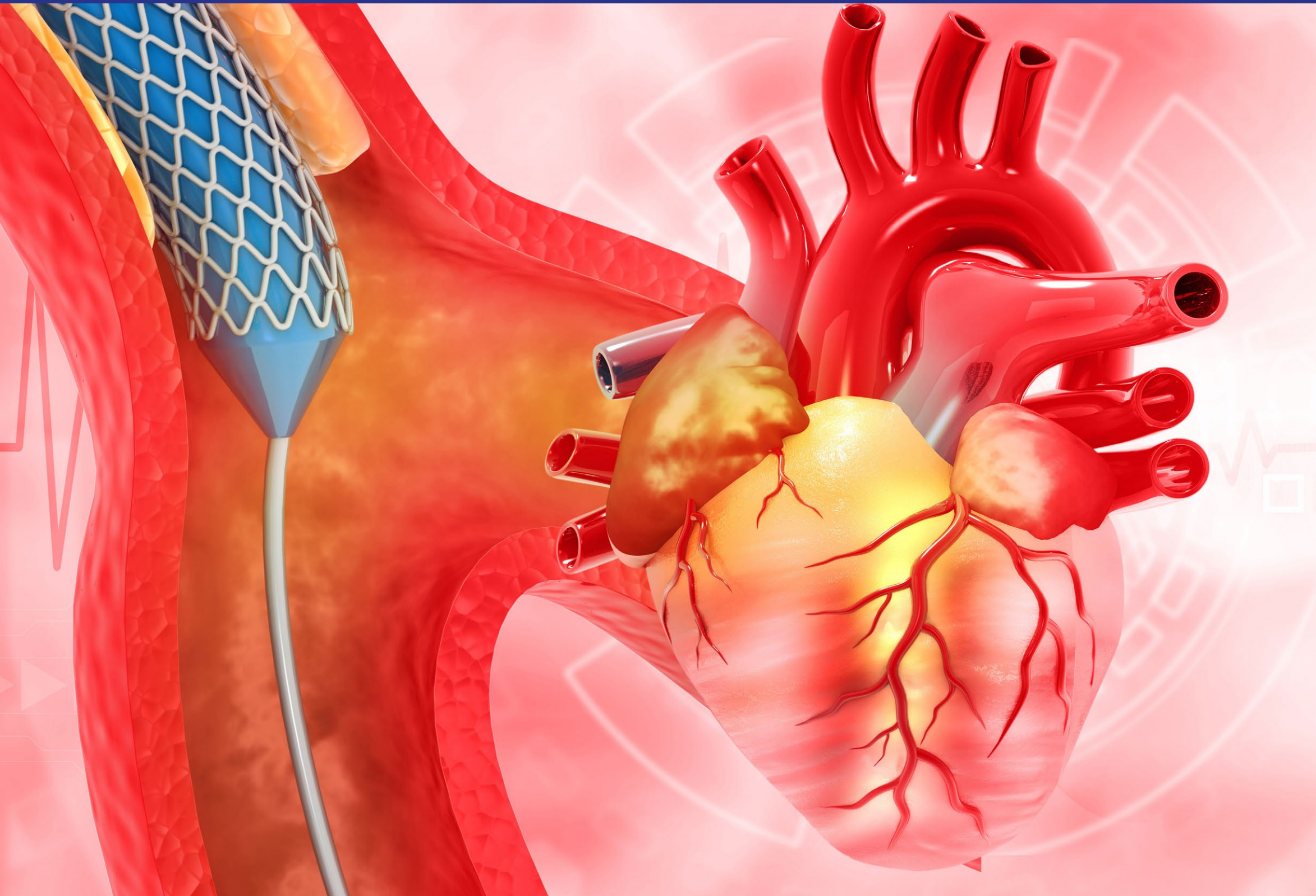




Developing the new era of zinc biodegradable stents

Plaque can build up in our blood vessels and arteries, blocking blood flow and causing heart attacks and strokes. This condition – known as atherosclerosis – is a key feature of coronary artery disease, the leading cause of death worldwide. Atherosclerosis treatment currently uses cardiovascular stents to open narrowed arteries. But these stents are permanent metal fixtures which can cause adverse reactions over time.

To overcome this problem, biodegradable stents that degrade and are excreted by the body are in development. The potential medical applications and reward for developing safe biodegradable stents make this a hot research topic among cardiologists, scientists, and biotech companies. Leading the research in this field is Professor Jaroslaw W

- Traditional cardiovascular stents treating the narrowing of blood vessels remain in situ for years and can cause long-term side effects.
- To address this, Jaroslaw W Drelich, Professor in Materials Science and Engineering at Michigan Technological University, USA, leads an ambitious programme exploring zinc alloys as prime candidates for biodegradable stents.
- During the last decade, Drelich and his team worked to overcome biomedical engineering challenges.
- Now, equipped with optimised materials, they aim to take developing biodegradable stents to the next level.

Drelich from Michigan Technological University, USA. In 2013, Drelich and his research team were the first to propose zinc as a promising material for biodegradable vascular stents. Since then, they have embarked on a journey of experimental work, encountering and addressing technical challenges along the way, with the aim to develop biodegradable stents.

Engineering meets medical science

A treatment for coronary artery disease and aorta coarctation (a birth defect in children where part of the aorta is narrowed) uses stents in combination with a balloon structure to widen the narrowed artery in a procedure known as angioplasty. The stent fits over the balloon to provide a scaffolding that remains in the vessel, giving mechanical support after the balloon has been inflated and removed. This keeps the vessel open, ensuring healthy blood flow, and allows the artery wall to strengthen and regain shape.

Such stents made of stainless steel and cobalt chromium only need to be in place for a few months to a year (at most) to achieve this. Currently, however, they remain in the vessel permanently. This unnecessary prolonged placement can cause adverse reactions such as clot formation near the stent, chronic inflammation, and

In 2013, Drelich and his research team were the first to propose zinc as a promising material for biodegradable vascular stents.

even damage to nearby vessels. Furthermore, permanent stents interfere with any imaging investigations or surgery needed to restore blood flow in the blocked vessels.

To address these problems, scientists are trying to develop biodegradable stents that provide mechanical support to the vessel for 6–12 months before corroding and being safely excreted. To ensure safety and efficacy, any candidate material must have specific mechanical and corrosion properties. Considerations include how long the metal will remain intact (mechanical integrity), its biocompatibility (fulfilling its purpose without causing harm), its design, structure, and strength (mechanical properties), and how quickly it corrodes or deteriorates.

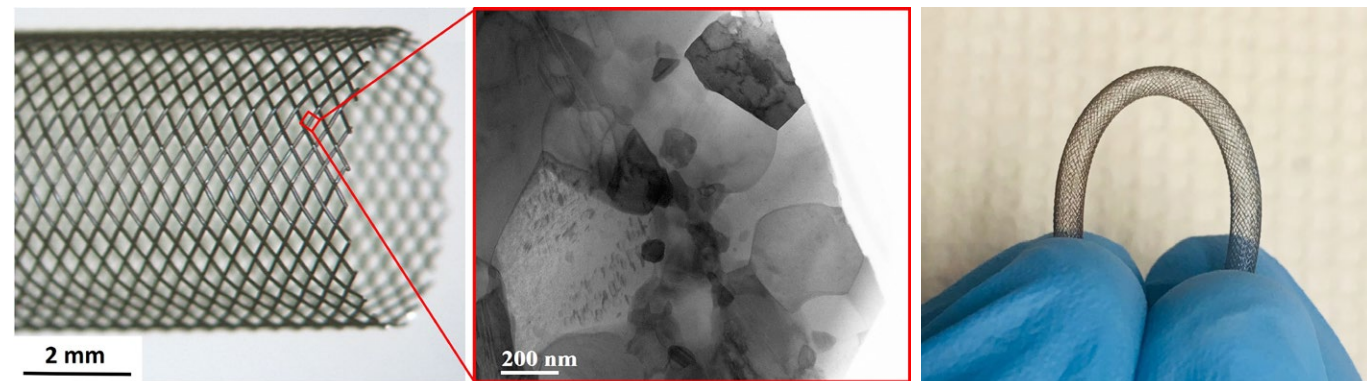


Image of the biodegradable stent prototyped at Michigan Technological University. Left: general view; middle: Transmission electron microscope (TEM) image of the stent strut; right: demonstration of stent flexibility.

Vascular scaffolds and bumps along the road

For decades, efforts focused on developing polymeric materials for use in biodegradable stents. Despite initial endorsement, such stents are no longer on the market due to safety concerns. Because of their superior strength, the attention briefly turned to metal stents with iron and magnesium, offering initial hope before they were deemed unsuitable.

Drelich and colleagues published a paper proposing zinc as a potentially suitable material for biodegradable stents in 2013. Zinc has natural physiological roles in the body, including regulating cell death, cell signalling, and gene expression. What caught the researchers' attention was zinc's antioxidant properties and its convenient ability to

stabilise the membranes lining blood vessels. Such properties may prevent formation of plaque inside blood vessels and therefore, be inherently useful in vascular stents.

Following concerns that pure zinc could not take enough stress before breaking (since it has low tensile strength), the team suggested that zinc alloys (a mixture of metals, combined to optimise its strength and desired properties) should be explored. However, they discovered that developing alloys involves a series of trade-offs because often, improvement of one aspect is at the expense of another, thus requiring a fine balancing act. For example, alloys can improve metal strength but affect corrosive properties.

After revealing zinc as a promising material for biodegradable stents, the team faced

challenges strengthening the metal and improving its mechanical properties. Experimenting with different metal compositions, the team published research investigating zinc alloys containing silver as well as alloys combined with magnesium as potential candidates.

Further, they discovered that the manufacturing methods to produce these biodegradable metals can alter their properties. Their research has provided valuable insights into which processing techniques negatively impact the desired properties of alloys. Other work by the team addressed the issue of natural ageing in the mechanical properties of zinc alloys – with the researchers adding copper and manganese to the alloy to reduce ageing and improve the alloy's strength and stability.

A new era of biodegradable stents

The field is transforming from focusing on the strength and properties of metals to recognising the importance of bioactivity of these metals. Now, the spotlight is on potential therapeutic and nutritional benefits of 'bioactive' stents for cells. For example, recent research suggests ions released from zinc biodegradable stents have beneficial biological properties such as targeting cells of scar tissue that commonly form in stented vessels. This would eliminate the need for stents to be artificially coated with drugs aimed to do exactly this.

Despite considerable progress in optimising materials for use in biodegradable stents, gaps in our knowledge persist. For example, we still do not know how well a stent maintains its mechanical strength in vivo and if there are any knock-on effects or reactions elicited by the degradation of these stents. The team mention that understanding how degradation by-products affect the local vascular environment is required to enhance their design. After researching and refining the characteristics of zinc alloys for use in stents, Drelich and colleagues move forward with a new direction and focus for future research in their quest for biodegradable stents.

Personal response

What led you to study materials science and engineering?

It is the result of the strange turns in my life. I moved from Poland to the US in 1989 to study mineral processing at the University of Utah. After completing my PhD and post-doctoral programmes, I began teaching courses in extractive metallurgy at Michigan Technological University in 1997. In 2000, the College of Engineering decided to restructure engineering programmes, giving me a choice to either join the Department of Mining or switch to teaching materials and materials characterisation. Because I was already working on programmes related to plastic and paper recycling and advanced characterisation of material surfaces using atomic force microscopy, I decided to stay in the field of materials and explore research opportunities with novel materials, material surface modifications, and advanced characterisation techniques.

What are the next steps to take zinc alloy stents forward into human studies?

It will take ten years or more before the zinc stents are considered for human studies. We are currently working on prototyping stents with the goal of conducting preclinical studies with larger animals, such as sheep or pigs, in the next couple of years. This preclinical study is needed to assess the stent's deliverability, recoil, stability, restenosis, toxicity, impairment of vessel growth, and the stent's degradation profile. This preclinical study will help guide the design of the anticipated good laboratory practice animal study that will be

performed as part of a commercialisation project that will follow the preclinical research. The commercialisation step will include a broader animal study, stent manufacturing verification and validation, regulatory work with the FDA, and early feasibility clinical study plans.

Could your work on zinc alloys have other medical applications besides cardiovascular scaffolds?

Since our report in *Advanced Materials* in 2013, many research laboratories worldwide have explored medical applications of zinc alloys as temporary vascular, bladder, neurovascular, tissue regeneration scaffolds, and various orthopaedic implants. The problem is that most of these laboratories limit the research developing alloys and basic testing of these alloys on toxicity using cell cultures, with no access to animal facilities. Without testing them on animals, there is no pathway to developing biodegradable implants as there is no such alternative yet.

I am assembling a team of researchers and clinicians who could propose and test new paediatric applications of our invented zinc alloys. Temporary implants are essential to children and teenagers whose organs and bones grow. To avoid painful second surgery to remove temporary implants, biodegradable implants could save lives and reduce the pain of many patients. Soon after we develop new applications for our zinc alloys, I will happily report them in *Research Features*.

Details



e: jwdrelic@mtu.edu
 w: www.surfi.mtu.edu
 w: scholar.google.com/citations?user=p8bFb0EAAAAJ&hl=en

Funding

- U.S. NIH National Institute of Biomedical Imaging and Bioengineering
- U.S. NIH National Heart, Lung, and Blood Institute
- American Heart Association
- State of Michigan
- Michigan Technological University

Collaborators

Professor Jeremy Goldman, Department of Biomedical Engineering, Michigan Technological University

Bio

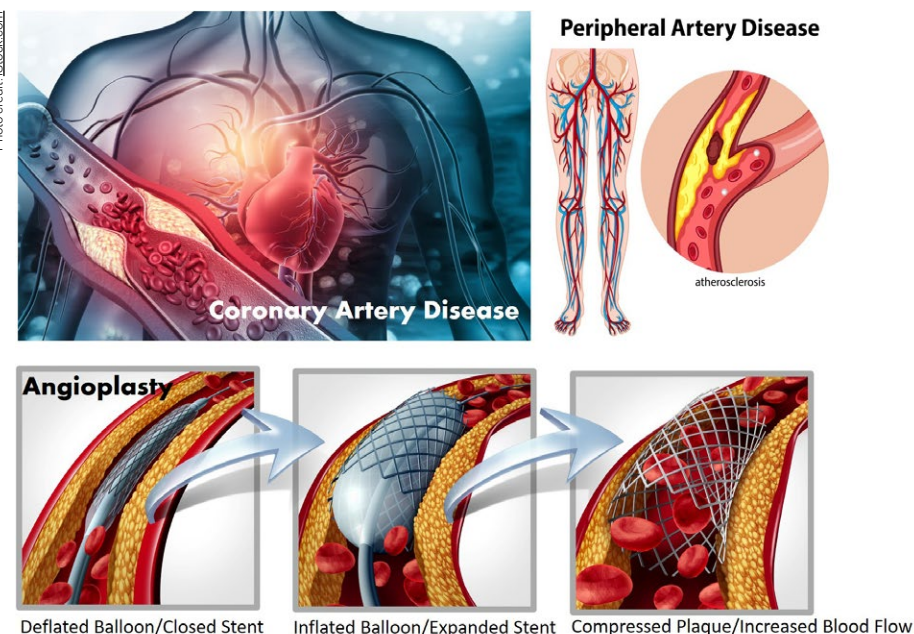
Professor Jaroslaw W Drelich is a TMS (The Minerals, Metals & Materials Society) Fellow and Distinguished

Professor at Michigan Technological University, USA. Over the past two decades, he has conducted research in biomaterials, with a recent focus on biodegradable medical materials. He has also introduced zinc alloys as new biodegradable materials for interventional medical applications.

Further reading

- Drelich, JW, Goldman, J, (2022) *Bioresorbable vascular metallic scaffolds: Current status and research trends. Current Opinion in Biomedical Engineering*, 24, 100411.
- Ralapanawa, U, Sivakanesan, R, (2021) *Epidemiology and the Magnitude of Coronary Artery Disease and Acute Coronary Syndrome: A Narrative Review. Journal of Epidemiology and Global Health*, 11(2), 169–177.

- Mostaed, E, et al, (2020) *Towards revealing key factors in mechanical instability of bioabsorbable Zn-based alloys for intended vascular stenting. Acta Biomaterialia*, 105, 319–335.
- Ardakani, MS, et al, (2020) *The effects of alloying with Cu and Mn and thermal treatments on the mechanical instability of Zn-0.05Mg alloy. Materials Science & Engineering A*, 770, 138529.
- Bowen, PK, et al, (2016) *Biodegradable metals for cardiovascular stents: from clinical concerns to recent Zn – alloys. Advanced Healthcare Materials*, 5(10), 1121–1140.
- Bowen, PK, Drelich, J, Goldman, J, (2013) *Zinc Exhibits Ideal Physiological Corrosion Behavior for Bioabsorbable Stents. Advanced Materials*, 25(18), 2577–2582.



Drawings of artery disease in coronary and peripheral arteries, and illustration of angioplasty stenting procedure.