Brainstorm summary of the working group of nuclear cardiology and cardiac CT on hot topics

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This summary reflects our brainstorm activities focused on the topic ***"…what we don't know but should know…"*** in the field of cardiac imaging and cardiology in general. On one hand we had stimulating talks as a basis for the following discussion parts. On the other hand we wanted to try a new platform for our exchange and our discussions: The "think – tanks". In these think – tanks we worked and discussed in smaller groups (5-6 participants) and shared our ideas with respect to different topics. The think – tank participants were randomly assigned to a group which were coached by experts in the field, allowing knowledge transfer from master to fellow and from fellow to master, allowing also discussions in an easy and stimulating atmosphere.

Please find summaries of the different think – tank topics below:

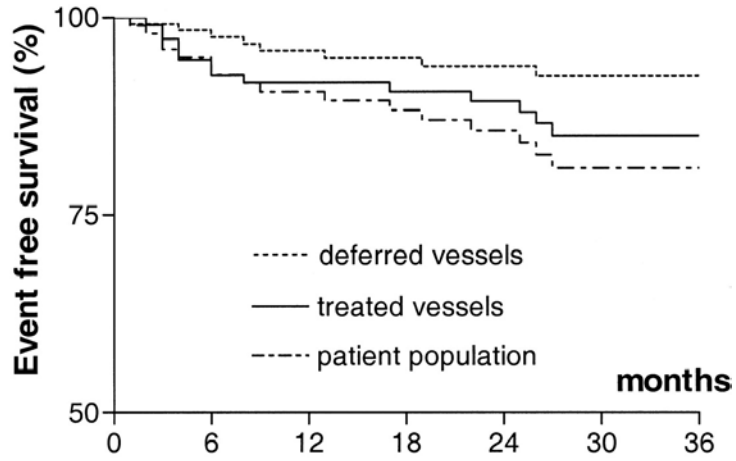
1. Merits and pitfalls of absolute flow quantification
2. Prerequisites for PCI in stable coronary patients: non-invasive and invasive assessment methods?
3. Hybrid imaging
4. Risk stratification – rock solid or still debatable
5. Tracer and translational research still strong or fading away
6. Working group and political activities
7. Working group's chair perspective

1. Merits and pitfalls of absolute flow quantification (H. Schelbert, M. Schwaiger)

Merits of absolute flow quantification:

- Quantitation is feasible by PET, MR and CT
- Rest/stress studies within 1 hour
- Diagnostic and predictive value shown only in single center studies-
- Absolute quantification allows detection of macro- and microvascular dysfunction and therapy monitoring

Cumulative major adverse cardiac events (combined end points of death, myocardial infarction, and target vessel revFFRascularization) rate curves (Kaplan-Meier) for treated, deferred vessels, and for the entire patient population



Deferred Vessels	113	111	103	92	76	64	48
Treated Vessels	127	112	107	93	78	71	57
Patients Population	102	102	81	71	57	46	34

Berger A. et al. JACC 2005

Pitfalls of absolute flow quantification:

- Lack of clinical data validating quantitative flow measurements
  - Evaluation of specific lesions (FFR)
  - Prognostic value for clinical outcome (PET driven revascularization strategy)
- Lack of simple and robust analysis methods
  - Choice of flow tracers
  - Analysis software
  - Training and education

Challenges of multimodality imaging

- Combination of PET/CTA and MRI
  - Coronary anatomy
  - Vascular wall imaging (structural & molecular)
  - Endothelial dysfunction
- Phenotyping of disease
- Endpoints of pharmacologic interventions

2. Prerequisites for PCI in stable coronary patients: non-invasive and invasive assessment methods? (U. Sechtem, M. Mazzanti)

The association between the degree of coronary artery stenosis as determined from coronary angiograms and regional ischemia remains elusive. Coronary disease with lesion in multiple vessels poses particular problems in this respect. Revascularisation of coronary stenoses that induce ischemia may improve a patient's functional status and outcome. Revascularisation of stenoses that do not induce ischemia, however, continues to be discussed controversially. The position of WG5 of the ESC in this issue is defined in this paper.

The recently published results of the FAME (Fractional Flow Reserve Versus Angiography in Multivessel Evaluation) study support the evolving strategy of revascularisation of ischemic lesions and medical treatment of nonischemic ones. This strategy leads to significantly reduced rates of mortality and myocardial infarction 1 and 2 years after the intervention as compared to angiographically guided revascularisation. Interestingly, this successful strategy is diametrically opposed to the currently held belief that complete revascularisation of all visible coronary artery stenoses during bypass surgery leads to improved outcomes.

FFR has obvious disadvantages. It is an invasive test with inherent risks and the pressure wire is expensive. Non-invasive determination of regional ischemia could be a less invasive and much cheaper but equally useful alternative to FFR measurements. In patients without regional ischemia coronary angiography could be postponed and a strategy of medical treatment might be pursued instead. Patients with regional ischemia would have coronary angiography and undergo revascularisation of the culprit lesion (with or without additional proof by FFR). Unfortunately no randomised study has yet shown that such a strategy leads to identical outcomes as were achieved in the FAME study.

Do we have data that support such an approach of stress imaging first in a patient population with chronic stable angina? It is clear that coronary angiography and subsequent revascularisation do not improve outcomes in low risk patients with stable coronary disease. Such low risk patients can be identified by a combination of clinical data combined with exercise stress testing but patients at low or high risk may be more precisely discriminated when stress imaging is employed. Hence, a strategy of not performing coronary angiography in a low risk population identified by stress imaging holds promise for saving unnecessary invasive examinations.

What is the evidence that selective revascularisation of an ischemic region identified by imaging gives a better outcome than revascularisation of all angiographically relevant (>50%) stenoses? In fact, the only data we have are from the nuclear substudy of the COURAGE trial. Revascularisation (PCI) resulting in a large reduction of ischemia demonstrated by myocardial perfusion imaging was associated with improved outcomes. However, one should not directly extrapolate from these data that revascularisation of regions identified by MPI led to prognostic improvement. The COURAGE data do not contain information whether the ischemia related lesions were successfully revascularised or whether revascularisation of all lesion was attempted in a given patient. Furthermore, the correlation between myocardial perfusion imaging and FFR for diagnosing regional ischemia has been suboptimal in some studies. This may be related to the fact that MPI requires at least one non-stenotic coronary artery for accurate interpretation of results. In patients with angiographic triple vessel disease no perfusion defect or a defect consistent with single vessel disease was seen in 54% of patients. In contrast, studies comparing myocardial perfusion CMR and FFR have come to more favourable results. Two

studies directly comparing the two modalities found sensitivities and specificities of CMR detecting FFR values ≤ 0,75 of around 90%. This suggests that CMR might be a modality matching FFR in its ability to preventing unnecessary coronary interventions.
Therefore, we need randomised clinical studies addressing the following questions:

1. Is there any clinical benefit in performing invasive coronary angiography in patients with chronic stable angina and no or only mild evidence of ischemia with perfusion imaging

2. Is perfusion imaging able to direct coronary intervention towards those vessels causing ischemia in a similar way as FFR and to prevent unnecessary revascularisation of vessels not causing ischemia?

3. Hybrid Imaging (O. Gaemperli, R. Underwood)

The appropriate management of patients with heart disease is based on integration of complementary information on cardiac anatomy, structure, pathophysiology, and pathobiology. For this purpose, the technological developments of the last decades have provided a large armamentarium of noninvasive imaging techniques including echocardiography, radionuclide imaging (SPECT and PET), magnetic resonance imaging, and computed tomography (CT). Hybrid imaging consists of the combination (or „fusion“) of images from more than one imaging technique and allows obtaining complementary structural and functional information in a single setting. The increasing availability of hybrid devices, where two imaging modalities are merged in a single scanner, has contributed to a steady growth of hybrid imaging during the last few years. However, hybrid imaging has also generated controversy with regard to which patients should undergo such integrated examinations for clinical effectiveness and minimization of costs and radiation dose, raising a general demand for objective data to support the use of hybrid imaging in general practice. Specifically, the following open questions have emerged: What is the best way of acquiring and delivering hybrid information? Are hybrid images summative or synergistic? Does every patient need to undergo hybrid imaging to be treated appropriately? Who is driving the field and what developments are envisaged in the hybrid imaging arena?

In recent years, a large number of hybrid devices by different manufacturers have entered commercial production and are now available in many diagnostic centers for use in cardiac patients. Nonetheless, it should be emphasized that hybrid imaging can easily be performed from standalone scanners by soft-ware based image fusion using commercially available software packages that provide simple and reliable co-registration of images from different modalities. Conversely, the use of hybrid devices with computer-aided co-registration does not preclude manual interaction to double-check and correct for potential misregistration. Finally, hybrid information can be presented using three-dimensional volume-rendered images and analyzed in multi-parameter databases.

A number of small single-center studies have documented the clinical value of hybrid imaging by demonstrating its superior diagnostic accuracy compared to corresponding single imaging techniques with a sensitivity of 90-96%, specificity of 95-100%, positive predictive value of 82-100% and a negative predictive value of 91-99%. However, the synergistic rather than summative value of hybrid images was revealed by another set of small cohort studies that compared hybrid imaging with the side-by-side reading of the corresponding modalities. These studies showed that hybrid imaging provides additional information by improving assignment of perfusion defects with particular coronary stenoses and thereby identifying hemodynamically relevant coronary lesions. This seems to be particularly useful in patients with multivessel disease or patients who have perfusion defects that are located in the inferior or inferolateral wall. A recent prospective study also documented an incremental prognostic value of hybrid imaging.

The use of hybrid imaging has recently been endorsed by a joint position statement by the European Association of Nuclear Medicine (EANM), the European Society of Cardiac Radiology (ESCR), and the European Council of Nuclear Cardiology (ECNC) which acknowledge its potential as a promising cardiac noninvasive imaging tool. They also note, however, that the clinical impact and the incremental value of hybrid imaging need to be evaluated in larger cohorts and multicentre investigations. Data is still lacking on the impact of hybrid imaging on clinical decision making and

management strategies, improved patient outcomes, and cost-effectiveness and, as to now, there are no hybrid imaging guidelines reflecting an international consensus on the appropriate use of this technique. It is unlikely that every patient will benefit from such an integrated imaging approach, and therefore the added costs and higher radiation exposure need to be considered whenever evaluating a patient for hybrid imaging. In centers with considerable expertise such as the University Hospital Zurich, approximately 10% of patients referred to noninvasive imaging undergo hybrid assessment, which reflects the number of patients in whom a hybrid approach may be considered beneficial.

It is likely that the increased availability of hybrid imaging will also have an impact onto the organization of diagnostic healthcare structures ushering in a “new imaging culture”. Modern diagnostic imaging centers will witness a shift from specializing in a particular technique that is applied by cross-sectional imaging to multiple organs, to an organ or system-based approach where the diagnostic expert is more concerned with function, the integration of results into clinical decision-making, and the impact of diagnostic imaging on clinical outcomes. Instead of getting a referral for a particular imaging modality, the future hybrid imager may be confronted with a particular clinical problem based upon which he will decide on the best imaging approach.

Cardiac hybrid imaging is a new and highly dynamic field of continuing research driven by the constant technological advances and innovation of noninvasive imaging and the increasing clinical interest. Open questions regarding clinical usefulness, impact on patient outcomes and management strategies, and cost-effectiveness should encourage further research and stimulate multi-centre collaborations. Results of ongoing prospective trials such as SPARC, EVINCI and PROMISE are eagerly awaited, Nonetheless, the support from industry is crucial to provide funding and coordinate multinational efforts to shed more light into the future of cardiac hybrid imaging. As the “multimodality culture” is spreading throughout Europe and the United States, so is the demand for dedicated hybrid cardiac scanners that may be more cost-effective for high-throughput centers than standalone devices.

4. Risk stratification – rock solid or still debatable (R. Gibbons, A. Kitsiou)

The think tank began by considering this question in the overall context of patients with coronary artery disease. The evidence in support of imaging with myocardial perfusion scintigraphy (MPS) or cardiac CT (CCT) for risk stratification is very different depending on the patient population. Five potential patient populations can be identified:

1. Asymptomatic patients being screened for suspected coronary artery disease.
2. Patients with stable symptoms and known or suspected coronary artery disease.
3. Patients being considered in the emergency department with possible acute coronary syndromes (ACS) for subsequent triage.
4. Patients admitted to the hospital with ACS who are managed non-invasively.
5. Patients undergoing evaluation early after myocardial infarction.

The panel began with the second group – patients with known or suspected coronary artery disease – since the evidence is strongest for MPS and CCT in this population. The panel used the framework suggested by Hlatky et al in a scientific statement from the American Heart Association (Table 1). Although this framework was originally developed for novel risk markers, the underlying scientific concepts seemed equally applicable to cardiac imaging.

For patients with stable symptoms and known or suspected coronary artery disease, there is an abundant literature for both MPS and CCT supporting the proof of concept that they can risk stratify patients. Both approaches have been prospectively validated and shown to provide incremental value to usual clinical assessment. The evidence in support of their ability to change treatment, and thereby demonstrate clinical utility, is less definitive. Much of the evidence relies on retrospective analyses of observational or randomized trial data that are primarily “hypothesis-generating”. These analyses have left a number of unresolved issues: (Table 2):

1. What is the threshold for a different clinical decision? For example, for stress MPS, some studies consider the summed stress score (SSS) and others rely on the summed different score (SDS). Clinical practice guidelines often suggest that a “large” area of ischemia is important, but do not rigorously define “large”. For cardiac CT, most studies of CT coronary angiography have relied on the identification of stenoses of 50% or greater, with only secondary analyses of 70% or greater, which was the definition customarily used in most of the original large randomized trials.
2. How to manage very elderly patients? Beginning in January, 2011, the “baby-boom” generation began to reach age 65. This is a world-wide trend that will affect virtually all countries in Europe, North America, Australia, and the Pacific rim. Elderly patients will therefore increasingly undergo non-invasive evaluation by either MPS or CCT, but there is currently little data regarding risk stratification in such patients.
3. What are the implications of discordant findings using clinical data, anatomic data (CCT), or functional data (MPS)? Although the simultaneous assessment of anatomy and perfusion by CCT and MPS has many potential advantages, including the detection of non-obstructive CAD, the increased detection of multi-vessel CAD, and the measurement of ischemia to determine which stenoses are physiologically significant, the available evidence from multiple studies suggests that there will be discordant findings when both approaches are employed. For example, a certain percentage of patients with obstructive CAD will have normal SPECT images, and

this will include some patients with high-risk CAD. There is currently little evidence to guide clinicians in reaching decisions about patients with such discordant results.
4. Are we using these tools in accordance with the evidence to demonstrate ischemia before interventional treatment? Both the ESC and ACC-AHA guidelines for the management of patients with stable angina recommend percutaneous intervention in patients with ischemia. However, there are many patients who have stable symptoms who proceed directly to invasive angiography and percutaneous coronary intervention without demonstration of ischemia. This reality in many countries is in conflict with the available evidence.

The final two steps in the phases of evaluation of imaging for CAD have little if any evidence. There have not been randomized trials showing improved clinical outcomes with the application of either MPS or CCT for risk stratification. In contrast, there is evidence of improved clinical patient outcomes (and cost-effectiveness) using fractional flow reserve during invasive coronary angiography. The FAME trial reported by Tonino et al demonstrated that an FFR-guided approach to intervention improved patient outcomes compared to an invasive angiography-based approach to intervention. Such data are not available for MPS or CCT.
The panel then turned its attention to the applications of CCT and MPS in asymptomatic individuals without known cardiovascular disease. This complex topic had been recently summarized in the position statement of the ESC Working Group on Nuclear Cardiology and Cardiac CT that was published online in July, 2010. The recommendations reflected in that position statement are nicely summarized in table 2 of that document which is reproduced here (figure 1). There is no recommended role for CT coronary angiography at this time. There is also no recommended role for cardiac CT calcium scoring for the “monitoring” of progression. In intermediate-risk patients, CT calcium score is recommended(Class IIa) to try to identify high-risk patients who are candidates for aggressive risk factor modification. In Type II diabetic subjects, CT calcium scoring is recommended(Class IIa) as a first step to try to identify patients who might then undergo MPS. If MPS identifies moderate or severe ischemia, invasive angiography can be considered. In first-degree relatives of patients with premature CAD, MPS may be considered as a first-line test, but this is a Class IIb recommendation.
The position statement of the working group summarizes all of the evidence in support of these recommendations. For example there is reference to the study by Annand et all (Eur Heart J 2006;27:713–721) in which subclinical atherosclerosis, measured by CT calcium score, was superior to the established cardiovascular risk factors for predicting silent myocardial ischemia and short-term outcome (2 year follow-up).
There is evidence of proof of concept, and prospective validation that these imaging approaches provide incremental value to usual clinical assessment. The potential clinical utility is for intensified risk factor modification or possible revascularization. However, as emphasized in the position statement, “neither the use of computed tomography for calcium imaging nor of myocardial perfusion scintigraphy have been proven to significantly improve clinical outcomes of primary prevention subjects in prospectively controlled trials”.
Similarly, the most recent ACCF/AHA guidelines for the assessment of risk in asymptomatic adults (Greenland P, et al. J Am Coll Cardiol 2010;56:e50-103) recommend the use of cardiac computed tomography for the assessment of CT calcium score for screening in subjects with intermediate Framingham Risk Score

(10%-20% risk over 10 years) in order to modify risk prediction and potentially alter therapy (Class IIa, level of evidence B).
Shortly after the Kitzbuehel meeting, the Early Identification of Subclinical Atherosclerosis by Noninvasive Imaging Research (EISNER) study was published (Rozanski A, et al. J Am Coll Cardiol 2011;57:1622-7). EISNER was a prospective randomized trial that compared the clinical impact of conventional risk factor modification to that associated with the addition of CT calcium scanning, in 2,137 volunteers. The primary endpoint was a 4-year change in CAD risk factors and Framingham Risk Score. Compared with no scanning, randomization to CT calcium score scanning was associated with superior coronary artery disease risk factor control without increasing downstream medical testing.

Table 1. Phases of evaluation (evidence development) for non-invasive imaging in the risk stratification of CAD.

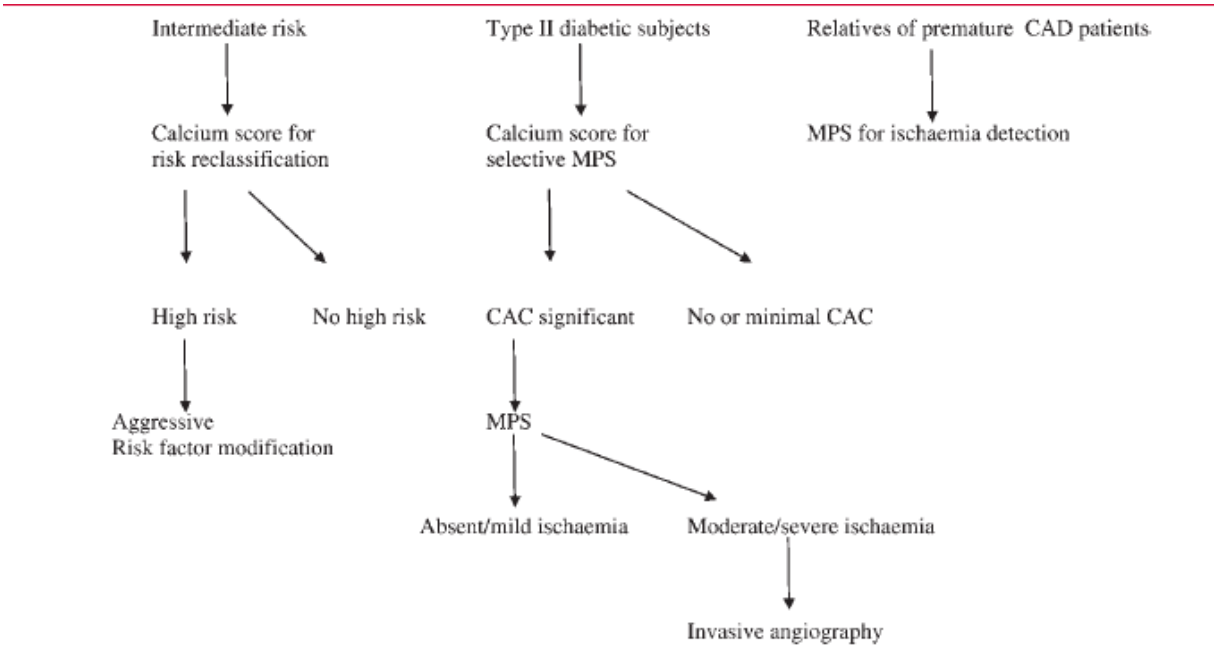
Proof of concept
Prospective validation
Incremental value to usual clinical assessment
Clinical utility – change treatment
Clinical outcome
Cost-effectiveness

Modified from Hlatky et al, Circ2009;119:2408

Table 2. Open questions in the application of non-invasive imaging for the risk stratification of patients with stable symptoms and known or suspected CAD.

What is the threshold to change clinical decision?
How to manage very elderly patients given very limited data?
How to manage patients with discordant findings (clinical vs anatomy vs function)?
Is there proof of ischemia before intervention?

Figure 1. Applications of CCT and myocardial perfusion scintigraphy in asymptomatic subjects without previous cardiovascular events. Reproduced with permission from Perrone-Filardi P, et al. Eur Heart J 2010, Position Statement of the Working Group on Nuclear Cardiology and Cardiac CT of the ESC.



5. Tracer and translational research still strong or fading away (F. Bengel, G. Sambuceti)

Translational research is a critical contributor to progress in the field of cardiovascular imaging. At present, there still seems to be a gap between A0) the very exciting molecular imaging techniques that are mostly employed in preclinical models, such as plaque-targeted imaging, imaging of stem cells, or imaging of LV remodeling; and B) the clinical imaging environment, which mostly looks at perfusion and coronary atherosclerosis. Translational research is defined as the bridge from basic science to clinical science, and back. Two major segments of translation were identified by the group. One is the bridge between animals and humans; the second is the bridge between a first-in-man application and clinical practice.

The translation of novel imaging techniques from experimental animals to the human setting provides major opportunities: New tracers may emerge for improved and more versatile clinical imaging applications. And the costs of drug development may be reduced by the implementation of serial noninvasive imaging techniques.
However, it also faces various challenges: First, the animal model needs to reflect the clinical setting most realistically. This is difficult to achieve, because the biology of small rodents (mice, rats) often differs significantly from humans. Experimental animals rarely develop true coronary artery disease or die of ischemia/infarction. Some imaging techniques, such as optical imaging, are also restricted to small animals. Intermediate steps, such as large animal studies, seem to be necessary to get closer to the clinical setting regarding heart size and body shape, but from a biologic point of view those do not provide a complete solution either.
Another challenge is the fact that there seems to be a good business model for researchers to rush from one proof of principle to the next, without spending time and additional effort to focus on translation. This is supported by the ease of getting high-ranked publications and funding with novel proof-of-principle work, and by the relative difficulty and high time demand of translational work, which may not be seen as truly innovative because of previously published proof-of-principle type of work.
Finally, the major challenges are the manifold regulatory hurdles, which inhibit a rapid move from animals to humans. Costs of providing the necessary safety and toxicology data are excessive and it is difficult to secure appropriate funding.

The translation from first-in-man to clinical practice provides the opportunity to establish novel approaches for more efficient clinical imaging. At the same time, there are also challenges: The market size (and thus the potential to recover development costs through sales revenue) for novel imaging agents is much smaller than that for therapeutic drugs. Yet, the developmental costs and the expenses for achieving approval are identical. Another problem in the new field of molecular-targeted imaging is that the increasing specificity of the molecular tracers may limit their broad clinical application and may thus reduce the market size even further.

The think thank group identified the following needs in the area of translational tracer research: 1.) The identification of true clinical demands and priorities should be clearly defined. Only by really knowing about the needs of clinical cardiology practice can the research and development efforts focus on useful new products. 2.) In order to facilitate the introduction of a new imaging test into the clinics, a most suitable way would be to link novel therapies with novel imaging tests from the beginning, i.e. in the preclinical stage. If the therapy reaches clinical acceptance (with the help of a

specific imaging technique to guide decision for or against it), then the respective imaging test will automatically be linked with the new therapy and it will also gain acceptance. Such joint efforts of therapeutic and imaging researchers would be along the line of personalized medicine. 3.) In order to have a sufficiently broad market despite the high molecular specificity of novel molecular agents, common grounds should be identified for such agents across the borders of various disciplines. Most molecular targets which are thought to play a role in plaque vulnerability also play a role in ischemic myocardial injury, but also in tumor progression and cerebrovascular disease, or diseases of other organs. And 4.), because translation is a complex topic, broad education , mentoring, interaction and networking across the framework of different disciplines and across various specialties will be beneficial to advance the field and to ascertain progress.

6. Working group and political activities (E.E. van der Wall, P. Perrone Filardi)

- Dissemination (publications, scientific sessions etc) based on disease-oriented imaging instead of modality-driven imaging
- Education in multimodality imaging at multilevel training:
  - Cardiology residency
  - Post-specialty
- Levels of training
  - local
  - centers of excellence
  - national (special training year within and/or outside cardiology training)
- More interaction between WG's in order to produce consensus papers; not only stimulating interaction between imaging WG's but also WG's and Associations outside imaging (revascularization, heart failure, congenital, valvular, cardiomyopathies)
- Improved penetration of the value of imaging modalities into the Guidelines

- Reimbursement; primary aim is to increase the knowledge instead of income! However!!!
- More involvement of nuclear medicine specialists and radiologists (EANM, ESR)
- Imaging Association?
- European Journal of Cardiovascular Imaging?
- Boosting ICNC (ASNC, EANM, ESC)?

- Database registration within Europe (cf. US)
- Engagement in multi-center studies (EVINCI)
  (US: SPARC, PARR, BioImaging)

7. Working group's chair perspective: a new era of intensified collaboration between non-invasive cardiac imaging modalities (Anastasia Kitsiou, Chair, WG on Nuclear Cardiology and Cardiac CT, ESC)

Our key motivation is to intensify the collaboration between the European Association of Cardiovascular Imaging, the Working Group on Cardiovascular Magnetic Resonance and the Working Group on Nuclear Cardiology and Cardiac CT within the European Society of Cardiology. This would address patients' needs by working together with experts representing all non-invasive imaging modalities and trying to identify the best cardiac imaging technique to answer each specific question in the most efficient way. Furthermore, the increasing budgetary constraints across Europe lead to major changes in reimbursement for diagnostic procedures. In this time of limited economic resources and responding to the challenges facing the cardiovascular field requires an effort from all specialties involved that is based on collaboration rather than competition. The European Heart Journal – Cardiovascular Imaging is an example of successful collaborative effort and members of our Working Group are actively participating in the Editorial Board and also submit their papers to the Journal. In addition, extensive collaboration exists between the three imaging constituent bodies in the organization of scientific meetings and in writing relevant position statements.