3rd Research Day of the Royal Brompton and Harefield Hospital

Royal Society of Medicine, Marcus Beck Library (3rd floor), London, United Kingdom
Wednesday, December 19, 2018 - 08.30 – 16.00h
Chairs: Kim Fox, Richard Grocott-Mason, Thomas F. Lüscher

FACULTY:

- Amir Lerman (excused)
- Alex Lyon (excused)
- Felix Mahfoud (excused)
- Jeroen Bax
- John Cleland
- John Deanfield
- Milton Packer
- Sanjay Prasad (morning only)
- Rod Stables (morning only)

GUESTS:

- Ruth Ashton (excused)
- Dorian Haskard (excused)
- Osama Samara (excused)
- Simon Davies
- Debra Dempster
- Ranil De Silva
- Allan Davies, Research Fellow
- Diana Gorog
- Vias Markides
- John Pepper
- Paula Rogers
- William Wijns
- Tom Wong
- Rosita Zakeri

Introduction

Kim Fox and Thomas F. Lüscher welcomed the participants (see Figure 1) in the name of the *Royal Bromp-ton & Harefield Foundation Trust*, as well as in the name of the *Institute of Cardiovascular Medicine & Science*, a collaboration between the *Royal Brompton and Harefield Hospitals* and the *Liverpool Heartand Chest Hospital*.

Thomas F. Lüscher introduced the meeting with a few slides outlining the spirit and strategy of the Research Days at the *Royal Society of Medicine*. It is the aim of such meetings to discuss ideas and outline and drafts of future clinical trials and the use of this sounding board of visiting experts from the United Kingdom, Europe and the USA for a true brainstorming and review of the presented materials. So far, this has been extremely productive and well-received by the participants and took place, for the first time, at *The Royal Society of Medicine* in London on December 20, 2017 – immediately after the first *Cardiology Update, London* 2017 – and now on December 19, at the end of the 2nd *Cardiology Update*, London. The topics discussed were mainly coronary intervention and prevention, as well as heart failure and atrial fibrillation. Other topics such as structural heart disease, congenital heart disease and cardiovascular surgery are on the list for future meetings.

So far, all Research Days have been paid for by the *Zürich Heart House – Foundation for Cardiovascular Research*. The support of this charity is, therefore, acknowledged.

Figure 1: Participants of the 3rd Research Day at the Royal Society of Medicine in London (Photo: Jan Lipton)

The Institute of Cardiovascular Medicine & Science

Rod Stables, from Liverpool, reported on the activities of the *Institute of Cardiovascular Medicine & Science* (ICMS) and its Annual Meeting, which took place this fall at The *Royal College of Physicians*.

Rod Stables further introduced new options to collect and analyse data based on his experience with AIMES^{R}, a start-up company and a spin-off of the University of Liverpool, with offices in Liverpool and now London as well. This company specializes in data collection for registries and trials. The audience was very impressed about the options that this start-up company made possible – collecting data, not only from excel sheets, but also from PDFs and other materials and their ability to link it with addresses and social status among other demographic data of patients. It is hoped that this will help to foster collaboration between Liverpool and London in the future.

Interventional Cardiology

The first scientific session on "interventional cardiology" chaired by William Wijns featured a presentation of several trials.

Thomas F. Lüscher presented the **ICONE Trial** (*Improvement of Cardiac and HemOdyNamic Function through Inhibition of Endothelin*) that has been submitted to the MRC and is now in its second round of reviews. The trial hypothesizes that endothelin (ET) plays a crucial role in

microvascular contraction and, in turn, left ventricular dysfunction in patients with Tako Tsubo Syndrome. Therefore, this trial will investigate whether Tezosentan, an ET_{AB}-receptor antagonist, will be able to reverse left ventricular dysfunction and apical ballooning, respectively in this patient population. This proof of concept study will involve 125 patients and randomize them to placebo or Tezosentan, respectively. It will involve patients at 8 sites, i.e. Southampton (Nick Curzon), Bart's Heart Centre (Andreas Baumbach), St. Thomas' Hospital (Bernard Prendergast), Harefield Hospital (Miles Dalby), Hertfordshire (Diana Gorog), Liverpool Heart & Chest Hospital (Rod Stables) and Newcastle (Azfar Zamarn).

Then the **REPLACE-ACS Trial** (*RevErsal of atherosclerotic PLaques with AliroCumab Evaluation in Acute Coronary Syndromes*) was presented. The trial would like to focus on patients with STEMI and plaques of non-subtotal hemodynamic significance in other than culprit arteries and would anticipate to randomize around 1,200 to 1,500 patients to either standard therapy or culprit primary PCI plus Alirocumab on top of a statin and ezetimibe in both groups. The hypothesis is that lowering LDL cholesterol to levels below 0.5 mmol/L will reverse or stabilize atherosclerotic plaques outside the culprit artery and reduce the number of deaths, myocardial infarction, rehospitalizations and revascularizations after hospital discharge.

It was extensively discussed whether, or not, it will be possible to pursue such a strategy on ethical and logistical grounds. Current practice, as Rod Stables pointed out, usually insists on evaluating the hemodynamics of significant and potential cause of ischemia of lesions outside the culprit artery using FFR for non-invasive perfusion tests at least in certain centers. It was discussed whether one should randomize patients after 30 days; however, this would certainly reduce the power of the study to detect any difference between the two groups. The presenter will come up with a revised version for further discussion. Of note, this trial has already been submitted to Amgen, Sanofi-Regeneron and the Medicines Company.

Furthermore, Thomas F. Lüscher presented an outcomes research project, i.e. the prospective **Heart-ACS registry** with a biobank at Harefield hospital. It is anticipated to recruit all patients presenting as primary patients to the Cath Lab at Harefield Hospital, to obtain oral consent on the table and after placing the sheet to obtain 60-100 ml of blood for the biobank. The coronary angiogram and eventually a procedure, if necessary, will be performed; the patients will be fully characterized with a specific eCRF and follow-up visits at 6 and 12 months, respectively.

Such a registry has been successfully developed in Switzerland with 5 centres recruiting over 5,000 patients. This network was extremely productive with over 30 publications in high impact journals such as the *European Heart Journal*, the *Journal of the American College of Cardiology*, the *International Journal of Cardiology* and the *New England Journal of Medicine* and many others. Therefore, such a prospective registry would be of utmost importance also for Harefield Hospital where around 1,400 patients with acute coronary syndrome are seen on a yearly basis.

Thomas F. Lüscher asked Rod Stables and Diana Gorog whether it would be possible to implement this also in Liverpool and Hertfordshire, respectively. This option will be further discussed with these centers, but certainly would represent a huge opportunity for all centres.

The next topic was **Clot Firmness in ACS Patients** and its importance for outcome, particulary in patients with STEMI. Thomas F. Lüscher presented some data of the PLATO sub-study looking at fibrin clot properties that independently predict adverse clinical outcomes for ACS patients, treated mainly with primary PCI. This study showed that the greater the firmness (i.e. turbidity and fibrinolysis) of the clot the higher mortality and the lower the firmness of the clot,

the higher the risk of bleeding. Therefore, there is a sweet spot which would provide an opportunity for a large, randomized trial in those who have a propensity to develop firm clots, testing the effects of a NOAC – in short *precision medicine*.

The suggestion was expanded by an excellent and well-documented presentation by Diana Gorog from Hertfordshire, where she showed based on her own data that, indeed, patients with delayed fibrinolysis have a 10-fold increase in risk after an acute event, and a 5-fold increased risk after correcting for traditional risk factors. Therefore, the group was very enthusiastic to pursue a trial in this patient population to test whether in those with delayed fibrinolysis a NOAC would be beneficial for outcome with a reduced bleeding risk (which was the major hurdle in ATLAS-ACS TIMI 51 and in part also in COMPASS).

Allan Davies, from the Royal Brompton & Harefield Hospital, then presented the concept of **microbiome and its product for cardiovascular disease**. He showed that our body contains about three times as many bacteria as we have cells that make up our body. These bacteria do eat what we eat and produce metabolites that are potentially harmful for cardiovascular health. In particular, trimethylamine (TMA) is produced by the microbiome of omnivores from carnitine contained in red meat, oxidized in the liver to TMAO and in turn facilitates the development of atherosclerotic plaques and stimulates tissue factor, both important mediators of ACS. Indeed, he showed studies between the University Hospital, Zürich and the Cleveland Clinic demonstrating a marked increasing risk of major adverse cardiovascular events in those with high TMAO levels and in a later study in press also in those with increased levels of trimethyllysine (TML), another microbiome product, which predicts mortality in patients after ACS. Finally, patients with diabetes and recent acute coronary syndrome exhibit markedly elevated levels of microbiome metabolites that are predictive for outcome, particularly in the highest quartile.

Figure 2: Discussants at the 3rd Research Day at the Royal Society of Medicine in London. From left to right: Richard Grocott-Mason, Tom Wong, Simon Davies and John Deanfield (Photo: Jan Lipton)

Therefore, Allan Davies and Thomas F. Lüscher propose to perform a **trial with microbiome transplantation** after an ACS in those within the highest quartile of TMAO levels to see whether this would normalize markers of inflammation and outcomes in these patients. John Deanfield (see Figure 2) argued that in primary prevention his studies did not find much of an effect of TMAO. Possibly, patients with established disease are indeed different, have been exposed to these bacterial metabolites for prolonged periods of time unlike healthy subjects exposed to the metabolites for only short periods.

Heart Failure

The next session chaired by Diana Gorog focused on heart failure.

The first speaker, Jeroen Bax from Leiden University in the Netherlands discussed how to measure and **image left ventricular ejection fraction** and how to define heart failure with preserved ejection fraction. He particularly focused on the fact that ejection fraction is just a volume change and may not necessary reflect the intrinsic contractile capacity of the left ventricle. Rather, longitudinal strain, which normally has a value of -20 might be a much more appropriate parameter to assess left ventricular function. This is particularly important to define the phenotypes of patients for future trials in heart failure with preserved ejection fraction.

Milton Packer, from Dallas, Texas talked about the role and the interaction of **diabetes and heart failure** and provoked the team with his statement that diabetes and heart failure may, in fact, be the same disease. Indeed, diabetics have an increased rate of heart failure and in heart failure patients the presence of diabetes worsens the course of the disease and clinical outcomes. Furthermoe, obesity is also related to both conditions. He again stressed the fact that inflammation derived from visceral obesity in the belly, as well as around the heart and the kidneys, may be important mediators providing inflammation and in turn fibrosis of both the myocardium and the kidney leading to stiff hearts and impaired renal function, respectively. Impaired renal function will lead to an increased plasma volume with which a stiffened heart has difficulties to cope with which will in turn lead to symptoms of heart failure such as breathlessness, orthpnea and bendopnea. He derived three major phenotypes of heart failure in obese patients that may be important subgoups to focus future trials on.

John Cleland finally discussed how to define **HFpEF from a trialist perspective**. He reviewed all the trials and the definitions of HFpEF that have been published in the past from CHARMS to HYVET and stressed a reasonable and feasible definition of HFpEF for future trials, i.e. (1) normal ejection fraction; (2) breathlessness and/or diuretic use (with diuretic use having more weight); (3) mild increases in NT-BNP (> 300, but less than 1'000 pg/ml) and (4) an enlarged atrium.

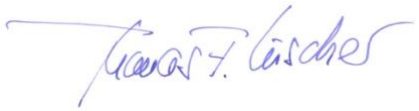
Finally, Rosita Zankeri presented on behalf of Ranil da Silva and his team the **Reducer in Microvascular Angina Trial**. She reminded the participants that a large proportion of patients undergoing PCI still have anginal symptoms, some even when all epicardial coronary arteries are unobstructed, the so-called INOCA (*Ischemia with non-obstructive coronary artery disease*) syndrome. Here, the REDUCER^{R}, a stent device implanted in the coronary sinus thereby obstructing venous outflow, may be a treatment option. Thus, they hypothesized that In patients with angina, unobstructed epicardial coronary arteries and CMR evidence of ischaemia secondary to microvascular dysfunction, coronary sinus obstruction with the REDUCER^{R} will improve symptoms, quality of life and myocardial perfusion. To that end they plan to recruit in three centers 165 patients with INOCA. The participants felt that this trial that has been submitted to the NIHR in a first round is interesting and may address a therapeutic gap. How-

ever, Kim Fox was somewhat concerned about the anticipated three year recruitment period and the availability of such patients at large. Ranil da Silva however argued that they do indeed see a considerable number of such patients at the Brompton and in other centers with an interest in this patient population.

Conclusion

Thomas F. Lüscher thanked the participants for a most stimulating meeting with excellent presentations and productive discussions and promised to organize a next meeting in spring 2019 for further discussions and development of common projects.

London, December 24th 2019



Professor Thomas F. Lüscher, FRCP
Director of Research, Education & Development