



Aortic Valve Replacement using Individualised Regenerative Allografts:
Bridging the Therapeutic Gap

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1 Introduction

In addition to presentations and publications, the ARISE consortium set the goal to introduce the concept of decellularized aortic homografts (DAH) for aortic valve replacement (AVR) to active professionals as well as young medical students in practical ways.

As a first step to reach that goal a 3D video, produced during the operation of the first ARISE patient, showing the operation technique of the aortic heart valve replacement in detail was created for the Techno-College of the European Association for Cardio-Thoracic Surgery (EACTS). The goal of the EACTS's Techno-College is to raise medical standards of professionals through education and training and is joined by several hundred surgeons and scientist each year. The video was presented during the EACTS conference 2015 in Amsterdam.

The second part of the goal was the organisation of a training workshop for surgeons. With the workshop the consortium wanted to share information about the ARISE project and the decellularized homograft technology, to disseminate latest results, create awareness of the topic and contribute to the education of especially young surgeons.

2 Preparation and organisation

The preparation of the training workshop was initiated during the 5th ARISE Steering Committee Meeting on the 3rd of December 2016 in Zurich. Prof. Pomar from IDIBAPS (partner 4) presented first ideas and different options for the workshop to discuss them with the whole consortium.

The most important topics for the workshop were discussed and the partners agreed on the following key aspects:

- the ARISE project and its funding by the European Commission's H2020 programme
- the rationale behind the decellularized homografts
- the homograft allocation process
- operative techniques and surgical pitfalls
- latest experiences and results

Furthermore the consortium decided to include practical lessons in the wet lab into the workshop.

Regarding the target audience it was decided to address cardiologists and cardiac surgeons, especially younger staff, as well as medical students, who would all benefit from the practical lessons. On top of that it was planned to invite some employees of tissue banks, transplant coordinators and, if possible, patients or members of patient organisations to the workshop, to reach as many audiences with connections to the projects topic as possible.

The Hospital Clinic of Barcelona (HCB) was chosen as the location for the workshop, since they offer handy and affordable venues, especially due to their direct connection to the Medical School of the University of Barcelona.

Lastly it was decided to schedule one of the next ARISE consortium meetings around the workshop. This would increase the visibility of the consortium and would give them the opportunity to interact and discuss the project with other professionals and interested people.



Image 1 and 2: Hospital Clinic of Barcelona

The further organisation of the workshop was carried out in cooperation of MHH (partner 1), IDIBAPS (partner 4) and LUH (partner 9), with updates for the consortium on different occasions. The 17th of November 2017 was set as the date for the workshop and the programme was further elaborated. As an additional topic it was decided to also share some information about ARISES's predecessor project ESPOIR. Furthermore a presentation by Dr. Harder from Corlife (partner 2) about the company Corlife and the reimbursement of the decellularized valves outside of the project, as well as a section by Dr. Jashari and Dr. Trias from the tissue banks in Brussels and Barcelona were integrated.

The workshop location, catering for the participants and equipment were arranged. An adequate room that is used for anatomic demonstrations at the basement of the Medical School of the University of Barcelona was adapted for the wet lab. Sixty pig hearts were conveniently procured from a local slaughterhouse the day before and stored in a fridge. Several pig's heart valves were decellularized by corlife to give the participants the opportunity to actually get to know the technology in a safe training environment. Twenty complete sets of instruments including scalpels, scissors, forceps, needle holders and sutures were prepared.

To advertise the workshop a flyer was prepared, including the programme as well as all other necessary information, like locations and registration, for interested parties. It was decided to not charge any registration fees, to encourage especially young medical professionals to join the workshop.

About ARISE

65,000 aortic valve replacements (AVR) are performed in Europe each year to treat acquired and congenital aortic valve diseases. Current AVR options are, however, limited for young patients - especially female patients - and those unwilling to accept life-long medical anticoagulation with its inherent risks. None of the currently available prostheses for AVR is tailored toward the individual patient or allows for individual regeneration. The ARISE project will bridge this therapeutic gap in a clinical study to determine the feasibility, safety and efficacy of **decellularized human heart valves (homografts) for aortic valve replacement**.

The ARISE consortium will address these challenges, integrating a network of six leading centres for cardio-thoracic surgery, each with proven track records in clinical research and an innovative small enterprise experienced in bringing human tissue products to the clinic and market and expertise in ethical and regulatory aspects of regenerative medicine.



**Implantation of decellularised aortic homografts for aortic valve replacement:
Training workshop for surgeons**

Friday November 17th 2017 08:30 – 18:00

Hospital Clinic Barcelona – Sala Ferreras Valenti

Programme

- 08:30**
Welcome and Introduction.
Dr. Axel Haverich and Dr. José L. Pomar
- 08:45**
What is the H2020 program of the European Union?
Marga Nadal and Maria Carol
- 09:05**
Why ARISE and ESPOIR got funding from the European Framework Programme.
Dr. Axel Haverich
- 09:30**
Summarizing the goals and rationale of the ARISE Project.
Dr. Samir Sarikouch
- 09:45**
The partners of the ARISE project.
Dr. Axel Haverich
- 10:00**
Why is this project important for you?
Dr. Jose Luis Pomar

- 10:15**
Let us explain to you how this technique works:
a) The first human implantation of a decellularized homograft in the ARISE project – Live-In-A-Box case
Dr. Igor Tudorache
b) The first implantation in our hospital - Live-In-A-Box case
Dr. Eduard Quintana
- 10:45**
How the Spanish and Catalan Transplantation Network could help to disseminate the project's results.
Dr. Ramadan Jashari and Dr. Esteve Trias
- 11:00**
Reimbursement of cell-free homografts beyond ARISE.
Dr. Michael Harder
- 11:15** *Coffee break*
- 11:45**
Current outcomes of the ESPOIR project.
Dr. Dietmar Böthig
- 11:55**
Current outcomes of the ARISE project.
Dr. Samir Sarikouch
- 12:05**
Reasons for concern? The Mayo Clinic report.
Dr. Axel Haverich
- 12:15**
Results from other researchers.
TBD
- 12:30**
Let's go to practice! - Wetlab: Tips and tricks for the implantation of decellularized homografts. Animal hearts and Live-In-A-Box cases.
Dr. Daniel Pereda and Dr. Eduard Quintana
- 14:00** *Lunch*
- 15:00**
Wetlab continuation.
- 17:30**
Conclusion for the media.

Registration

Until November 10th 2017 via mail to: acamos@clinic.ub.es

Costs for the workshop will be covered by the ARISE Consortium. Costs for travel and accommodation have to be covered by the participant.

Location

Hospital Clinic Barcelona, Villarroel 170
Room Ferreras Valenti, Stairway 9 – 3rd floor



Aortic Valve Replacement using Individualised Regenerative Allografts: Bridging the Therapeutic Gap

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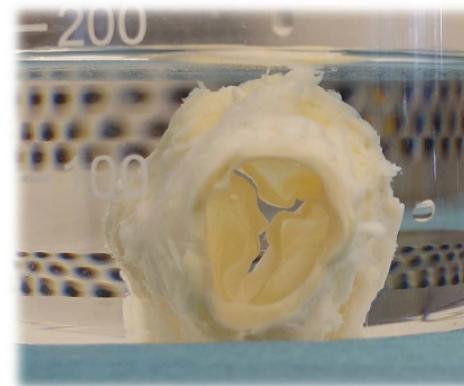


Image 3 and 4: ARISE Training Workshop Flyer

The flyer as well as information on the workshop in general was disseminated by all partners to their respective clinics and universities, to different partner clinics and networks like the European Association of Cardiothoracic Surgery (EACTS), the Association for European Paediatric Cardiology (AECPC), the German Society for paediatric cardiology (DGPK), the Spanish Society of Cardiology (SEC) and Cardiovascular Surgery (SECTV), Catalan Society of Cardiology (SCC) and the Catalan Society for Cardiac Surgery (SCCC).

3 Programme and implementation

The opening of the workshop was done by the coordinator of the ARISE project Prof. Haverich (partner 1) and Prof. Promar from the Hospital Clinic of Barcelona, as host of the workshop. Both welcomed the participants and introduced them to the general topic of the workshop. The whole workshop was also filmed by the technical team of the Hospital Clinic, to enable later dissemination via the internet (please see the chapter 4 for further information).

3.1 What is the H2020 program of the European Union?

Since the ARISE project couldn't have been realized without the funding by the European Commission, the consortium decided to start the workshop with a presentation about the European Union's H2020 programme. Juan Abolafia, member of the European and International Projects Research Management Office "Fundació Clínic per a la Recerca Biomèdica", introduced the participants to the funding programme for research and innovation, its goals and challenged based approach. He outlined the structure of the funding programme with its three pillars "Excellent Science", "Industrial Leadership" and "Societal Challenges". Special focus was laid on the Societal Challenge "Health demographic change and wellbeing", due to its connections to the subject of the ARISE project. To help any young researchers, or those who haven't worked on a H2020 project yet, get an idea on how to participate, he outlined the participation rules and funding range. Furthermore he gave some helpful tips on how to read the work programme and finding the right calls.

Additionally Mr. Abolafia informed the participants about three calls with similarities to the topic of the ARISE project: "SC1-BHC-09-2018: Innovation platforms for advanced therapies of the future", "SC1-BHC-16-2018: Global Alliance for Chronic Diseases (GACD) - Scaling-up of evidence-based health interventions at population level for the prevention and management of hypertension and/or diabetes" and "SC1-BHC-07-2019: Regenerative medicine: from new insights to new applications".



Image 5: Overview H2020

3.2 Why ARISE and ESPOIR got funding from the European Framework Programme

As an introduction to the ARISE project and to give the participants an impression of the development of a research idea, the coordinator Prof. Haverich outlined the story and evolution of the two EU funded projects ESPOIR and ARISE.

After the development and refinement of the decellularization technique, the decellularized heart valves were first put to test in animals, where they showed very good histological results. The first clinical application of pulmonary heart valves was done 2002 in Chisinau (Moldova), with further patients following in Chisinau as well as Hannover. An important discovery was made later, when check-up of the first two patients showed, that the valves had actually grown inside the patients, opening up the possibility to develop implants that would grow with the patient and would therefore be especially suitable for young recipients.

During the ESPOIR study especially the approval of the valves by PEI and the different national regulations of the involved partners were a major challenge, which was overcome with the dedicated work of the whole team. This achievement as well as the strong team that had formed in form of the ESPOIR consortium served as a basis for the ARISE project.

Prof. Haverich explained, that one of the main success criteria for both the ESPOIR and the ARISE project, was the clear goal, that had already been set before the work on the proposals started. For both projects the idea was to initiate a multicentre clinical trial to investigate the potential and benefits of decellularized heart valves. He underlined the significance of serendipity in this context, showing how not only in famous cases like the discovery of penicillin, but also regarding e.g. the growth potential of decellularized heart valves unexpected findings by the scientists were a very

important factor. He elaborated that a clear goal and dedication to do the work are key, while also having open eyes for new discoveries and findings by all members of the team. He further explained the importance of the dedication put into the proposals for both projects as well as the exploration of the benefits both projects could have for special groups like children and young women.



Image 6: Prof. Haverich and Prof. Pomar during the ARISE training workshop

3.3 Summarizing the goals and rationale of the ARISE Project

To introduce the participants to the rationale of the ARISE project, Prof. Sarikouch started off by first illustrating the course of the ESPOIR project. Just like ARISE, ESPOIR focused on evaluating the efficacy and benefits of decellularized fresh homografts, focusing on pulmonary valves instead of aortic ones. The ESPOIR consortium had to master a lot of challenges to, but managed to receive approval of the decellularized valve by Paul-Ehrlich-Institute, establish first connections to different national authorities and tissue banks in Europe and collect data of 121 patients operated during the ESPOIR study. All of this helped to enable a smooth start of the ARISE clinical trial.

He continued by explaining the rationale behind the idea of using DAH for AVR. Traditional options for AVR have different kinds of disadvantages for the patients. Xenogeneic valve degenerated quickly, mechanical valves demand the use of blood thinners, patients treated with the ROSS procedure need a lot of reoperations and cryopreserved homografts have a major issue with calcification. Animal data for decellularized allografts on the other hand, has shown convincing mechanical stability and less calcification. Main objective of the ARISE study is therefore to determine the feasibility, safety and efficacy of DAH for AVR within a multi-centre clinical study.

Prof. Sarikouch furthermore added some information about the project's structures and work packages, the Ethics and Governance Council (EGC) of ARISE and some information about the study protocols.



Image 7: Prof. Sarikouch during the ARISE training workshop

3.4 The partners of the ARISE project

The workshop participants were introduced to the different partner organisations involved in the ARISE project. They got an overview of the ARISE partners, clinics outside of the two consortium that have implanted aortic decellularized valves and provide their data to the database, as well as the different tissue banks in Europe that provided the heart valves for the projects.



Image 8: The organisations involved in the ARISE study

3.5 How the Spanish and Catalan Transplantation Network could help to disseminate the project's results

Dr. Ramadan Jashari from the European Homograft Bank (EHB) in Brussels and Dr. Esteve Trias from the Barcelona Tissue Bank (BST) joined the workshop to explain the role of the tissue banks for the ARISE project and to raise awareness of the topic of tissue donation and allocation in general.

In his presentation Dr. Jashari explained the role of the tissue banks in the ARISE as well as the ESPOIR project. EHB was one of the members of the ESPOIR consortium and is now the most active provider of heart valves for the ARISE study. The tissue banks are responsible for the consent and donation process, the harvesting, first test (e.g. histological) of the donated tissue and the allocation process to the patient. Corlife provides the decellularization as a service and is responsible for the quality management of the decellularized valve. Additionally Dr. Jashari explained the complex and diverse rules in Europa regarding organ and tissue donation and by showing some recent numbers illustrated the serious percentage differences regarding the amount of tissue donated in the different EU countries. As a conclusion he shared the importance of the active involvement of surgeons into the tissue donation process, especially in case of non-transplantable hearts.

Dr. Trias opened his presentation with some general words about heart valve transplantation. A tissue donation is a unique gift, which needs to be given with consent and full information. Following ethical guidelines for donation and procurement procedures as well as fulfilling technical, quality and safety requirements are of the highest importance. With new ways to process donated tissue, like it is the case with the decellularization, regulations and a positive health technology assessment (HTA) are important to ensure safety, efficacy, effectiveness, appropriateness and implementation. He underlined that for the HTA especially follow up data is needed, while for the implementation and to ensure availability of the new technology, national and international cooperation between clinics, tissue banks and other stakeholders is needed.



Image 9: Dr. Jashari and Dr. Trias during the ARISE training workshop

3.6 Reimbursement of cell-free homografts beyond ARISE

Dr. Harder from corlife introduced the workshop participants to the topic of reimbursement for processed human heart valves. According to Guiding Principle No. 5 of the World Health Organisation, the human body and its parts (e.g. donated tissue) must not be a source of financial gain. The need to cover legitimate costs of procurement and of ensuring the safety, quality and efficacy of human cell and tissue products and organs for transplantation is seen as acceptable though, as long as it is done at a fair price. Corlife's policy is to act according to this guideline, providing and charging a price only for the service of the decellularization, while not participating in the allocation process itself.

Dr. Harder explains that reimbursement procedures are country-specific and extremely complex and are one of the major challenges for Corlife to ensure sustainability and availability for their product around Europe. Corlife tries to establish a model procedure according to the European Network for Health Technology Assessment (EUNETHTA), for the positive Health Technology Assessment, follow-up data by all clinics participating in the ARISE study is need though. For Germany, Austria and Switzerland, reimbursement is provisionally organized and must now be maintained, appropriate applications are also being prepared for Belgium and the Netherlands.

3.7 Current outcomes of the ESPOIR project

To give the participants a better impression of the results on decellularised fresh homografts generated so far, Dr. Böthig presented some outcomes of the ESPOIR project.

Within the ESPOIR Registry data of 231 patients has been integrated so far, adding up to a total follow-up time of 629 years. Survival rate at 10.6 years so far is 97%. A total of 5 patients died, none of them due to valve related reasons. Dr. Böthig explained several calculations done for different kinds of indicators used to determinate the efficacy of the treatment, like valve insufficiency levels, mean peak valvular gradients or right ventricular outflow track gradients. In summary, more than 3/4 of the patients treated with decellularized pulmonary homografts remained free from dysfunction or intervention within 10 years.

Dr. Böthig continued with the presentation of some results generated from a matched triple comparison study done with the data of patients treated with decellularized homografts, conventional homografts and bovine jugular veine. Decellularised homografts showed very good results, especially regarding appropriate size development. The data showed that after 12 years only the decellularized conduits and none of the conventional alternatives developed its size appropriately. Overall the statistical results indicated that fresh decellularised pulmonary valves in pulmonary position preserve their function longer, show more adaptive size development and need less explantation or intervention than alternative conduits.

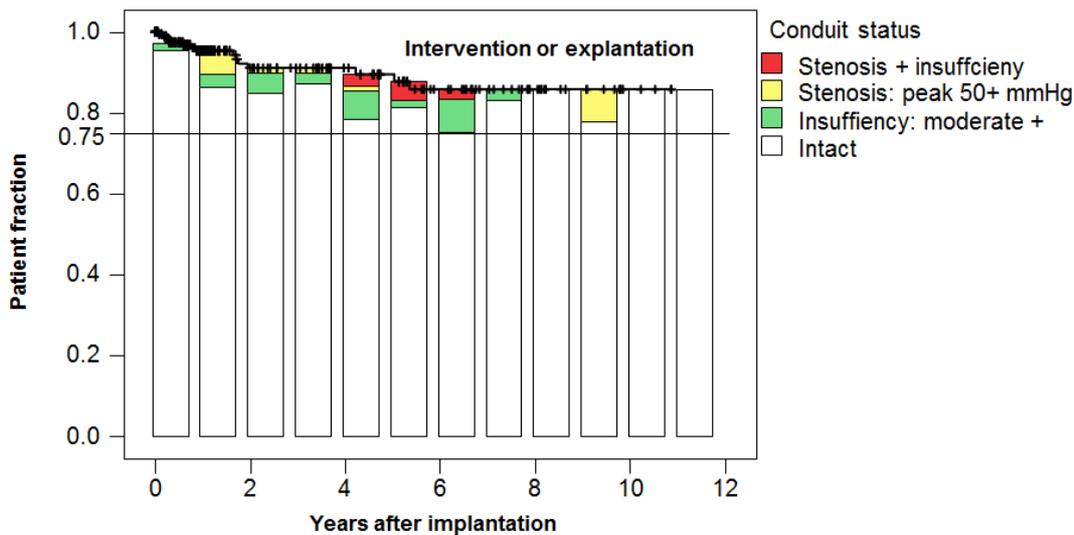


Image 10: Conduit status development

3.8 Current outcomes of the ARISE project

Until the day of the workshop, data of 142 patients had been integrated into the ARISE Registry, with 99 of them having been operated within the ARISE study. Prof. Sarikouch presented the participants some of the latest result generated with the data.

Within the ARISE study, 13 severe adverse events occurred, with 2 of them being related to the study valve. In both patients early endocarditis occurred. The original adverse events calculation for ARISE, that was used in the proposal for the project, was done for a group of adults with a good starting health status (no preceding procedures), on the basis of data for biological and mechanical valve replacement. So far, patients operated with DAH for AVR with the ARISE study have not only been young, but also a great share of them already had (multiple) pre-operations. Even looking at the original calculation, the adverse event rate is still in the calculated range. When plotting the number of adverse events with data adjusted to the amount of children included, the amount of adverse events is actually even surpassing the expectations. This gives a great first indication, that the decellularized valves are not only safe and feasible, but that they might even be a safer option than alternative procedures used so far. Additionally Prof. Sarikouch added information on some specific cases and histological results.

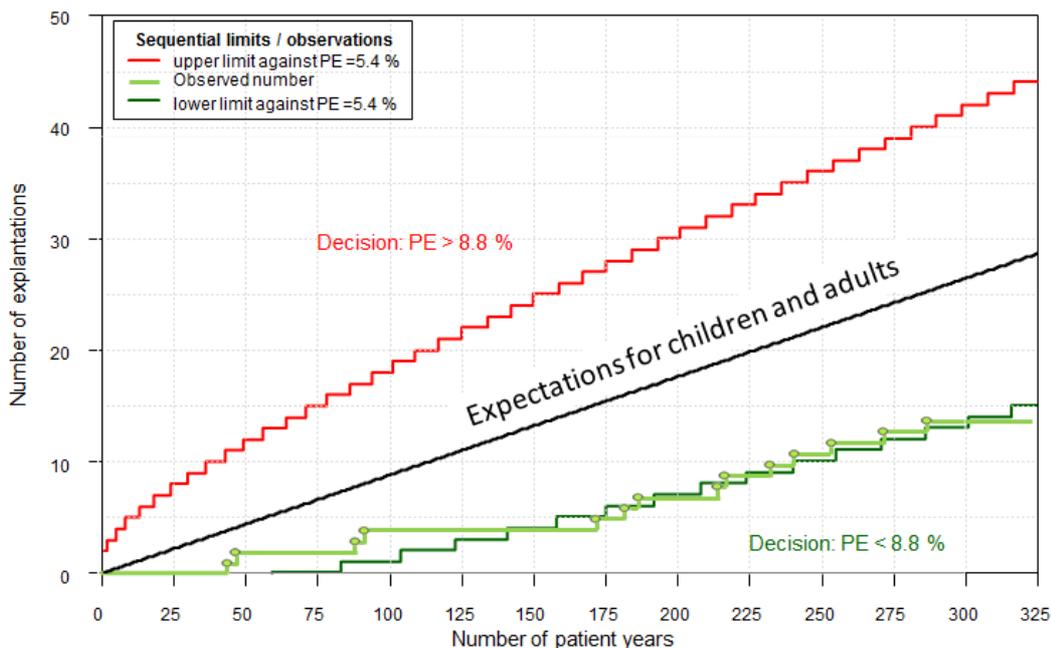


Image 11: Adverse event expectations for the ARISE clinical trial for children and adults

3.9 Reasons for concern? The Mayo Clinic report

As an example of a study on decellularized homografts done by other research groups, Prof. Sarikouch presented the case of a study¹ on late durability of decellularized cryopreserved allografts (synergrafts) for aortic valve replacement done by the Mayo Clinic in Rochester (USA).

In this retrospective study freedom from reoperation at 10 years was 51 % in the decellularized aortic valve allograft (DAVA) group, compared to 80% in the standard cryopreserved group. Survival was 76% in the DAVA group, compared to 57% in the cryopreserved group. With p-values of 0.06 and 0.09 both results were not significant though. Reasons for reoperations of the synergrafts were endocarditis (26%), aortic stenosis (29%) and aortic regurgitation (31%).

Prof. Sarikouch discussed that the paper shows the importance of long-term follow-up, but it generalizes its findings, without paying attention to the fact, that not every decellularized valve is the same and that there may be different results depending on aspects like the decellularization technique used. In case of the Mayo clinic report for example, the homografts have been cryopreserved and radiated before implantation. Both of these procedures have been demonstrated to impact the ultrastructure. In contrast, the ARISE trial is evaluating fresh, non-cryopreserved and non-radiated DAH for AVR.

Dr. Sarikouch and Prof. Haverich therefore published a letter on behalf of the consortium, sharing their thoughts and some results of the ARISE valve. Several reviewers answered to the letter, agreeing with the fact that different decellularization techniques should not be generalized, but also pointing out that the aortic decellularized valve ARISE will also need long term follow up to ensure safe results.

¹ Helder, Kouchoukos, Zehr, Dearani, Maleszewski, Leduc, Heins, Schaff: "Late durability of decellularized allografts for aortic valve replacement: A word of caution." In: European Journal of Cardio-Thoracic Surgery October 2016.

3.10 Let us explain to you how this technique works – Live-In-A-Box cases

Two Live-In-A-Box cases were explained to the participant as video presentations, commented by Dr. Tudorache from MHH and Dr. Quintana from HCB. Dr. Tudorache presented the first human implantation of a DAH in the ARISE project, while Dr. Quintana presented the case of the first patient operated with a DAH in Barcelona. The diagnoses of the patients, their condition before and after the operation as well as the actual implantation process were explained. The surgeons shared insight on their thought process, challenges and the techniques used for the operations.

3.11 Wet lab: Tips and tricks for the implantation of decellularized homografts

The practical section of the workshop was done in an adequate room that is used for anatomic demonstrations at the basement of the Medical School of the University of Barcelona. Pig's hearts and heart valves were prepared for the lesson. Both pulmonary and aortic valves were available and had been decellularized by Corlife in advance. This way the participants had the chance to work with the actual product, handle it, touch it and learn how to assess the quality of the valve as a surgeon.

The participants had to operate the valves to the hearts, while more experienced surgeons from Hannover (Germany), Barcelona (Spain) and Zurich (Switzerland) supervised and tutored them. Handling and cutting of the valves as well as the techniques for the implantation were explained. Twenty complete sets of instruments including scalpels, scissors, forceps and needle holders were distributed for the aortic root dissection and the decellularized homografts were implanted with propylene sutures of 4/0 and 5/0.

Additional to the surgeons some non-surgeons, e.g. the participating members of the EGC, had the chance to participate in the wet lab training as well, to get a better impression and understanding of the work done in the ARISE project.

After the workshop the wet lab participants were provided with a certificate, confirming their participation.



Image 12: Decellularized valves for the workshop



Image 13: Participating surgeons during the wet lab session



Image 14: Participating surgeons during the wet lab session



Image 15: Participating surgeons during the wet lab session



Image 16: Examination of the decellularized valve



Image 17: Dr. Quintana demonstrating the operation technique to non-surgeons

4 Dissemination

About 35 people joined the ARISE workshop, most of them being medical professionals and a few students. The participants included employees of the European Homograft Bank (EHB) in Brussels and the Blood and the Barcelona Tissue Bank (BST) as well as the EGC members James Lawford

Davies and Marte Jystad, member of the patient organisation “European Congenital Heart Disease Organisation” and some cardiovascular surgeons.

A summary of the workshop was submitted to the communication department of HCB and IDIBAPS for subsequent dissemination in the media. The AV department is preparing a video clip and graphic support to be distributed through social media.

To further disseminate the content of the workshop as well as the ARISE project in general the workshop was filmed by the technical team of HCB. The video will be available on the ARISE website. Information about it will be shared with the members of the ARISE consortium and via them to their respective clinics. The option to share the video via other networks, like the EACTS, or during presentations in some future meetings (e.g. at the International Update in Cardiology and Cardiovascular Surgery - UCCVS) will also be explored.



Image 18: Cookies with the ARISE logo and EU stars prepared for the catering