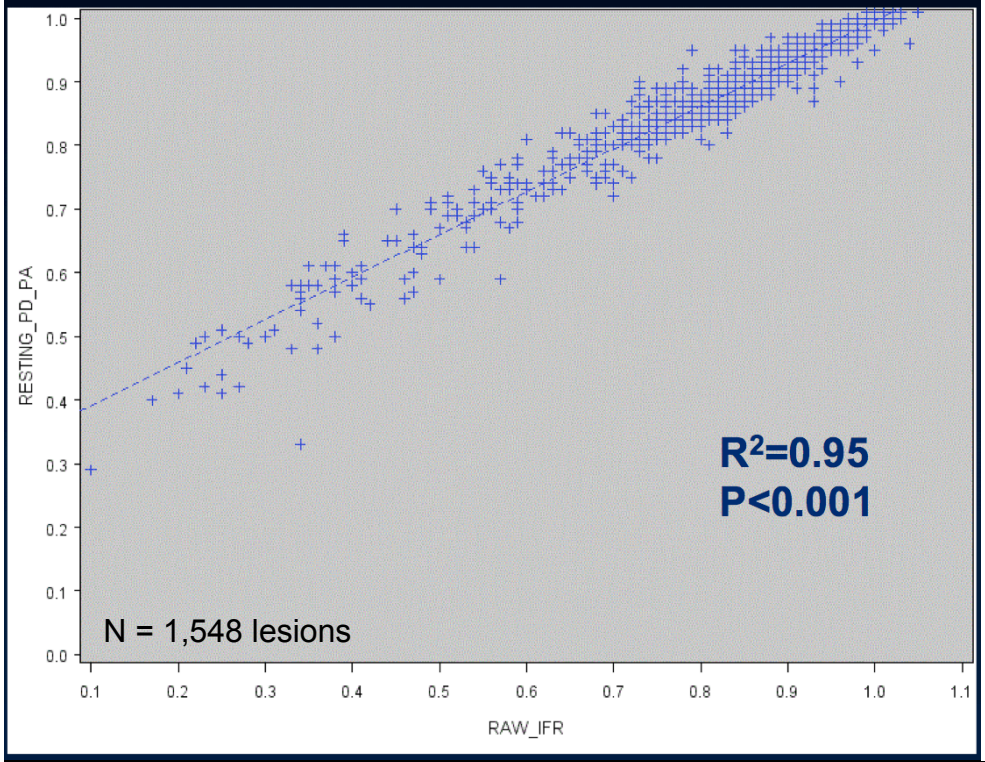


Figure 3B of Johnson NP, *JACC* 2013;61(13):1428-35.

Using *Volcano algorithm*



Slide 20 of Jeremias A, CPI 2013, Montréal, Québec (January 30, 2013).

Not Volcano algorithm

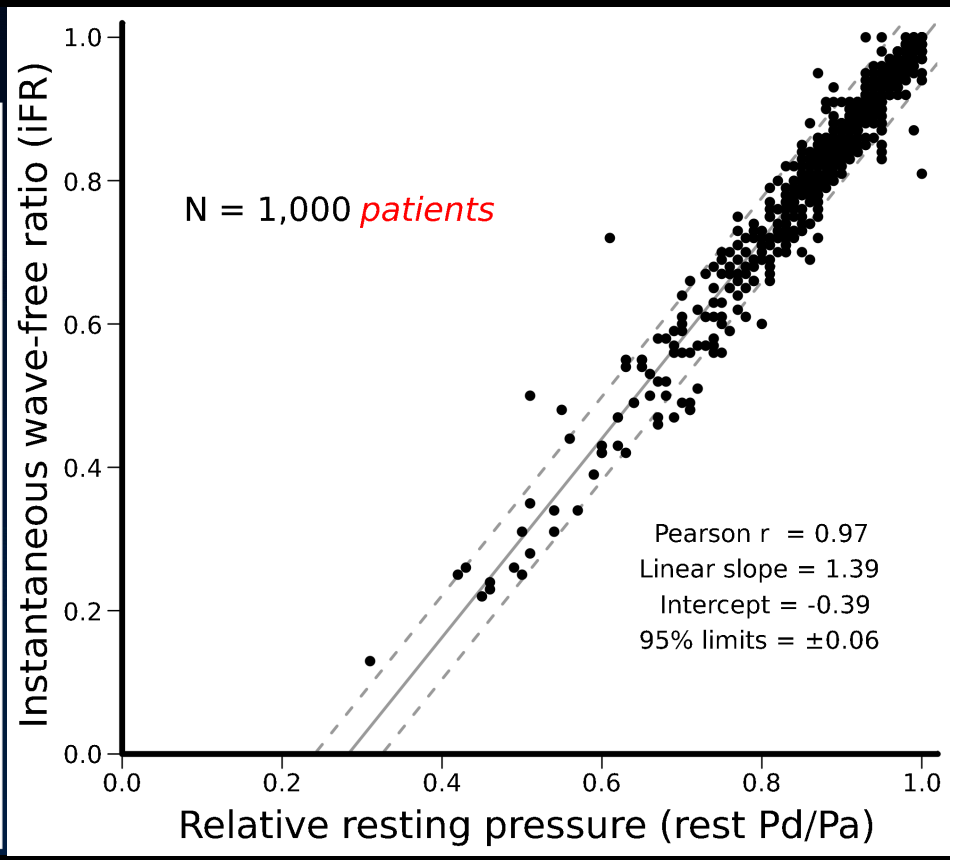


Figure 5 of Johnson NP, *JACC* 2013;61(13):1428-35.

Rest Pd/Pa predicts *95%* of iFR variation

the methodology and algorithms used to measure iFR, which, we believe, could be at variance with the methodology applied in our paper, thus explaining the different results of the correlation.

Text from Sen S, *JACC* 2012;59(21):1917-8.

It would thus appear that the details of the methodology for calculating iFR might impact its accurate measurement

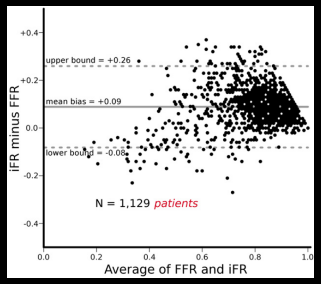
Text from Samady H, *JACC* 2013;61(13):1436-9.

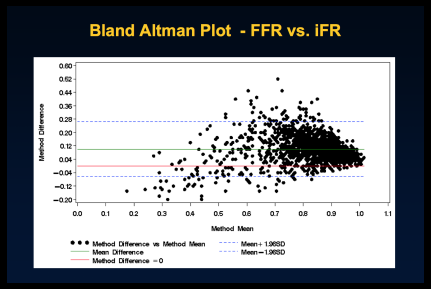
Does *algorithm* matter?

Not Volcano

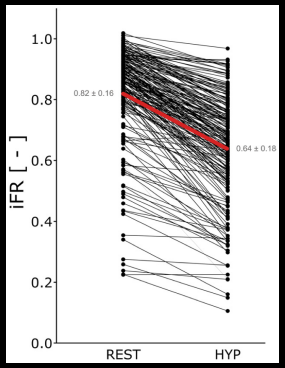
Volcano algorithm

Bias/scatter

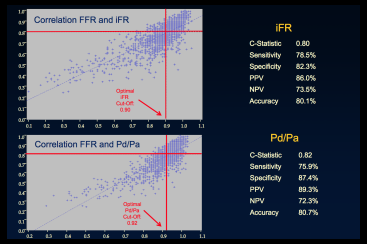




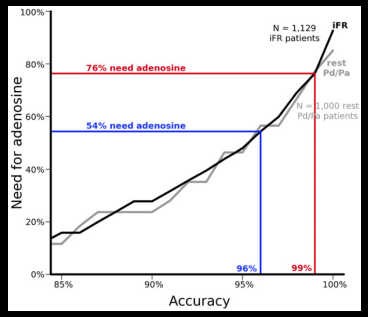
iFR decrease with adenosine

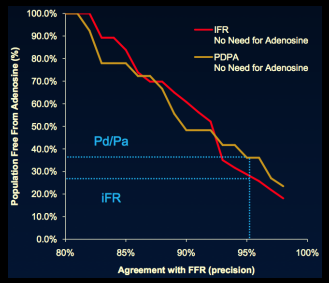


iFRa had significantly lower values than FFR and iFR (median iFRa 0.74 [0.58, 0.85] versus median FFR 0.84 [0.70, 0.89] and median iFR 0.93 [0.83, 0.98], p < 0.001 for both).

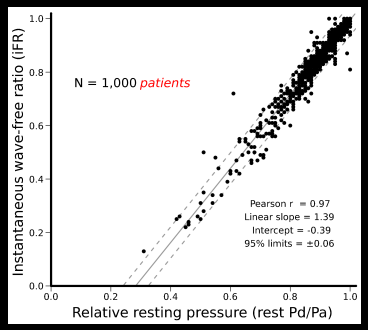


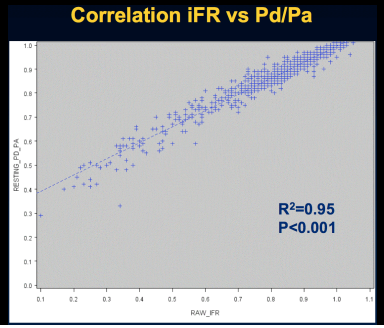
Equivalence of rest Pd/Pa





95% of iFR explained by rest Pd/Pa





Summary

1. iFR "numerically similar" to FFR
   - No, iFR≠FFR (iFR larger and more imprecise)
2. Resistance during wave-free period equivalent to hyperemia
   - No, resistance 2.5-fold higher during wave-free period
3. iFR more reproducible than FFR
   - iFR less reproducible and more influenced by HR and BP
4. Very high "adjusted" accuracy for iFR
   - Invalid method for "adjusting" accuracy
5. VERIFY has reported "fluctuating" accuracy
   - Accuracy depends on iFR cutoff, which has fluctuated
6. Accuracy of iFR better than rest Pd/Pa
   - Both offer same tradeoff between accuracy and adenosine
7. Exact details of iFR algorithm make crucial difference
   - No, key results hold regardless of iFR algorithm

nothing < rest < hyperemia

rest Pd/Pa *or* iFR