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PERSPECTIVE

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Translational Science in Vascular Aging: From Bench to Bedside—Insights from a VascAgeNet Roundtable

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Abstract

Translating vascular aging research from bench to bedside presents both significant opportunities and challenges. This paper summarizes insights from a roundtable discussion at the Artery 23 conference, featuring perspectives from basic science, clinical trials, regulation, and industry. The main conclusions of the discussion are as follows: basic science research must align with clinical relevance, using appropriate animal models and standardized measurement techniques. Pragmatic and registry-based clinical trials offer viable alternatives to traditional randomized controlled trials, facilitating real-world applicability. The regulatory landscape, particularly for software medical devices, must evolve to keep pace with technological advancements like artificial intelligence. Industry efforts focus on developing devices or solutions for vascular aging assessment and treatment strategies, yet face hurdles in large-scale adoption and reimbursement. Despite significant progress, the development of pharmacological interventions to mitigate vascular aging remains a critical need. This discussion underscores the importance of interdisciplinary collaboration to overcome barriers and translate scientific discoveries into clinical practice effectively.

Keywords Bench to bedside, Translational science, Vascular aging

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1 Introduction

Cardiovascular disease (CVD) remains the leading cause of death worldwide, contributing to one-third of all deaths [1] and imposing tremendous costs on healthcare systems [2]. Vascular aging, which describes early and mainly asymptomatic changes in the arterial system [3], is a promising concept for the early detection of preclinical cardiovascular disease and, consequently, for cardiovascular prevention.

The European Cooperation in Science and Technology (COST) Action VascAgeNet ("Network for Research in Vascular Aging") was launched in 2019 to address the unmet needs of measuring vascular aging in clinical practice. The network focuses on refining, harmonizing, and promoting the use of vascular aging biomarkers with the goal of improving clinical practice and reducing the burden of CVD [4]. An important aspect of this initiative is the translation of research findings from bench to bedside for the benefit of society [5]. However, several obstacles hinder the integration of these advancements into clinical practice and guidelines. Some of these barriers for clinicians include the costs of devices, the time required for measurements, the lack of validated devices and biomarkers, the absence of guidelines, and the lack of reimbursement [6, 7].

Translational science offers a pathway to overcome these barriers and to achieve full transition from bench to bedside. It covers the translation of findings from basic science to human studies and then into clinical decision-making [8–10], see Fig. 1. The first phase consists of basic research studies, preclinical studies, and innovation and intellectual property management. The second phase comprises clinical trials and data management, guideline development and policy makers' engagement, and finally, approval for application in humans and use in routine clinical practice. This complex process is supported by transversal topics, such as product/procedure development and regulatory requirements, which are crucial but often neglected [11]. It is important to highlight that different stakeholders are involved at various stages of the innovation process [12]. This article summarizes a roundtable discussion held at the Artery 23 conference, focusing on the translational process in vascular aging from the perspective of four of the key stakeholders: a basic scientist, a medical doctor, a regulatory specialist, and an industry representative.

2 Methods

Within the European Cooperation in Science and Technology (COST) Action VascAgeNet ("Network for Research in Vascular Aging"), we have put emphasis on the translational process to move the concept of vascular aging from bench to bedside [4, 5]. One of our main activities included hosting roundtable discussions at training schools and conferences. One such event was conducted during the Artery 23 conference, held in Bonn, Germany on 6th of October 2023. The format of the roundtable was as follows: (i) a brief introduction, (ii) presentations by speakers (LR, PB, VG, AS) addressing four distinct perspectives (see Fig. 2), and (iii) a general discussion moderated by EB and CCM, focusing on identifying barriers and opportunities, discussing personal motivations, and guidance on navigating the translational process and fostering interaction. The key points from these discussions are summarized below.

3 Results

3.1 The View from Basic Science Research

The translational process involves moving scientific discoveries from the laboratory to practical applications in healthcare. Unfortunately, many fundamental research findings are never further explored in clinical trials,

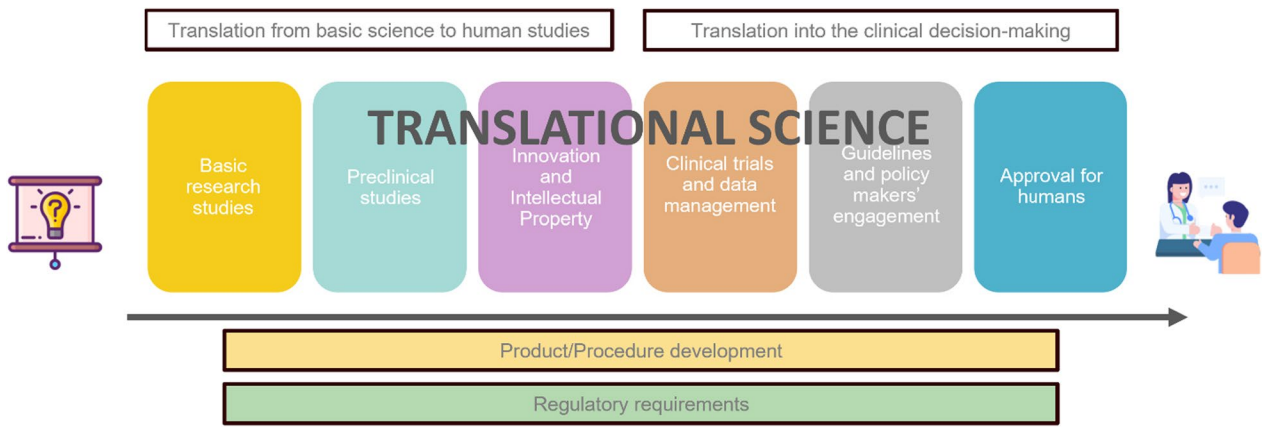

Fig. 1 Translational Science—the process from bench to bedside

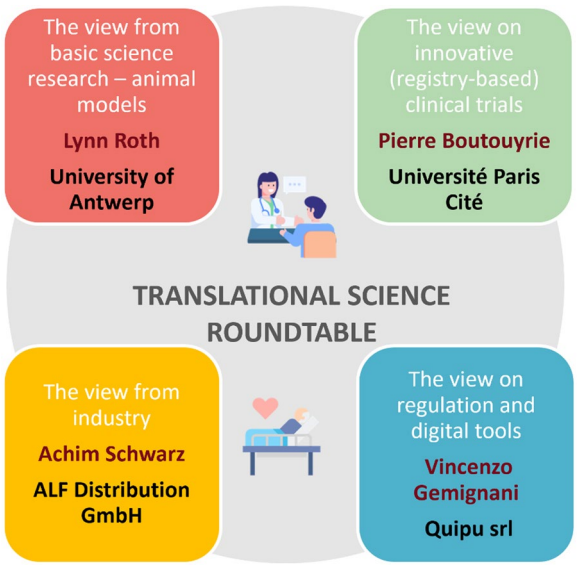

Fig. 2 The stakeholders of the roundtable discussion on translational science in vascular aging

resulting in a waste of resources, funding, and time. To improve the translational perspective of basic science studies, a strong emphasis should be placed on the clinical relevance of the proposed research. Starting at the 'bedside' and engaging with clinicians to understand their additional insights and knowledge requirements might be an effective approach to ensure this. In addition, appropriate experimental studies are necessary to bring research findings from the laboratory to clinical practice. Therefore, the use of appropriate animal models and techniques for the evaluation of vascular aging is necessary.

At present, mice remain the preferred model for studying vascular aging, mainly due to their ease of handling, relatively low housing costs, and shorter lifespan compared to humans. Interestingly, mice exhibit fundamental signs of vascular aging, such as progressive arterial stiffening, inflammation, wall thickening, collagen and proteoglycan deposition, reduced elastin content, and elastic fiber fragmentation [13–15]. However, using old mice to investigate vascular aging can be time-consuming, often taking nearly 2 years to complete a study. Alternatively, if there is an interest in the role of specific proteins, genes or molecular pathways in the pathophysiology of vascular aging process, the use of genetically or pharmacologically altered mice is another valid approach. For instance, when studying the influence of elastic fiber integrity in arterial stiffening, mice with mutations in elastin ($Eln^{\pm}$) or microfibril-associated proteins ($Fbln4^{-/-}$, $Fbln5^{-/-}$, $Fbn1^{C1039G/+}$) can be adequate tools [16–19]. However, it is important to consider that all these models have advantages and disadvantages that should be considered when designing a study.

In addition to the choice of animal model, reliable and reproducible methods for measuring vascular aging are essential for ensuring clinical relevance. However, this remains challenging. For example, measuring arterial stiffness in animal models presents various complexities and variations. In mice, pulse wave velocity (PWV) can be assessed in vivo by measuring pulse transit time or by calculating it based on vessel distensibility. While the first approach provides an integrated measure of stiffness over a certain distance, the second approach provides the PWV at a specific location in the artery. Thus, measures may be difficult to compare, as in humans [20]. Furthermore, PWV is also affected by fluctuations in blood pressure and heart rate, which means that type of anesthetic used to sedate the animal during the measurement may introduce variability [21]. To avoid these in vivo confounding factors, it is also possible to assess arterial stiffness ex vivo after isolation of the arterial segment of interest [22]. However, different set-ups and experimental techniques exist to assess ex vivo stiffness, which makes it difficult to compare results between research groups. Thus, guidelines describing how to correctly interpret data from a specific set-up and how to compare it with other techniques are essential in this regard.

In summary, translating basic research into clinical applications presents many challenges, including formulating relevant research questions, selecting suitable (animal) models, designing reliable experiments, and achieving consensus on research techniques. Reproducibility is a critical factor in translational research, highlighting the need for established guidelines for study protocols and techniques to measure vascular aging in preclinical studies.

3.2 The View on Innovative Clinical Trials–Pragmatic and Registry-Based Trials

Randomized clinical trials (RCTs) have transformed clinical practice in cardiovascular medicine, by validating treatment strategies that saved millions of lives worldwide [23]. However, though RCTs have played a major role in moving from empirical to evidence-based medicine, they present several limitations. In addition to being extremely cost-inefficient, the processing times for initiation of the trial are significantly long due to increasing bureaucratic and regulatory burden. Furthermore, the population under study is usually highly selected, and thus the results cannot be easily translated into a real clinical setting. The funding for RCTs, typically driven by the pharmaceutical industry, often overlooks rare diseases or clinical conditions with little economic benefit. While the pharmaceutical labs are compensated by

marketing the drugs, the economic burden of these trials eventually falls in the hands of the taxpayer [23].

Consequently, there has been an important movement in favor of optimizing clinical research toward pragmatic trials [23]. These pragmatic trials are designed with input from the healthcare stakeholders rather than the industry and often use electronic medical registries and national healthcare or insurance datasets to follow-up patients and assess outcomes [24]. Additionally, these trials are developed with an aim to include diverse, representative study populations from real-world healthcare settings facilitating the incorporation of the results into routine clinical practice. A recent example is the trial comparing hydrochlorothiazide and chlorthalidone for CVD outcome reduction [25]. The strength of evidence from these trials is intermediate of that from observational studies and RCTs. In general, all forms of bias, such as lack of generalizability, Hawthorne bias, confounding bias, user bias, and observer bias, within pragmatic clinical trials are believed to fall somewhere between those observed in observational studies and those in RCTs [26]. The design of pragmatic trials leads to its applicability to real-life situations, which is one of the biggest advantages over conventional trials.

One method of developing a pragmatic trial involves grounding it on health registries. Results from registry-based trials can evaluate available therapeutic options and be indicative of actual clinical care. Registry-based trials can be successful in guiding or modifying therapy within a short span of time and are particularly useful for assessing efficacy of treatments which are already in clinical practice, possibly for other purposes than the one intended to test, but require the existence of a registry with linkage to national healthcare datasets, such as in the case of the Swedeheart registry [27]. Decentralized trials are also increasingly planned, especially after COVID pandemics, including home-based assessments with wearables and web result transmission [28]. Finally, pharmacoepidemiology studies using observational data may be used though they require sophisticated statistical tools to provide robust results; for instance, a registry-based trial based on a nationwide digitized medical and pharmaceutical records demonstrated that the use of cyproterone acetate, an anti-androgenic and contraceptive agent, was associated with meningioma in women [29].

In relation to vascular assessment, a very ambitious classical RCT that aimed to develop a Strategy for Preventing cardiovascular complications based on Arterial stiffness (SPARTE study) was unable to provide the expected outcome due to barriers associated with RCTs [30]. This leaves several unanswered questions related to the cost–benefit ratio of arterial stiffness assessment and its application in modifying therapeutic strategies, which need to be answered using alternative approaches. This could include the use of home-monitoring devices, home-based assessment of drug adherence, telemedicine, and existing healthcare system datasets to quantify treatment status and cardiovascular events. Shifting healthcare from hospitals to homes could prove to be one of the most efficient methods for improving patient outcomes.

3.3 The View on Regulation and Digital Tools

Medical devices for assessing vascular aging can be categorized into four groups: (i) devices based on medical imaging, (ii) devices based on non-invasive sensors, (iii) intravascular devices, and (iv) software devices [31–35]. At Quipu (CG is co-founder), they have more than 10 years of experience in developing and commercializing software as a medical device.

Quipu started their activities in 2011, a time when most software was classified as low-risk devices using a process of self-certification that did not require a rigorous analysis by a notified body. Several software devices were not even classified as medical devices, allowing them to be placed on the market without any certification. However, the situation has completely changed over the last decade, especially in Europe, where the new EU Medical Device Regulation 2017/745 (MDR) has been adopted. The MDR explicitly includes software among medical devices if they are used for diagnosis, prevention, monitoring, prediction, prognosis, treatment or alleviation of disease, injury or disability, or even if they are used for investigating a physiological or pathological process or state. Any software used for the assessment of vascular aging will thus fall within the definition of medical device. In addition, the MDR has more clearly defined the risk class of software devices. If they provide a measurement, they should be classified at least in the middle risk class (II-a or II-b), and this means that requirements for the manufacturers in terms of risk analysis/management, clinical evaluation, and product traceability are even more rigorous.

If on the one hand, MDR now clearly includes software devices, then on the other hand, it still lacks coverage of all aspects of the new technologies involved. In these years, in Quipu, they have experienced several issues in the product certification process because regulatory requirements were tailored for apparatus, i.e., physical devices, and not for intangible devices. Although some rules have been updated with the new MDR, technology is continuously evolving. An example is the use of artificial intelligence technologies, increasingly adopted in medical devices, which might require the implementation of further requirements. In general, regulatory requirements struggle to keep up with new technologies

and, for this reason, manufacturers of digital medical devices may perceive the regulatory framework as an obstacle to innovation.

To have a clearer picture of the role of the regulatory framework, one should take into consideration all steps of medical device development. The biodesign process is defined in as and divided into three main phases: (i) Identify: Needs Finding and Curation, conducted by clinicians, (ii) Invent: Product Development Support, led by inventors, and (iii) Implement: Business Implementation and Execution, made by developers [36]. Regulatory requirements involve all three steps of the development [37]. For this reason, they should be discussed and shared among all stakeholders, who should also actively participate in defining the rules. With this vision, regulatory requirements may become a "common language" among stakeholders involved in the biodesign process, and a tool that helps the transition of ideas into the market.

3.4 The View from Industry

The industry of medical devices and pharmaceutical products has demonstrated a profound interest in vascular aging over the past several decades, beginning with the first non-invasive measurements of pulse wave velocity. The development of a novel marker for cardiovascular risk stratification, which will exceed the diagnostic information of existing markers and will drive better patient outcomes, is intriguing, as from a market perspective, cardiovascular diseases are very prominent around the globe, with a global net revenue in treatment amounting to USD 440 billion in 2024 [38].

The aim of the industry effort is to establish the new marker and its related treatment strategies on a large-scale level, meaning that vascular aging measurement and its treatment will become a standard of clinical care. However, broad adoption requires the reimbursement of the test and subsequent treatment by the payors in the healthcare industry, mainly insurance companies which cover the costs of medical treatment and intervention strategies. Payors rely on data not only demonstrating improved patient outcomes, but also considering a cost–benefit ratio prior to endorsing a new technique.

In this context, about a decade ago, the ARTERY society endorsed a guidance on the role of vascular biomarkers in primary and secondary prevention. This detailed work described the criteria for a marker to qualify as a clinical surrogate endpoint [39] and has served as a cookbook for industry efforts. Today, it needs to be stated that although a tremendous amount of work has been accomplished to address the criteria set forth in this guidance document, more data is still needed to fulfill its requirements.

Another major challenge the industry faces in its endeavor is the wealth of different biomarkers covered under the umbrella term of "vascular aging." These biomarkers are categorized into "molecular and cellular", "functional and structural," and "composite biomarker predictors" [40]. Considering the different biomarkers and the multiple sensor techniques implemented in measurement devices for vascular aging, which are not always interchangeable, a concerted approach to pursue clinical adoption is more complex to design.

In recent years, the industry has been investigating multiple pathways to penetrate the market even before obtaining reimbursement from insurance companies. These include programs offering vascular age testing directly to patients and identifying use cases which address specific, well-defined diseases or interventions, rather than the very broad approach of implementing vascular aging in "cardiovascular prevention for all," which requires a large investment in the studies needed to fulfill the criteria. Among these efforts, promising results have been shown in the early prediction of preeclampsia [41], the treatment of isolated systolic hypertension in the young [42], the growth prediction of abdominal aortic aneurysm [43], and the improved selection of patients qualifying for renal denervation to lower blood pressure [44, 45], to name only a few.

Lastly, it should be noted that even though the medical device industry has advanced significantly in its effort to provide easy, cost-effective, and clinically useful measures of vascular aging, we still lack drugs from the pharmaceutical industry that can reverse or at least halt the progress of vascular aging. A "de-stiffening" drug could be a game-changer in promoting the broad adoption of vascular aging assessments in clinical medicine.

4 Discussion and Conclusion

The results highlight key perspectives on translating research findings in vascular aging into clinical practice. From basic science research, the emphasis lies on aligning research with clinical relevance and utilizing appropriate experimental designs and animal models. Challenges persist in measuring vascular aging with precision and accuracy in animals, necessitating standardized protocols. Pragmatic and registry-based clinical trials, as well as decentralized and pharmacoepidemiology studies, offer promising alternatives to traditional randomized trials, enabling real-world applicability and rapid evaluation of therapeutic strategies. Regulatory frameworks, though adapting to include software devices, struggle to keep pace with advancing technologies like artificial intelligence. Collaboration among stakeholders is crucial to navigating regulatory requirements and fostering innovation in digital medical devices. The industry's interest in

vascular aging underscores the potential for novel markers to drive better patient outcomes in cardiovascular medicine. However, challenges remain in establishing these markers on a large scale and addressing the diversity of biomarkers and sensor techniques. Despite progress, the development of drugs to counteract vascular aging remains a critical focus for future advancements.

During the discussion following the presentations, not only the experts and sessions chairs leading the roundtable but also the entire audience was invited to debate about translational science in vascular aging. There was unanimous agreement that vascular aging represents a significant and promising concept, yet it lacks some important steps to reach clinical practice on large scale beyond research settings. The main practical reason for implementing vascular aging measures is because it is an opportunity to stratify patients better and earlier. However, therapies or drugs specifically targeting vascular aging to modify it and improve clinical outcomes are still unidentified. Thus, currently, clinicians cannot always exploit the potential clinical benefits of measuring vascular aging [6, 7]. An effective and desirable approach for clinicians would be coupling measuring with targeted therapy. One proposed solution is the development of preclinical systems for drug development and/or testing, which could not only advance the field and increase awareness, but also fortuitously identify drugs capable of regressing arterial stiffness. As an example, studying the effects of new anti-diabetes drugs (e.g., sodium–glucose linked transporter 2 (SGLT2) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists) might provide advancement in the field because of their protective effects on the cardiovascular system, in terms of lowering blood pressure and arterial stiffness [46–48]. The positive effects on arterial aging may contribute to the demonstrated beneficial effect of these drugs beyond diabetes treatment [49, 50].

Another important aspect is the lack of reimbursement, closely related to the missing studies and data on vascular aging measures as therapy outcomes. Understandably, reimbursement by insurers and healthcare systems is not yet as needed. To facilitate advancements in the field, one should consider alternative payment and financing models, as mentioned previously, and alternative markets such as well-being, where the demand is huge. Measures of vascular aging are not only for diagnosis or illness detection but can also be tailored to improve quality of life.

Safety is paramount for all medical devices, but compliance with regulatory requirements often demands significant effort from researchers creating innovative healthcare technologies. Furthermore, administrative burdens exist as funding is largely consumed by bureaucracy and thus does not wholly reach innovators and researchers. There is a cultural aspect involved as well. Many research institutions and universities have decades or centuries of history with an embedded culture of basic and applied research, but not as much a culture of translation. Consequently, much research performed in universities and research centers is excellent in the pursuit of knowledge, but translation from the bench to the bedside often ends up being from the bench to the shelf or in a research article. Thus, there is need for an important culture shift in universities and research institutes. While bright minds create brilliant ideas, they often cannot translate them to the society due to a lack of translational skills and institutional barriers. These institutions can play an important role in supporting researchers and innovators in the field of vascular aging, including lobbying to enable a pathway for the validation and certification of medical devices, generating the needed additional clinical evidence and facilitate contacts with the industry.

To conclude, invited experts raised the importance of (simpler) communication, collaboration, and networking as crucial aspects to ensure research findings are effectively translated into clinical practice.

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Data availability
Not applicable.

Declarations

Competing interest
Elisabetta Bianchini and Vincenzo Gemignani are co-founders of QUIPU s.r.l., Pisa, Italy, a spin-off company of the Italian National Research Council and the University of Pisa, developing software as medical device. Achim Schwarz is the founder of ALF Distributions, which sells medical devices. For the remaining authors, there are no conflicts of interest.

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