Eindhoven dissertation prize 2010

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Interuniversity Cardiology Institute of the Netherlands

For the 22nd time in a row, starting in 1990, the Netherlands Society of Cardiology (NVVC) and the Interuniversity Cardiology Institute of the Netherlands (ICIN-Netherlands Heart Institute), together with Sanofi-Aventis, supported the competition for the best three cardiovascular PhD theses published in the year 2010. The dissertation prize carries the name of one of the greatest Dutchmen in the history of cardiovascular medicine: Willem Einthoven, who in 1902 recorded the human ECG for the first time, for which he received the Nobel Prize in 1924.

This time the jury received a total of 24 PhD dissertations. The jury members were very impressed by the high scientific quality of the PhD fellows. Based on originality, the number of articles in first-rate journals, the contribution as a first author (or shared first author) to the papers, and the number of citations, the jury finally selected three nominees: Alexander Hirsch (AMC, Amsterdam), Pim Tonino (Catharina Hospital, Eindhoven), and Laurens Tops (LUMC, Leiden). The three candidates presented their PhD theses at the annual Spring Congress of the NVVC in Papendal on 31 March 2011. The ultimate winners of the first, second, and third prize were chosen by the audience. Summaries of the three nominated PhD theses are given below.

Chairmen of the jury

W.H. van Gilst, E.E. van der Wall

Clinical and functional outcomes after revascularisation strategies in acute coronary syndromes

The term acute coronary syndrome (ACS) refers to a range of acute myocardial ischaemic states, including unstable angina, non-ST-elevation myocardial infarction (NSTEMI), and ST-elevation myocardial infarction (STEMI). This thesis describes several studies on clinical and functional outcomes after different revascularisation strategies in patients with ACS.

Early invasive versus selective invasive management for NSTEMI

The first part concerns a large multicentre Dutch study, the ICTUS trial, which compared an early invasive with a selective invasive treatment strategy in patients with NSTEMI. In total 1200 patients were randomly assigned either to an early invasive strategy, including early routine catheterisation and revascularisation where appropriate, or to a more selective invasive strategy, where catheterisation was done if the patient had refractory angina or recurrent ischaemia. In summary, the ICTUS trial did not show that an early invasive strategy was better than a more selective invasive strategy. With optimised medical treatment and a revascularisation rate around 55% to 60% at 1 year, an early invasive treatment may not be necessary for all patients with NSTEMI. Furthermore, several factors for additional risk stratification could be identified including NTproBNP and cystatin C. However, these factors were not helpful in identifying a subgroup of patients that benefit from an early invasive treatment strategy in the ICTUS trial.

Clinical and functional outcomes after primary percutaneous coronary intervention

Cardiovascular magnetic resonance (CMR) is emerging as an important diagnostic and prognostic tool in ACS. The

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second part of the thesis describes the assessment of cardiac function, infarct size, and especially microvascular obstruction (MVO) by CMR in patients after STEMI. The relation of these CMR measurements with current known risk factors was investigated and the predictive value on functional recovery infarction was examined. In conclusion, we recommend late gadolinium enhancement CMR as the preferred technique to assess MVO. It can be successfully used for risk stratification after ACS and is superior to several commonly used angiographic and electrocardiographic techniques. This technique can be useful in selecting STEMI patients at high risk for future events that may benefit from adjunctive therapy.

Cell therapy as an adjunctive therapy for STEMI

The third part concerns another Dutch multicentre study, the HEBE trial. In this trial the concept of improving left ventricular function by intracoronary infusion of mononuclear cells from bone marrow or peripheral blood in the subacute phase after STEMI, was tested. First, a pilot study was performed to evaluate the safety and feasibility in all participating centres. Second, the cell isolation protocol used in the HEBE trial was validated with regard to the quantity and quality of isolated cells by comparing it with processing protocols used in other clinical trials for cell therapy. Finally, the randomised controlled HEBE trial was performed, in which 200 patients with first STEMI were enrolled in eight hospitals. After 4-months follow-up, there were no significant differences between the treatment groups and standard therapy in the efficacy endpoints that were evaluated, including the primary endpoint of percentage of dysfunctional segments at baseline with improved segmental wall thickening and the secondary endpoints of change in LVEF, volumes, mass and infarct size. Therefore, to date this type of cell therapy is not a valuable tool in preventing heart failure-related morbidity or mortality.

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Fractional flow reserve to guide percutaneous coronary intervention in multivessel coronary artery disease

Revascularisation by percutaneous coronary intervention (PCI) should be targeted at relieving myocardial ischaemia.¹ However, non-invasive stress testing and coronary angiography will not always provide adequate or complete information about the functional importance of coronary artery narrowings.^{2–4} Particularly in patients with multi-

vessel coronary artery disease (CAD), it can be difficult to determine which out of several lesions cause myocardial ischaemia and therefore warrant revascularisation.

The index Fractional Flow Reserve (FFR) is considered the gold standard for the detection of stenosis-related myocardial ischaemia.⁵ By using FFR in patients with multivessel disease, the interventional cardiologist is able to accurately distinguish coronary stenoses that induce myocardial ischaemia from stenoses that do not induce ischaemia. Consequently, it is possible to treat selectively the functionally significant (ischaemic) stenoses by stenting and leave the non-ischaemic stenoses for medical treatment. This led to the hypothesis that, compared with commonly practised angiography-guided stenting, a strategy of FFR-guided stenting would decrease the number of stents and stent-related complications, but still result in complete relief of myocardial ischaemia, thereby improving clinical outcome.⁶ That was the rationale to perform the Fractional Flow Reserve versus Angiography in Multivessel Evaluation (FAME) study.⁷ This international, multicentre study compares angiography-guided PCI with FFR-guided PCI in patients with multivessel CAD. In both treatment arms the coronary intervention is performed with drug-eluting stents. In little more than a year, 1005 patients were randomised in 20 centre in Europe and in the USA. The results of the FAME study after 1 year showed a significant reduction in the primary, combined endpoint of death, myocardial infarction, and repeat revascularisation for the FFR-guided strategy. While using less stents per patient, the FFR-guided approach resulted in a similar relief of anginal symptoms as with the angiography-guided approach. The use of FFR in these patients did not prolong procedure time and even reduced the amount of contrast agent used.

After 2 years of follow-up in the FAME study, the favourable results of an FFR-guided strategy were maintained.⁸ The combination of death and myocardial infarction, both very important endpoints from a clinical and patient's perspective, were significantly reduced at 2 years.

An in-depth analysis of the patients in the FFR-guided arm of the FAME study confirms the poor performance of coronary angiography in predicting the presence of inducible myocardial ischaemia, related to a coronary stenosis.⁹ Of all coronary stenoses with an angiographic severity of 50%–70%, two-thirds are functionally non-significant and only one-third is functionally significant by FFR. Even in more severe stenoses between 71% and 90% angiographic stenosis severity, 20% of such lesions are non-ischaemic.

Therefore, in patients with multivessel CAD, one cannot rely on the angiogram to identify ischaemia-producing lesions when assessing stenoses between 50% and 90%. In fact, this is probably one of the key explanations for the superior clinical outcome of FFR-guided stenting in the FAME study; by selectively stenting ischaemic stenoses,

‘collateral damage’ from unnecessary stenting of non-ischæmic coronary stenoses is prevented, with similar relief of myocardial ischaemia as with angiography-guided stenting.

An extensive economic evaluation of the FAME study shows that a FFR-guided strategy also saves health care resources and improves health outcomes at 1 year.¹⁰ Combining the economic and clinical outcome of the FAME study reveals that FFR-guided placement of drug-eluting stents in patients with multivessel CAD is one of those rare situations in which a new technology not only improves outcomes, but also saves resources.

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Multimodality imaging to guide cardiac interventional procedures

In recent years, a number of new cardiac interventional procedures have been introduced. Catheter ablation procedures for atrial fibrillation (AF) have been refined and are now considered a good treatment option in patients with drug-refractory AF. In cardiac pacing, cardiac resynchronisation therapy (CRT) is now standard of care for patients with drug-refractory heart failure. At the same time, CRT may also be beneficial in patients with heart failure after long-term right ventricular (RV) apical pacing. Finally, new percutaneous procedures for valvular heart disease have been introduced for patients who are deemed inoperable. At the same time, various imaging modalities have been further developed and important advances have been made in the integration of different imaging modalities. The aim of the present thesis was to explore the role of multimodality imaging in cardiac interventional procedures.

In Part I, the integration of different imaging modalities during catheter ablation procedures for AF was studied. It was demonstrated that the integration of different imaging modalities (Multi-slice Computed Tomography (MSCT), electroanatomic mapping, intracardiac echocardiography) is feasible, and provides additional information during catheter ablation procedures. In addition, the effects of these procedures on left atrial (LA) and left ventricular (LV) size and function were investigated. It was demonstrated that LA and LV function improve in patients who maintain sinus rhythm after the catheter ablation procedure.

Part II studied the effects of RV apical pacing on LV dyssynchrony and mechanics, and the effect of upgrade to CRT. In the present studies, about half of the patients with long-term RV apical pacing developed significant LV dyssynchrony and exhibited deterioration of LV function. By restoration of synchronous contraction, CRT may (partly) reverse the detrimental effects of long-term permanent RV apical pacing. Importantly, LV dyssynchrony may be present immediately after onset of RV apical pacing. More studies are needed to identify patients who are at risk for development of LV dyssynchrony and deterioration of LV function after long-term RV apical pacing.

Finally, in Part III the role of multimodality imaging in new percutaneous procedures for valvular heart disease was explored. The present studies demonstrate that cardiac

imaging provides critical information for percutaneous valve procedures. In particular, MSCT plays an important role in the selection of patients referred for these procedures. This 3D imaging technique clearly visualises the relation between the coronary arteries, coronary veins and affected valves. Both for percutaneous mitral valve procedures using coronary sinus annuloplasty and transcatheter aortic valve replacement, this relation is of utmost importance. Furthermore, after the implantation procedure, MSCT allows visualisation of the prosthesis and the relation with surrounding structures.

In conclusion, multimodality imaging plays an important role in new cardiac interventional procedures such as AF ablation, cardiac pacing and percutaneous valve procedures. Image integration can facilitate these procedures by better visualization of important anatomical structures.

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