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Metrics of coronary physiology. Are they all equal?

Bernard De Bruyne, MD, PhD

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Department of Cardiology, Lausanne University Center Hospital, Lausanne, Switzerland

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Disclosure of Conflicts of Interest

Bernard De Bruyne, MD, PhD

- **Institutional Research Support/Grants** (for the CV Research Center Aalst)

  Abbott Vascular, Medtronic, Biotronic, St Jude Medical

- **Institutional Consultancies** (for the CV Research Center Aalst)

  St Jude Medical, Boston Scientific, Opsens

- **Investment Funds/Equities in Medical Companies**

  Siemens, GE, Philips, Bayer, Philips, HeartFlow, Edwards Life Sciences, Sanofi, Ceyliad

- **Involvement in Contract Research Organizations**:

  None

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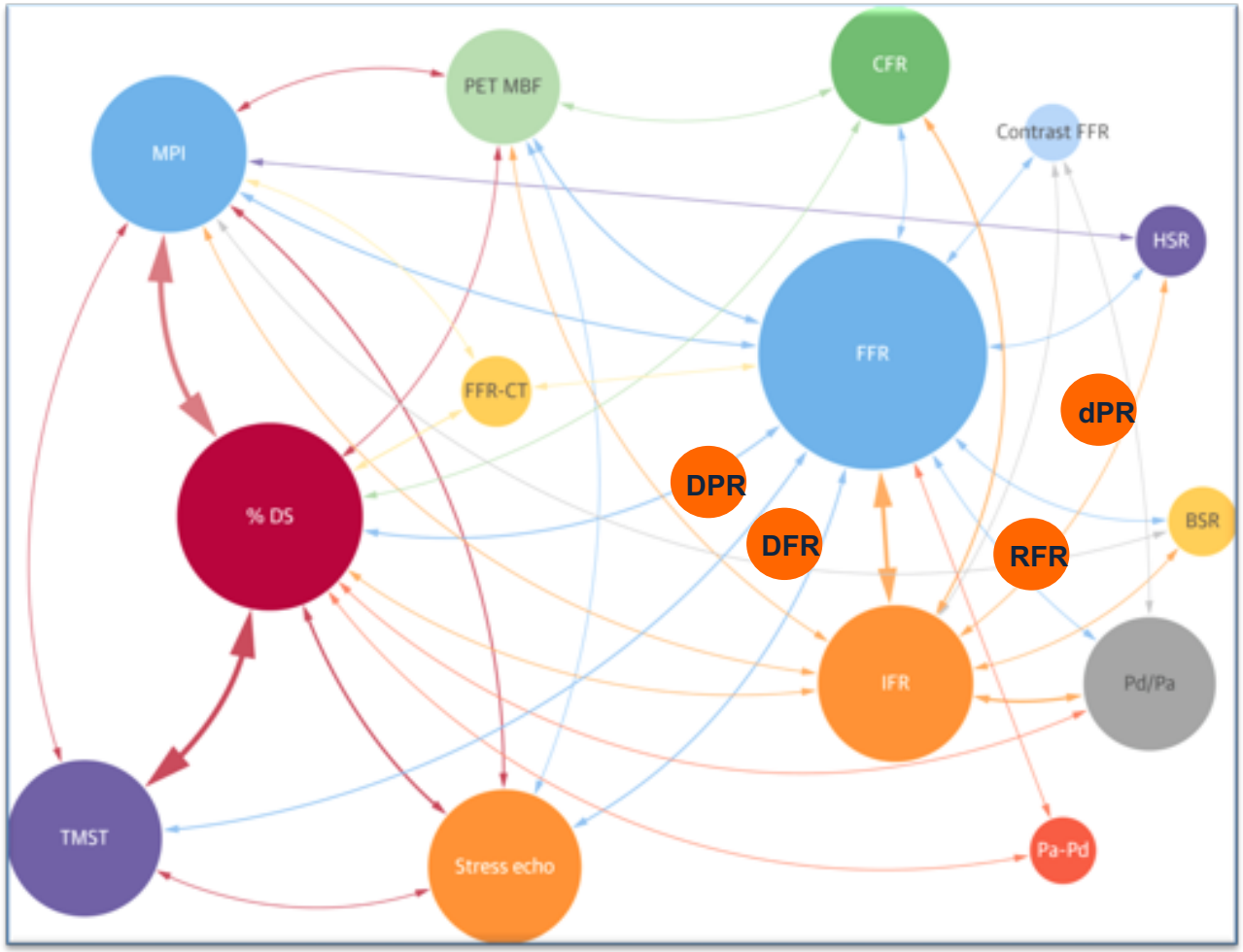
The Universe of Ischemic Clinical Testing



Kern MJ and Seto AH. JACC 2017,70:2124

Before I came here I was confused about this subject. Having listened to your lecture I am still confused. But on a higher level. (Enrico Fermi)

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Metrics of coronary physiology

1. The 2 compartments model
2. Are all NHPR's equal?
3. FFR or NHPR's?
4. The microcirculation

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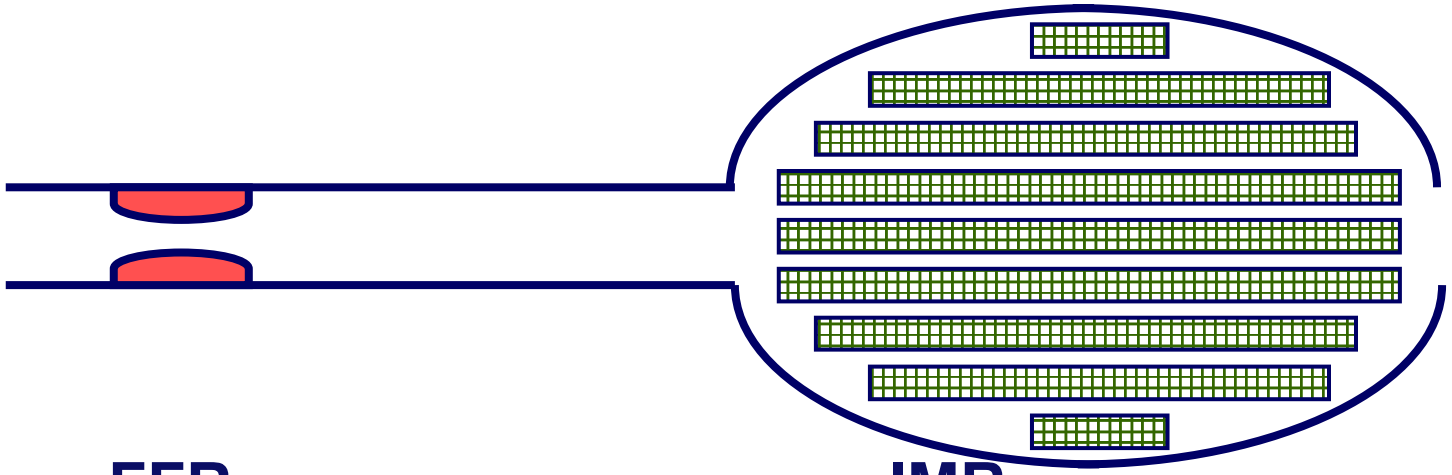
Two-Compartment Model of the Coronary Circulation

Epicardial Artery | **Microvasculature**



FFR

IMR

Absolute **M**icrovascular **R**esistance

P_d/P_a
*i*FR
dPR
DPR
dFR
RFR

} **NHPR's**

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Non Hyperemic Pressure Ratio

(P_d/P_a, *i*FR, dPR, DPR, dFR, RFR)

Good idea

- **Faster**
- **Cheaper**
- **No side effects**

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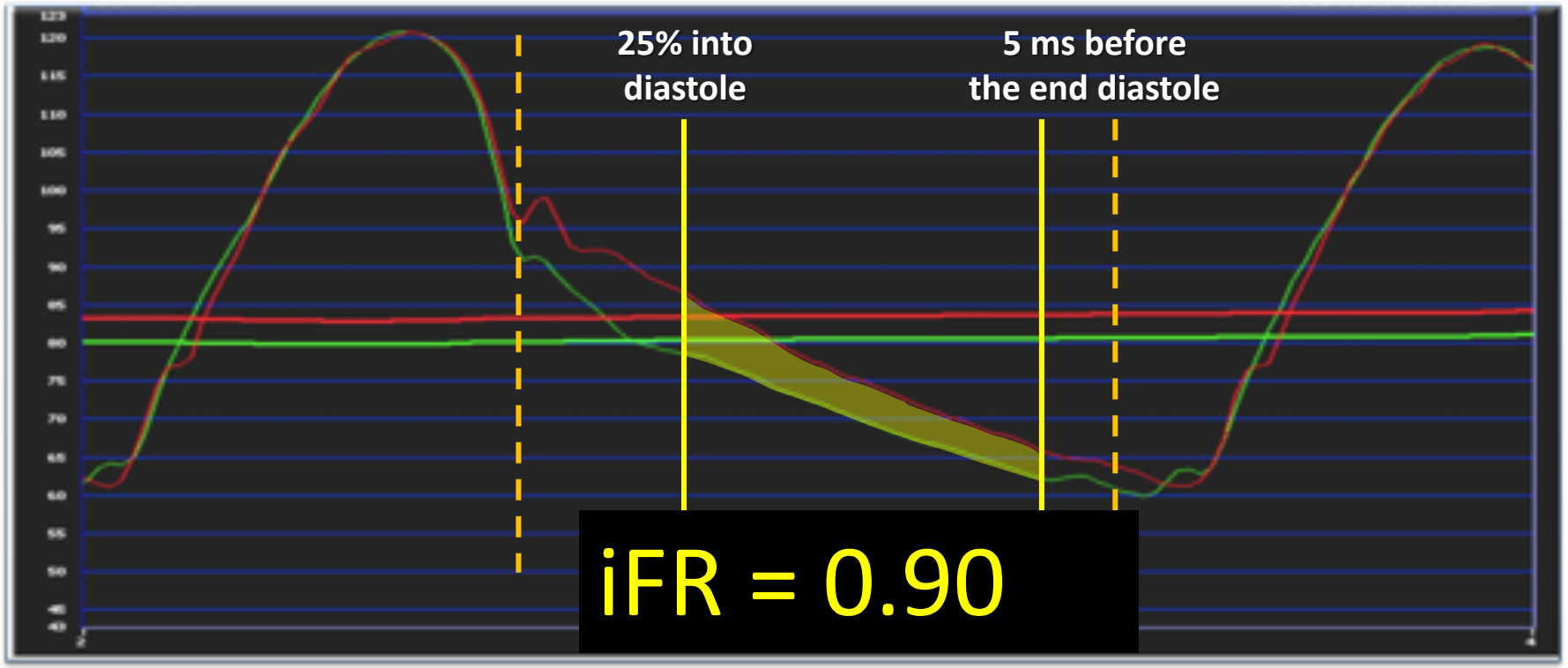
P_d/P_a and iFR



iFR = P_d / P_a during the "wave free period"
"when resistance is *naturally* minimized"

Sen S et al JACC 2012

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The Wave-Free Period

Vascular Structure and Function

Wave Separation, Wave Intensity, the Reservoir-Wave Concept, and the Instantaneous Wave-Free Ratio

Presumptions and Principles

Nico Westerhof, Patrick Segers, Berend E. Westerhof

Novelty and Significance

What Is New?

- Wave intensity analysis wrongly suggests that there is a wave-free period (diastole) in the cardiac cycle.

What Is Relevant?

- Methods based on this assumed wave-free period, the reservoir-wave concept and the Instantaneous wave-Free Ratio of pressure and flow are, therefore, physically incorrect.

Summary

The reservoir-wave concept and the Instantaneous wave-Free Ratio should not be used.

Westerhof N et al. J Hypertens. 2015 33:926-7

Westerhof N et al. Artery Research doi.org/10.1016/j.artres.2017.03.001

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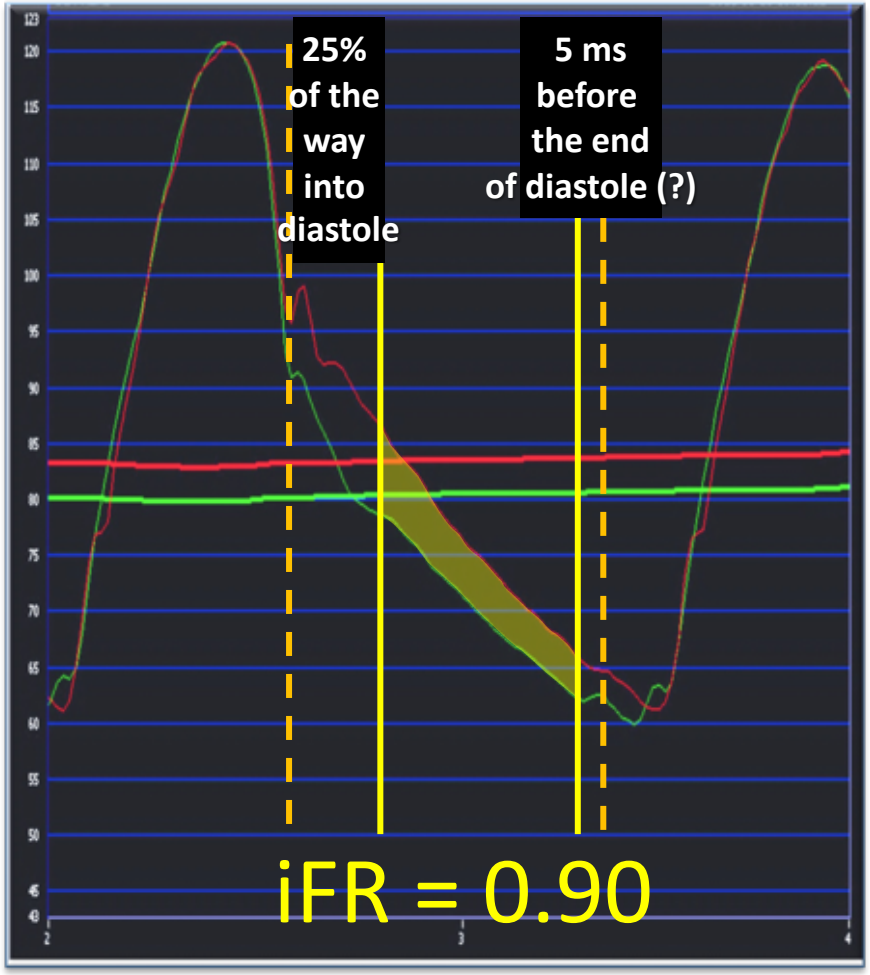
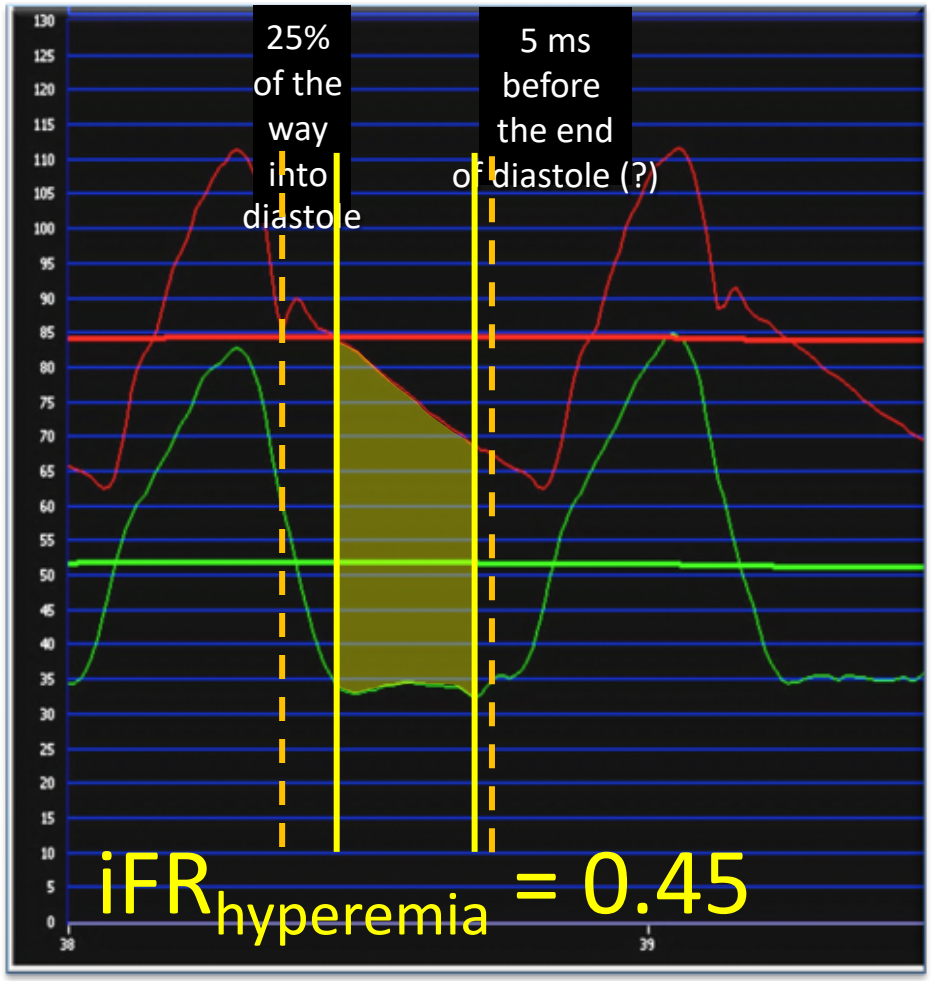
Microvascular Resistance Are not Minimized During Diastole





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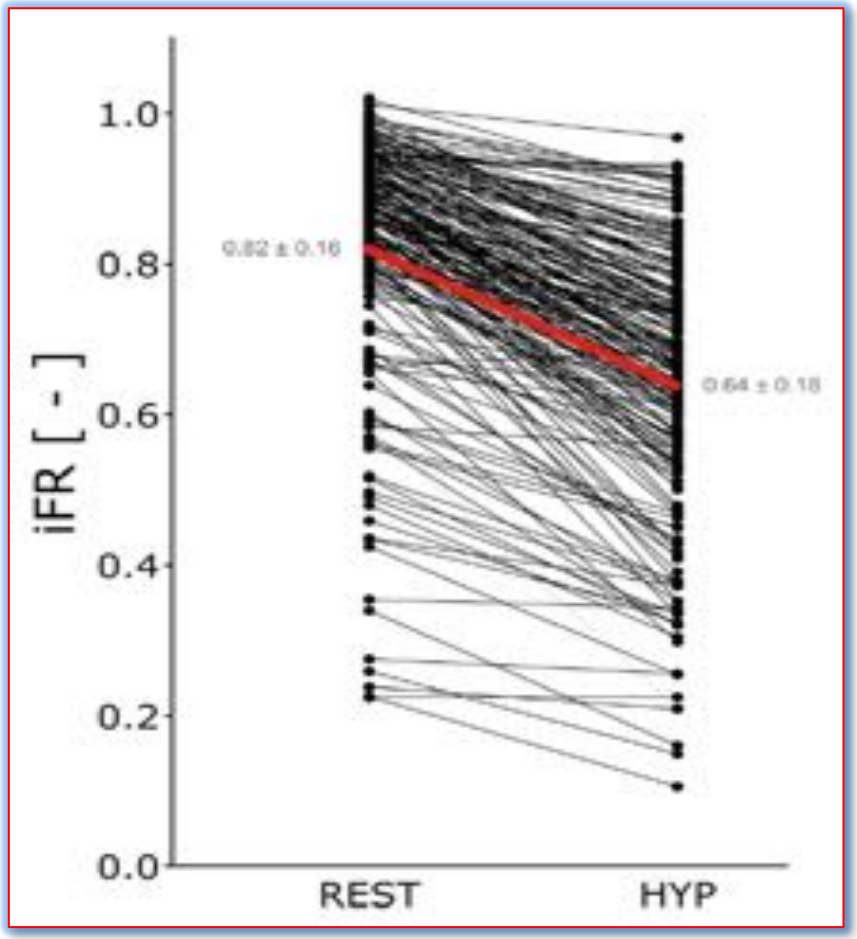
Microvascular Resistance Are not Minimized During Diastole



iFR = P_d / P_a during the "wave free period"

"when resistance is *naturally* minimized"

Berry C et al JACC 2013

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Is this a Problem?

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Metrics of coronary physiology

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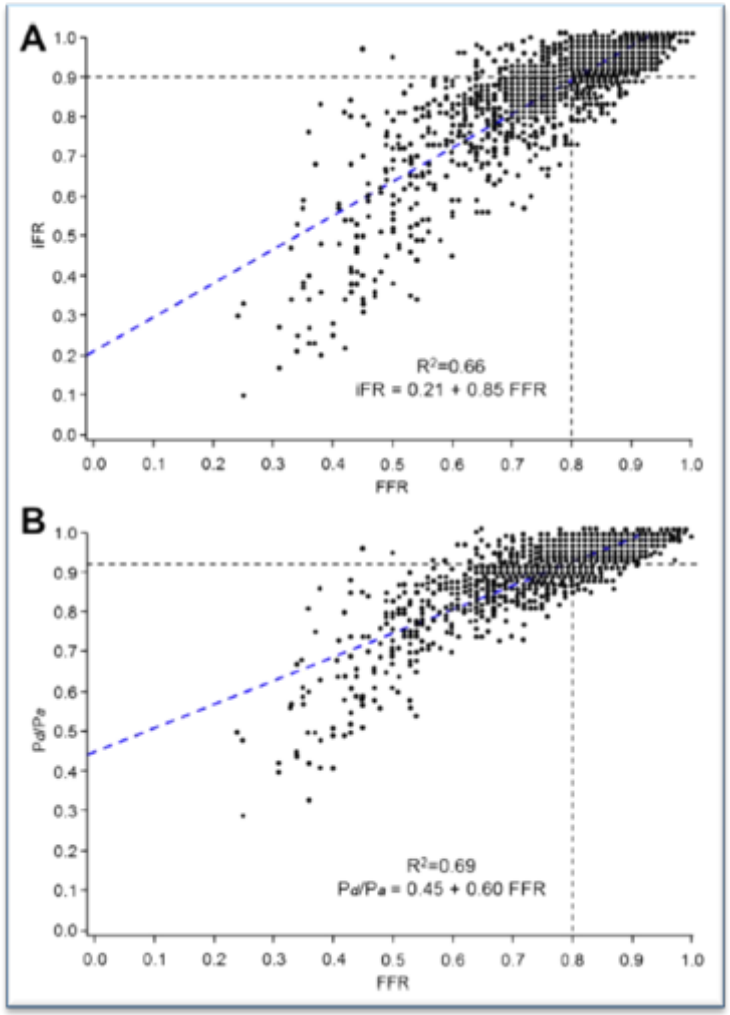
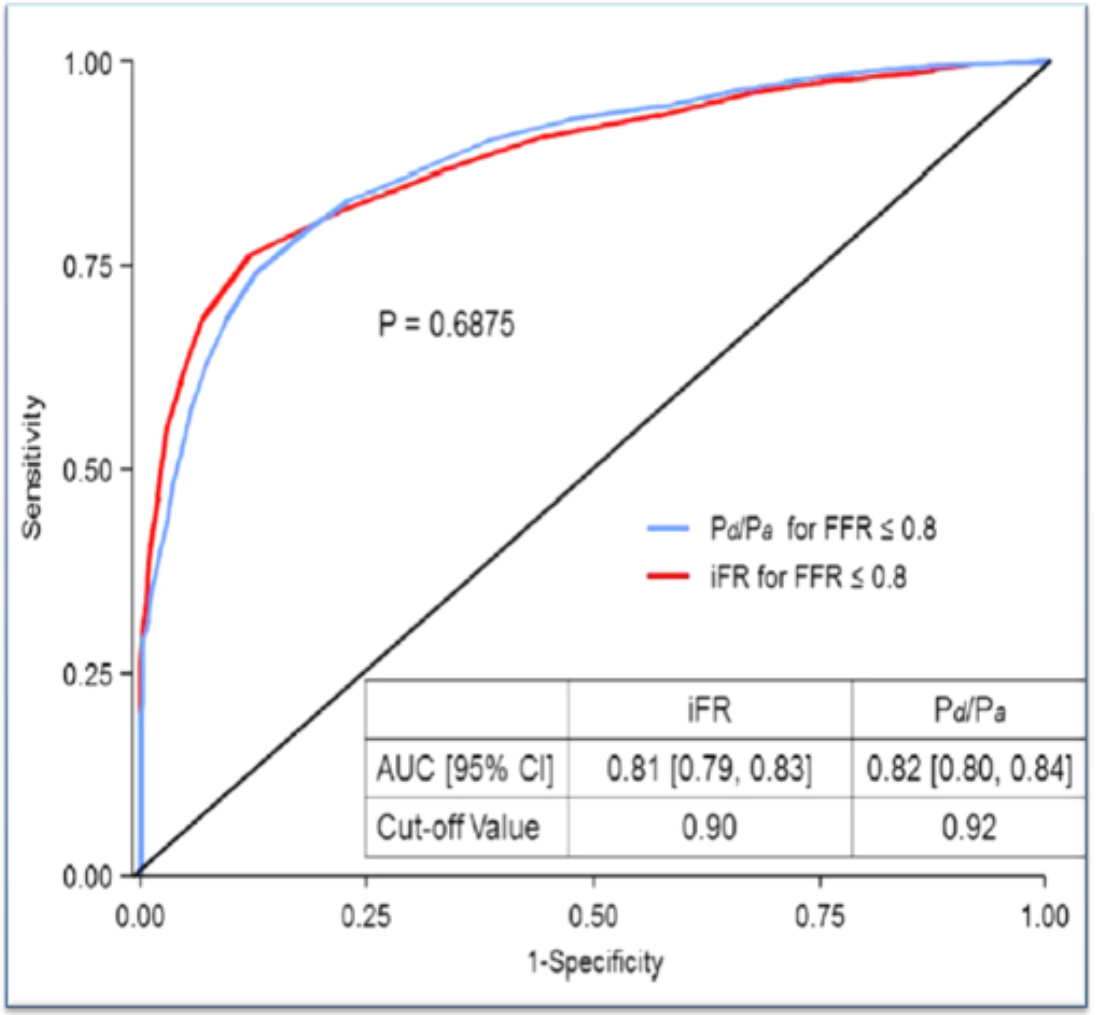
How do iFR (and the NHPR's) Compare to FFR?

Multicenter Core Laboratory Comparison of iFR and Resting P_d / P_a to FFR





	iFR	Pd/Pa
AUC [95% CI]	0.81 [0.79, 0.83]	0.82 [0.80, 0.84]
Cut-off Value	0.90	0.92

A. Jeremias et al. JACC 2014;53:1253

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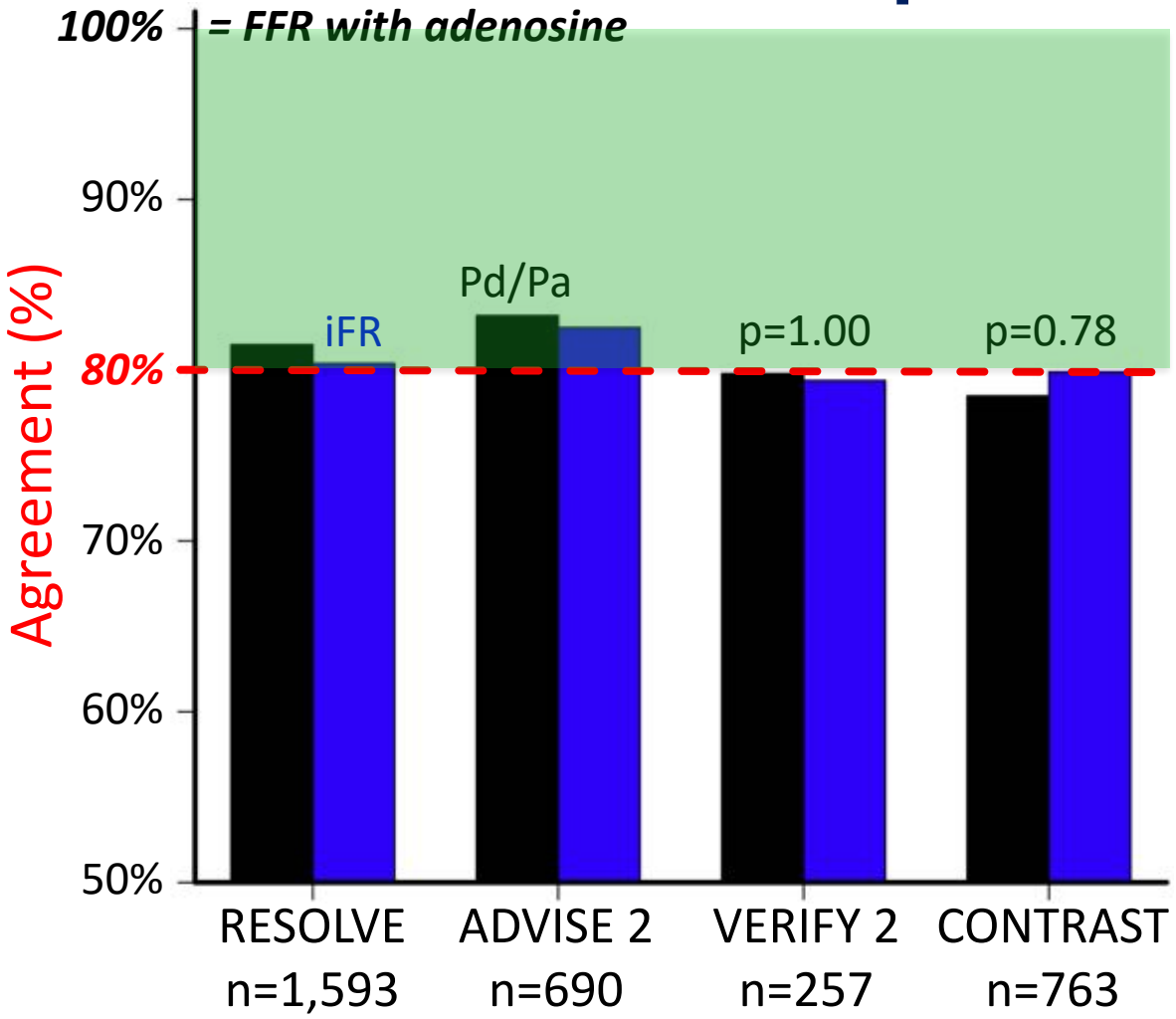

Key conclusion

- *80% agreement*
- *3,300+ lesions*
- *multiple studies*

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ADVISE 2 = Escaned J, *JACC Cardiovasc Interv*. 2015,8:824-33
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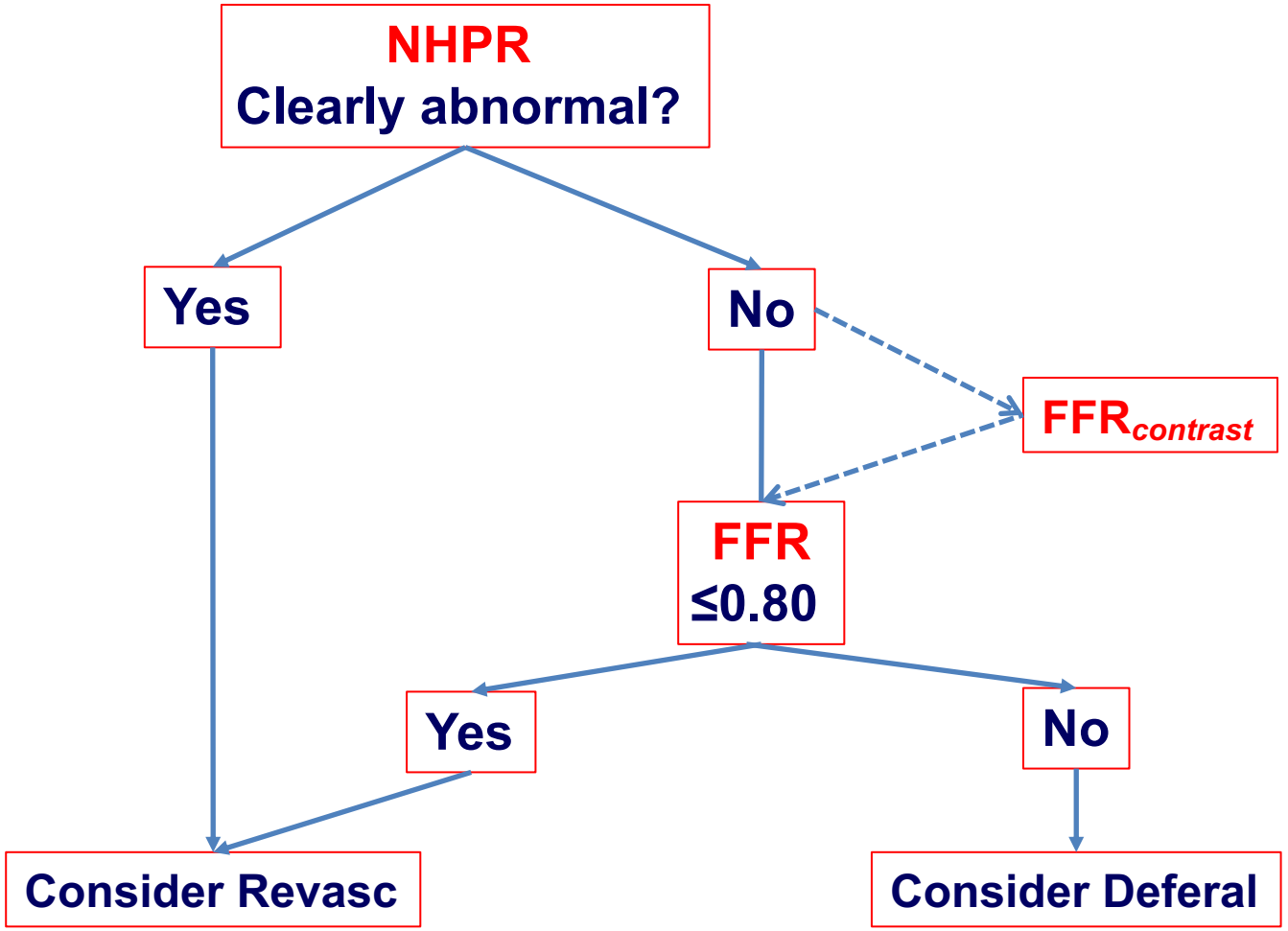
Hybrid Approach



No 'deferral' based on 'normal' resting indices

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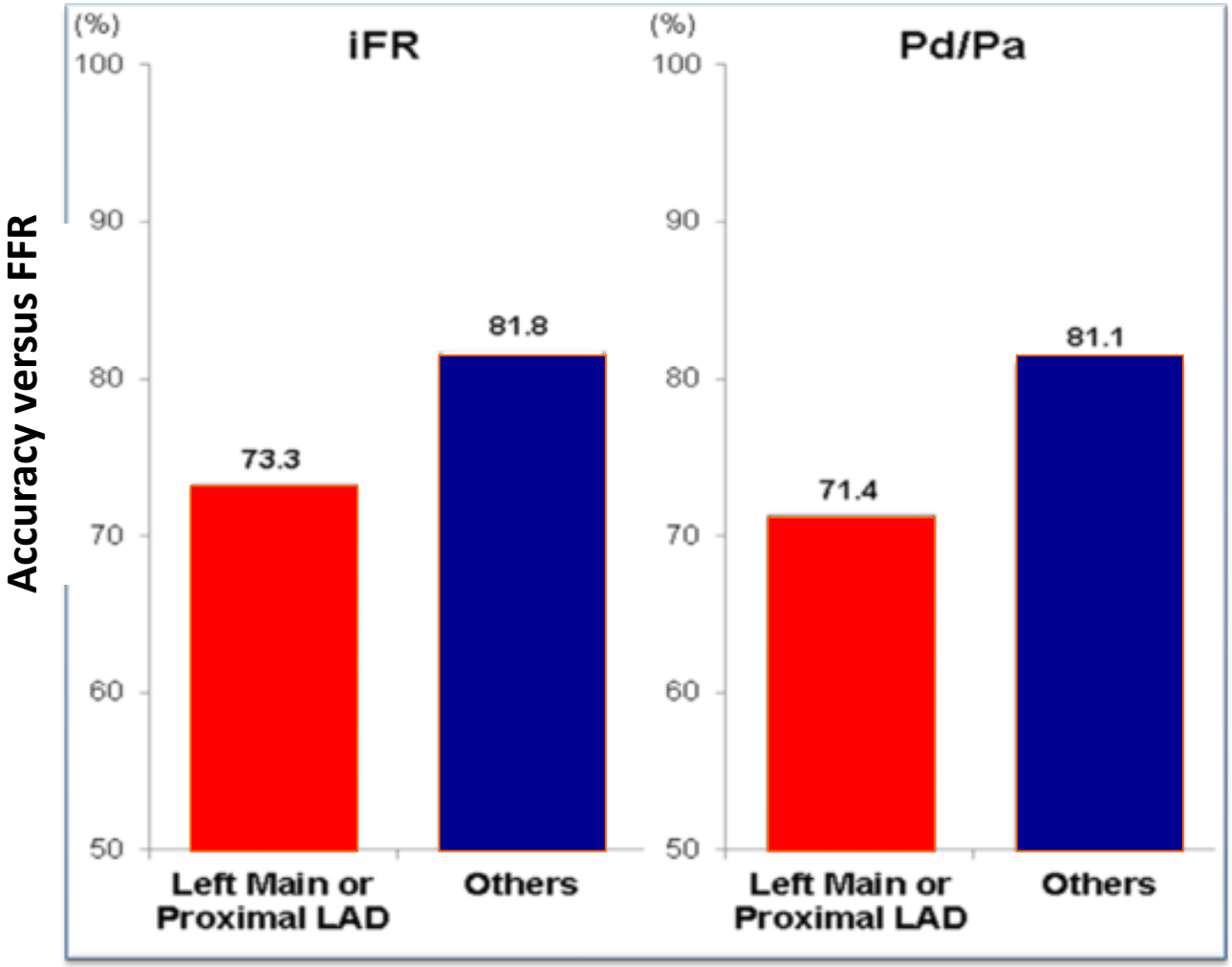
How do the Resting Indices Compare to FFR?



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Kobayashi Y, JACC Cardiovasc Interv. 2016;9:2390-2399

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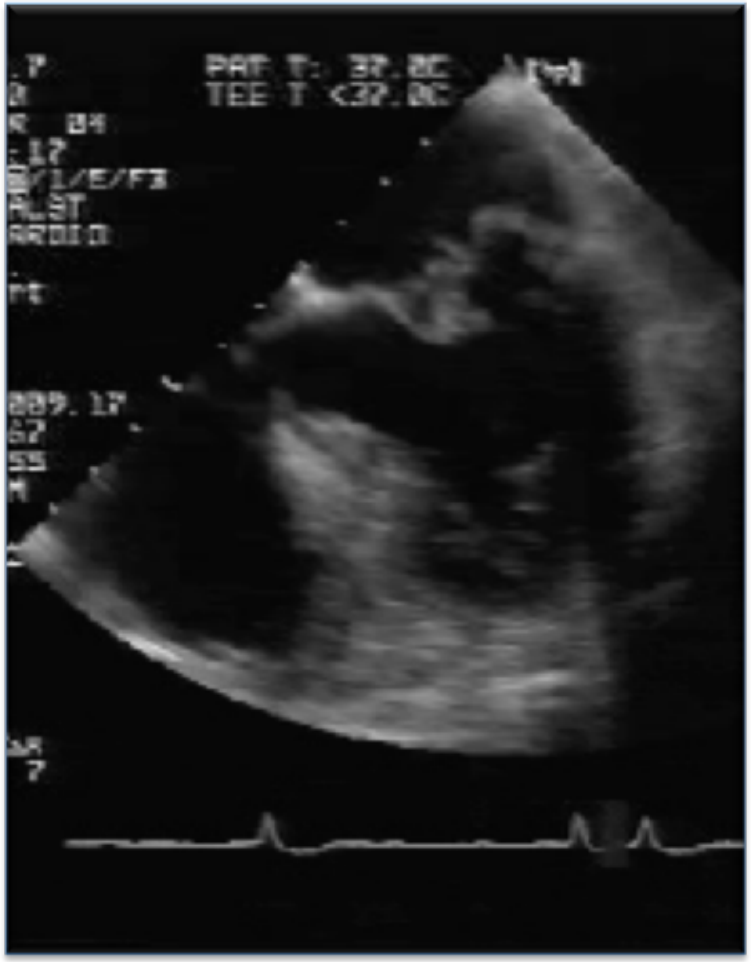
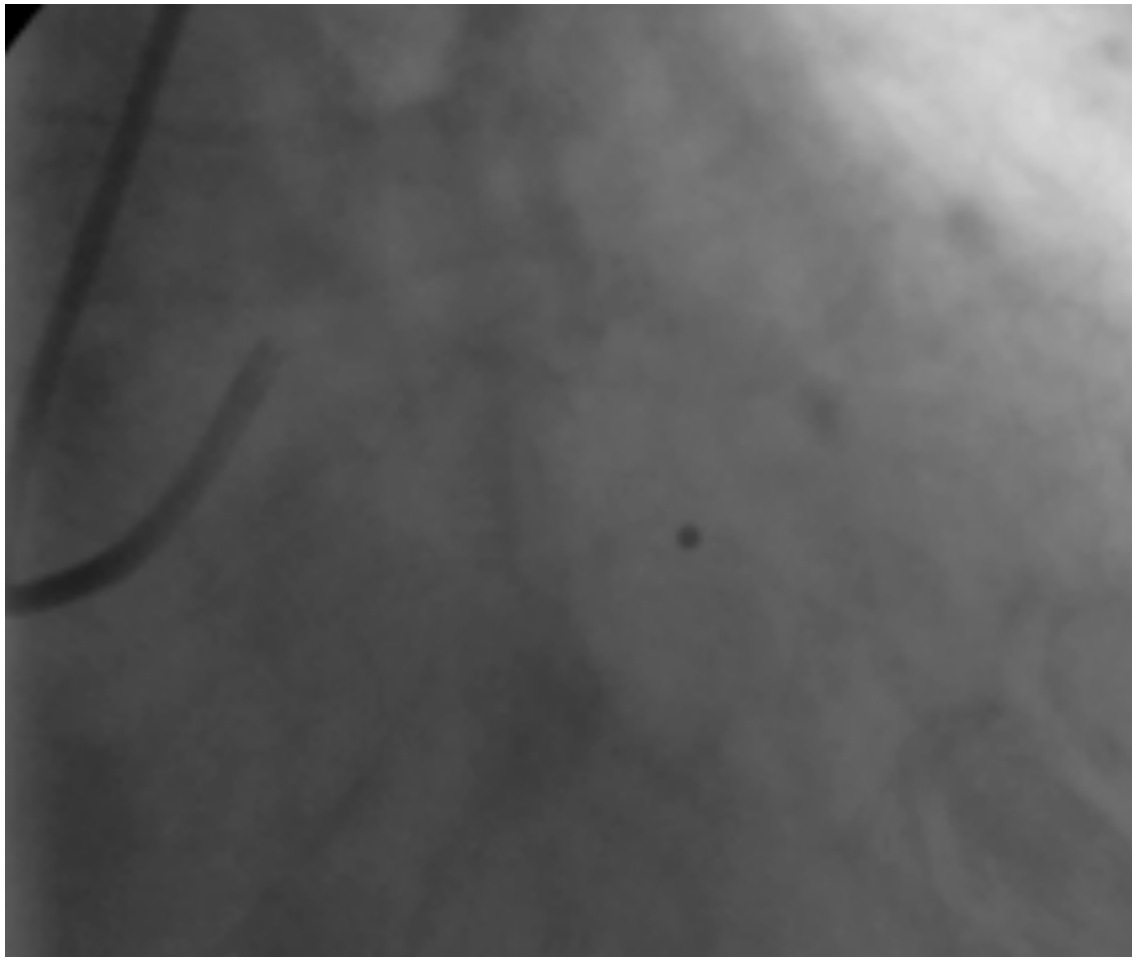
77-y-old lady
Dyspnoe NYHA 3
Mitral Regurgitation 4 (Barlow)





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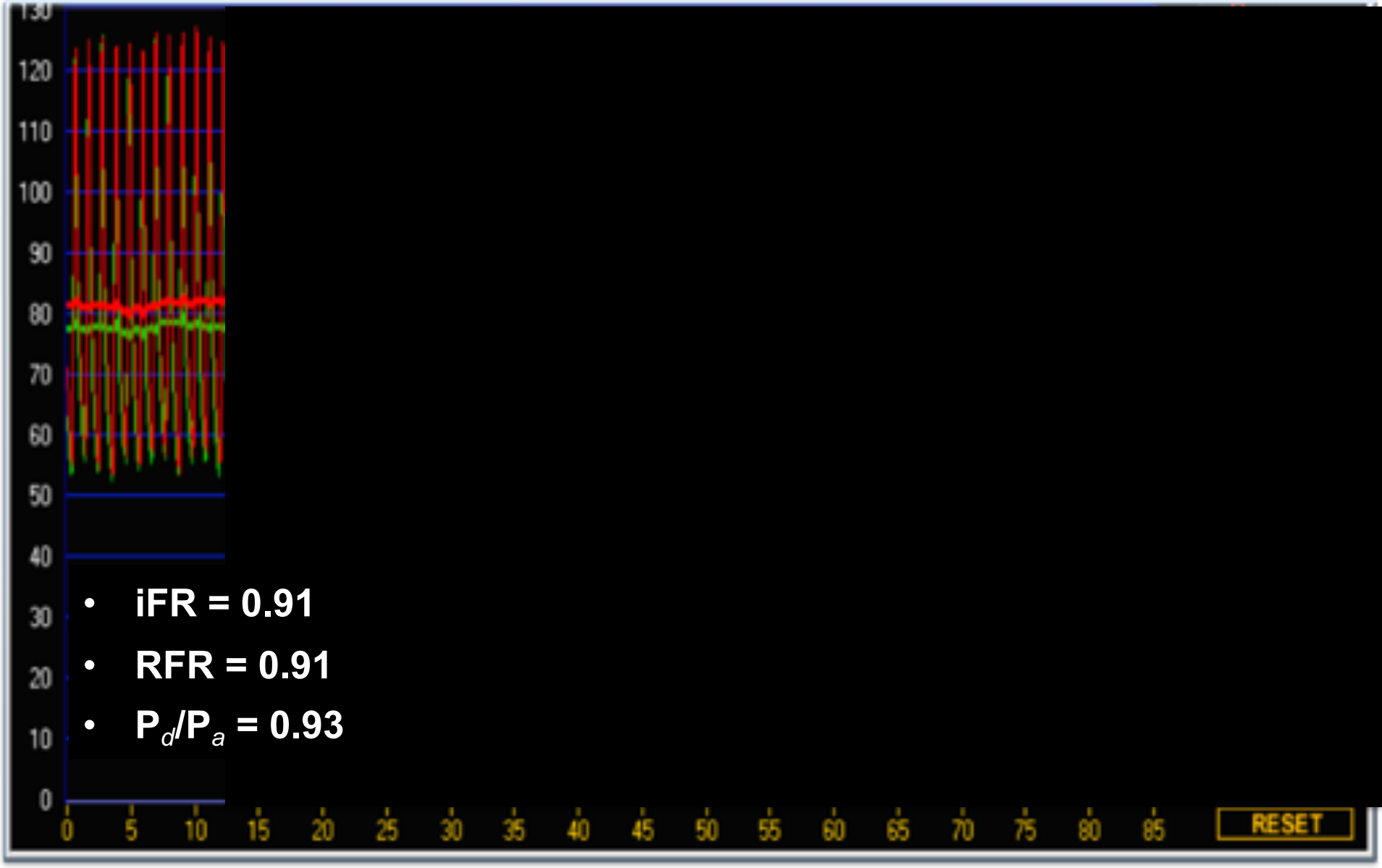

- iFR = 0.91
- RFR = 0.91
- P_d/P_a = 0.93

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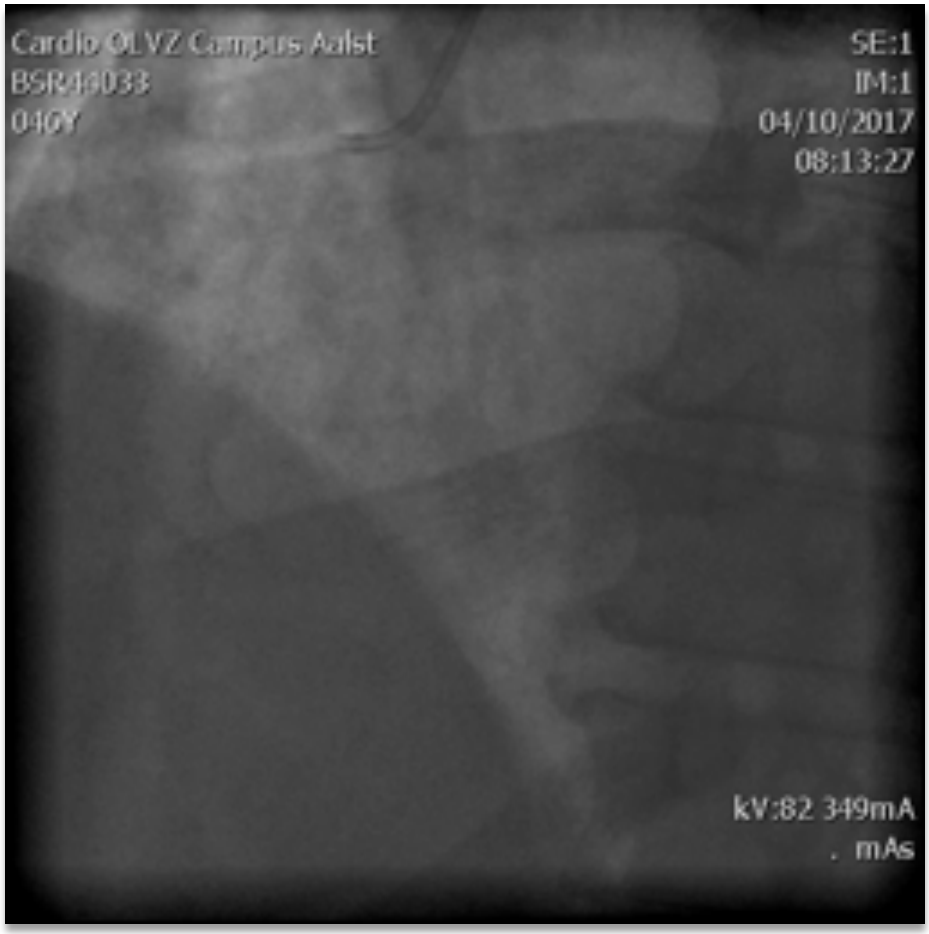
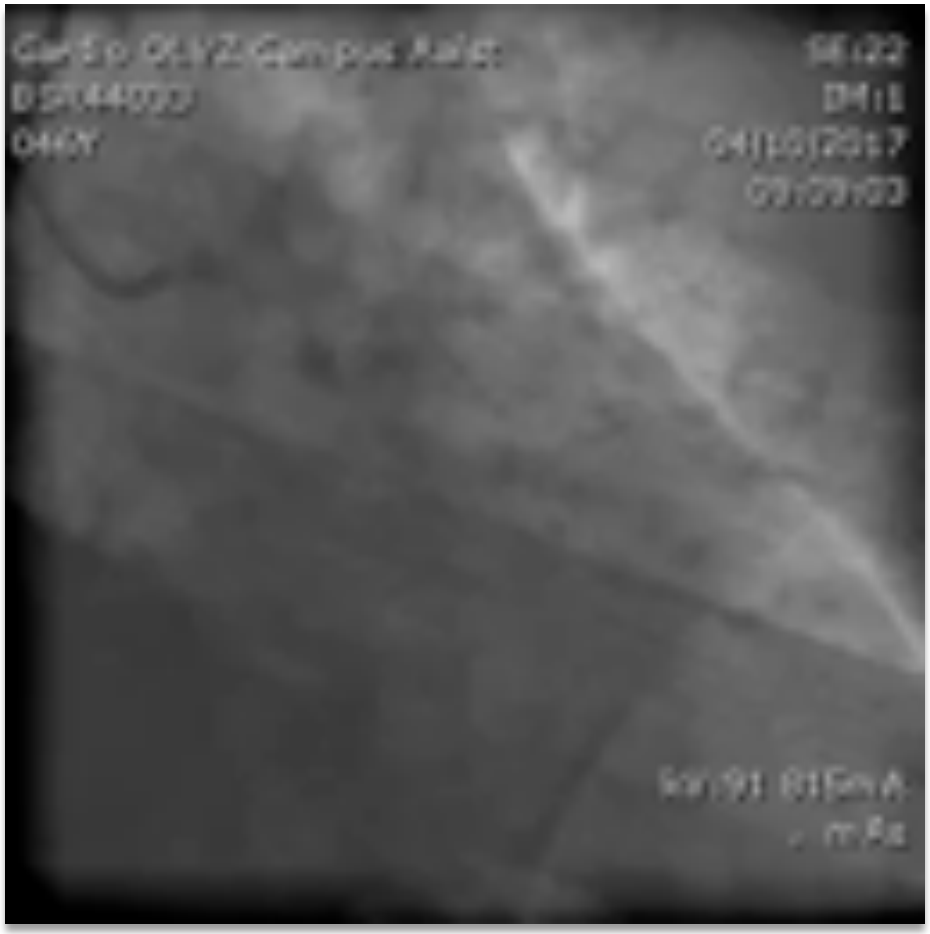
48-y-old man
Crescendo angina
Normal LV EF





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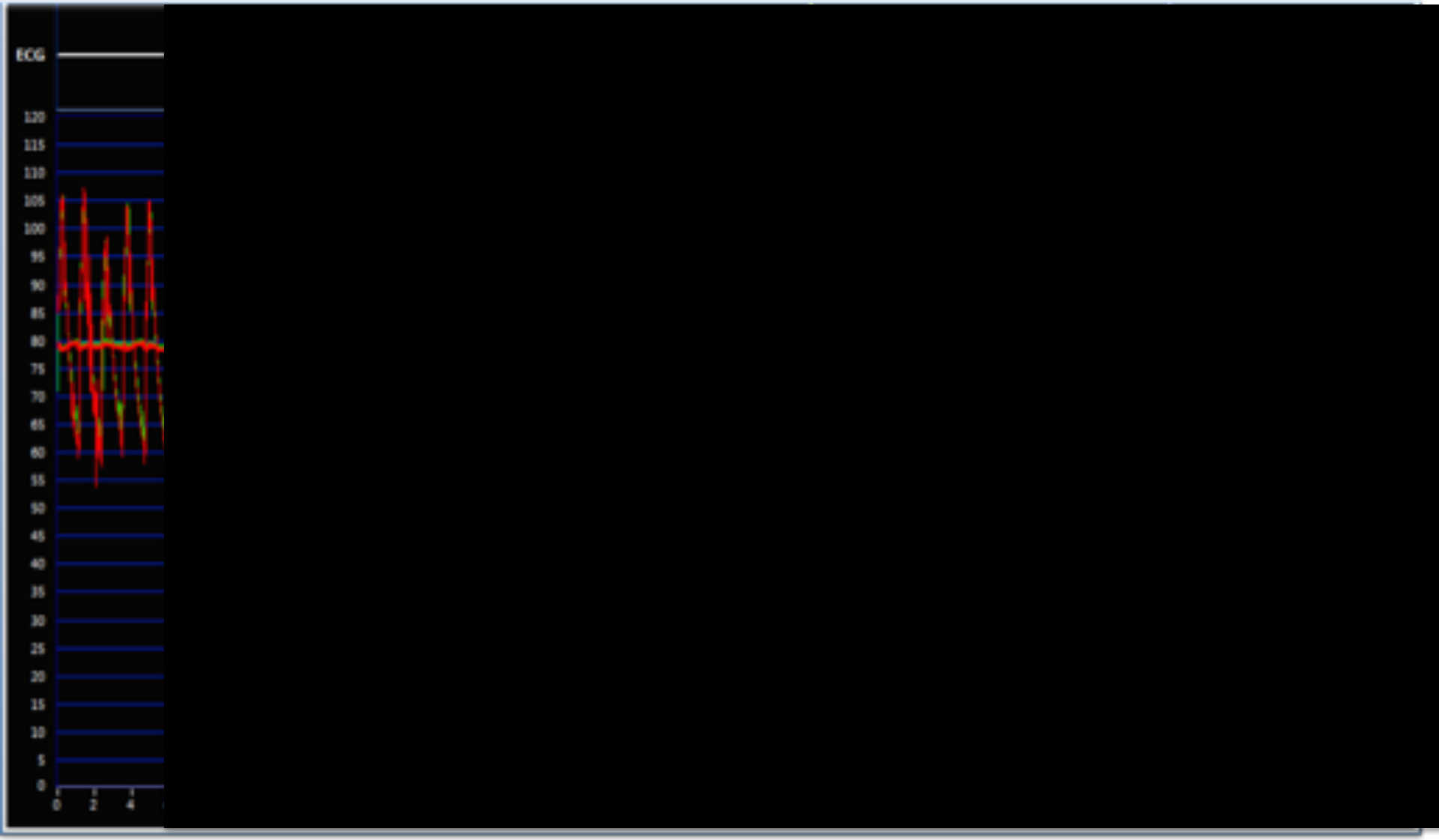

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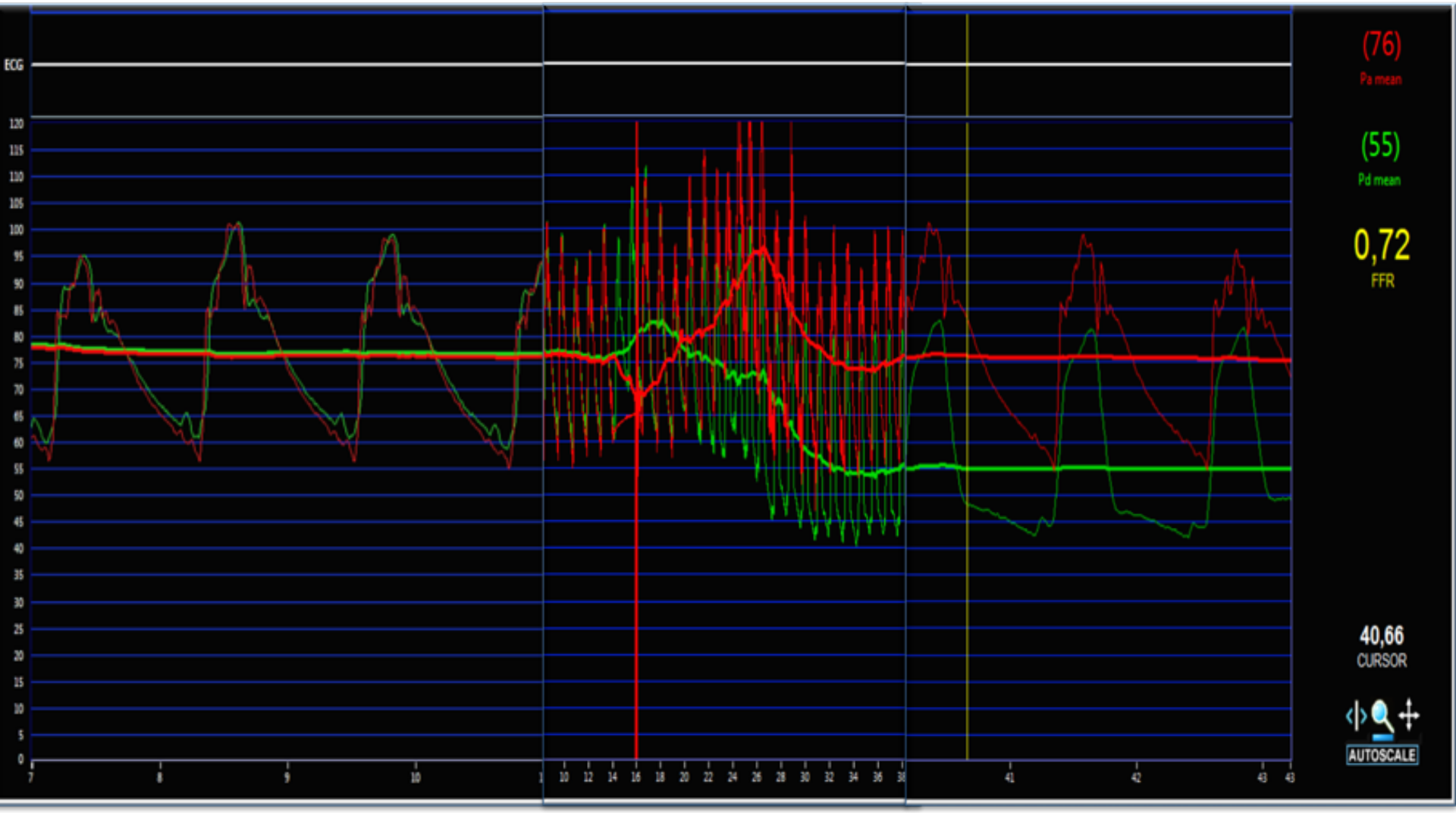

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Outcome

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Clinical Outcome Data Based on Physiological Indices

Lesions/Patients Settings	FFR	NHPR's
Intermediate lesions/Low Risk Patients	+	+
Intermediate lesions/All Round patients	+	-
Left Main	+	-
Post-CABG	+	-
Small vessels	+	-
MVD	+	-
Post MI setting	+	-
Proximal LAD	+	-

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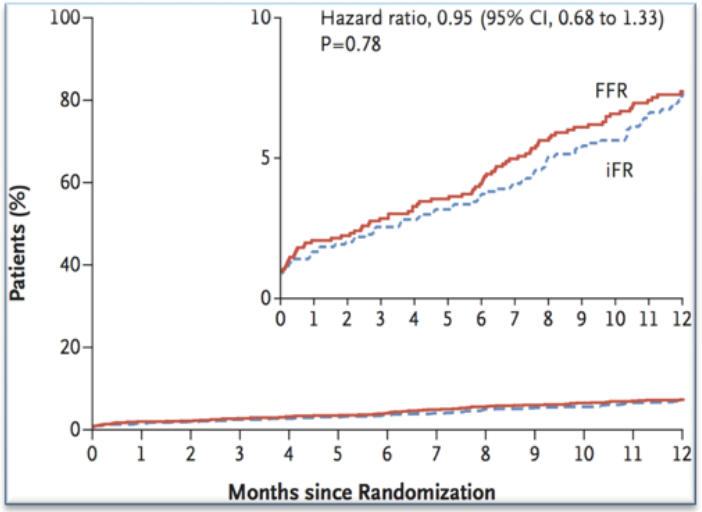
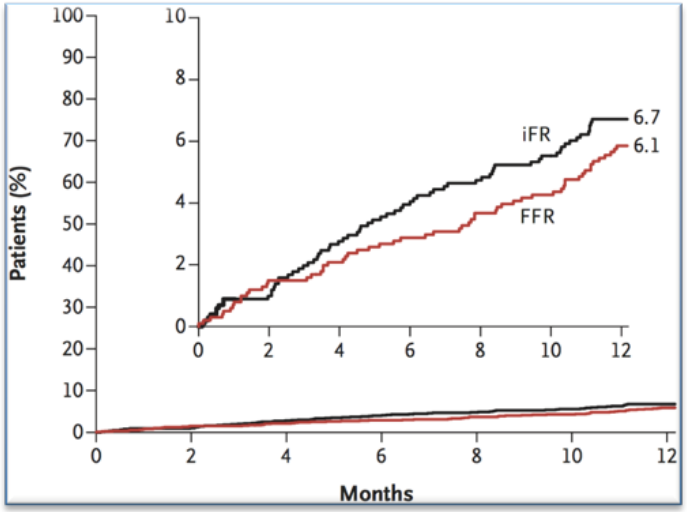
iFR trials: Conclusions



Davies JE, NEJM. 2017



Götberg M, NEJM. 2017

CONCLUSIONS

Coronary revascularization guided by iFR was noninferior to revascularization guided by FFR with respect to the risk of major adverse cardiac events at 1 year. The rate of adverse procedural signs and symptoms was lower and the procedural time was shorter with iFR than with FFR. (Funded by Philips Volcano; DEFINE-FLAIR ClinicalTrials.gov number, NCT02053038.)

CONCLUSIONS

Among patients with stable angina or an acute coronary syndrome, an iFR-guided revascularization strategy was noninferior to an FFR-guided revascularization strategy with respect to the rate of major adverse cardiac events at 12 months. (Funded by Philips Volcano; iFR SWEDEHEART ClinicalTrials.gov number, NCT02166736.)

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Caveats

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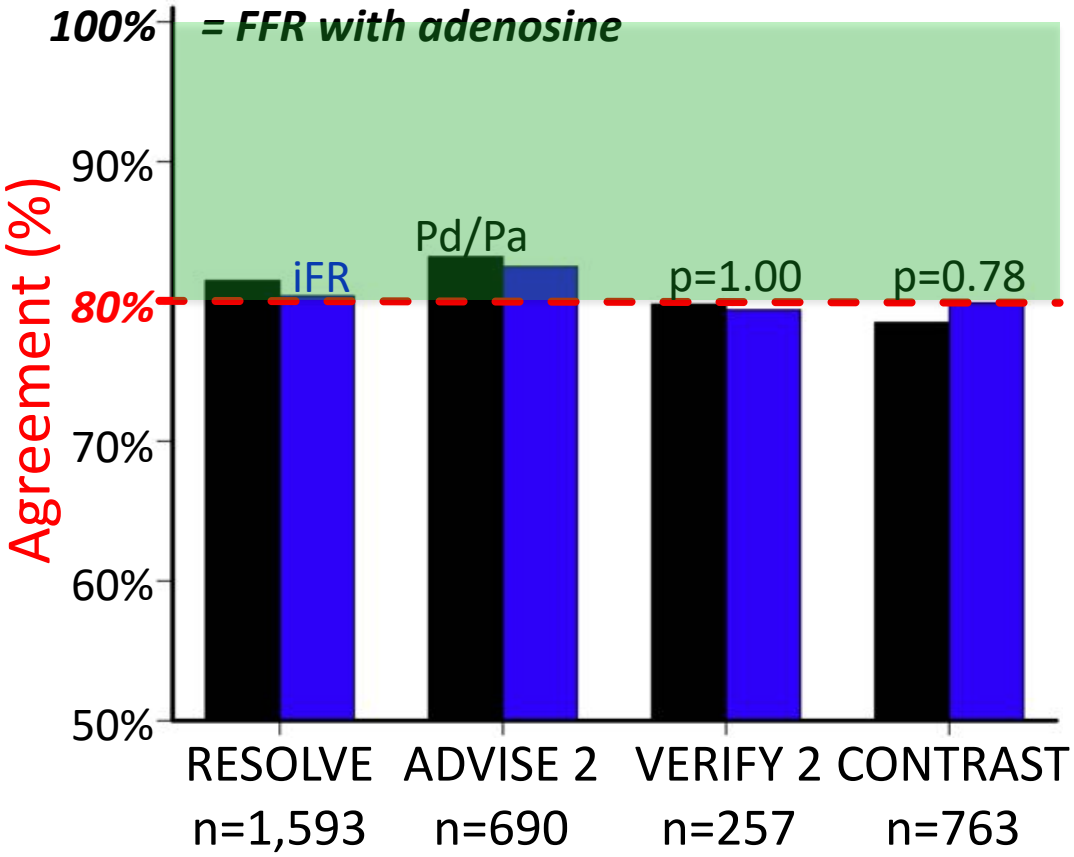
#1 A Priori Knowledge

80% of cases FFR and iFR are in agreement



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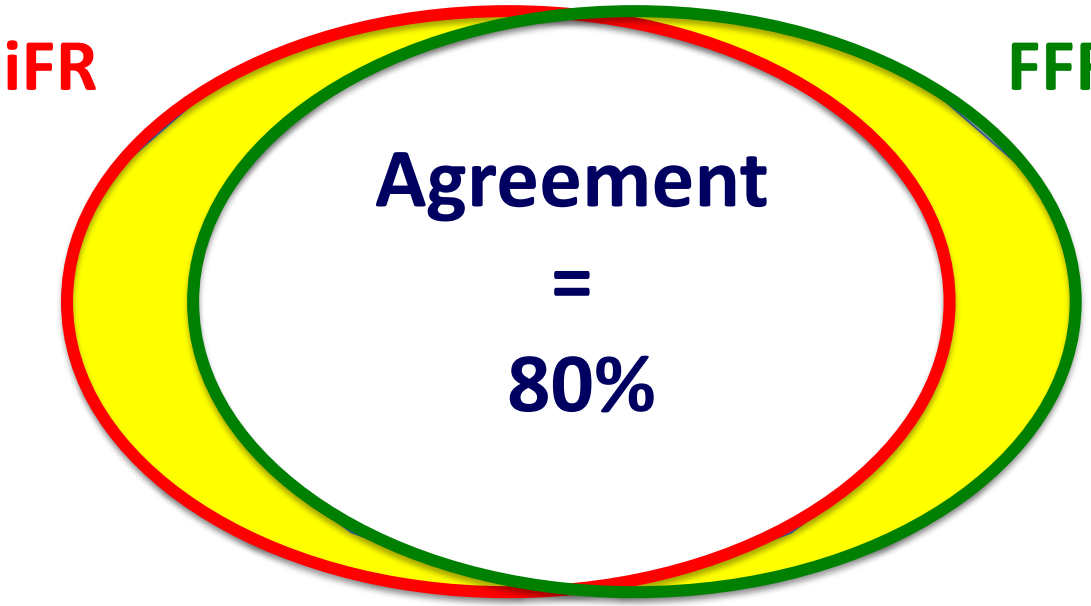
#1 A Priori Knowledge



A potential difference could only arise from 20% of population

➔ An non-inferiority trial CANNOT fail

Functional Underpowered

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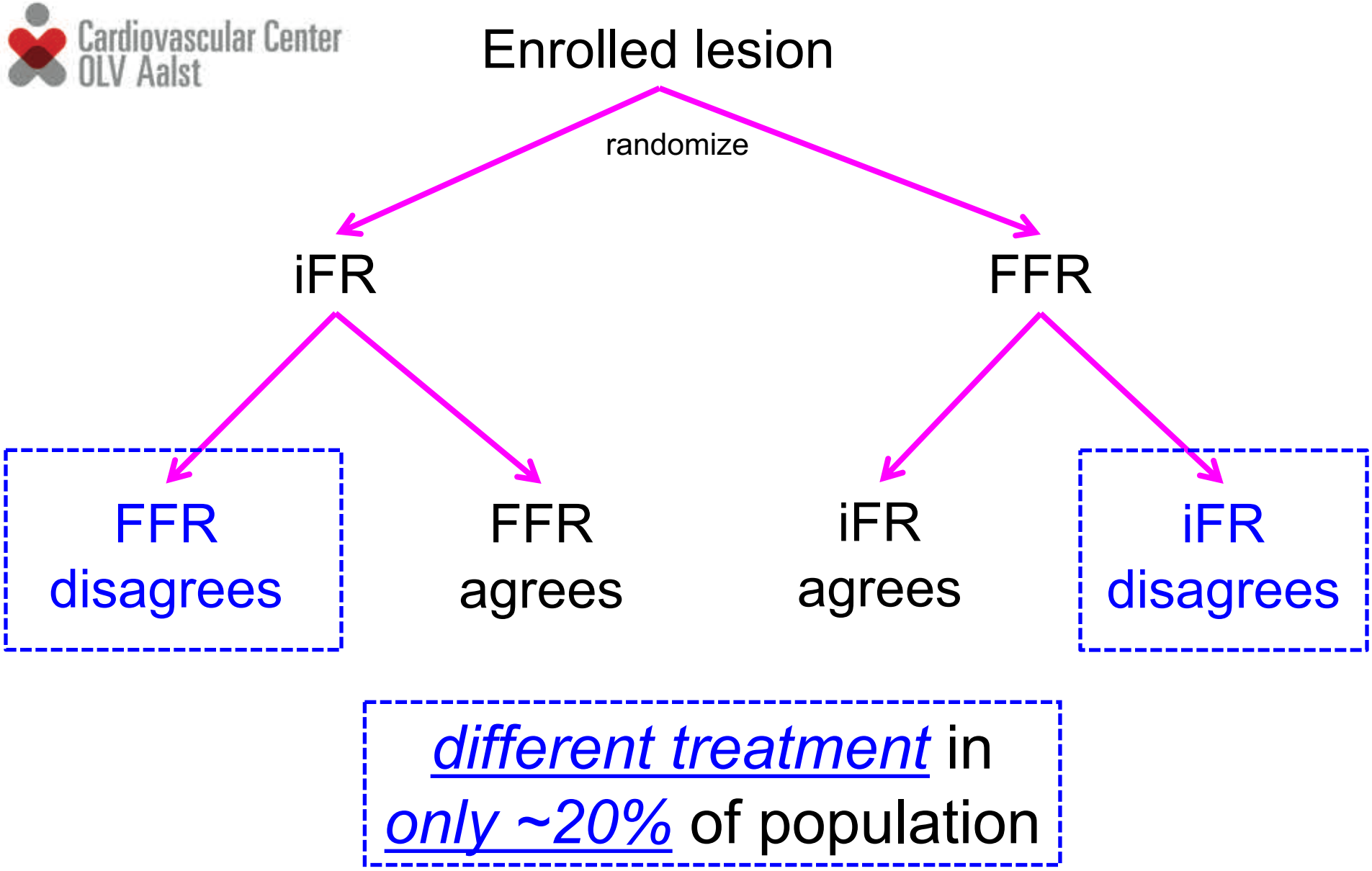

different treatment in *only ~20%* of population

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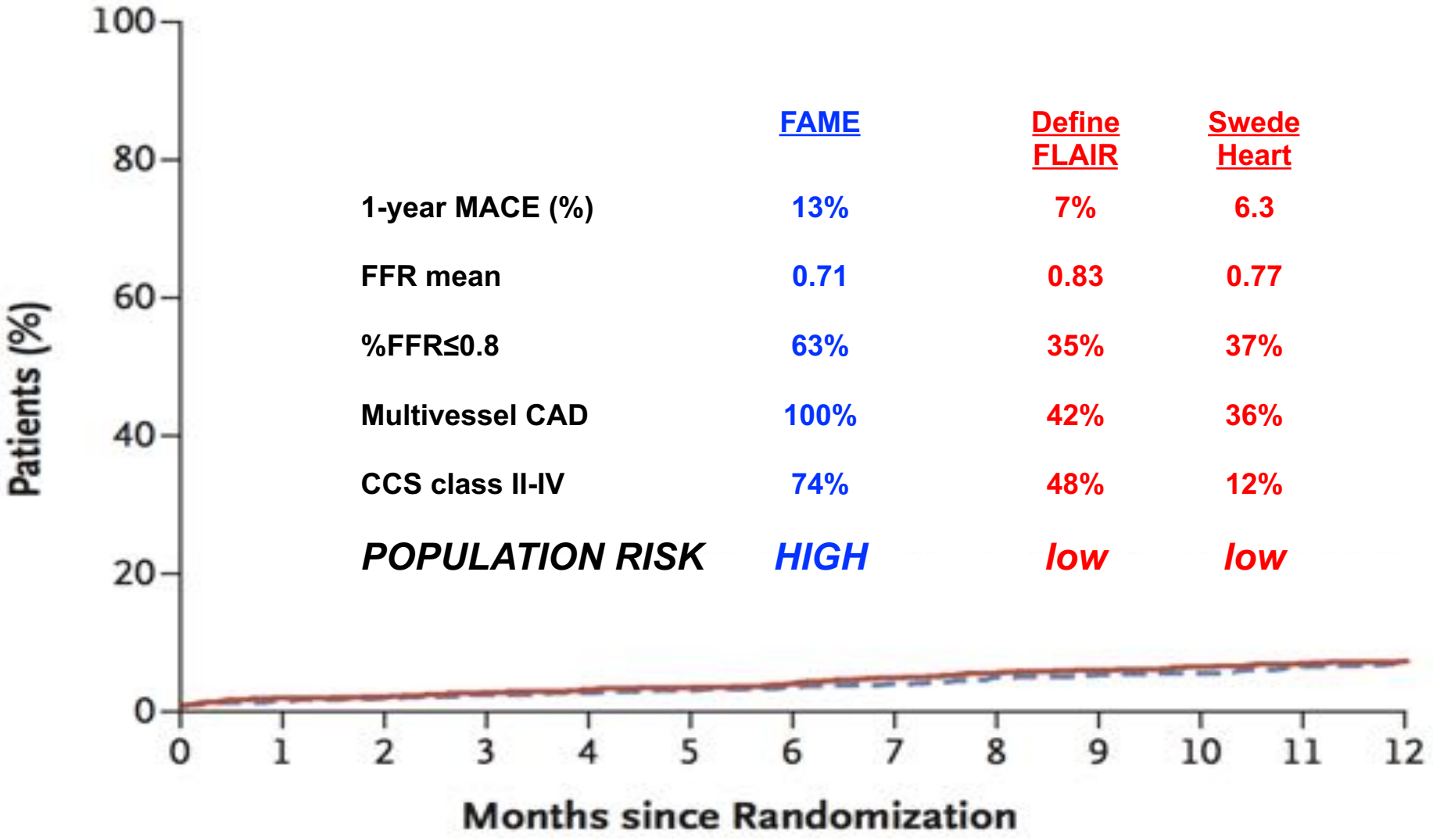
#2 Low Event Rate

	FAME	Define FLAIR	Swede Heart
1-year MACE (%)	13%	7%	6.3
FFR mean	0.71	0.83	0.77
%FFR≤0.8	63%	35%	37%
Multivessel CAD	100%	42%	36%
CCS class II-IV	74%	48%	12%
POPULATION RISK	*HIGH*	*low*	*low*



An angio-guided arm would certainly also be “non-inferior”

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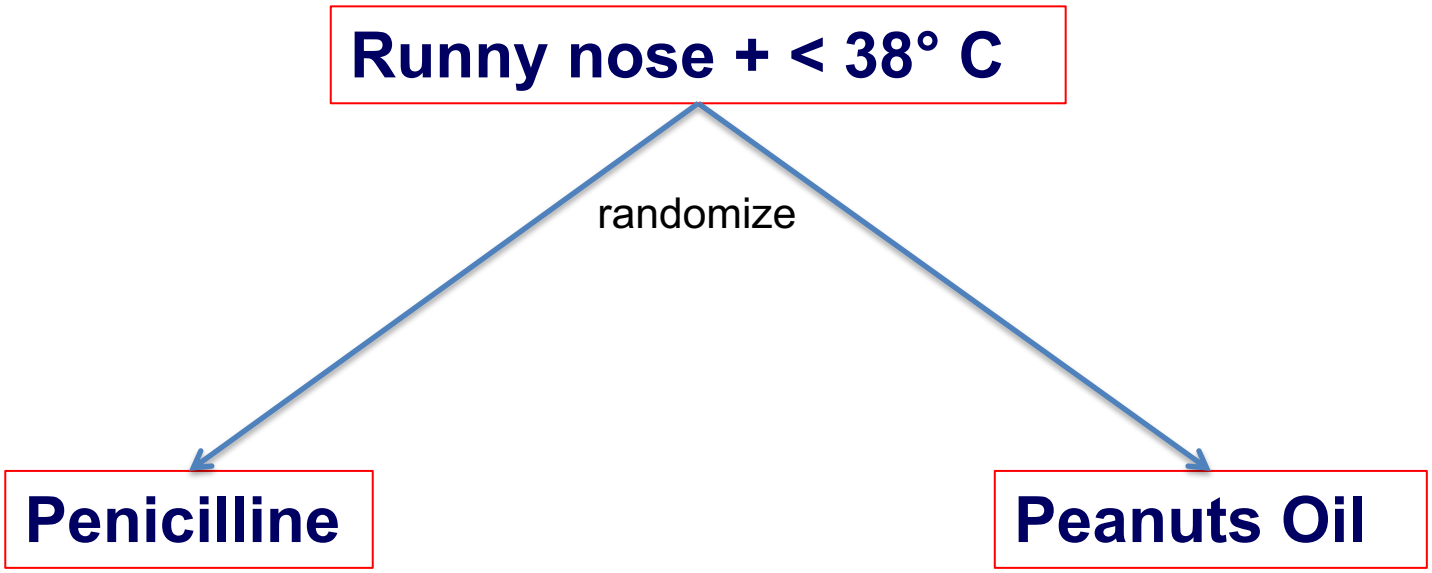
#2 Low Event Rate



Non-Inferior ?

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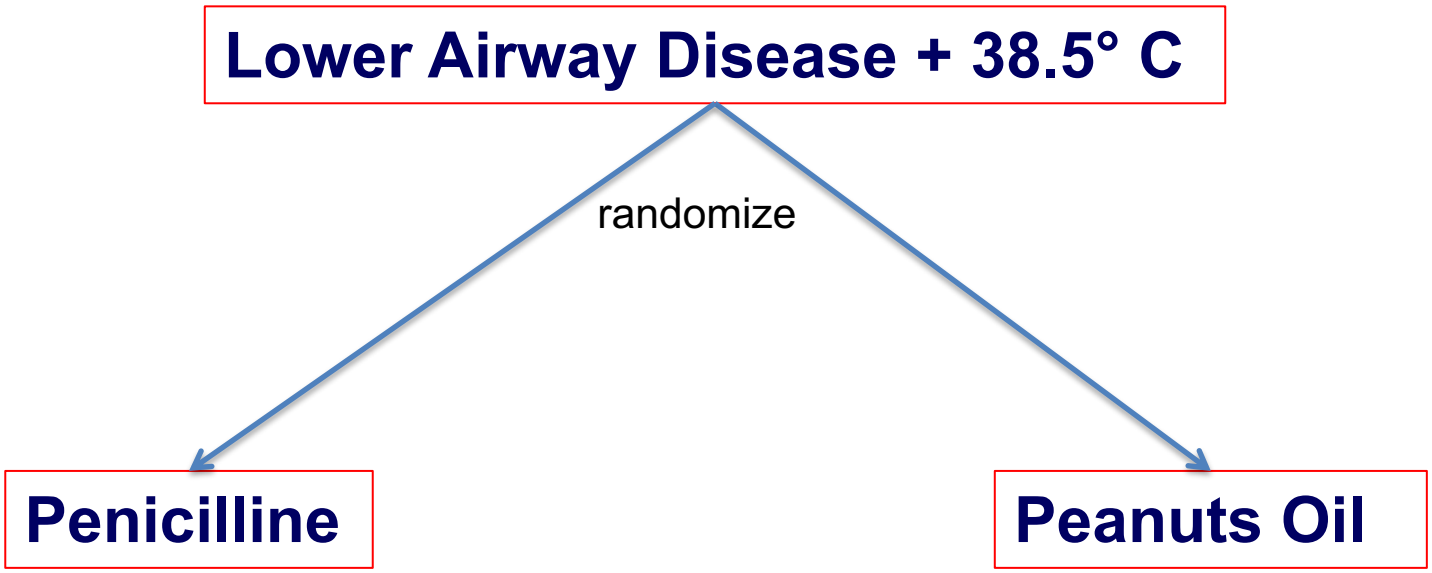

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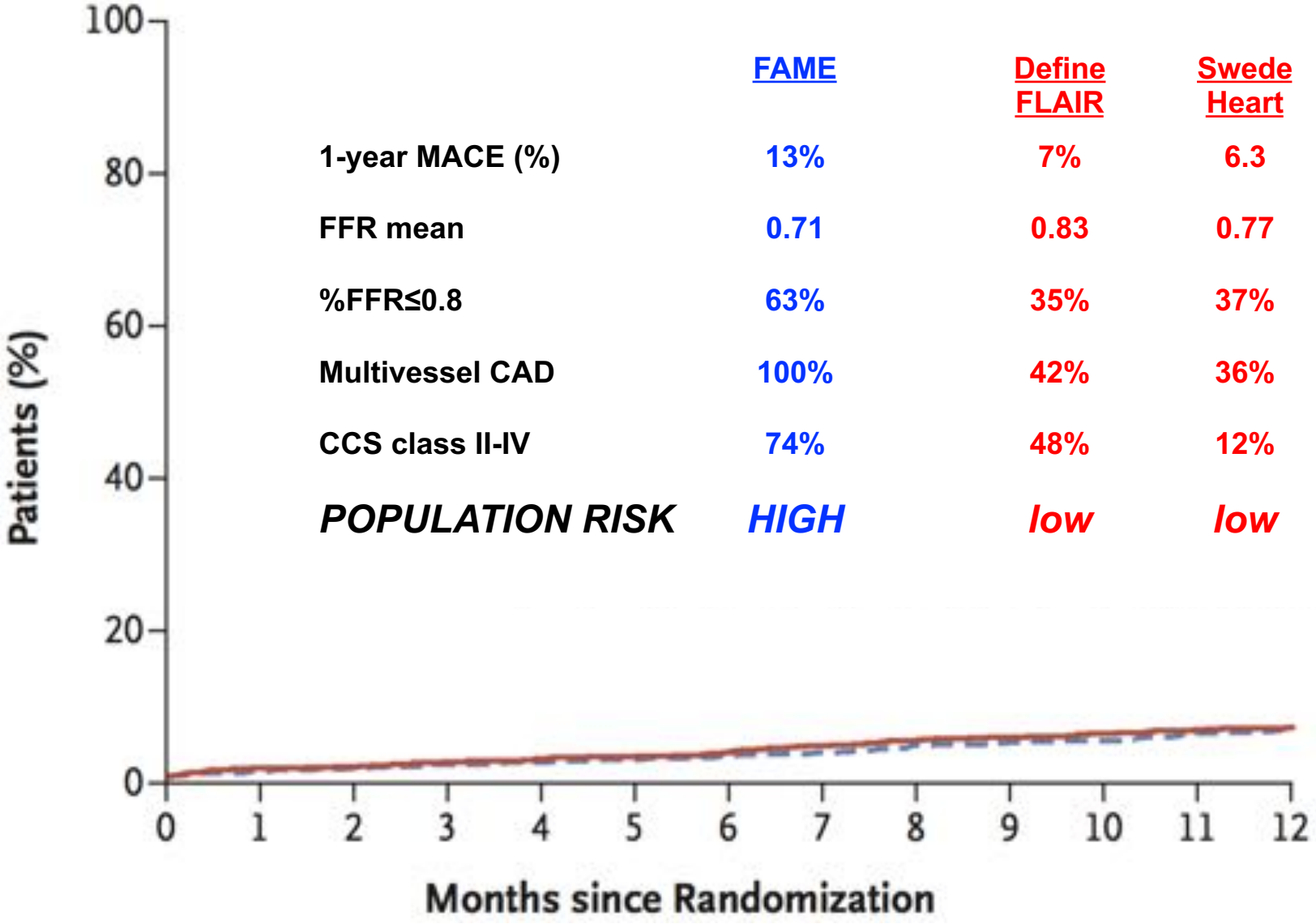

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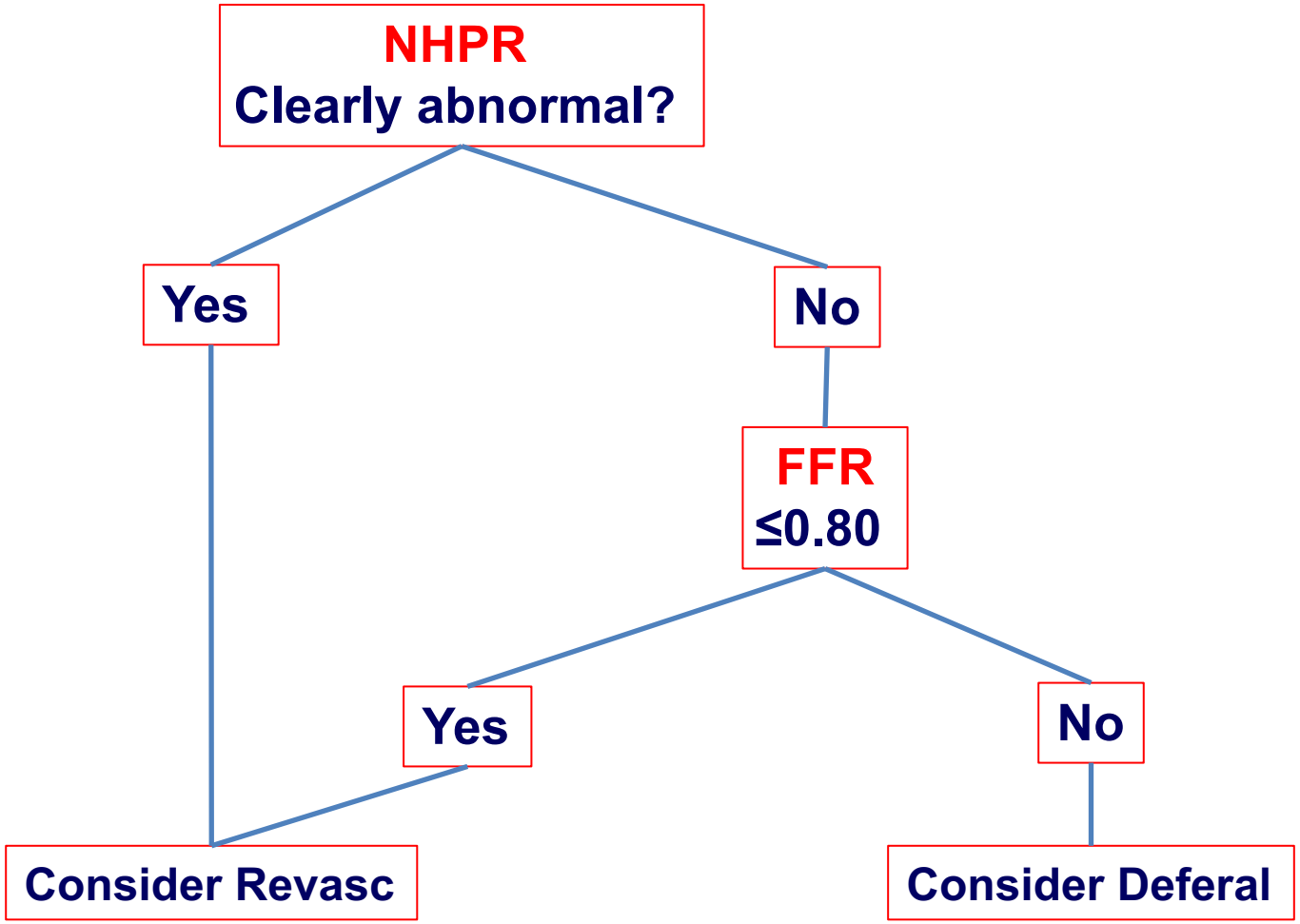
Hybrid Approach



No 'deferral' based on 'normal' resting indices

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NHPR
Non-Hyperemic Pressure Ratio's

NHPR	Name	Definition	Company
P_d/P_a	Resting whole cycle Pd/Pa	Average Pd/Pa during the entire cardiac cycle	Generic
iFR	Instantaneous Wave-Free Ratio	Average Pd/Pa during the wave-free period (WFP)	Proprietary Philips
DPR	Diastolic Pressure ratio	Averagen Pd/Pa during the entire diastole	Generic –Opsens, Acist
dPR	Diastolic Pressure Ratio	Pd/Pa during the "flat" period of the dP/dt signal	Generic Erasmus MC/Rotterdam
RFR	Resting Full-Cycle Ratio	Lowest mean Pd/Pa ratio during the mean Pa ending at systole entire cardiac cycle	Proprietary-Abbott/coroventis
DFR	Diastolic Hyperemia-Free Ratio	Average Pd/Pa during the period between Pa<mean Pa ending at systole	Proprietary-Boston Scientific

Source: Tiren Technology, Mona Tiren

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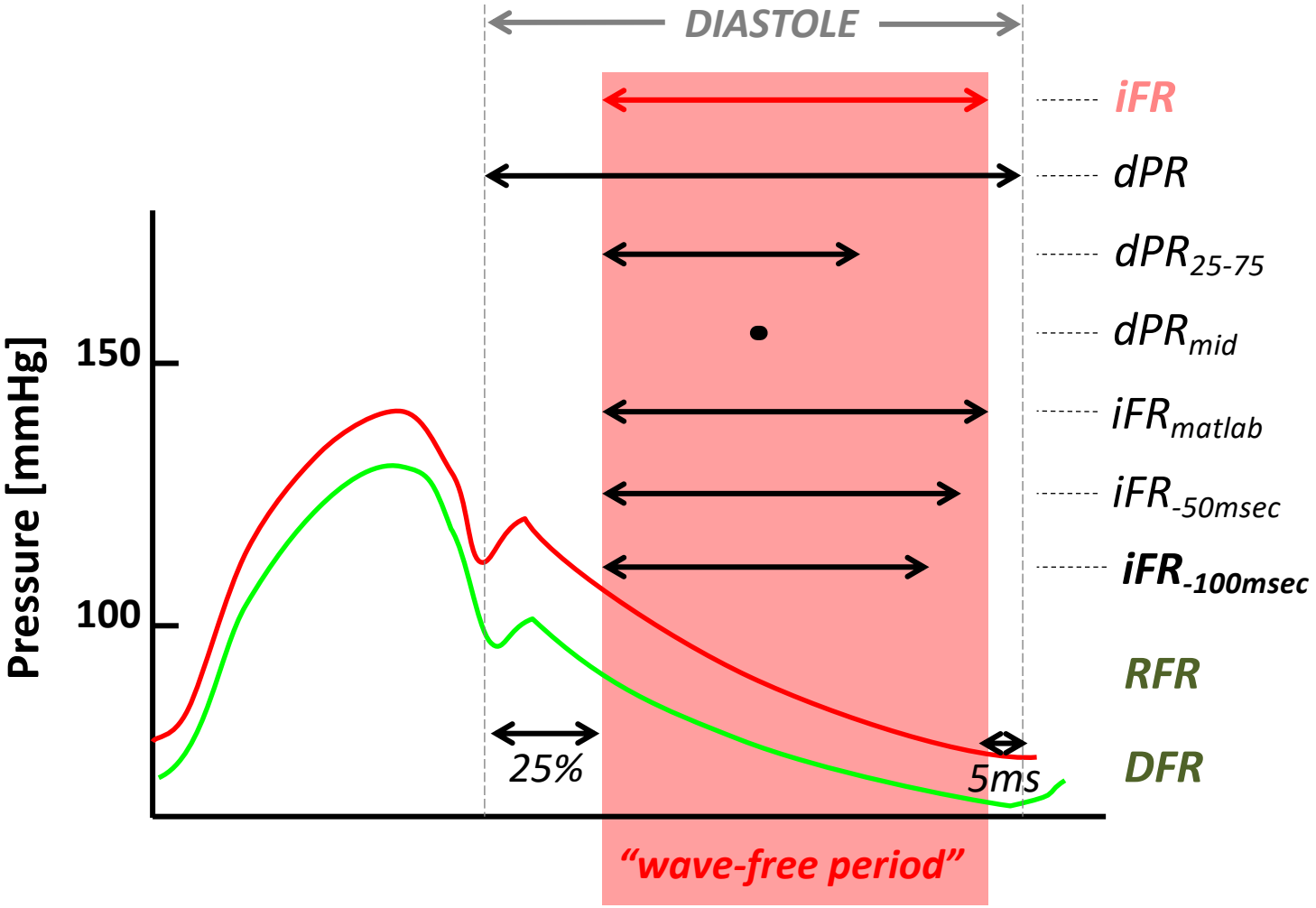
Are all NHPR's equal?

- 257 stenoses
- iFR by Volcano
- Various other diastolic indices



Van 't Veer M et al JACC 2017

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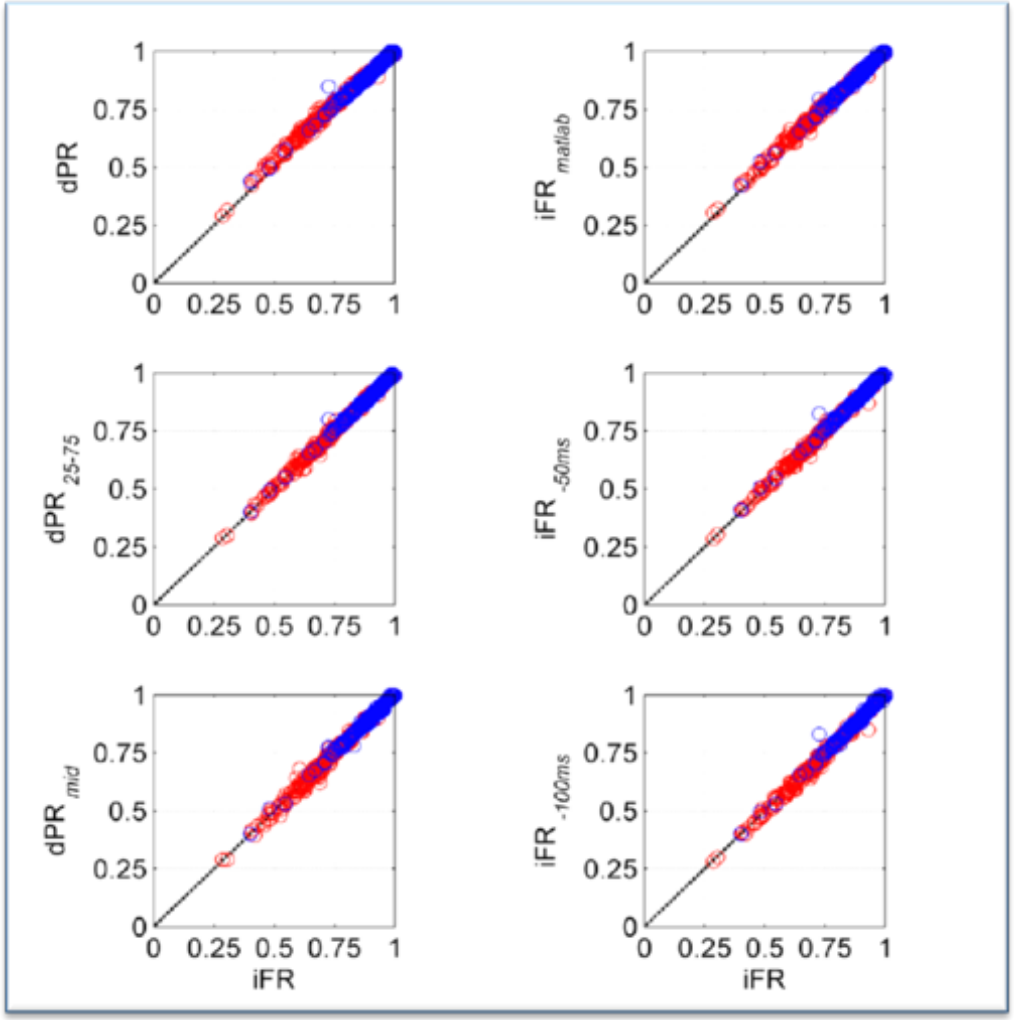

index	difference with iFR ± stdev		
dPR	0.0059	±	0.0108
dPR_{25-75}	0.0012	±	0.0065
dPR_{mid}	0.0012	±	0.0081
iFR_{matlab}	0.0054	±	0.0088
$iFR_{-50msec}$	0.0026	±	0.0083
$iFR_{-100mse}$	0.0009	±	0.0086

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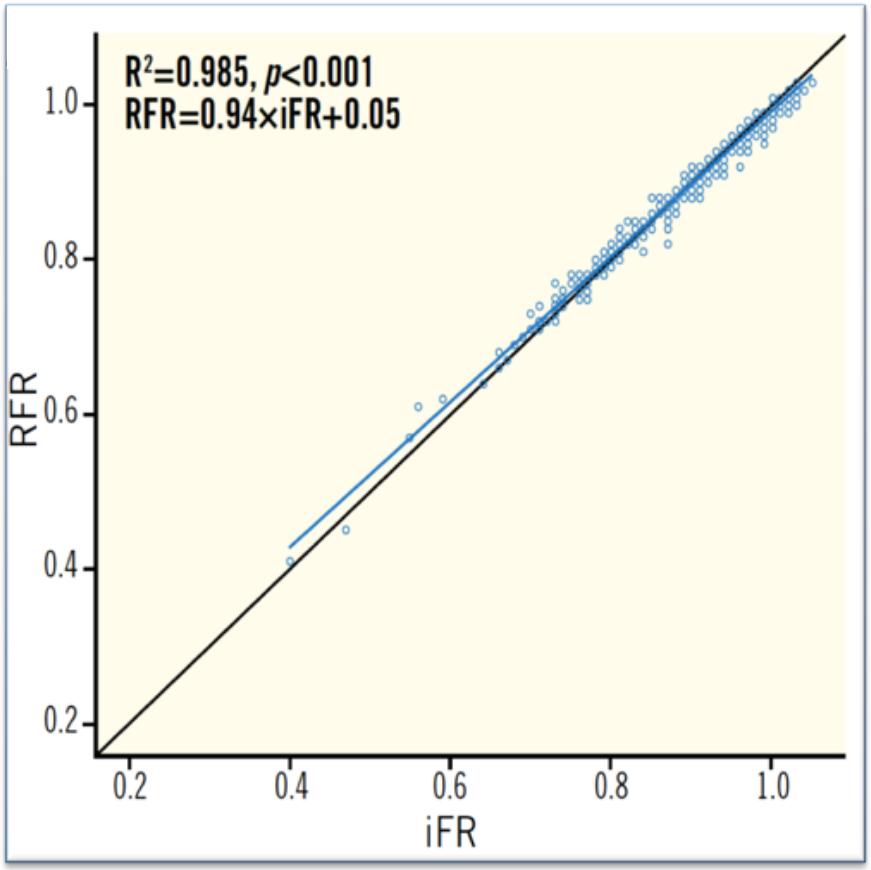
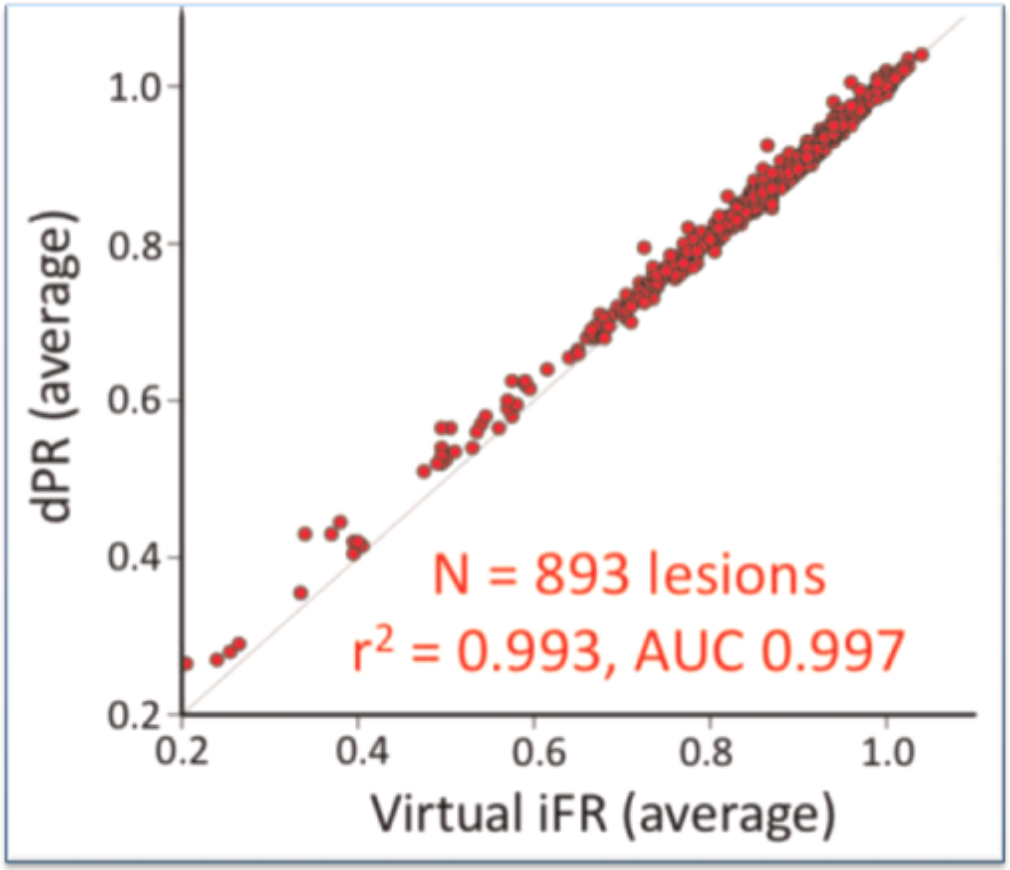
Are all NHPR's equal?

RFR vs iFR



Johan Svanerud et al. EuroInterv 2018;14:806-814

dPR vs iFR



Nils Johnson et al Eur Heart J 2019, In Press

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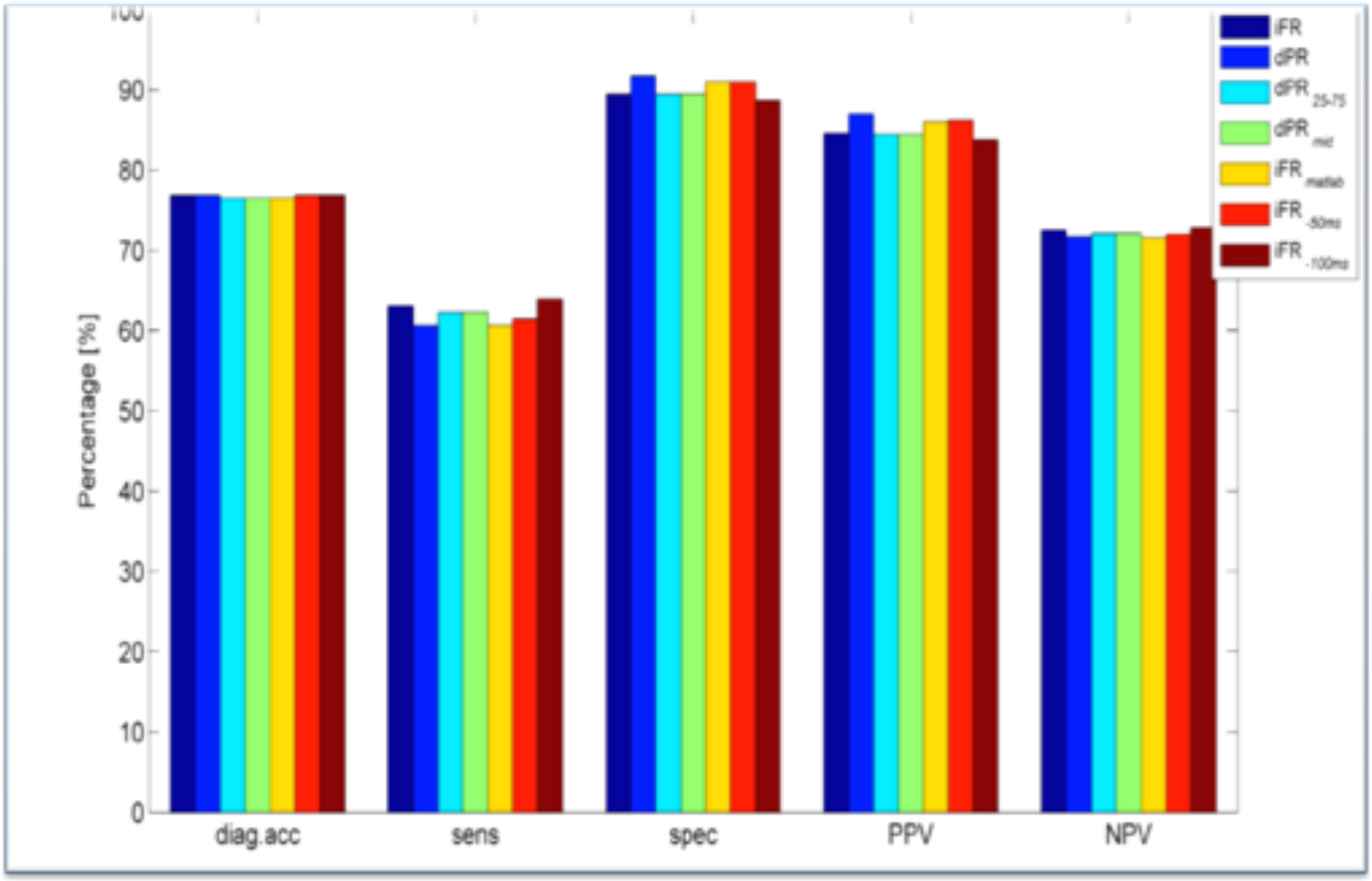
Diagnostic Accuracy

Of NHPR's (0.89) vs FFR (0.80)



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Equality
(Mathematics)

$$A = B$$

And

$$B = C$$

Then

$$A = C$$

And A can always be replaced by B or by C

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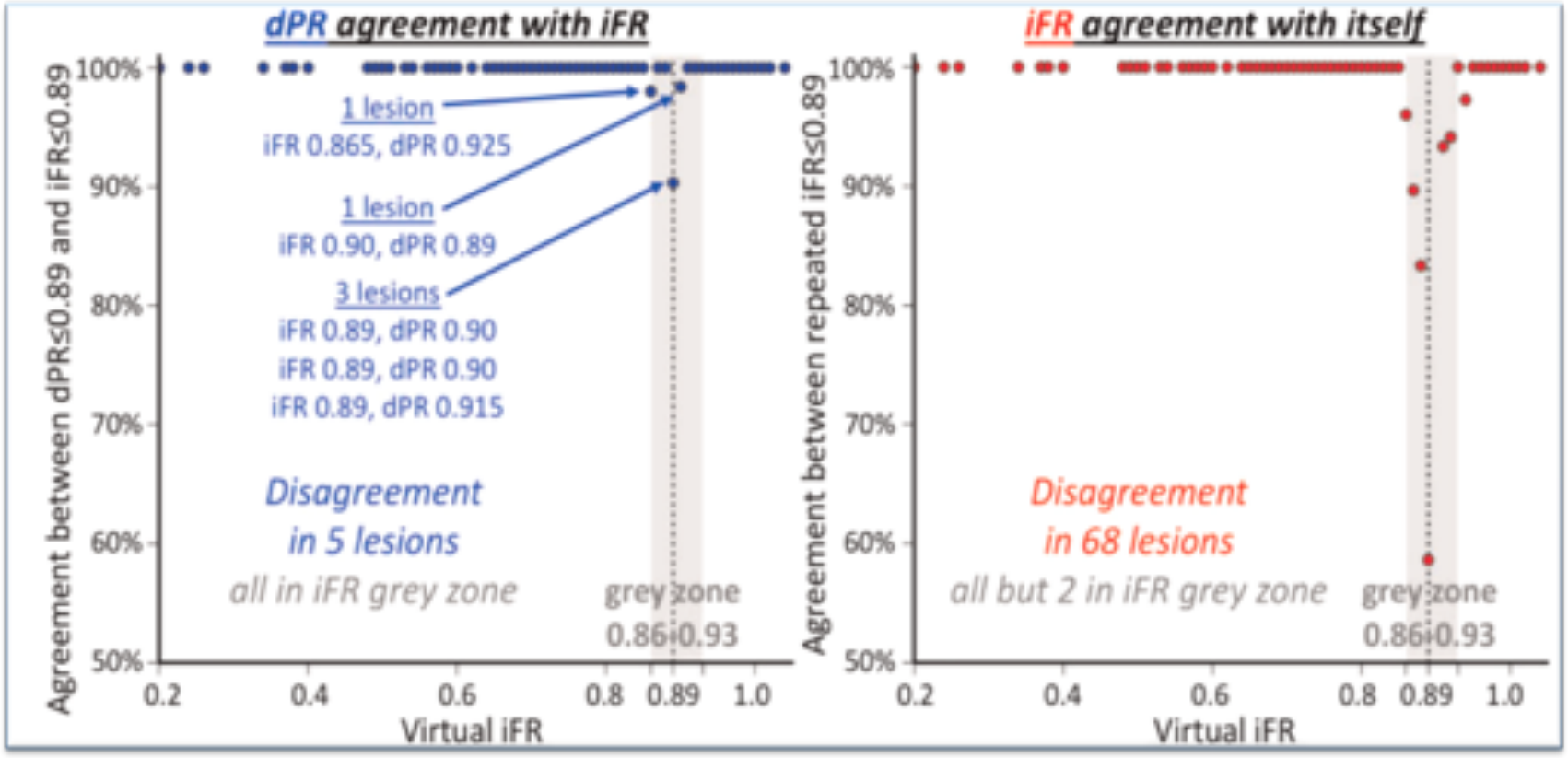
Numerical Equivalence

When the difference between 2 repeated measurements of A is similar to the difference observed between A and B, then A and B can be considered numerically equivalent



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≈ Generics

(They are biologically equivalent, NO new outcomes studies needed!)

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Conclusive Remarks

1. A “hybrid approach” with NHPR’s may be attractive but

   ✓ Only in low risk patients/lesions
   ✓ Cave deferral based on ‘normal’ NHPR’s

2. All NHPR’s are numerically equal and interchangeable with respect to cut-off values, clinical recommendation, and guidelines…

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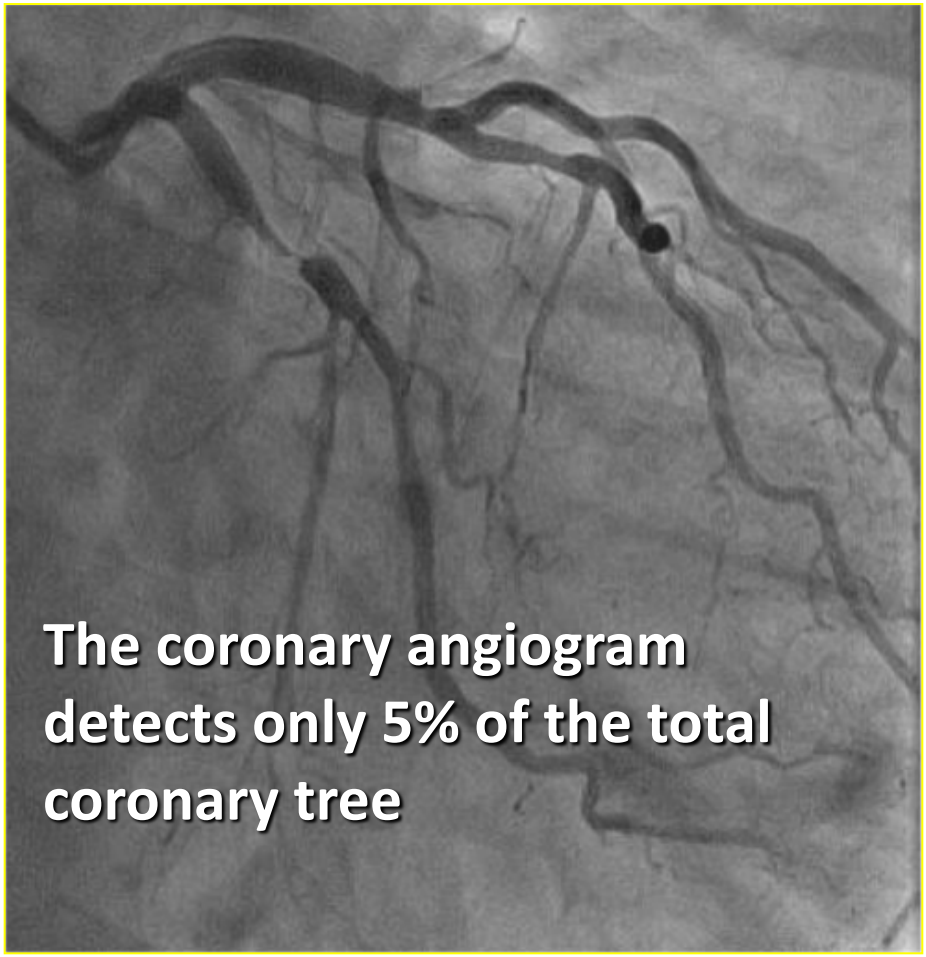
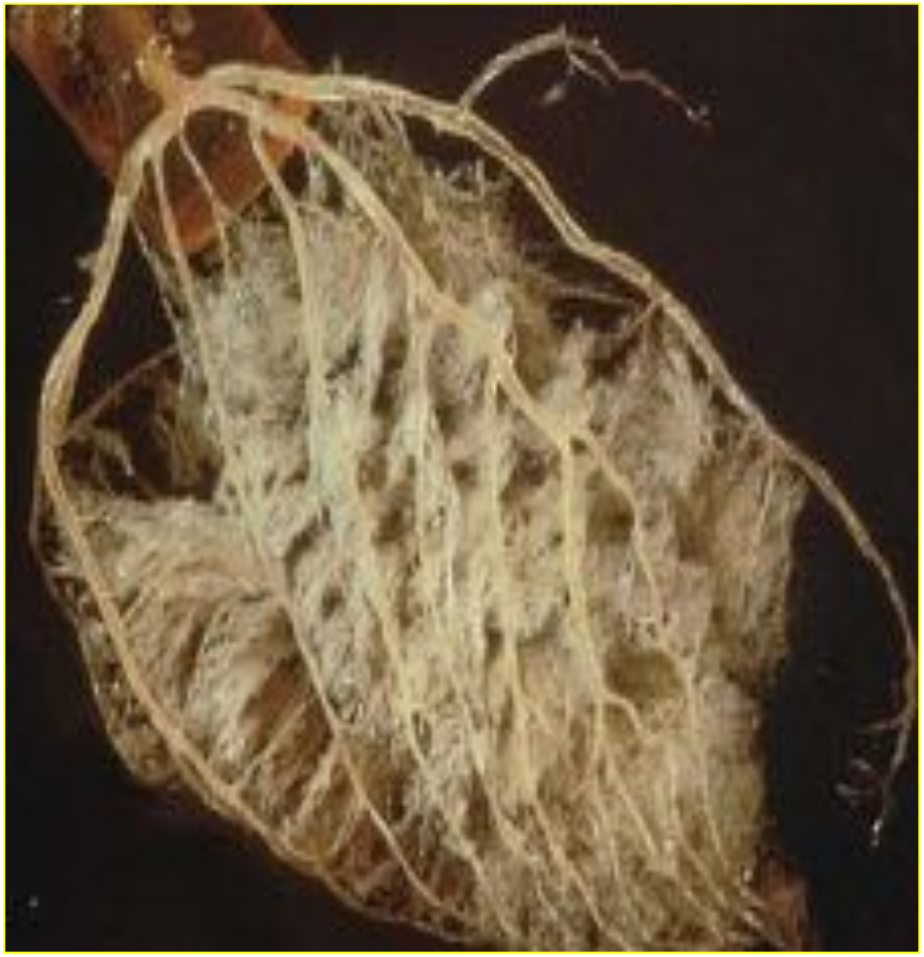
Two-Compartment Model of the Coronary Circulation





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Part of the World Known at the Time of Babylonia

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Absolute Coronary Flow and Resistance

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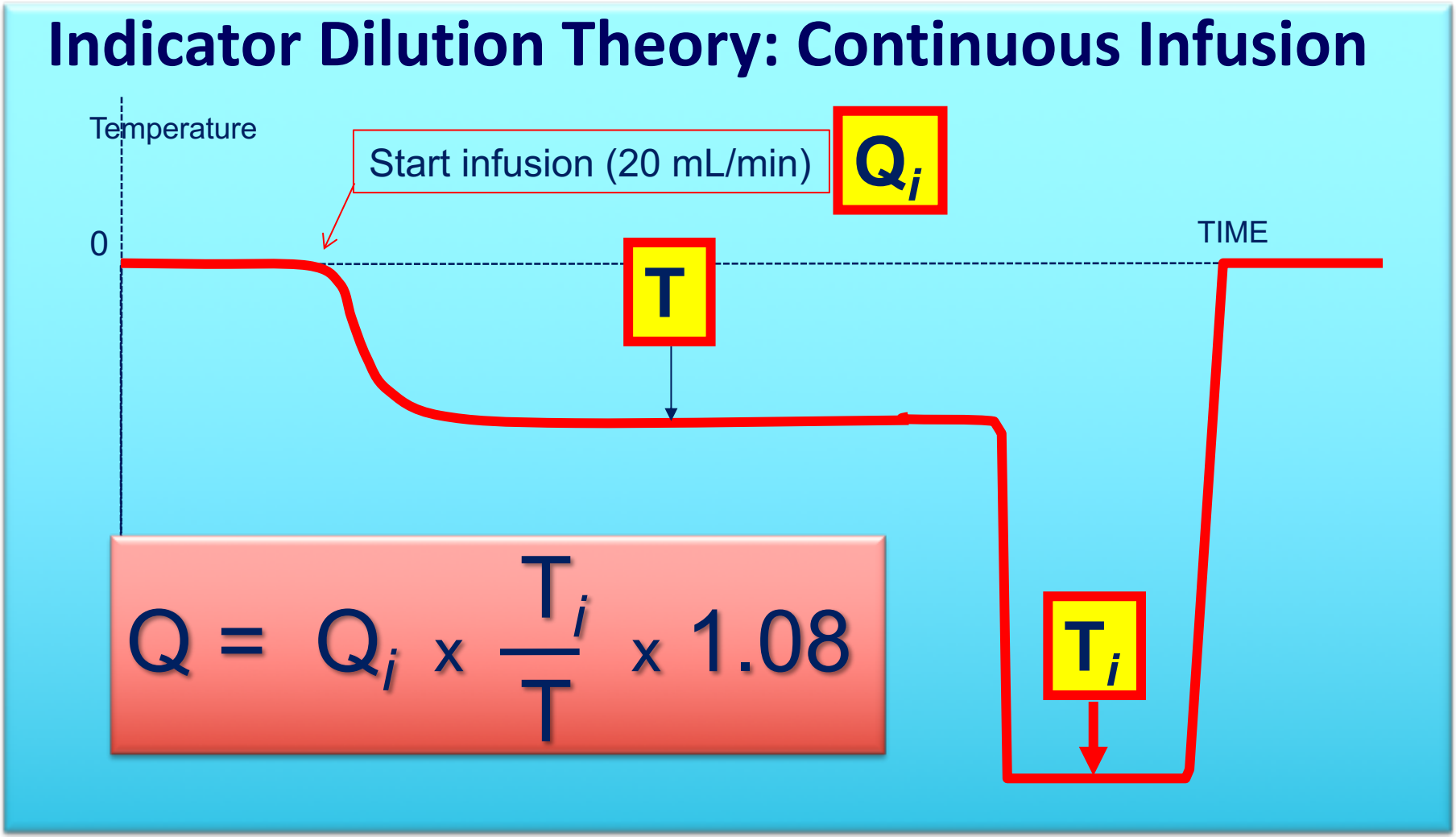
Absolute Coronary Flow and Resistance



Aarnoudse W et al J Am Coll Cardiol 2007;50:2294

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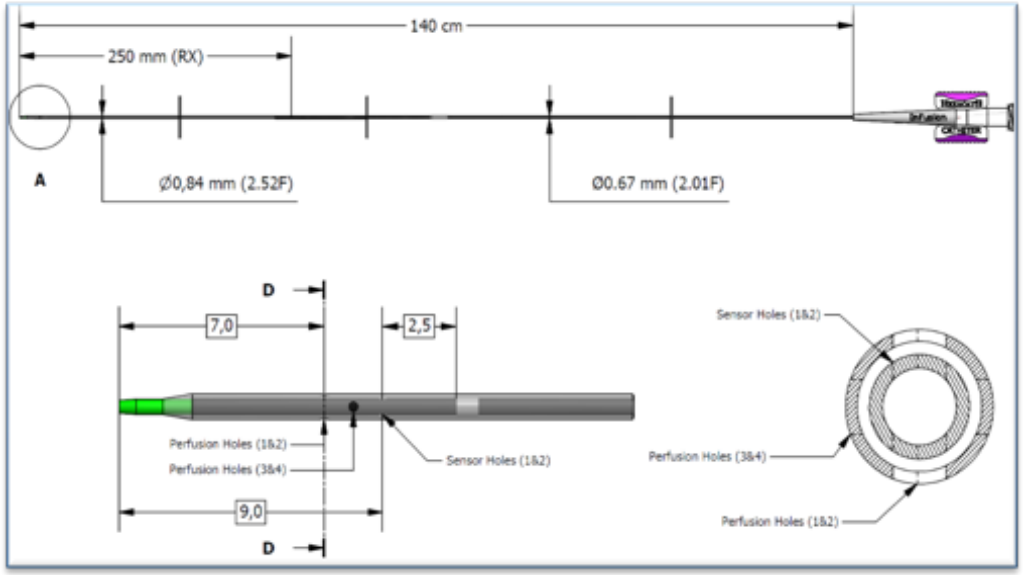
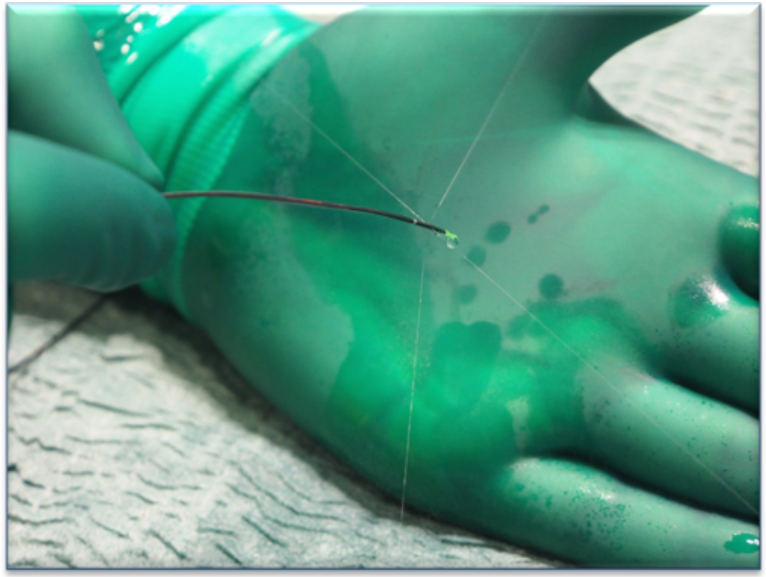
Absolute Coronary Flow

Development of a novel monorail infusion catheter





- **Monorail** (2.5 F or 0.8 mm outer diameter)
- **4 outer holes (mixing)**
- **2 inner holes (T_i)**

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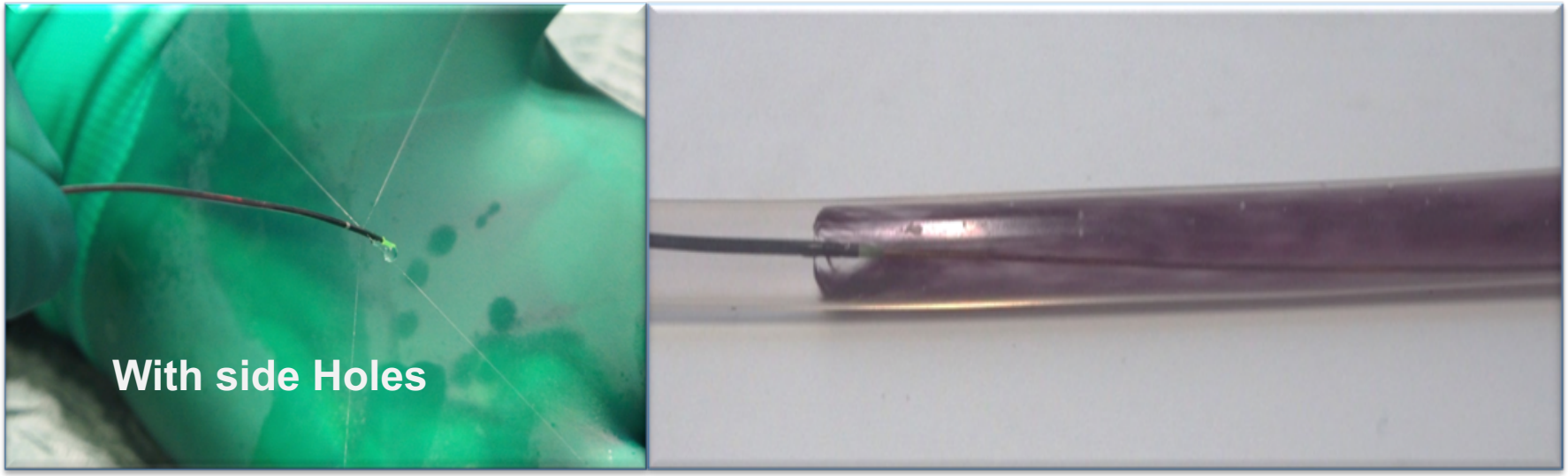
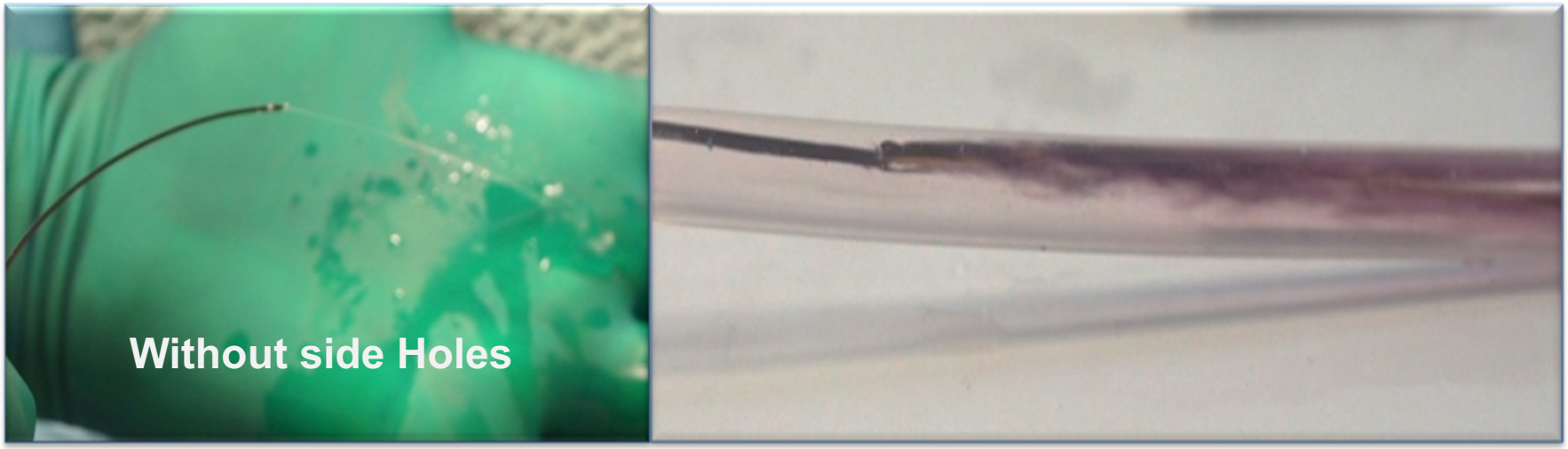
Absolute Coronary Flow

Importance of complete and immediate mixing





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Units

Vascular resistance

Refers to the resistance that must be overcome to push blood through the circulatory system and create flow

$$R = \frac{P}{Q}$$

P → **mm Hg**

Q → **L/min**

Units of resistance

- Dynes.s/cm^5
- MPa.s/m^3
- Wood Units (mm Hg/L/min)

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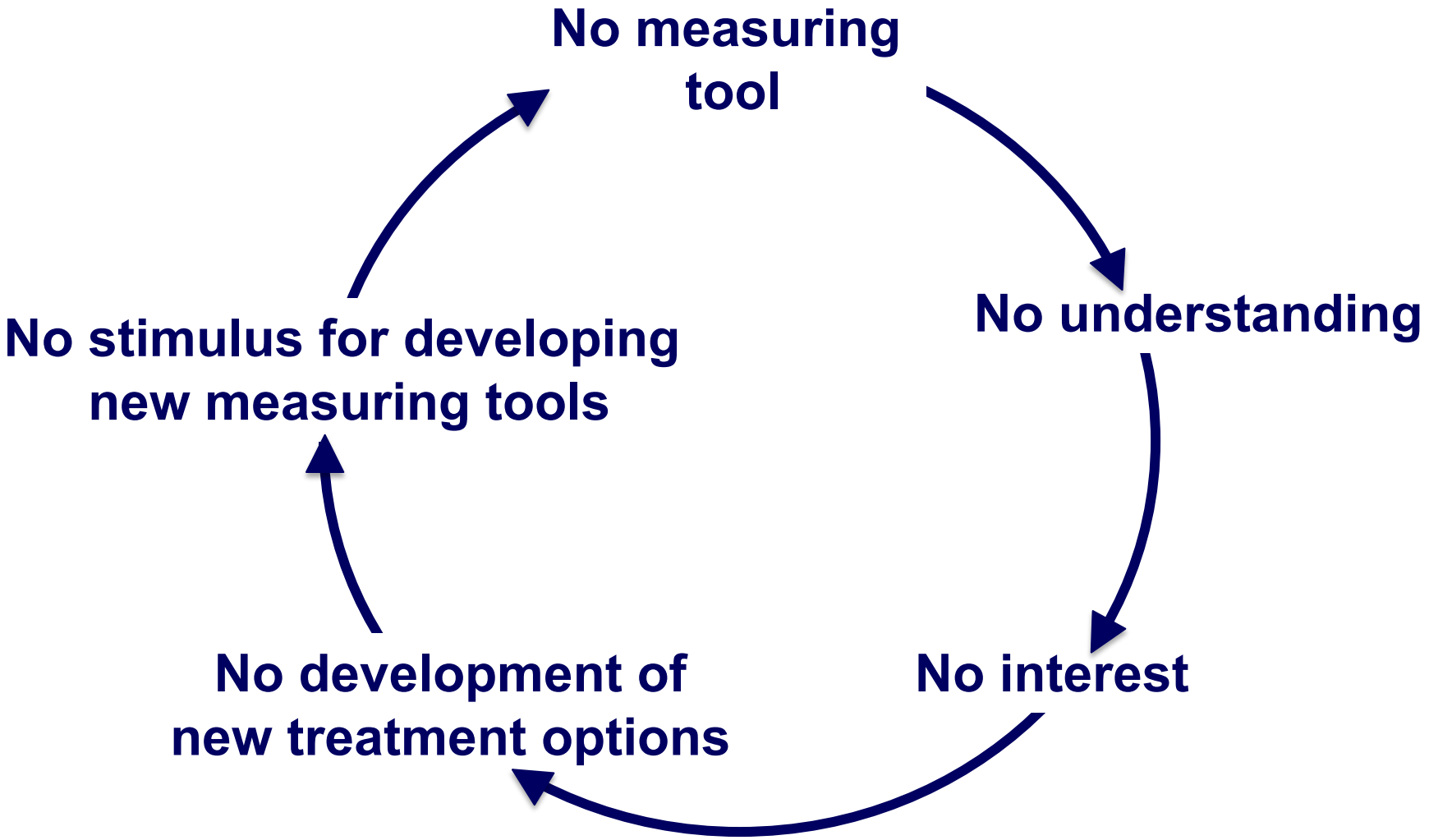
Microvascular's Catch 22



One cannot treat if one cannot measure

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BMJ

BMJ 2012;344:e1553 doi: 10.1136/bmj.e1553 (Published 15 March 2012)

RESEARCH

Credibility of claims of subgroup effects in randomised controlled trials: systematic review

- The authors of trial reports, however, often do not prespecify hypotheses for subgroups, fail to carry out a statistical test for interaction, and undertake a large number of subgroup analyses. ***Given these limitations, it is perhaps not surprising that many inferences from subgroup analyses have proved spurious.***
- Authors often claim subgroup effects in their trial report. However, the credibility of subgroup effects, even when claims are strong, is usually low. ***Users of the information should treat claims that fail to meet most criteria with scepticism.***

Sun X, *BMJ*. 2012 Mar 15;344:e1553. (Title and ***quotes***)

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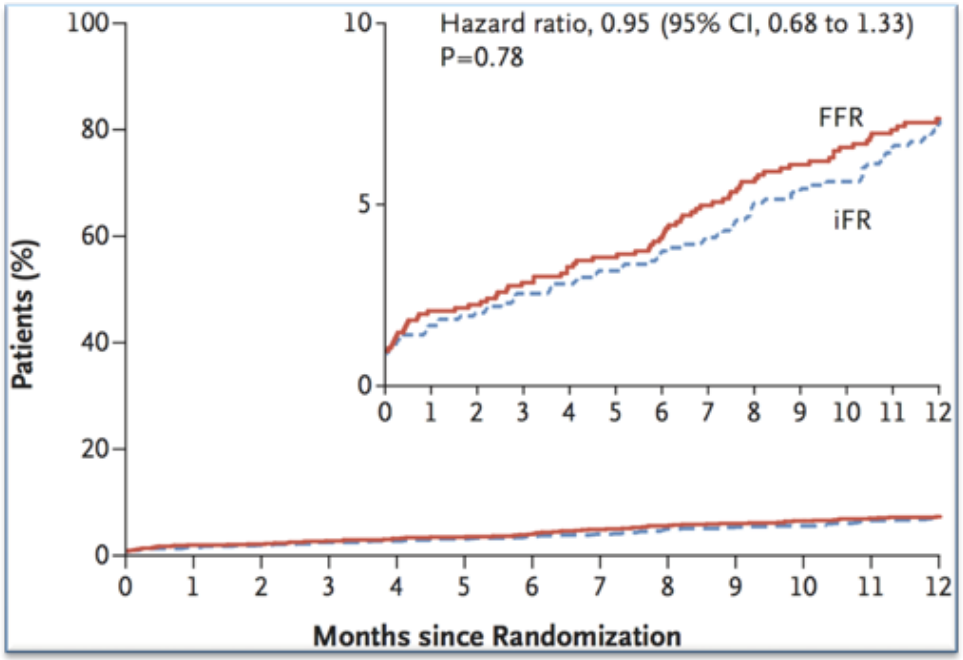
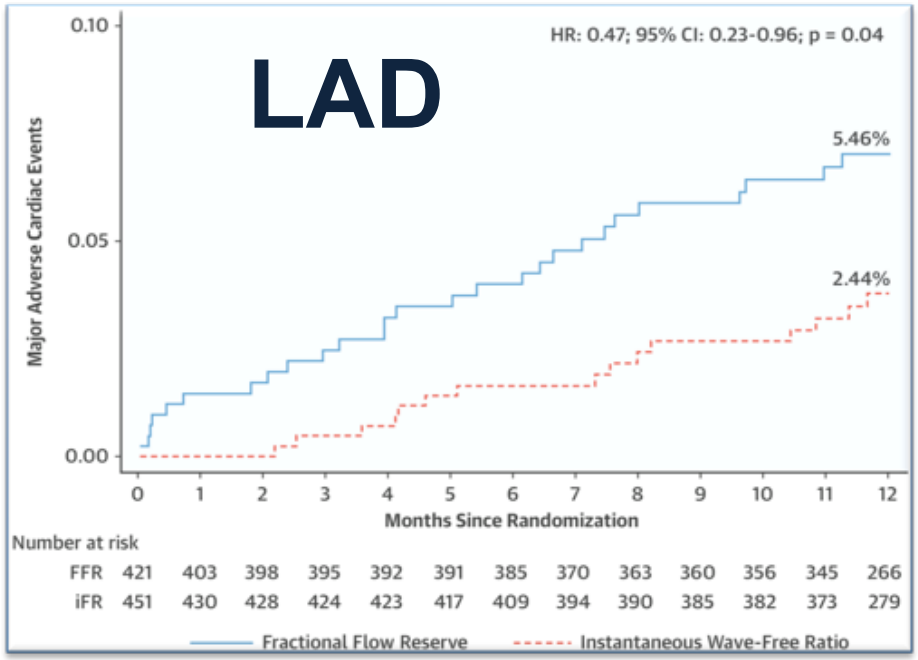
Define FLAIR trial



Davies JE, NEJM. 2017



Sen JACC 2019

Where are the RCA's and the LCx's?

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BMJ

Criteria of credibility of claims of subgroup effects in randomized trials

Ten criteria used to assess credibility of subgroup effect

Design

- Was the subgroup variable a baseline characteristic?
- Was the subgroup variable a stratification factor at randomisation?*
- Was the subgroup hypothesis specified a priori?
- Was the subgroup analysis one of a small number of subgroup hypotheses tested (≤5)?

Analysis

- Was the test of interaction significant (interaction P<0.05)?
- Was the significant interaction effect independent, if there were multiple significant interactions?

Context

- Was the direction of subgroup effect correctly prespecified?
- Was the subgroup effect consistent with evidence from previous related studies?
- Was the subgroup effect consistent across related outcomes?
- Was there any indirect evidence to support the apparent subgroup effect—for example, biological rationale, laboratory tests, animal studies?

*Item was not included in our previously published list of criteria for subgroup credibility

Sun X, BMJ. 2012 Mar 15;344:e1553.

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Criteria of credibility of claims of subgroup effects in randomized trials

Ten criteria used to assess credibility of subgroup effect

Design

- Was the subgroup variable a baseline characteristic? ***Yes***
- Was the subgroup variable a stratification factor at randomisation?* ***No***
- Was the subgroup hypothesis specified a priori? ***No*** (not in online protocols at NEJM)
- Was the subgroup analysis one of a small number of subgroup hypotheses tested (≤5)? ***No*** (EuroPCR had 6 subgroups)

Analysis

- Was the test of interaction significant (interaction P<0.05)? ***No*** (not performed in JACC paper, p=0.11 using their #'s)
- Was the significant interaction effect independent, if there were multiple significant interactions? ***No*** (not performed)

Context

- Was the direction of subgroup effect correctly prespecified? ***No*** (not in online protocols at NEJM)
- Was the subgroup effect consistent with evidence from previous related studies? ***No*** (not consistent with Muller study)
- Was the subgroup effect consistent across related outcomes? ***No*** (not provided)
- Was there any indirect evidence to support the apparent subgroup effect—for example, biological rationale, laboratory tests, animal studies? ***No*** (not consistent with De Bruyne *Circulation* 1994 PET and Pijls *NEJM* 1996 studies)

*Item was not included in our previously published list of criteria for subgroup credibility

1 of 10 criteria satisfied

Sun X, BMJ. 2012 Mar 15;344:e1553.