European Heart House

Coronary Physiology in the Catheterization Laboratory

Thursday 25 – Saturday 27, 2013

Conclusive Remarks

Bernard De Bruyne, MD, PhD
Cardiovascular Center Aalst
OLV-Clinic Aalst, Belgium

European Heart House

Coronary Physiology in the Catheterization Laboratory

Thursday 25 – Saturday 27, 2013

Selection Bias

www.cardio-aalst.be

"*People who wish to analyze nature without using mathematics must settle for a reduced understanding*",
- Richard P Feynman, PhD, Nobel Laureate of Physics in 1965

People who wish to treat CAD without physiology must settle for a reduced understanding

- **Clinical outcome data**
- **Microvasculature**
- **KISS principle**

www.cardio-aalst.be

Unmet clinical need

Clinician's request to engineers/industry

(Not the contrary)

The value of FFR in terms of

Clinical Outcome

Has been validated in patients with...

1.	**Intermediate stenoses**	*(Pijls et al. New Engl J Med 1996)* *(Bech et al Circulation 2001)* *(Pijls et al. JACC 2010)*
2.	**Post-myocardial setting**	*(De Bruyne et al Circulation 2001)* *(Ntalianis et al. JACCInterv 2010)*
3.	**Multivessel disease**	*(Tonino et al. NEJM 2009)* *(Berger et al JACC 2005)* *(Botman et al CCI 2004)* *(De Bruyne et al NEJM 2012)*
4.	**Left main stenosis**	*(Hamilos et al. Circulation 2009)*
5.	**Proximal LAD stenosis**	*(Muller et al. JACCInterv 2011)*
6.	**Bifurcation lesions**	*(Koo et al. Eur Heart J 2010)*
7.	**Hybrid revascularization**	*(Davidavicius et al Circulation 2005)*
8.	**Post CABG**	*(Botman et al Ann Thor Surg 2007)*
9.	**Small vessel**	*(Puymirtat et al Circ Interv 2011)*

FAME 3

PI: William F Fearon

All Comers with 3 V CAD
(not involving LM)

↓

Amenable to PCI/CABG and meet inclusion criteria
No exclusion criteria met and patient consents

↓

Heart team identifies lesions for PCI/CABG
and then patient is randomized

↙ ↘

FFR-Guided PCI with DES
Stent all lesions with FFR < 0.80
(n=750)

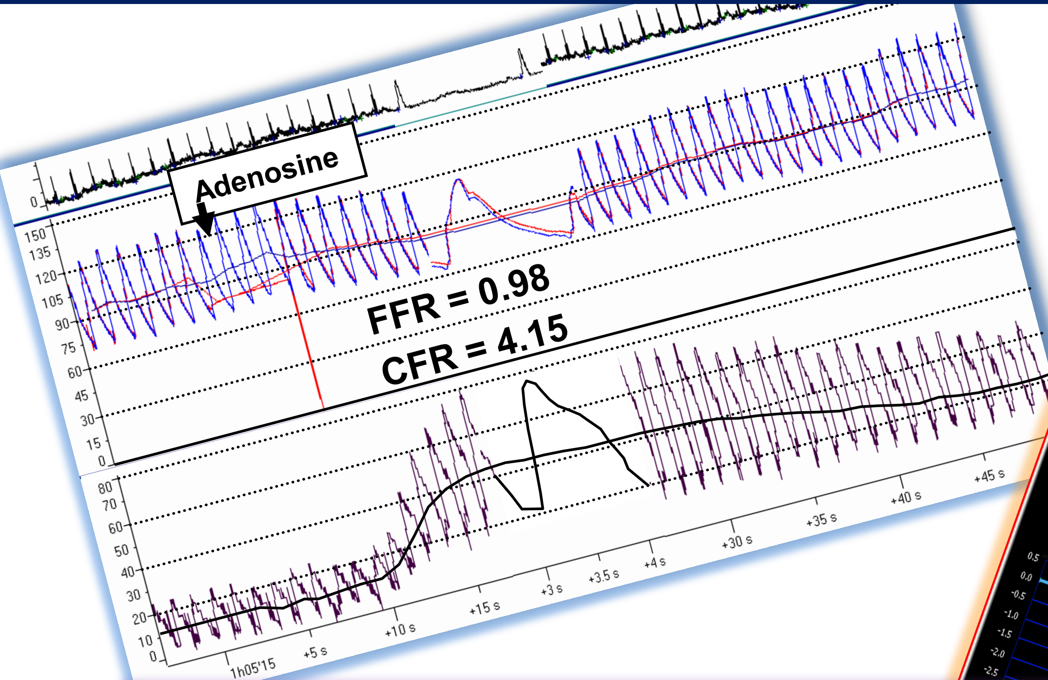
Perform CABG based on
coronary angiogram
(n=750)

↘ ↙

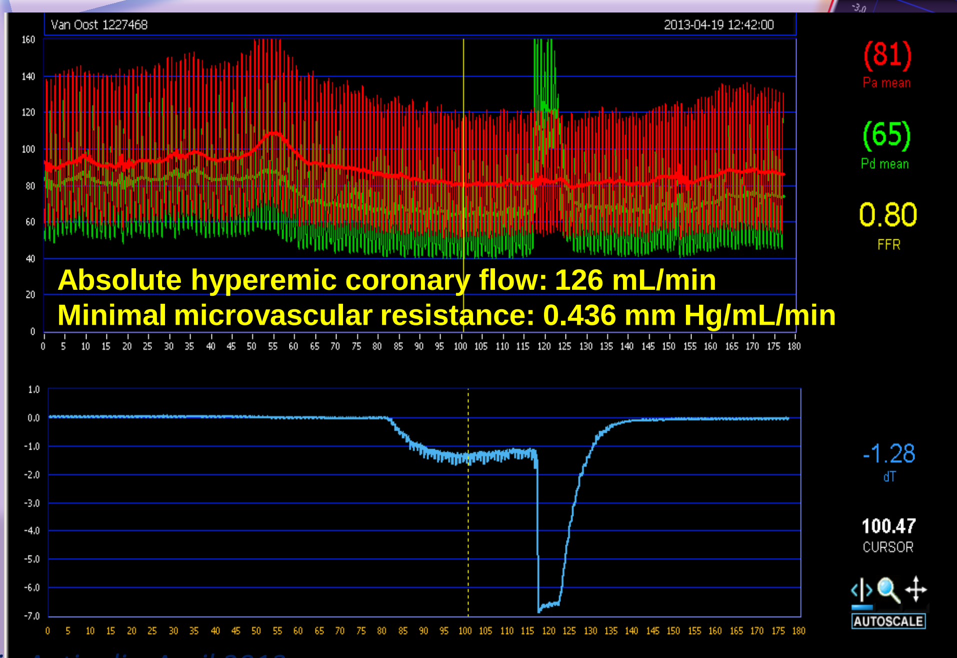
One Year follow-up for MACCE
(1 month, 3 and 5 year follow-up)

- **Clinical outcome data**
- **Microvasculature**
- **KISS principle**

ETP Course: Conclusions



www.cardio-aalst.be



- **Clinical outcome data**
- **Microvasculature**
- **KISS principle**

The "KISS" Principle:

Keep It Simple, Stupid!

Appendix

It should be kept in mind that all of the theoretical considerations in this appendix apply to a system at maximum vasodilation. Therefore, the resistances R and R_c are minimal and constant.

First, it will be proved that the ratio between mean arterial pressure (P_a) and coronary wedge pressure (P_w), both after subtraction of venous pressure (P_v), is constant. For that purpose, suppose in Figure 1, at any arbitrary pressures P_a and P_v, that $R_s=\infty$ and $Q_s=0$, as with total occlusion; then, $Q=Q_c$ and $P_d=P_w$ by definition. In that case:

$$P_a-P_v=Q(R+R_c)$$

and

$$P_w-P_v=QR$$

Therefore

$$\frac{P_a-P_v}{P_w-P_v}=\frac{(R+R_c)}{R}=1+\frac{R_c}{R}=C_1 \quad (A1a)$$

Equation A1a can also be rearranged into the following two forms, which will be helpful in later considerations:

$$\frac{P_w-P_v}{P_a-P_w}=\frac{R}{R_c}=C_2 \quad (A1b)$$

and

$$\frac{P_a-P_v}{P_a-P_w}=\frac{R}{R_c}+1=C_3 \quad (A1c)$$

where C_1, C_2, and C_3 are all different constants characterizing collateral resistance relative to the resistance of the myocardial bed supplied by the collaterals at maximum vasodilation.

The second step is the calculation of fractional flow reserve of the stenotic coronary artery (FFR_{cor}). By definition,

$$FFR_{cor}=\frac{Q_s}{Q_s^N}=\frac{Q-Q_c}{Q^N-Q_c^N}$$

Because $Q_c^N=0$:

$$FFR_{cor}=\frac{Q-Q_c}{Q^N}$$

$$=\frac{(P_d-P_v)/R-(P_a-P_d)/R_c}{(P_a-P_v)/R}$$

$$=\frac{(P_d-P_v)-(P_a-P_d)\cdot R/R_c}{(P_a-P_v)}$$

Substitution of the constant value C_2, obtained from Equation A1b, gives the following:

$$FFR_{cor}=\frac{(P_d-P_v)(P_a-P_w)-(P_a-P_d)(P_w-P_v)}{(P_a-P_v)(P_a-P_w)}$$

$$=\frac{P_d-P_w}{P_a-P_w} \quad (A2a)$$

$$=1-\frac{\Delta P}{P_a-P_w} \quad (A2b)$$

Next, fractional flow reserve of the myocardium (FFR_{myo}) is calculated as follows:

$$FFR_{myo}=\frac{Q}{Q^N}=\frac{(P_d-P_v)/R}{(P_a-P_v)/R}=\frac{P_d-P_v}{P_a-P_v} \quad (A3a)$$

$$=1-\frac{\Delta P}{P_a-P_v} \quad (A3b)$$

Equation A3 has been derived previously by Gould.[1,5]

The contribution of collateral flow to total flow now is calculated as follows. By definition,

$$Q=Q_c+Q_s \quad (A4a)$$

Therefore:

$$\frac{Q_c}{Q^N}=\frac{Q}{Q^N}-\frac{Q_s}{Q^N}$$

and because $Q_s^N=Q^N$, this can be written as the following:

$$Q_c=(FFR_{myo}-FFR_{cor})\cdot Q^N \quad (A4b)$$

In case of interventions, it should be realized that flow at maximum vasodilation is directly proportional to the driving pressure P_a-P_v. Therefore, the ratio between maximum flow through the coronary artery before (situation 1) and after the intervention (situation 2) can be written as the following:

$$\frac{Q_s^{(2)}}{Q_s^{(1)}}=\frac{Q_s^{(2)}}{Q_s^{(2)N}}\cdot\frac{Q_s^{(2)N}}{Q_s^{(1)N}}\cdot\frac{Q_s^{(1)N}}{Q_s^{(1)}}$$

$$=FFR_{cor}^{(2)}\cdot\frac{P_a^{(2)}-P_v^{(2)}}{P_a^{(1)}-P_v^{(1)}}\cdot\frac{1}{FFR_{cor}^{(1)}}$$

$$=\frac{FFR_{cor}^{(2)}}{FFR_{cor}^{(1)}}\cdot\frac{P_a^{(2)}-P_v^{(2)}}{P_a^{(1)}-P_v^{(1)}}$$

By substitution of Equations A1c and A2a:

$$\frac{Q_s^{(2)}}{Q_s^{(1)}}=\frac{P_d^{(2)}-P_w^{(2)}}{P_d^{(1)}-P_w^{(1)}} \quad (A5a)$$

Note that for evaluation of the functional improvement of a stenotic artery after PTCA, $FFR_{cor}^{(2)}/FFR_{cor}^{(1)}$ theoretically is a better measure than $Q_s^{(2)}/Q_s^{(1)}$ because the first expression is independent of arterial pressure. From Equation A2b it is clear that

$$\frac{FFR_{cor}^{(2)}}{FFR_{cor}^{(1)}}=\frac{P_d^{(2)}-P_w^{(2)}}{P_a^{(2)}-P_w^{(2)}}\cdot\frac{P_a^{(1)}-P_w^{(1)}}{P_d^{(1)}-P_w^{(1)}}$$

$$=\left(1-\frac{\Delta^{(2)}P}{P_a^{(2)}-P_w^{(2)}}\right):\left(1-\frac{\Delta^{(1)}P}{P_a^{(1)}-P_w^{(1)}}\right) \quad (A5b)$$

The expression $FFR_{cor}^{(2)}/FFR_{cor}^{(1)}$ represents the improvement of FFR_{cor} of th...

called pressure-corrected maximum flow ratio (MFR_c) in a previous study.[11]

Equation A5a can also be derived directly from Figure 1 by the following:

$$\frac{Q_s^{(2)}}{Q_s^{(1)}}=\frac{Q^{(2)}-Q_c^{(2)}}{Q^{(1)}-Q_c^{(1)}}=\frac{(P_d^{(2)}-P_v^{(2)})/R-(P_a^{(2)}-P_d^{(2)})/R_c}{(P_d^{(1)}-P_v^{(1)})/R-(P_a^{(1)}-P_d^{(1)})/R_c}$$

and by substituting Equation A1a.

Theoretically, maximum blood flow through the myocardium can be compared before and after the intervention by:

$$\frac{Q^{(2)}}{Q^{(1)}}=\frac{(P_d^{(2)}-P_v^{(2)})/R}{(P_d^{(1)}-P_v^{(1)})/R}=\frac{P_d^{(2)}-P_v^{(2)}}{P_d^{(1)}-P_v^{(1)}} \quad (A6a)$$

or, if correction for pressure changes is made, by:

$$\frac{FFR_{myo}^{(2)}}{FFR_{myo}^{(1)}}=\frac{P_d^{(2)}-P_v^{(2)}}{P_a^{(2)}-P_v^{(2)}}\cdot\frac{P_a^{(1)}-P_v^{(1)}}{P_d^{(1)}-P_v^{(1)}}$$

$$=\left(1-\frac{\Delta^{(2)}P}{P_a^{(2)}-P_v^{(2)}}\right):\left(1-\frac{\Delta^{(1)}P}{P_a^{(1)}-P_v^{(1)}}\right) \quad (A6b)$$

Finally, the theoretical relation between collateral flow at different degrees of stenosis can be obtained. From Figure 1, it is clear that $Q_c=(P_a-P_d)/R_c$. Therefore:

$$\frac{Q_c^{(2)}}{Q_c^{(1)}}=\frac{(P_a^{(2)}-P_d^{(2)})/R_c}{(P_a^{(1)}-P_d^{(1)})/R_c}=\frac{\Delta^{(2)}P}{\Delta^{(1)}P} \quad (A7a)$$

or, if correction for pressure changes is made:

$$\frac{Q_c^{(2)}}{Q_c^{(1)}}=\frac{\Delta^{(2)}P}{P_a^{(2)}-P_v^{(2)}}:\frac{\Delta^{(1)}P}{P_a^{(1)}-P_v^{(1)}} \quad (A7b)$$

In fact, Equation A7 states that decrease of ΔP by improved stenosis geometry after PTCA induces a proportional decrease of the relative contribution of collateral flow to total myocardial flow, which will be further clarified in the following examples.

Application of these equations in clinical practice also will be demonstrated.

Example 1

The first example is based on the simple hemodynamic case in which systemic pressures (P_a and P_v) are unchanged during PTCA. Therefore, according to Equation A1a, wedge pressure (P_w) also is constant.

Before and after PTCA of one of the coronary arteries, pressure measurements are performed by the pressure-monitoring guide wire at maximum coronary hyperemia induced by intracoronary administration of papaverine or adenosine. Mean arterial pressure (P_a) is 90 mm Hg both before and after the procedure; transstenotic pressure gradient ΔP is reduced from 50 mm Hg before to 10 mm Hg after the procedure; and venous pressure (P_v) is 0 both before and after the procedure. P_w measured during balloon inflation, is 20 mm Hg. Therefore, $P_a^{(1)}=P_a^{(2)}=90$ mm Hg, $P_d^{(1)}=40$ mm Hg, $P_d^{(2)}=80$ mm Hg, $P_v^{(1)}=P_v^{(2)}=0$ mm Hg, and $P_w^{(1)}=P_w^{(2)}=20$ mm Hg.

With Equations A6b, A5b, and A7b, the following is obtained:

$$FFR_{myo}^{(2)}/FFR_{myo}^{(1)}=(1-10/90):(1-50/90)=2.0$$

$$FFR_{cor}^{(2)}/FFR_{cor}^{(1)}=(1-10/70):(1-50/70)=3.0$$

In other words, maximally achievable blood flow through the myocardium increased by a factor 2; maximally achievable blood flow through the dilated artery increased by a factor 3; and collateral blood flow decreased by a factor 5.

By using Equations A2b, A3b, and A4b (both before and after PTCA), one obtains the values of all flow parameters expressed as a fraction of normal maximum myocardial blood flow expected in the absence of a stenosis and normalized for pressure changes:

$$FFR_{myo}^{(1)}=4/9=28/63=0.44$$

$$FFR_{myo}^{(2)}=8/9=56/63=0.89$$

$$FFR_{cor}^{(1)}=2/7=18/63=0.29$$

$$FFR_{cor}^{(2)}=6/7=54/63=0.86$$

$$Q_c^{(1)}=4/9-2/7=10/63=0.15$$

$$Q_c^{(2)}=8/9-6/7=2/63=0.03$$

or, in summary:

	Before PTCA	After PTCA
Fractional myocardial flow	0.44	0.89
Fractional coronary flow	0.29	0.86
Fractional collateral flow	0.15	0.03

Such a matrix completely describes the distribution of flow in the coronary circulation both before and after PTCA.

Example 2

The second example demonstrates the calculations when mean arterial and venous pressure do change during PTCA.

PTCA is performed of one of the coronary arteries. At maximum coronary hyperemia, mean arterial pressure is 96 mm Hg before and 80 mm Hg after PTCA; ΔP is 45 mm Hg before and 15 mm Hg after the procedure; and venous pressure is 6 mm Hg before and 5 mm Hg after the procedure. P_w is 23 mm Hg during balloon inflation. Mean arterial pressure during balloon inflation is 92 mm Hg, and mean venous pressure during balloon inflation is 6 mm Hg.

In this case, with changing P_a and P_v, at first $P_w^{(1)}$ and $P_w^{(2)}$ have to be calculated because $(P_w-P_v)/(P_a-P_v)$ is constant according to Equation A1a: Because $P_w^{(1)}=24$ mm Hg, and $P_w^{(2)}=20$ mm Hg, in an identical way as in example 1, Equations A6b, A5b, and A7b are used to calculate the following:

$$FFR_{myo}^{(2)}/FFR_{myo}^{(1)}=(1-15/75):(1-45/90)=1.6$$

$$FFR_{cor}^{(2)}/FFR_{cor}^{(1)}=(1-15/60):(1-45/72)=2.0$$

$$Q_c^{(2)}/Q_c^{(1)}=15/75:45/90=1:2.5$$

In other words, maximally achievable blood flow through the myocardium increased by a factor 1.6, maximally achievable blood flow through the dilated artery increased by a factor 2, and collateral flow decreased by a factor 2.5.

By using Equations A2b, A3b, and A4b (both before and after PTCA), one obtains the values of all flow parameters, expressed as a fraction of normal maximum myocardial blood flow expected in the absence of a stenosis and normalized for pressure changes:

	Before PTCA	After PTCA
Fractional myocardial flow	0.50	0.80
Fractional coronary flow	0.375	0.75
Fractional collateral flow	0.125	0.05

www.cardio-aalst.be

Pijls NHJ et al Circulation 1993

The "KISS" Principle:

Keep It Simple, Stupid!

"Le contraire du vrai n'est pas le faux mais le complexe"

André Comte-Sponville
Petit traité des grandes vertus
PUF, 1995, p 245

The contrary of 'true' is not 'false', but 'complicated'

The “KISS” Principle:

Keep It Simple, Stupid!

- FFR_{myo}, FFR_{cor}, FFR_{coll}
- RA pressure measurements
- Serial stenoses equations

$$FFR = \frac{P_d}{P_a}$$

During hyperemia

www.cardio-aalst.be

CARDIOVASCULAR CENTER AALST

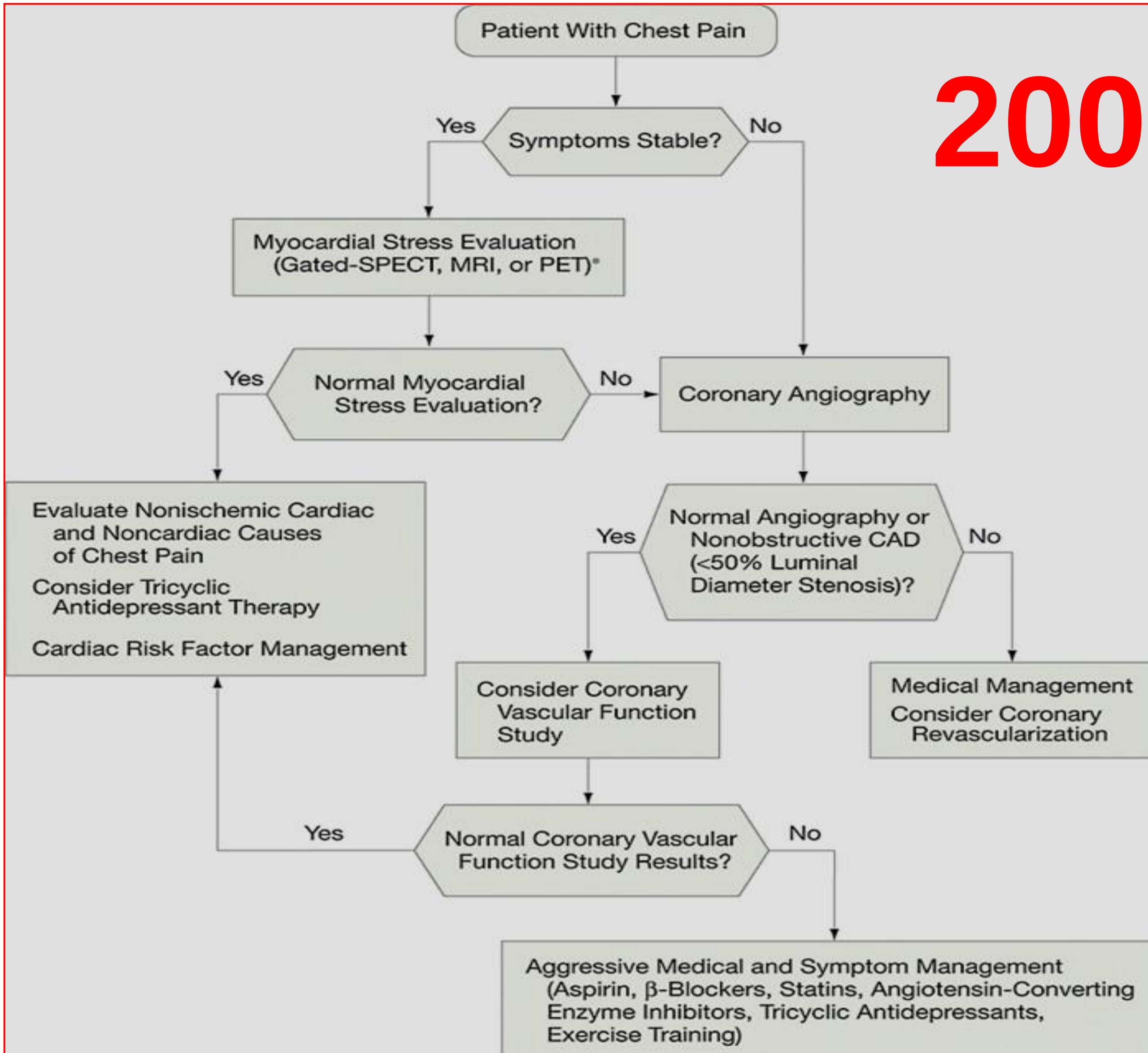
The "KISS" Principle:

Keep It Simple, Stupid!

Hyperemia

- Adenosine IV (140 µg/kg/min)
- Adenosine IC (100 – 200 µg bolus)
- Regadenosone IV bolus (IV peripheral bolus)

Diagnostic Algorithm in patients with (suspected) stable CAD

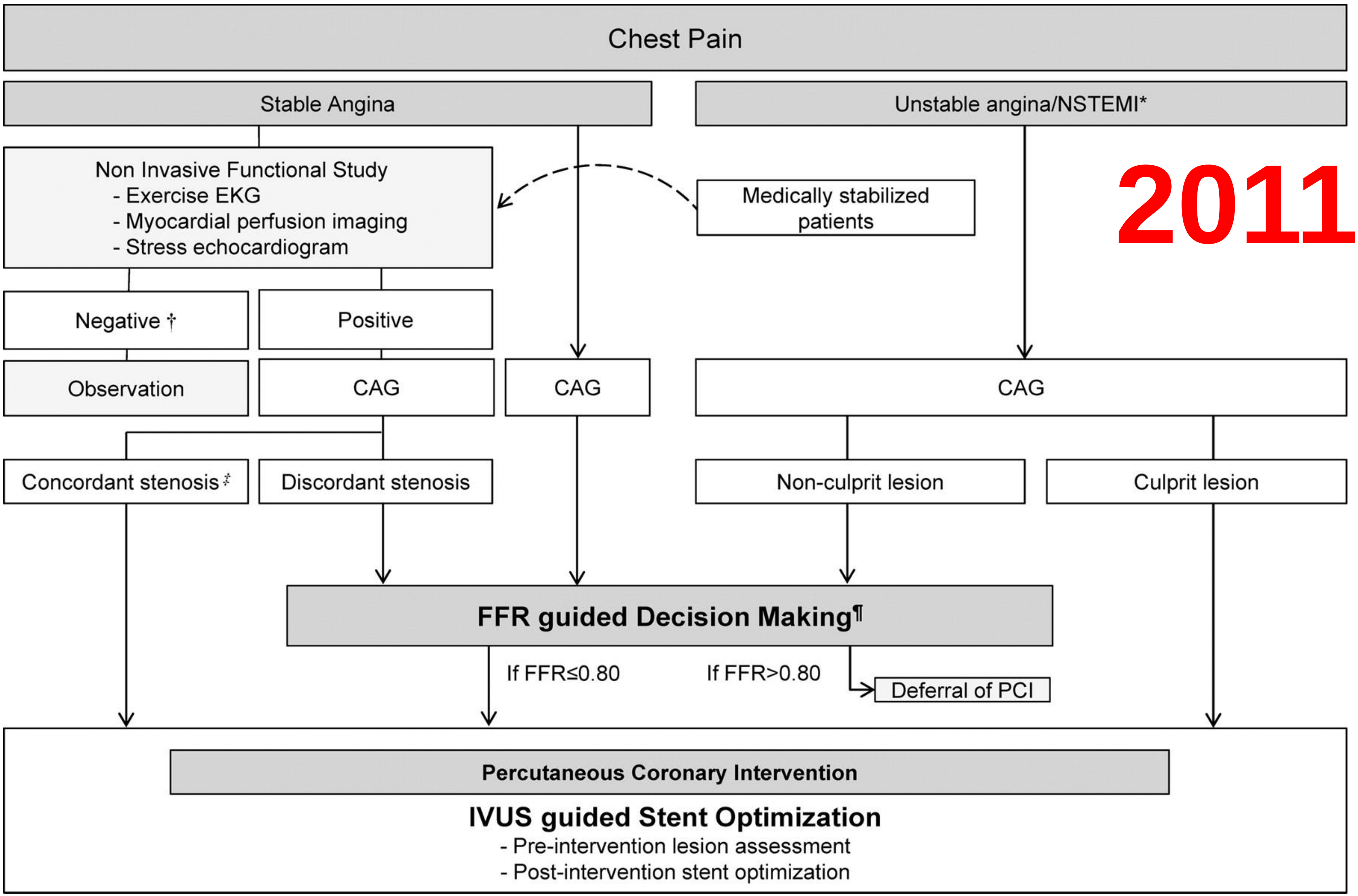


2005

www.cardio-aalst.be

Bugiardini et al, JAMA, 2005

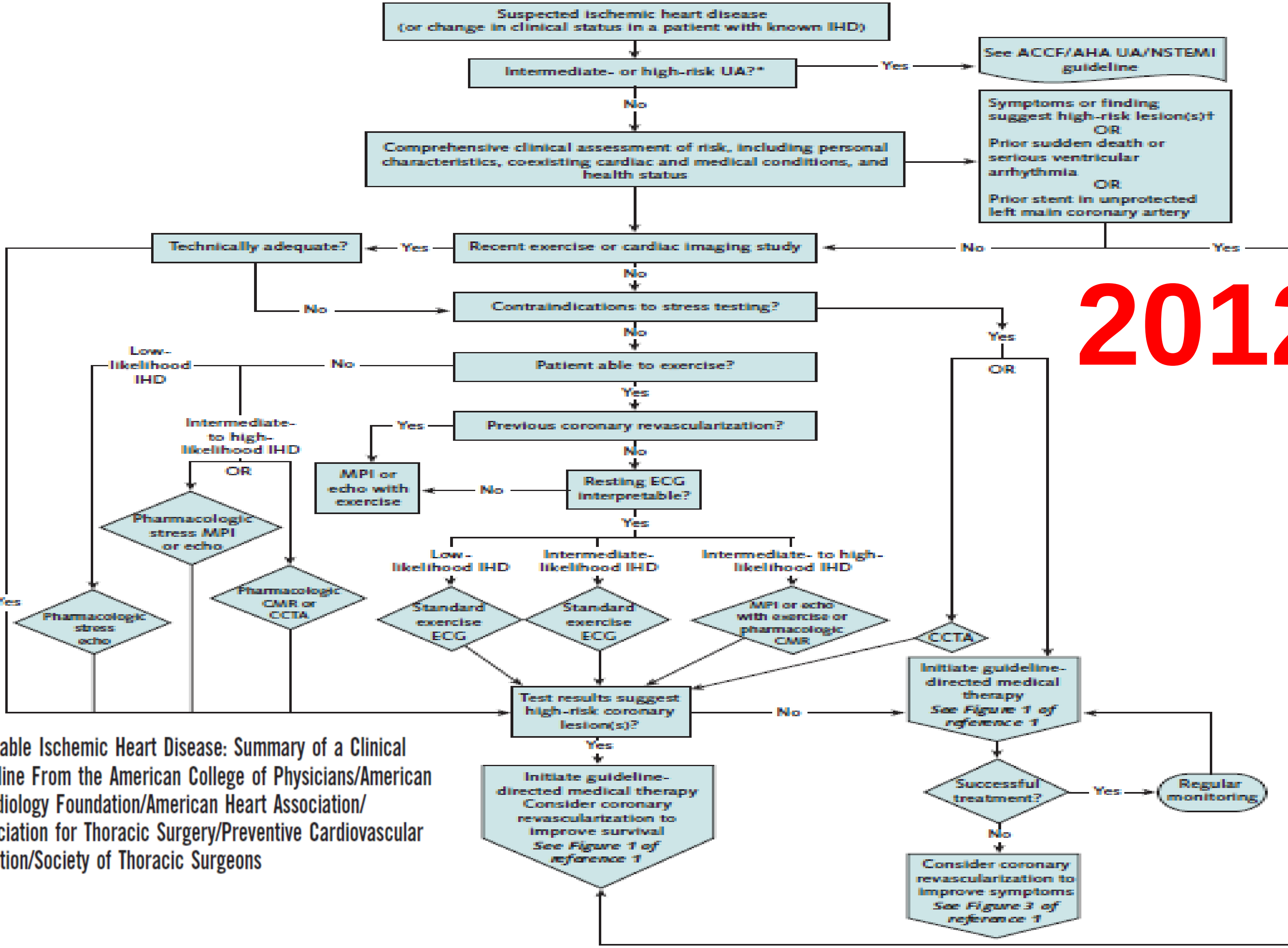
Diagnostic Algorithm in patients with (suspected) stable CAD



www.cardio-aalst.be

Park SJ et al. Circulation 2011;124:951

Diagnostic Algorithm in patients with (suspected) stable CAD

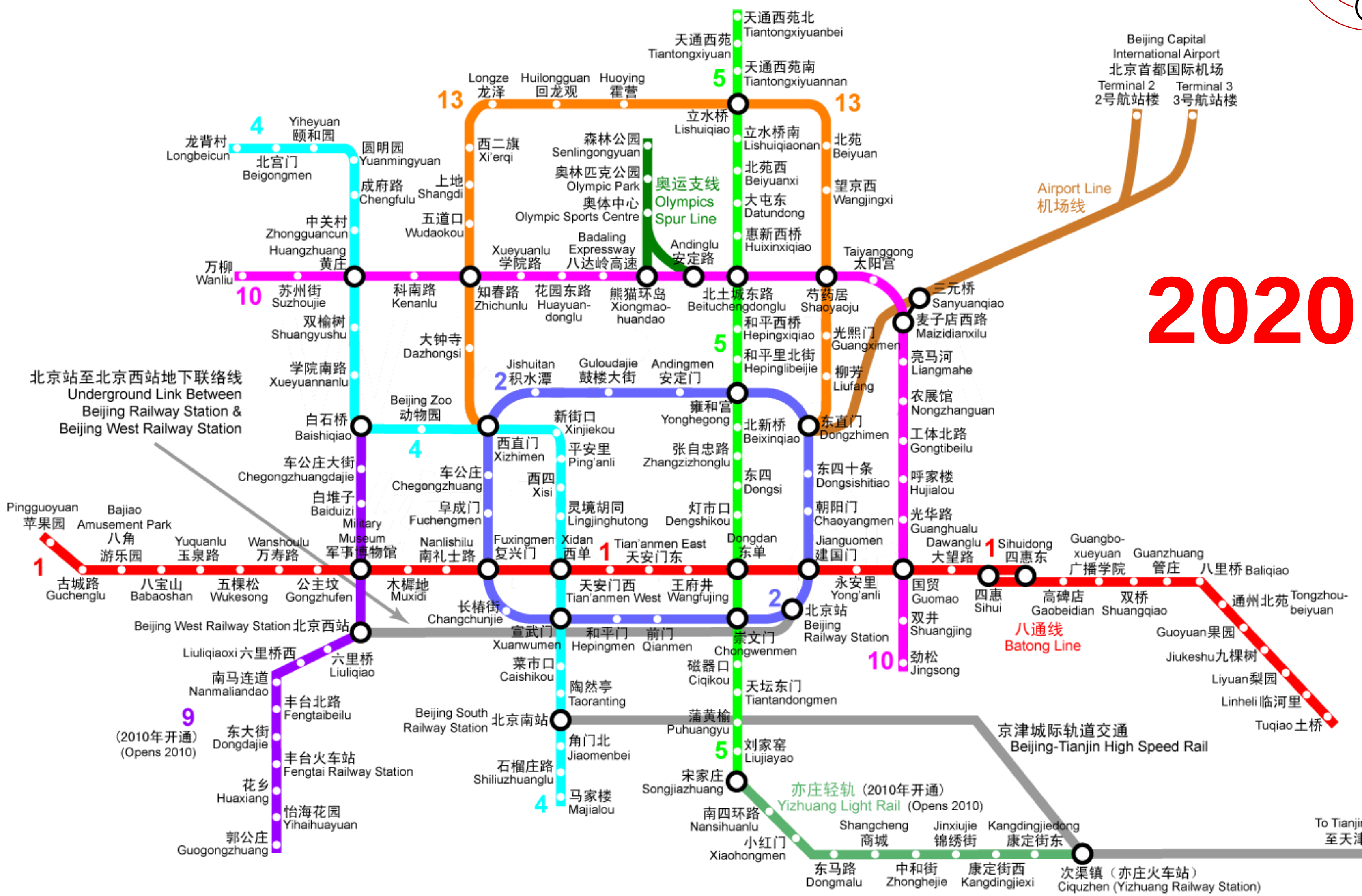


2012

Diagnosis of Stable Ischemic Heart Disease: Summary of a Clinical Practice Guideline From the American College of Physicians/American College of Cardiology Foundation/American Heart Association/ American Association for Thoracic Surgery/Preventive Cardiovascular Nurses Association/Society of Thoracic Surgeons

Qasem A et al Annals Int Med, 2012,157,729

Diagnostic Algorithm in patients with (suspected) stable CAD



2020 ?

www.cardio-aalst.be

Things have to be made as simple as possible, but not simpler

The "KISS" Principle:

Keep It Simple, Stupid!

Suspected Ischemic Heart Disease

↓

Medical History
(+ Body Language !)

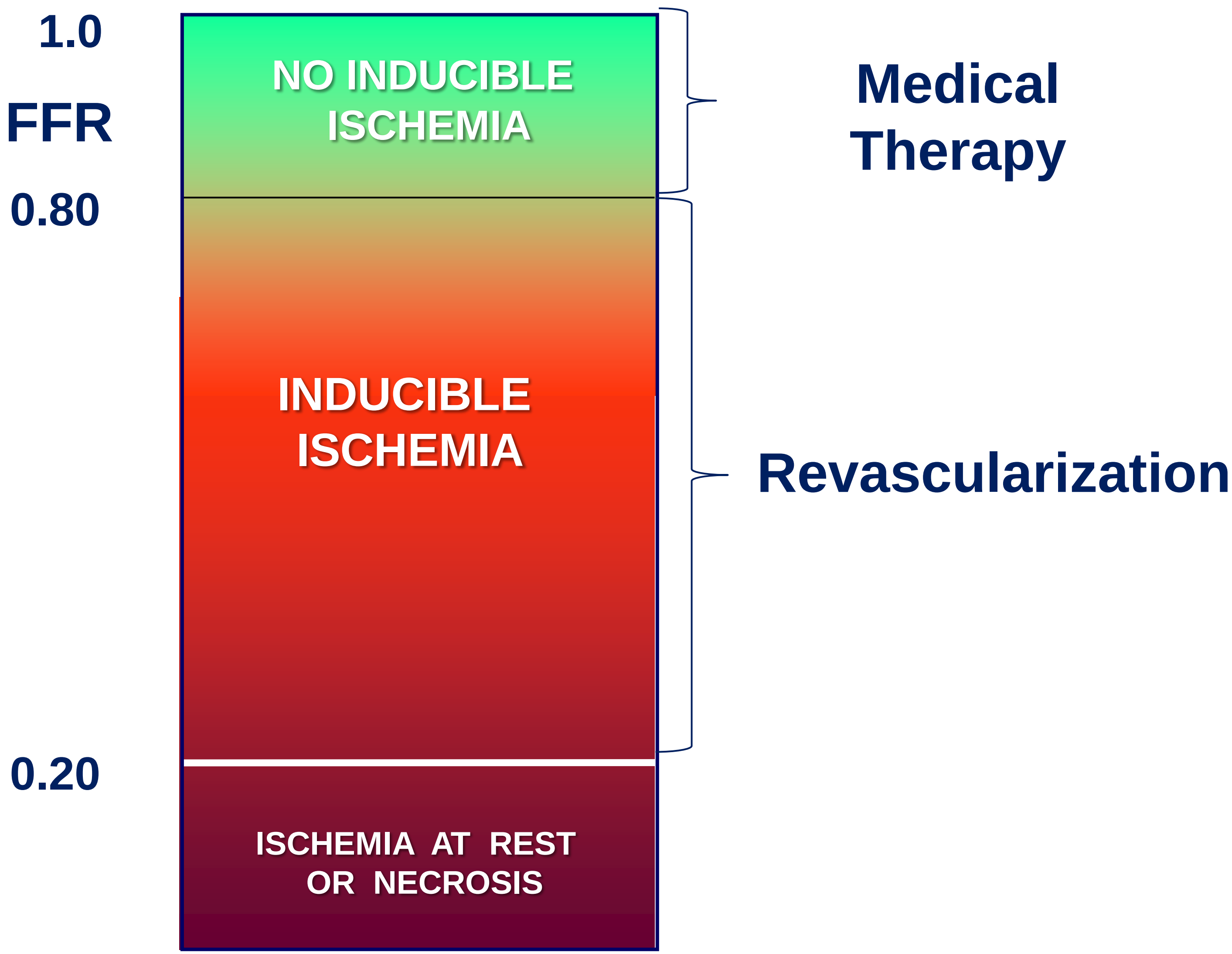
↓

Coronary Angiogram + FFR, IMR, ...
± ad hoc appropriate treatment

2013 ?

www.cardio-aalst.be

FFR, ... life can be so simple



www.cardio-aalst.be

"People who wish to analyze nature without using mathematics must settle for a reduced understanding",
- Richard P Feynman, PhD, Nobel Laureate of Physics in 1965

People who wish to treat CAD without physiology must settle for a reduced understanding

Thank you !!

www.cardio-aalst.be