The CERC Chronicle

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HIGH TECH MARSEILLE

CERC at HIGH TECH 2023

CERC, as a long-standing partner of **High Tech**, is very pleased to attend yet another edition of this innovative and highly educative event.

Many of our members will be on stage to share the latest knowledge, the results of the trials that might change the practice and foster education.

Meet CERC TEAM

We are delighted to meet you and discuss the newest trends in the cardiovascular field, new ideas for clinical research and share the innovations we are bringing to this area.

Meet CERC booth 33

New Clinical Trials at CERC

REVERSE
Randomized, controlled trial: DCB vs DES in patients with large vessel CAD in Asia

MENA - TAVI
The use of ACURATE Neo 2 valve in patients with symptomatic aortic stenosis in the Middle East..

GLYCAR
A clinical investigation of GLYCAR Bovine pericardial patch with EnCap technology in cardiac and vascular repair or reconstruction surgery

TRANSFORM 2
Randomised, controlled trial: DCB vs DES in patients with small CAD

e-ULTRA 10K
A Post-Market Registry of the BioFreedom™ Ultra CoCr Biolimus A9™ coated coronary stent system

EVERGREEN
Evaluation of the Valiant Captivia custom made fenestrated stent-graft system for treatment of aortic arch and descending aorta pathologies

An Interview with Roxana Mehran, MD, FSCAI

A Mount Sinai Professor in Cardiovascular Clinical Research and Outcomes and director of interventional cardiovascular research and clinical trials at The Zena and Michael A. Weiner Cardiovascular Institute at The Icahn School of Medicine at Mount Sinai, New York, NY.

By Dragica Paunovic

Professor Mehran, it is a great honor and a privilege to have you contributing to CERC Chronicle. Given this unique opportunity, please allow me to ask you a few questions.

Q1. What was the most important driving force behind your passion for clinical research?

For me it has always been the curiosity to answer questions clinicians face and patients care about. And this has led me to clinical research focused on outcomes of patients. I also wanted to be there at the table to be sure that we had fair assessment of our devices, procedures, and new therapies, with good clinical equipoise. These were fundamental to me.

Q2. Clinical research has evolved over the years, but could we do more to accelerate innovation in clinical trials?

We must and can do better. We need to be more inclusive in our patient enrollment and trial criteria, more innovative with our approach, more pragmatic with our questions, and how we answer them, and more applicable to daily practice. This means that we have a finite time to evaluate therapies for given conditions, using comparative effectiveness methodology to answer the questions, with current technologies to speed up the trial timelines. Otherwise, our work and final results will not be applicable.

Q3. How can we all mobilize to improve diversity in clinical trials?

To improve diversity requires intentional work with real results, and not just window dressing for our trials. If we want diverse patients, we should include diverse investigators who serve those patients often not included in our trials. Trial leadership will also need to be more diverse, and our methodology can also be curtailed to make sure we have diverse patients included. This can be done through capping certain populations and focusing on women and minorities until we have met our quotas, there are many ways. We must find the way.

Q4. As we are so close to gender equality, could you briefly tell us how you and Marie Claude came to the idea to found the Women as One initiative?

I have always admired and looked up to Prof Morice. She was the true "Trailblazer" of our time Early in the years PCI and new devices were being examined, she was the only one who led the way for other women. She an I had a discussion, and she was all in... We wanted an organization that was completely focused on a simple mission of promoting talented women in medicine. And this is how Women as One was born. Simple, doable, provocative, and most importantly intentional.

Q5. You are a great friend and supporter of the CERC. Is it about your admiration for our founder, Marie Claude, CERC's DNA to embrace and unconditionally support trials with a hypothesis to change clinical practice and improve patient care?

I love the concept of CERC, clinical trials by clinicians in practice, who answer questions for patients through collaboration, friendship and inclusion. A dream come through. CERC is completely transparent, collaborative, and effective in delivering the answer that matter for clinicians, and patients. CERC is also a beacon for regulatory trials and provides the best and most comprehensive services that is topline, with highest quality and with the best efficient and timely delivery.

Q6. Finally, what is the hottest research subject in your mind right now?

Well, the fact that DCB is still not approved in US and not on our shelves is something to deal with, and we now have several trials that hopefully will prove them to be safe and effective. There is much excitement in heart failure therapies, which are device based. Also, in the valve arena, there are many important new devices on the horizon. The current wearable technologies are giving us many important opportunities to follow patients for important endpoints, and even think about tech-based enrollment in trials. Primary and secondary prevention on top of device/interventional /surgical therapies will be reducing the burden of disease and improve outcomes. Finally, Artificial Intelligence will be front and center in choosing best possible ways forward.

CERC "Entreprise à mission"

By Ghada Khoury Martin

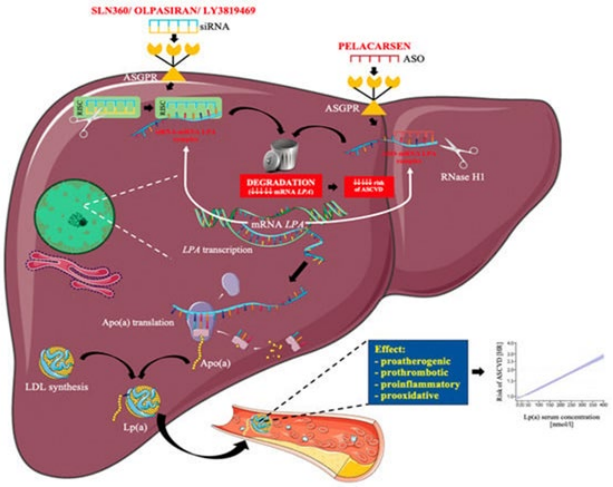
CERC has adopted a corporate form, "Entreprise à mission", that means pursuing voluntarily a social and environmental purpose with specific sustainability goals. CERC's purpose is to promote optimal healthcare in order to improve the clinical outcomes and quality of life of patients, to spearhead trial design innovations and to carry a ground-breaking clinical research, while incorporating respectful environmental and societal practices into daily activities. Going further in the integration of eco-social responsibility in the business strategy, CERC has undertaken sponsoring a local Massy Essonne Handball sport club, with whom CERC shares similar values. On a regular basis, setting up projects with a positive impact, without distinction of age, gender, social class, origins or culture. It accomplishes solidarity-based and eco-friendly actions such as plogging operations, creating a sports brand targeting the elderly and the sick people, collecting food for precarious students, visiting children in hospitals, organizing sporting event to support the fight against breast cancer and in favor of screening tests, celebrating International Women's Day by honoring ambitious female players, etc.. A perfect fit between high societal value partners!

Lp(a), the molecule of the year

By Pieter Smits

Lipoprotein [Lp(a)], commonly referred to as "Lp little a", is increasingly appreciated as a major driver of risk in atherosclerotic vascular disease and aortic valve stenosis. Elevated Lp(a) levels occur approximately in 20% of the Western world and is solely genetically determined.

Recently new pharmaceutical treatments have been developed to lower Lp(a) blood levels. These new treatments aim at the synthesis mechanism of Lp(a), through interfering with the transcription of RNA. Some companies, like Novartis, aim at inhibiting mRNA of the LPA gene in the liver cells by monthly subcutaneous injections with Pelacarsan, a single strand antisense oligopeptide. Phase 2 studies have shown that Pelacarsan can reduce Lp(a) blood levels ranging from 29 to 67%. The ongoing HORZON Phase 3 trial with Pelacarsan will show whether lowering Lp(a) will reduce MACE in patients with proven atherosclerotic disease and elevated Lp(a) of >70 mg/dl.



Mechanism of action of SLN360, olpasiran, LY3819469 and pelacarsen. ASGPR—asialoglycoprotein receptor; ASO—antisense oligonucleotides; siRNA—small interfering RNA; LPA—lipoprotein (a) gene; LDL—low density lipoprotein; ASCVD—atherosclerotic cardiovascular disease; Lp(a)—lipoprotein (a); apo (a)—apolipoprotein (a); RICS—RNA-induced silencing complex. The following was used in the preparation of the figure: https://smart.servier.com (accessed on 29 October 2022; free-access). Sonowska et al. Pharmaceuticals 2022 (open-access).

Other companies, like Amgen, Silent Therapeutcs and Eli-Lilly, aim at inhibiting mRNA that encodes for Lp(a) by injection of small interfering RNA (siRNA) strands that form inert complexes with mRNA and prevent translation of mRNA into Lp(a). On top, the inert complex of siRNA and mRNA is recognized by the cell as abnormal and eventually degraded. These small interfering RNA therapies against Lp(a) are also very effective. The recent phase 2 trial with Olpisaran (Amgen) showed a more than 95% reduction in patients with elevated Lp(a) and atherosclerotic vascular disease. The OCEAN Phase 3 trial with Olpiseran has recently started to recruit patients. The phase 2 trial with SLN360 from the company Silent Therapeutics in subjects with elevated Lp(a), also showed an amazing reduction of Lp(a) by 98%. The phase 2 results of the LY3819469 compound by Eli-Lilly are to be awaited this year.

CERC has great interest in these new developments and aims to be part of research in this field.

Lost in MDR Translation? CERC can help!

By Ute WINDHÖVEL Windhövel and Dragica Paunovic

The announcement of the EU Medical Device Regulation (EU 2017/745) (MDR) several years back has delighted academia and medical practitioners as it promised increased scrutiny of patient safety, extensive and meaningful clinical evidence, and support for innovations. The medical device industry embraced these Regulation goals with the hope of streamlined processes and complete transparency about the requirements for placing devices on the EU market. All European stakeholders hoped that the MDR would consolidate and strengthen this market, ensure patient safety, and preserve sufficiently fast access to innovation for patients. As time passed, and as the Regulation was implemented, key gaps and uncertainties emerged, contributing to collective anxiety about the MDR transition period's feasibility and the future of EU healthcare system.

The medical device industry has committed significant resources to comply with new requirements and make a success of the new regulatory system. Still, lack of clarity and lack of certification capacity by Notified bodies, forced many companies to prioritize their portfolio leading to shortages of many legacy devices. Furthermore, manufacturers' R&D, clinical and regulatory resources were drained into the ongoing MDR recertification processes, reducing new developments and innovation. The small and highly innovative companies changed their strategies by prioritizing markets with more unpredictable regulatory processes, leaving European patients in a long queue for their innovative, sometimes life-changing or lifesaving, products.

CROs and Academic research organizations after years of delivering ground-breaking science found themselves in a paradoxical situation to assist the industry and healthcare system to continue benefiting from the devices, sometimes on the market for more than 20 years with an excellent safety and performance track record. This new type of research, mainly single-arm observational registries, besides being scientifically unattractive are changing the real meaning of clinical research, meant to find new and better ways to detect, diagnose, treat, and prevent disease. The cost of those registries is not negligible, reducing the medical device industry's resources to support academia in further developing strong and more impactful clinical evidence that would contribute to advancing patient care and medical practice in general.

To ease the burden of our medical device industry partners, we at CERC developed a comprehensive, cost effective, all-in-one, PMCF strategy fully compliant with MDR requirements. Furthermore, benefitting from our strong cardiovascular therapeutic area expertise we offer a full partnership in developing clinical evaluation strategy, clinical evaluation plan and report throughout the product life cycle.

CERC and ARC initiatives

By Philippe Garot & Davide Capodanno

The Academic Research Consortium (ARC) is a collaborative forum of stakeholders founded in 2006 to develop and disseminate consensus definitions for pivotal clinical trials of medical devices. Under the auspices of ARC, CERC is coordinating two initiatives in the domains of structural and coronary interventions.

VARC-HBR Initiative - The Valve Academic Research Consortium (VARC) is an ARC derivative devoted to the field of heart valve interventions. Recently, the VARC-3 provided an overview of risk assessment after TAVI that included definitions of bleeding, but factors contributing to this risk were not discussed. Standardized bleeding definitions for cardiovascular clinical trials were previously introduced by the Bleeding Academic Research Consortium (BARC).

The risk of major bleeding after TAVI is non-negligible and has been consistently associated with an increased risk of mortality. Compared to percutaneous coronary intervention (PCI), TAVI is more invasive and is directed to older patients with frequent comorbidities that make them at high bleeding risk (HBR). Although conditions associated with bleeding related to PCI have been defined by the ARC-HBR initiative in 2019 (another initiative run by CERC!), they remain insufficiently explored after TAVI. A recent post-hoc analysis of the SCOPE-2 trial demonstrated that patients with and without HBR according to the ARC definition for PCI experience similar rates of BARC bleeding type 3 or 5. HBR criteria should, therefore, be defined in a way that is specific to TAVI patients, especially for risk assessment prior to the selection of the strategy and for the selection of post-TAVI antithrombotic regimens based on individualized bleeding risk profiles.

To better characterize the profile of HBR patients with valve disease, CERC has designed a new ARC initiative, named VARC-HBR, mixing contributions of experts from the BARC, VARC and ARC-HBR groups, including worldwide physicians, representatives of the US Food and Drug Administration and the Japanese Pharmaceuticals and Medical Devices Agency, as well as observers from the pharmaceutical and medical device industries. Factors contributing to higher risk of severe bleeding are consensually discussed and will be determined in early 2023.

Language around DAPT – an ARC initiative – In patients undergoing PCI, the use of antiplatelet therapy comes at the expense of an increased risk of bleeding complications. Finding the optimal intensity of platelet inhibition needed according to the clinical presentation of atherosclerotic cardiovascular disease and individual patient factors is a daily clinical challenge. Modulation of antiplatelet therapy is a medical action that is frequently performed in practice to balance the risk of thrombotic or ischemic events and the risk of bleeding. This aim may be achieved by reducing (i.e., de-escalation) or increasing (i.e., escalation) the intensity of platelet inhibition by changing the type, dose or number of antiplatelet drugs. Because de-escalation or escalation can be achieved in different ways, with a number of emerging approaches, confusion arises with terminologies that are often used interchangeably.

To address this issue, this ARC collaboration will provide an overview of different strategies of antiplatelet therapy modulation for patients with coronary artery disease, including but not limited to those undergoing PCI, and consensus statements on standardized definitions.

Latest Milestones of CERC Trials

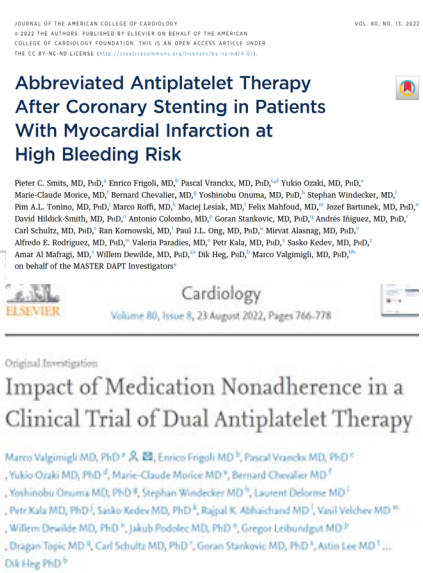
Enrolment Completed
1. KISS
2. ABILITY
3. REFORM
4. COMPRE HBR 60-90

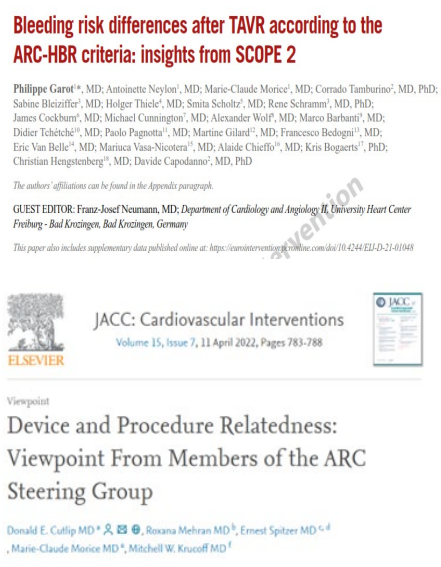
50% of Target Enrollment Reached
1. COLIBRI
2. TARGET FIRST
3. IONMAN

25% of Target Enrollment Reached
1. Selution DeNOVO

Enrollment Started
1. COMPARE STEMI ONE

Selected Publications





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