Chapter 8

General considerations and future perspectives

Jan G.J. Groothuis

GENERAL CONSIDERATIONS

General considerations

Until recently, the non-invasive diagnostic work-up of patients with chest pain and low to intermediate likelihood of having significant CAD was based on detection or ruling out of myocardial ischemia, by X-ECG, dobutamine stress echocardiography or nuclear myocardial perfusion imaging. Such a strategy is in line with recent studies that have confirmed the superiority of ischemia driven revascularization rather than anatomy based therapy. *(1.2)* However, with the growing use of CTCA the diagnostic evaluation of patients with suspected CAD is more and more based on the assessment of coronary anatomy rather than ischemia. Although CTCA can reliably rule-out significant CAD, the positive predictive value for detection of hemodynamically significant CAD is low. Therefore, to avoid large numbers of unnecessary invasive procedures, additional non-invasive functional testing is warranted when obstructive CAD is detected by CTCA.

In this thesis we have shown that CMR may be the ideal functional test in addition to CTCA. We proposed a new diagnostic workup of patients with chest pain and low to intermediate pre-test likelihood. CTCA is used as first line technique to reliably rule out significant CAD. When obstructive CAD is detected by CTCA, patients will undergo CMR for the evaluation of the hemodynamic significance of the lesions. This work-up improves diagnostic accuracy for detection of significant CAD, reduces the number of patients that will undergo myocardial perfusion imaging and allows the detection of alternative (extra-) cardiac causes of chest pain, without the cost of additional radiation. However, several issues of such a new non-invasive diagnostic evaluation of patients with suspected CAD remain unanswered.

Additional value of CTCA to CCS

The additional value of CTCA to CCS remains question of debate. In clinical practice most cardiac CT protocols consist of two parts, coronary calcium scan and coronary angiography. Due to beam hardening artifacts, the image quality of CTCA in patients with extensive calcified plaques (high coronary calcium scores) is reduced and therefore exclusion of significant CAD is less reliable. (3) For this reason, one might decide ad hoc, to abort the CT coronary angiography when the calcium score is high. However, with the rapid technological development of CTCA image quality is becoming better, even in calcified coronary arteries, and observers are becoming more experienced. Furthermore, recently it was shown that in addition to CCS, the pre-test probability of the patient has large impact of the diagnostic accuracy of CTCA. (4). Therefore we believe that an exact threshold of CCS to abort the CTCA does not exist. Most important is the assessment of the patients pre-test probability of suspected CAD. Only patients with low to intermediate risk should then be referred for cardiac CT. Conversely, as the prevalence of significant lesions in patients without coronary calcification is very low (3, 5) one might decide to abort the CT coronary angiography when the CCS is zero. However, conflicting data exist about the

exact prevalence of significant CAD in patients with a CCS of zero. (6). Especially in the younger patients and/or with more acute symptoms, significant CAD without any calcification is not rare (6, 7). As cardiac CT is used as (definitive) first line rule-out technique to exclude suspected CAD, we recommend that CTCA should not be aborted in patients with a coronary calcium score of zero.

Management of non-significant CAD on CTCA

In our proposed non-invasive diagnostic work-up, CTCA is used as first line technique as it can reliably exclude significant CAD and is able to detect (non-significant) CAD. In clinical practice patients with non-significant CAD on CTCA often are prescribed medication (statin, ace-inhibitor and aspirin). Although several studies have shown that CAD detected by CT has additional prognostic value to more conventional risk factors, especially in intermediate risk patients (8), no study has yet shown that patients with non-significant CAD on CTCA should receive medication. However, with the growing wealth of data on the prognostic value of CAD detected by CT (9), it may be unethical to start a study randomizing patients with non-significant CAD to placebo or medication. Moreover, large patient cohorts are needed to perform such research given the low incidence of cardiac events in patients with a low-intermediate risk profile and non-significant CAD on CT.

Validation of new diagnostic strategies

Although several studies have shown the superiority of CTCA and CMR myocardial perfusion imaging over X-ECG for the detection of CAD (10-12), it remains unknown whether a combined strategy of CTCA and CMR myocardial perfusion imaging will improve risk stratification when compared with X-ECG. While it has been shown that X-ECG cannot reliably detect significant CAD (13), its prognostic value has been validated extensively (14). Recently several studies have shown the significant prognostic value of either CTCA or CMR (9, 15-21), however, studies that directly compared the prognostic value of X-ECG with CTCA or CMR are scarce (22, 23). In contrast, several studies have shown the additional prognostic value of SPECT myocardial perfusion imaging to X-ECG. (24, 25) Therefore, long term outcome studies are needed in which patients with low or intermediate likelihood CAD are randomized to either a conventional work-up consisting of X-ECG or CTCA and/or CMR.

Cost effectiveness of new diagnostic strategies

It is clear that with increasing health costs, the cost-effectiveness becomes increasingly important when introducing new diagnostic techniques. Although the cost-effectiveness depends on many factors such as downstream test utilization and local organization of health costs, and these factors may vary overtime, several studies have investigated the cost effectiveness of either CTCA and CMR and showed promising results. (26-28). In a study

by Min et al (27) is was shown that using CTCA instead of nuclear SPECT myocardial perfusion imaging as first line technique in patients with intermediate likelihood of disease is more cost-effective. Furthermore, recently Francis et al (28) showed that CMR perfusion imaging is more cost-effective than nuclear perfusion imaging for the evaluation of patients with intermediate pre-test probability CAD.

In contrast, studies comparing the cost-effectiveness of the combined use of CTCA/CMR and conventional strategies using X-ECG and SPECT do not exist. However, we believe that the combination of CTCA and CMR can be cost effective. In addition to data on the superior diagnostic accuracy of both CTCA over X-ECG(10-11), and CMR in relation to SPECT, (29-30) and the cost effectiveness of either CTCA or CMR in relation to conventional strategies (26-28), further supportive data are the suggested prices of different diagnostic modalities presented by the Nederlandse Zorgautoriteit (31), see table 1. Given the relatively high price of X-ECG and the combined stress and rest SPECT myocardial perfusion imaging, the cost-effectiveness of a combined CTCA-CMR work-up seems promising.

Table 1. Recommended prices of different diagnostic modalities according to the Nederlandse Zorg Autoriteit

Diagnostic modality	cost price (euro)*
X-ECG	97,74
Echocardiography	51,35
CT heart	195,83
MRI thorax (heart not available)	160,01
SPECT myocardium	265,08 (stress), 199,41 (rest)
Invasive coronary angiography	789,35

*According to the Nederlandse Zorg Autoriteit. (31)

FUTURE PERSPECTIVES

The growing wealth of data showing that CTCA and CMR each are very powerful new modalities for the non-invasive diagnostic work-up of patients with suspected CAD and the growing availability of both techniques will result in a significant increase of use in clinical practice. However, further research and development is needed.

New developments of cardiac CT

The rapid technical improvements from 16-row to 64- and even 320-row multidetector CT and the use of dual source scanners have improved temporal resolution significantly while reducing radiation dose. (32, 33) In this way, image quality is less dependent on (slow) heart rates and patients will not need high doses of beta-blocker before CT scanning. (34, 35) On the other hand, higher temporal resolution will lead to higher image quality that may result in higher diagnostic accuracy. In contrast to ICA, CTCA visualizes not only the vessel lumen, but also the vessel wall, together with other (thoracic) structures. Therefore it is able to optimally visualize distinct abnormalities, such as coronary anomalies, with their relation to other cardiac structures. See addendum 1 and 2 for two case examples. With the growing availability of CTCA we believe that CTCA will be performed regularly in addition to, or instead of, ICA for further evaluation when such abnormalities are suspected. On the other hand, as more patients undergo (non-invasive) evaluation of coronary anatomy, more coronary anomalies may be detected. (36) This may herald outcome studies to investigate how these patients should be managed.

In contrast to ICA, CTCA visualizes coronary plaque in addition to the vessel lumen, therefore plaque burden can be measured. In figure 1 a case example is presented that shows how CTCA provides additional information to ICA about plaque burden, that was confirmed by intravascular ultrasound (IVUS). Recently, several studies have focused on coronary plaque characterization by CTCA (37, 38). Among risk characteristics for plaque rupture as detected by IVUS are the amount of necrotic core tissue and the density of thin-cap fibroatheroma. Several studies have shown a correlation between plaque composition measured by CTCA and IVUS data. (39-41). However, these were only small single center studies and the clinical consequences of these new data remains unknown.

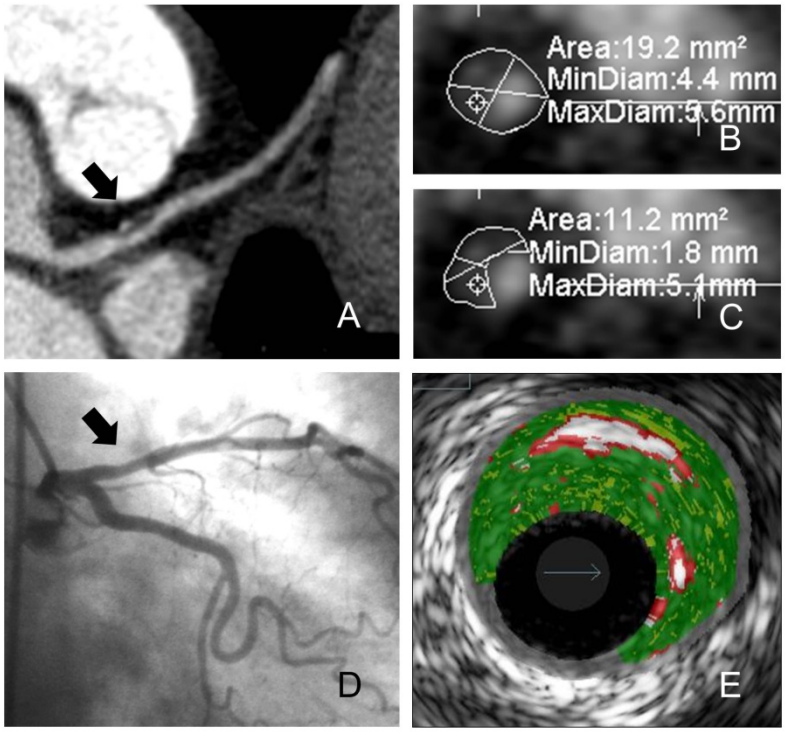

Figure 1. Underestimation of coronary plaque burden by ICA as compared to CTCA and IVUS. Panel A: CTCA curved multiplanar reconstruction of left anterior descending coronary artery (LAD) showing a mixed plaque (calcified and non-calcified plaque), arrow. Panel B and C: CT coronary angiography image showing cross sectional view of LAD at the sight of the mixed plaque with total vessel area of 19.2 mm and plaque area of 11.2 mm. Panel D: Invasive coronary angiography image of right anterior oblique view of LAD showing only mild stenosis in proximal LAD (arrow). Panel E: intravascular ultrasound image at the sight of lesion in LAD confirming large plaque burden (60%) consisting mainly of fibrotic tissue (green) and calcified plaque (white).

In a recent case report we showed how CTCA could visualize a myocardial perfusion defect in an acute traumatic myocardial infarction (see addendum 4). Recently, several studies have shown that myocardial perfusion imaging using CTCA can accurately detect significant CAD as defined by SPECT, ICA and FFR. (43-46) In contrast to CMR, CTCA has the advantage, that the concentration of ionated contrast agents has a linear relation to its signal intensitity. Although these data are promising, further research is needed to overcome several issues such as the injection of high volumes of ionated contrast agents, high radiation dosage and the optimal timing of the perfusion scans.

Recently a novel CT derived FFR method was presented, using computational fluid dynamic-based algorithms to calculate a fractional flow reserve from CTCA data. Although the diagnostic accuracy of CT-FFR for detection of hemodynamically relevant CAD was high in a single center study, (47), this could not be reproduced in a larger multi-center study. (48)

New developments of CMR

Recently several studies have investigated the performance of first pass myocardial perfusion imaging on systems with higher field strength (3 Tesla) (49, 50). The higher signal to noise ratio can be used to increase spatial and/or temporal resolution and thus results in better image quality. It was shown that CMR perfusion imaging at 3 Tesla resulted in a significantly higher diagnostic accuracy for detection of significant CAD than at 1,5 Tesla (51, 52). Furthermore, higher spatial resolution, and thus image quality, may result in better differentiation of subepicardial from transmural and endocardial defects and this may lead to more insights into the pathophysiology of microvascular function. (53-54). Although CMR perfusion imaging at 3 Tesla seems promising, cine imaging using steady state free precession (SSFP), that is the corner stone of CMR imaging and an important part in a CMR ischemia protocol, is less stable and more susceptible to artifacts at 3 Tesla. (55) Therefore, further research in this field is needed.

Recently several new techniques have been introduced to further accelerate myocardial perfusion imaging and thus improving temporal resolution. Highly constrained back-projection reconstruction (56), and compressive sensing (57) are promising new techniques. For quantitative analysis of myocardial perfusion imaging more research is needed to overcome the problem of the non-linear relation between contrast concentration and signal intensity. Although several possible correction methods have been presented (58-60), these need further incorporation into clinically available post-processing software. Furthermore, development of motion correction software and automatic contour detection of CMR myocardial perfusion images will be pivotal to reduce analysis time and increase observer reliability. Then, automatic quantitative analysis can be very important in clinical decision making, eg. for detection of (balanced) 3-vessel disease. It will provide many research applications e.g. in the field of myocardial perfusion related to microvascular dysfunction and follow-up of new therapies.

Although CTCA has surpassed MR coronary angiography for the detection of CAD, recently, several studies have shown promising results using 3D whole heart coronary angiography imaging sequences. (61, 62). Using this sequence, prognostically important left main disease and 3 vessel disease could be reliably ruled out (negative predictive value 99%). Especially in heavily calcified coronary arteries CMR may have additional value (63). However, acquisition time can be very long (> 15 minutes) and spatial resolution is still relatively low. With the development of new sequences at higher field strengths, these problems may be overcome and MR coronary angiography may be integrated in a CMR ischemia scan protocol.

Although CT-MR hybrid scanners do not exist, recently image fusion software for CTCA and CMR images was presented, in line with hybrid techniques using PET-CT or SPECT-CT. (64-65) It was shown that by using this technique the culprit atherosclerotic coronary segment could be allocated exactly to the corresponding perfusion defect. However, we believe that in low to intermediate risk patient population, a step wise strategy, rather than

hybrid protocol is more appropriate, thus taking maximal advantage of the high negative predictive value of CTCA, which will decrease the number of patients that will undergo additional functional testing.

REFERENCES

1. Tonino PA, De Bruyne B, Pijls NH, et al; FAME Study Investigators. Fractional flow reserve vs angiography for guiding percutaneous coronary intervention. N Engl J Med. 2009;360(3):213-224.
2. Shaw LJ, Berman DS, Maron DJ, Mancini GB, Hayes SW, Hartigan PM, Weintraub WS, O'Rourke RA, Dada M, Spertus JA, Chaitman BR, Friedman J, Slomka P, Heller GV, Germano G, Gosselin G, Berger P, Kostuk WJ, Schwartz RG, Knudtson M, Veledar E, Bates ER, McCallister B, Teo KK, Boden WE; COURAGE Investigators. Optimal medical therapy with or without percutaneous coronary intervention to reduce ischemic burden: results from the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial nuclear substudy. Circulation. 2008 Mar 11;117(10):1283-91
3. Nieman K, Galema TW, Neefjes LA, Weustink AC, Musters P, Moelker AD, Mollet NR, de Visser R, Boersma E, de Feijter PJ. Comparison of the value of coronary calcium detection to computed tomographic angiography and exercise testing in patients with chest pain. Am J Cardiol. 2009 Dec 1;104(11):1499-504.
4. Arbab-Zadeh A, Miller JM, Rochitte CE, Dewey M, Niinuma H, Gottlieb I, Paul N, Clouse ME, Shapiro EP, Hoe J, Lardo AC, Bush DE, de Roos A, Cox C, Brinker J, Lima JA. Diagnostic accuracy of computed tomography coronary angiography according to pre-test probability of coronary artery disease and severity of coronary arterial calcification. The CORE-64 (Coronary Artery Evaluation Using 64-Row Multidetector Computed Tomography Angiography) International Multicenter Study. J Am Coll Cardiol. 2012 Jan 24;59(4):379-87.
5. Cheng VY, Lepor NE, Madyoon H, Eshaghian S, Naraghi AL, Shah PK. Presence and severity of noncalcified coronary plaque on 64-slice computed tomographic coronary angiography in patients with zero and low coronary artery calcium. Am J Cardiol. 2007 May 1;99(9):1183-6. Epub 2007 Mar 15.
6. Ronen Rubinshtein, Tamar Gaspar, David A. Halon, a Jacob Goldstein,
Nathan Peled, Basil S. Lewis Prevalence and Extent of Obstructive Coronary Artery Disease in Patients With Zero or Low Calcium Score Undergoing 64-Slice Cardiac Multidetector Computed Tomography for Evaluation of a Chest Pain Syndrome Am J Cardiol 2007;99:472– 475)
7. Henneman MM, Schuijf JD, Pundziute G, van Werkhoven JM, van der Wall EE, Jukema JW, Bax JJ.Noninvasive evaluation with multislice computed tomography in suspected acute coronary syndrome: plaque morphology on multislice computed tomography versus coronary calcium score. J Am Coll Cardiol. 2008 Jul 15;52(3):216-22.
8. Greenland P, LaBree L, Azen SP, Doherty TM, Detrano RC. Coronary artery calcium score combined with Framingham score for risk prediction in asymptomatic individuals. JAMA. 2004 Jan 14;291(2):210-5. Erratum in: JAMA. 2004 Feb 4;291(5):563
9. Abdulla J, Asferg C, Kofoed KF. Prognostic value of absence or presence of coronary artery disease determined by 64-slice computed tomography coronary angiography a systematic review and meta-analysis. Int J Cardiovasc Imaging. 2011 Mar;27(3):413-20.
10. Maffei E, Seitun S, Martini C, Palumbo A, Tarantini G, Berti E, Grilli R, Tedeschi C, Messalli G, Guaricci A, Weustink AC, Mollet NR, Cademartiri F. CT coronary angiography and exercise ECG in a population with chest pain and low-to-intermediate pre-test likelihood of coronary artery disease. Heart. 2010 Dec;96(24):1973-9.
11. Dewey M, Dübel HP, Schink T, Baumann G, Hamm B. Head-to-head comparison of multislice computed tomography and exercise electrocardiography for diagnosis of coronary artery disease. Eur Heart J. 2007 Oct;28(20):2485-90.
12. Greulich S, Bruder O, Parker M, Schumm J, Grün S, Schneider S, Klem I, Sechtem U, Mahrholdt H. Comparison of exercise electrocardiography and stress perfusion CMR for the detection of coronary artery disease in women. J Cardiovasc Magn Reson. 2012 Jun 14;14:36.

13. Gianrossi R, Detrano R, Mulvihill D, Lehmann K, Dubach P, Colombo A, et al. Exercise-induced ST depression in the diagnosis of coronary artery disease. A meta-analysis. Circulation 1989 Jul;80(1):87-98.
14. Gibbons RJ, Balady GJ, Bricker JT, Chaitman BR, Fletcher GF, Froelicher VF, Mark DB, McCallister BD, Mooss AN, O'Reilly MG, Winters WL, Gibbons RJ, Antman EM, Alpert JS, Faxon DP, Fuster V, Gregoratos G, Hiratzka LF, Jacobs AK, Russell RO, Smith SC; American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Committee to Update the 1997 Exercise Testing Guidelines. ACC/AHA 2002 guideline update for exercise testing: summary article. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1997 Exercise Testing Guidelines). J Am Coll Cardiol. 2002 Oct 16;40(8):1531-40.
15. Min JK, Shaw LJ, Devereux RB, et al. Prognostic value of multidetector coronary computed tomographic angiography for prediction of all-cause mortality. J.Am.Coll.Cardiol. 2007 Sep 18;50(12):1161-70.
16. Chow BJ, Wells GA, Chen L, et al. Prognostic value of 64-slice cardiac computed tomography severity of coronary artery disease, coronary atherosclerosis, and left ventricular ejection fraction. J.Am.Coll.Cardiol. 2010 Mar 9;55(10):1017-28.
17. Pundziute G, Schuijf JD, Jukema JW, et al. Prognostic value of multislice computed tomography coronary angiography in patients with known or suspected coronary artery disease. J.Am.Coll.Cardiol. 2007 Jan 2;49(1):62-70.
18. Jahnke C, Nagel E, Gebker R, et al. Prognostic value of cardiac magnetic resonance stress tests: adenosine stress perfusion and dobutamine stress wall motion imaging. Circulation 2007 Apr 3;115(13):1769-76.
19. Steel K, Broderick R, Gandla V, et al. Complementary prognostic values of stress myocardial perfusion and late gadolinium enhancement imaging by cardiac magnetic resonance in patients with known or suspected coronary artery disease. Circulation 2009 Oct 6;120(14):1390-400.
20. Bertaso AG, Richardson JD, Wong DT, et al. Prognostic value of adenosine stress perfusion cardiac MRI with late gadolinium enhancement in an intermediate cardiovascular risk population. Int J Cardiol. 2012 Jun 2. [Epub ahead of print]
21. Buckert D, Dewes P, Walcher T, Rottbauer W, Bernhardt P. Intermediate-term prognostic value of reversible perfusion deficit diagnosed by adenosine CMR: a prospective follow-up study in a consecutive patient population. JACC Cardiovasc Imaging. 2013 Jan;6(1):56-63.
22. Dedic A, Genders TS, Ferket BS, Galema TW, Mollet NR, Moelker A, Hunink MG, de Feyter PJ, Nieman K. Stable angina pectoris: head-to-head comparison of prognostic value of cardiac CT and exercise testing. Radiology. 2011 Nov;261(2):428-36.
23. Cho I, Shim J, Chang HJ, Sung JM, Hong Y, Shim H, Kim YJ, Choi BW, Min JK, Kim JY, Shim CY, Hong GR, Chung N. Prognostic value of multidetector coronary computed tomography angiography in relation to exercise electrocardiogram in patients with suspected coronary artery disease. J Am Coll Cardiol. 2012 Nov 20;60(21):2205-15.
24. Hachamovitch R, Berman DS, Kiat H, Cohen I, Cabico JA, Friedman J, Diamond GA. Exercise myocardial perfusion SPECT in patients without known coronary artery disease: incremental prognostic value and use in risk stratification. Circulation. 1996 Mar 1;93(5):905-14.
25. Schinkel AF, Boiten HJ, van der Sijde JN, Ruitinga PR, Sijbrands EJ, Valkema R, van Domburg RT. Prediction of 9-year cardiovascular outcomes by myocardial perfusion imaging in patients with normal exercise electrocardiographic testing. Eur Heart J Cardiovasc Imaging. 2012 Nov;13(11):900-4.
26. Genders TS, Ferket BS, Dedic A, Galema TW, Mollet NR, de Feyter PJ, Fleischmann KE, Nieman K, Hunink MG. Coronary computed tomography versus exercise testing in patients with stable chest pain: comparative effectiveness and costs. Int J Cardiol. 2012 Apr 18. [Epub ahead of print]
27. Min JK, Gilmore A, Budoff MJ, Berman DS, O'Day K. Cost-effectiveness of coronary CT angiography versus myocardial perfusion SPECT for evaluation of patients with chest pain and no known coronary artery disease. Radiology. 2010 Mar;254(3):801-8.

28. Francis S, Cohen J, Olchanski N, Coelho-Filho OR, Heydari B, Shah R, Leavitt MB, Gewirtz H, Kwong R. Stress CMR myocardial perfusion imaging (CMR-MPI) is cost-effective compared to nuclear SPECT: a retrospective cost-effectiveness analysis J Cardiovasc Magn Reson. 2012; 14(Suppl 1): O3.Published online 2012 February 1.
29. Schwitter J, Wacker CM, Wilke N, Al-Saadi N, Sauer E, Huettle K, Schönberg SO, Debl K, Strohm O, Ahlstrom H, Dill T, Hoebel N, Simor T; MR-IMPACT investigators. Superior diagnostic performance of perfusion-cardiovascular magnetic resonance versus SPECT to detect coronary artery disease: The secondary endpoints of the multicenter multivendor MR-IMPACT II (Magnetic Resonance Imaging for Myocardial Perfusion Assessment in Coronary Artery Disease Trial). J Cardiovasc Magn Reson. 2012 Sep 2;14:61.
30. Greenwood JP, Maredia N, Younger JF, et al. Cardiovascular magnetic resonance and single-photon emission computed tomography for diagnosis of coronary heart disease (CE-MARC): a prospective trial. Lancet. 2012 Feb 4;379(9814):453-60
31. Nederlandse Zorg Autoriteit (ww.nza.nl, tarieflijst medisch specialistische behandelingen 2012)
32. Dewey M, Zimmermann E, Deissenrieder F, Laule M, Dübel HP, Schlattmann P, Knebel F, Rutsch W, Hamm B. Noninvasive coronary angiography by 320-row computed tomography with lower radiation exposure and maintained diagnostic accuracy: comparison of results with cardiac catheterization in a head-to-head pilot investigation. 320 Circulation. 2009 Sep 8;120(10):867-75.
33. Chao SP, Law WY, Kuo CJ, Hung HF, Cheng JJ, Lo HM, Shyu KG. The diagnostic accuracy of 256-row computed tomographic angiography compared with invasive coronary angiography in patients with suspected coronary artery disease. Eur Heart J. 2010 Aug;31(15):1916-23.
34. Achenbach S, Marwan M, Ropers D, Schepis T, Pflederer T, Anders K, Kuettner A, Daniel WG, Uder M, Lell MM. Coronary computed tomography angiography with a consistent dose below 1 mSv using prospectively electrocardiogram-triggered high-pitch spiral acquisition. Eur Heart J. 2010 Feb;31(3):340-6.
35. Leber AW, Johnson T, Becker A, von Ziegler F, Tittus J, Nikolaou K, Reiser M, Steinbeck G, Becker CR, Knez A. Diagnostic accuracy of dual-source multi-slice CT-coronary angiography in patients with an intermediate pretest likelihood for coronary artery disease. Eur Heart J. 2007 Oct;28(19):2354-60.
36. Cademartiri F, La Grutta L, Malagò R, Alberghina F, Meijboom WB, Pugliese F, Maffei E, Palumbo AA, Aldrovandi A, Fusaro M, Brambilla V, Coruzzi P, Midiri M, Mollet NR, Krestin GP. Prevalence of anatomical variants and coronary anomalies in 543 consecutive patients studied with 64-slice CT coronary angiography. Eur Radiol. 2008 Apr;18(4):781-91.
37. Boogers MJ, Broersen A, van Velzen JE, de Graaf FR, El-Naggar HM, Kitslaar PH,Dijkstra J, Delgado V, Boersma E, de Roos A, Schuijf JD, Schalij MJ, Reiber JH,Bax JJ, Jukema JW. Automated quantification of coronary plaque with computedtomography: comparison with intravascular ultrasound using a dedicated registration algorithm for fusion-based quantification. Eur Heart J. 2012 Apr;33(8):1007-16.
38. Sun J, Zhang Z, Lu B, Yu W, Yang Y, Zhou Y, Wang Y, Fan Z. Identification and quantification of coronary atherosclerotic plaques: a comparison of 64-MDCT and intravascular ultrasound. AJR Am J Roentgenol. 2008 Mar;190(3):748-54.
39. Takaoka H, Ishibashi I, Uehara M, Rubin GD, Komuro I, Funabashi N. Comparison of image characteristics of plaques in culprit coronary arteries by 64 slice CT and intravascular ultrasound in acute coronary syndromes. Int J Cardiol. 2012 Oct 4;160(2):119-26.
40. Nakazato R, Shalev A, Doh JH, Koo BK, Dey D, Berman DS, Min JK. Quantification and characterisation of coronary artery plaque volume and adverse plaque features by coronary computed tomographic angiography: a direct comparison to intravascular ultrasound. Eur Radiol. 2013 Apr 4. [Epub ahead of print]
41. Pundziute G, Schuijf JD, Jukema JW, Decramer I, Sarno G, Vanhoenacker PK, Reiber JH, Schalij MJ, Wijns W, Bax JJ. Head-to-head comparison of coronary plaque evaluation between multislice computed tomography and intravascular ultrasound radiofrequency data analysis. JACC Cardiovasc Interv. 2008 Apr;1(2):176-82.

42. Iriart X, Brunot S, Coste P, Montaudon M, Dos-Santos P, Leroux L, Labeque JN,Jais C, Laurent F. Early characterization of atherosclerotic coronary plaques with multidetector computed tomography in patients with acute coronary syndrome: a comparative study with intravascular ultrasound. Eur Radiol. 2007 Oct;17(10):2581-8. Epub 2007 Jun 5.
43. Ko BS, Meredith IT, Leung M, et al. Computed tomography stress myocardial perfusion imaging in patients considered for revascularization: a comparison with fractional flow reserve. Eur Heart J. 2012;33:67–77.
44. Ko BS, Cameron JD, Leung M, Meredith IT, Leong DP, Antonis PR, Crossett M, Troupis J, Harper R, Malaiapan Y, Seneviratne SK. Combined CT coronary angiography and stress myocardial perfusion imaging for hemodynamically significant stenoses in patients with suspected coronary artery disease: a comparison with fractional flow reserve. JACC Cardiovasc Imaging. 2012 Nov;5(11):1097-111.
45. Tamarappoo BK, Dey D, Nakazato R, Shmilovich H, Smith T, Cheng VY, Thomson LE, Hayes SW, Friedman JD, Germano G, Slomka PJ, Berman DS. Comparison of the extent and severity of myocardial perfusion defects measured by CT coronary angiography and SPECT myocardial perfusion imaging. JACC Cardiovasc Imaging. 2010 Oct;3(10):1010-9.
46. George RT, Arbab-Zadeh A, Miller JM, Vavere AL, Bengel FM, Lardo AC, Lima JA. Computed tomography myocardial perfusion imaging with 320-row detector computed tomography accurately detects myocardial ischemia in patients with obstructive coronary artery disease. Circ Cardiovasc Imaging. 2012 May 1;5(3):333-40.
47. Koo BK, Erglis A, Doh JH, et al. Diagnosis of ischemia-causing coronary stenoses by noninvasive fractional flow reserve computed from coronary computed tomographic angiograms. Results from the prospective multicenter DISCOVER-FLOW (diagnosis of ischemiacausing stenoses obtained Via noninvasive fractional flow reserve) study. J Am Coll Cardiol. 2011;58:1989–97.
48. Min JK, Leipsic J, Pencina MJ, Berman DS, Koo BK, van Mieghem C, Erglis A, Lin FY, Dunning AM, Apruzzese P, Budoff MJ, Cole JH, Jaffer FA, Leon MB, Malpeso J, Mancini GB, Park SJ, Schwartz RS, Shaw LJ, Mauri L.Diagnostic accuracy of fractional flow reserve from anatomic CT angiography. JAMA. 2012 Sep 26;308(12):1237-45.
49. Lockie T, Ishida M, Perera D, Chiribiri A, De Silva K, Kozerke S, Marber M, Nagel E, Rezavi R, Redwood S, Plein S High-resolution magnetic resonance myocardial perfusion imaging at 3.0-Tesla to detect hemodynamically significant coronary stenoses as determined by fractional flow reserve. J Am Coll Cardiol. 2011 Jan 4;57(1):70-5.
50. Cheng ASH, Pegg TJ, Karamitsos TD, Searle N, Jerosch-Herold M, Choudhury RP, Banning AP, Neubauer S, Robson MD, Selvanayagam JB (2007) Cardiovascular magnetic resonance perfusion imaging at 3-Tesla for the detection of coronary artery disease. J Am Coll Cardiol 49:2440–2449
51. Bernhardt P, Walcher T, Rottbauer W, Wöhrle J. Quantification of myocardial perfusion reserve at 1.5 and 3.0 Tesla: a comparison to fractional flow reserve. Int J Cardiovasc Imaging. 2012 Dec;28(8):2049-56.
52. Plein S, Schwitter J, Suerder D, Greenwood JP, Boesiger P, Kozerke S. k-space and time sensitivity encoding-accelerated myocardial perfusion MR imaging at 3.0 T: comparison with 1.5 T. Radiology 2008;249:493–500.
53. Vermeltfoort IA, Bondarenko O, Raijmakers PG, Odekerken DA, Kuijper AF, Zwijnenburg A, van der Vis-Melsen MJ, Twisk JW, Beek AM, Teule GJ, van Rossum AC. Is subendocardial ischaemia present in patients with chest pain and normal coronary angiograms? A cardiovascular MR study. Eur Heart J. 2007 Jul;28(13):1554-8. Epub 2007 May 15.
54. Panting JR, Gatehouse PD, Yang GZ, Grothues F, Firmin DN, Collins P, Pennell DJ. Abnormal subendocardial perfusion in cardiac syndrome X detected by cardiovascular magnetic resonance imaging. N Engl J Med. 2002 Jun 20;346(25):1948-53.
55. Schar M, Kozerke S, Fischer SE, Boesiger P. Cardiac SSFP imaging at 3 Tesla. Magn Reson Med. 2004;51(4):799-806.

56. Mistretta CA. Undersampled radial MR acquisition and highly constrained backprojection (HYPR) reconstruction: potentialmedical imaging applications in the post-Nyquist era. J Magn Reson Imaging 2009;29(3):501–516.36.
57. Otazo R, Kim D, Axel L, Sodickson DK.Combination of compressed sensing andparallel imaging for highly accelerated firstpasscardiac perfusion MRI. Magn ResonMed 2010;64(3):767–776.35
58. Takashi Ichihara, Masaki Ishida, Kakuya Kitagawa, Yasutaka Ichikawa,Takahiro Natsume, Noriyasu Yamaki, Hisato Maeda, Kan Takeda, Hajime Sakuma Quantitative Analysis of First-Pass Contrast-Enhanced Myocardial Perfusion MRI Using a Patlak Plot Method and Blood Saturation Correction. Magn Reson Med 62:373–383, 2009.
59. Ishida et al.: Development of a universal dual-bolus injection scheme for the quantitative assessment of myocardial perfusion cardiovascular magnetic resonance. Journal of Cardiovascular Magnetic Resonance 2011 13:28.
60. Hsu LY, Kellman P, Arai AE. Nonlinear myocardial signal intensity correction improves quantification of contrast-enhanced first-pass MR perfusion in humans. J Magn Reson Imaging 2008;27:793-801.
61. Kato S, Kitagawa K, Ishida N, et al. Assessment of coronary artery disease using magnetic resonance coronary angiography: a national multicenter trial. J Am Coll Cardiol 2010;56:983–91.
62. Pouleur AC, le Polain de Waroux JB, Kefer J, Pasquet A, Vanoverschelde JL, Gerber BL. Direct comparison of whole-heart navigatorgated magnetic resonance coronary angiography and 40- and 64-slice multidetector row computed tomography to detect the coronary artery stenosis in patients scheduled for conventional coronary angiography. Circ Cardiovasc Imaging 2008;1:114 –21.
63. Xin Liu, Xihai Zhao, Jie Huang, Christopher J. Francois David Tuite Xiaoming Bi Debiao Li James C. Carr Comparison of 3D Free-Breathing Coronary MR Angiography and 64-MDCT Angiography for Detection of Coronary Stenosis in Patients with High Calcium Scores AJR 2007; 189:1326–1332
64. Stolzmann P, Alkadhi H, Scheffel H, et al. Image fusion of coronary CT angiography and cardiac perfusion MRI: a pilot study. Eur Radiol;20:1174–9.
65. Olivio F Donati, Hatem Alkadhi, Hans Scheffel, Caroline Kuehnel, Anja Hennemuth, Christophe Wyss, Naim Azemaj, André Plass, Sebastian Kozerke, Volkmar Falk, Sebastian Leschka, Paul Stolzmann 3D fusion of functional cardiac magnetic resonance imaging and computed tomography coronary angiography: accuracy and added clinical value. Investigative radiology. 46(5):331-40.