

Stop invasive coronary angiography as the gold standard for the diagnosis of stable angina!

“...invasive coronary angiography carries nonnegligible risks, has limited accuracy in demonstrating the functional importance of a coronary artery stenosis and its place as gold standard for the diagnosis of coronary artery disease is changing.”

Keywords: coronary angiography • coronary artery disease • fractional flow reserve • gender • microvascular coronary disease

An accurate diagnosis is of great importance for appropriate treatment and estimation of prognosis in patients with ischemic heart disease. The current gold standard for the diagnosis of stable coronary artery disease (CAD) is invasive coronary angiography [1]. Although its invasive nature carries a non-negligible risk and adds significant costs [2], an immediate invasive strategy is even recommended for risk stratification in symptomatic patients at high risk, in patients with typical angina and a reduced left ventricular ejection fraction (<50%) and in patients who are candidates for other cardiac surgery [1]. In addition, according to the 2013 European Society of Cardiology (ESC) guidelines on stable CAD, invasive coronary angiography can also be considered for patients who are not able to exercise or who have nondiagnostic stress-testing results. Importantly, although patients without objective evidence of ischemia historically are believed to have a benign prognosis, coronary revascularization is recommended for patients with any stenosis >50% with limiting angina or angina equivalent that is unresponsive to optimal medical treatment [1].

Unnecessary invasive coronary angiography

Several large registries have shown that the majority of patients, who have invasive coronary angiography, have no obstructive

CAD [3,4]. This accounts for nearly two-thirds of women with stable angina pectoris and a third of men. In the Swedish Coronary Angiography and Angioplasty (SCAAR) registry, it was shown in patients with stable angina that almost 80% of women and 40% of men below 60 years of age had (near) normal findings at coronary angiography [5]. Moreover, a quarter of all patients undergoing coronary angiography have no symptoms at all [6]. To limit the number of patients without visible obstructive CAD prior noninvasive testing is recommended [1]. However, up to 50% of patients undergoing elective coronary angiography has no preprocedural risk stratification with any type of stress testing [7]. Among patients who had prior noninvasive tests before invasive coronary angiography, results of noninvasive tests predict obstructive CAD; but these tests have minimal incremental value beyond clinical factors for predicting obstructive disease [4]. Patient characteristics are key factors that affect the efficacy of stress testing in symptomatic patients. Before percutaneous coronary interventions (PCI), older patients and those with comorbidities are less likely to undergo prior stress testing. Although older age increases the probability of obstructive CAD, the presence of functional ischemia is crucial in determining whether the revascularization is appropriate [4].

Nanette Borren

Department of Cardiology, Isala klinieken, Zwolle, The Netherlands



Angela HEM Maas

Department of Cardiology, Radboud University Medical Center, Nijmegen, The Netherlands



Jan Paul Ottervanger

Author for correspondence:
Department of Cardiology, Isala klinieken, Zwolle, The Netherlands
Tel.: +31 38 4242374
Fax: +31 38 4243222
j.p.ottervanger@isala.nl

Future
Medicine part of fsg

Limited accuracy of invasive coronary angiography

The agreement between anatomical coronary artery disease and functional coronary artery disease is poor [8]. In aging populations, even in patients without anginal complaints, the number of intermediate stenoses as seen by invasive coronary angiography increase. Invasive coronary angiography, however, is not able to assess the hemodynamic relevance of coronary stenoses [8,9]. Instead, coronary angiography may either overestimate or underestimate the functional severity of a stenosis [10,11]. An incorrect indication for coronary angiography can, therefore, even lead to an inappropriate PCI [6]. Furthermore, a wide interobserver variability with poor agreement between observers regarding the diameter stenosis has been demonstrated [12]. Physician and system factors are important predictors of the diagnosis obstructive CAD. Angiograms performed by interventional cardiologists as opposed to invasive cardiologists have been shown to be more likely to demonstrate obstructive CAD, as were angiograms performed at hospitals with PCI capability [13]. Similarly, quantitative coronary angiography has failed to accurately predict the functional significance of coronary lesions [9]. In a subanalysis of the Fractional Flow Reserve Versus Angiography for Multivessel Evaluation study, only 14% of patients with angiographic three-vessel CAD had concordant three-vessel functional CAD as determined by invasive fractional flow reserve (FFR) measurements [14]. Clinical and lesion-specific factors associated with angiographic overestimation of hemodynamic lesion severity include advanced age, nonleft anterior descending artery location, absence of plaque rupture, short lesion length and greater minimal lumen diameter [15]. Conversely, factors associated with angiographic underestimation are younger age, left anterior descending artery location, the presence of plaque rupture and a smaller minimal lumen area [15]. Remarkably, even if there are no differences in angiographic diameter stenosis or lesion length, FFR is higher in women [16]. This may also result in a higher frequency of visual overestimation of coronary lesions in women, with the risk of unnecessary procedures.

Invasive coronary angiography in females

In women, angiography has lower positive predictive value of obstructive CAD in the epicardial arteries and is less effective to demonstrate the causes of the complaints [16]. In a multicenter study in Canada, it was shown that important predictors of a normal angiography are the absence of traditional risk factors, female gender and the presence of atypical symptoms [17].

Despite the lower rate of severe stenoses in women, the number of intermediate stenoses is higher in women as compared with men [18]. Although the prognosis of nonobstructive CAD in symptomatic women has historically been interpreted as benign, more recent data have shown that this confers an increased risk of major adverse cardiovascular events (MACE) and all-cause mortality [18,19]. In symptomatic middle-aged women at intermediate risk, ischemic heart disease is often caused by a combination of nonobstructive CAD with outward remodeling and functional impairment due to coronary microvascular dysfunction [20,21]. In aging women, endothelial function deteriorates faster after menopause with a relative larger role for inflammation compared with similarly aged men [22]. In 2014, the American Heart Association (AHA) launched evidence-based gender-specific guidelines for noninvasive testing that promote selective functional and anatomic testing with noninvasive imaging techniques in women at intermediate risk [23]. These are helpful to avoid the still too large number of unnecessary and inconclusive angiograms in this patient population.

Complications of invasive coronary angiography

In experienced hands, the risk of invasive coronary angiography is low, but complications do occur; these include access site bleeding, deterioration of renal function, (cerebral) embolism and allergic reactions [2]. In addition, there is exposure to radiation that accumulates with other diagnostic procedures (e.g., mammograms) during lifetime. Although the risk of bleeding is less after a radial than femoral approach, there is an increased risk of closure of the radial artery especially after repeated procedures. Furthermore, women undergoing coronary angiography and PCI have a higher risk of femoral vascular access site complications compared with men. Radial access is an effective method to reduce these complications; however, crossover rate to femoral access is higher in women [24].

Conclusion

In conclusion, invasive coronary angiography carries nonnegligible risks, has limited accuracy in demonstrating the functional importance of a coronary artery stenosis and its place as gold standard for the diagnosis of CAD is changing. Even a simple calcium score can exclude or demonstrate the presence of coronary artery disease with a high evidence-based prognostic significance. In high-risk patients or in patients with already proven CAD, functional tests, either invasive or noninvasive, are important to demonstrate ischemia, particularly if coronary revascularization is considered. Particularly in females, invasive coronary angiography

is of limited value, since coronary lesions are more frequently overestimated and the importance of both intermediate stenosis and microvascular disease is undetermined by invasive angiography.

Future perspective

The clinical value of invasive coronary angiography without the possibility of additional functional testing is losing clinical relevance. Fractional flow reserve measurement is more frequently required to guide appropriate coronary revascularization. More research should be performed on the clinical importance of

both intermediate stenoses and coronary microvascular disease, especially in women.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties. No writing assistance was utilized in the production of this manuscript.

References

- Task Force Members, Montalescot G, Sechtem U *et al.* 2013 ESC guidelines on the management of stable coronary artery disease: the Task Force on the management of stable coronary artery disease of the European Society of Cardiology. *Eur. Heart J.* 34(38), 2949–3003 (2013).
- Jolly SS, Amlani S, Hamon M, Yusuf S, Mehta SR. Radial versus femoral access for coronary angiography or intervention and the impact on major bleeding and ischemic events: a systematic review and meta-analysis of randomized trials. *Am. Heart J.* 157, 132–140 (2009).
- Jespersen L, Abildstrom SZ, Hvelplund A *et al.* Burden of hospital admission and repeat angiography in angina pectoris patients with and without coronary artery disease: a registry-based cohort study. *PLoS ONE* 9(4), e93170 (2014).
- Patel MR, Dai D, Hernandez AF *et al.* Prevalence and predictors of nonobstructive coronary artery disease identified with coronary angiography in contemporary clinical practice. *Am. Heart J.* 167, 846–852 (2014).
- Johnston N, Schenck-Gustafsson K, Lagerqvist B. Are we using cardiovascular medications and coronary angiography appropriately in men and women with chest pain? *Eur. Heart J.* 32(11), 1331–1336 (2011).
- Bradley SM, Spertus JA, Kennedy KF *et al.* Patient selection for diagnostic coronary angiography and hospital-level percutaneous coronary intervention appropriateness: insights from the National Cardiovascular Data Registry. *JAMA Intern. Med.* 174(10), 1630–1639 (2014).
- Hannan EL, Samadashvili Z, Cozzens K *et al.* Appropriateness of diagnostic catheterization for suspected coronary artery disease in New York state. *Circ. Cardiovasc. Interv.* 7, 19–27 (2014).
- Tonino PA, Fearon WF, de Bruyne B *et al.* Angiographic versus functional severity of coronary artery stenoses in the FAME study fractional flow reserve versus angiography in multivessel evaluation. *J. Am. Coll. Cardiol.* 55, 2816–2821 (2010).
- Chen SL, Xu B, Chen JB *et al.* Diagnostic accuracy of quantitative angiographic and intravascular ultrasound parameters predicting the functional significance of single *de novo* lesions. *Int. J. Cardiol.* 168, 1364–1369 (2013).
- Tonino PA, de Bruyne B, Pijls NH *et al.* FAME Study Investigators. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. *N. Engl. J. Med.* 360, 213–224 (2009).
- 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.* 334, 1703–1708 (1996).
- Zir LM, Miller SW, Dinsmore RE, Gilbert JP, Harthorne JW. Interobserver variability in coronary angiography. *Circulation* 53, 627–632 (1976).
- Wijeyesundera HC, Qiu F, Bennell MC *et al.* Impact of system and physician factors on the detection of obstructive coronary disease with diagnostic angiography in stable ischemic heart disease. *Circulation* 7, 648–655 (2014).
- Christou MA, Siontis GC, Katritsis DG, Ioannidis JP. Meta-analysis of fractional flow reserve versus quantitative coronary angiography and noninvasive imaging for evaluation of myocardial ischemia. *Am. J. Cardiol.* 99, 450–456 (2007).
- Park SJ, Kang SJ, Ahn JM *et al.* Visual-functional mismatch between coronary angiography and fractional flow reserve. *JACC Cardiovasc. Interv.* 10, 1029–1036 (2012).
- Kang SJ, Ahn JM, Han S *et al.* Sex differences in the visual-functional mismatch between coronary angiography or intravascular ultrasound versus fractional flow reserve. *JACC Cardiovasc. Interv.* 6(6), 562–568 (2013).
- Levitt K, Guo H, Wijeyesundera HC *et al.* Predictors of normal coronary arteries at coronary angiography. *Am. Heart J.* 166(4), 694–700 (2013).
- Jespersen L, Hvelplund A, Abildstrøm SZ *et al.* Stable angina pectoris with no obstructive coronary artery disease is associated with increased risks of major adverse cardiovascular events. *Eur. Heart J.* 33, 734–744 (2012).
- Gulati M, Cooper-DeHoff RM, McClure C *et al.* Adverse cardiovascular outcomes in women with nonobstructive coronary artery disease: a report from the Women's Ischemia Syndrome Evaluation Study and the St James Women Take Heart Project. *Arch. Intern. Med.* 169, 843–850 (2009).
- Reis SE, Holubkov R, Conrad Smith AJ *et al.* WISE Investigators. Coronary microvascular dysfunction is

- highly prevalent in women with chest pain in the absence of coronary artery disease: results from the NHLBI WISE study. *Am. Heart J.* 141, 735–741 (2001).
- 21 Shaw LJ, Bugiardini R, Merz CN. Women and ischemic heart disease: evolving knowledge. *J. Am. Coll. Cardiol.* 54(17), 1561–1575 (2009).
 - 22 Elias-Smale SE, Günal A, Maas AH. Gynecardiology: distinct patterns of ischemic heart disease in middle-aged women. *Maturitas* 7 (15) 00665–00669 (2015).
 - 23 Mieres JH, Gulati M, Bairey Merz N *et al.* Role of noninvasive testing in the clinical evaluation of women with suspected ischemic heart disease: a consensus statement from the American Heart Association *Circulation* 130(4), 350–379 (2014).
 - 24 Pandie S, Mehta SR, Cantor WJ *et al.* Radial versus femoral access for coronary angiography/intervention in women with acute coronary syndromes: insights from the RIVAL trial (Radial Vs femoral access for coronary intervention). *JACC Cardiovasc. Interv.* 8(4), 505–512 (2015).