The Common but Complicated Tool: Review of Embolic Materials for the Interventional Radiologist

Shamar Young, MD[1] Nassir Rostambeigi, MD[2] Jafar Golzarian, MD[1]

[1] Department of Radiology, University of Minnesota Medical Center, Minneapolis, Minnesota
[2] Department of Radiology, Washington University School of Medicine, St. Louis, Missouri

Address for correspondence Shamar Young, MD, Department of Radiology, University of Minnesota Medical Center, Minneapolis, MN 55455 (e-mail: Youn1862@umn.edu).

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Abstract

Embolization is an important and widely utilized technique in interventional radiology. There are a variety of different categories and individual products which can be utilized to perform embolization. Understanding the different classes of embolic agents, the important features of each of these classes including strengths and limitations, and the variation in individual products within the classes is critical for interventional radiologist to practice safely and effectively. This article reviews the different kinds of embolics and relays some of the pertinent physical and chemical properties of individual products which should be considered when determining which embolic to select for a given purpose.

Keywords
- interventional radiology
- embolization
- devices
- techniques

Embolization is a fundamental technique of interventional radiology and has applications which vary from cancer care, benign growths, to hemorrhage control.[1–4] Often the published class and specific embolic utilized vary even within the same indication.[1,2,4] As the specialty has matured, the types and breath of embolic materials have blossomed as well. A knowledge of the various classes of embolics and the differences among products is important for interventional radiologist to be able to deliver optimal care. This review aims to give an overview of various types of embolics highlighting key characteristics that vary from product to product (►**Table 1**, ►**Fig. 1**).

Particle Embolics

Particles were the first embolics described and have been a mainstay of various treatments since conception.[5] The first embolization technique reported was done with autologous blood clot and early devices included lead shot and Silastic, which had sizes on the order of 1 mm.[6–8] Particles have come a long way and now typically have sizes reported in micrometers. Particles can be subdivided into groups in several ways; however, the authors will first divide materials by whether or not they are resorbable. Resorbable particles are so termed because the material is resorbed by the body overtime. The theoretical advantage of these materials is that they will limit the blood flow temporarily, and then allow flow to be resumed, negating the need for the body to rely on or form collateral circulation in the long term. The removal of the material from the body also reduces the risk of long-term inflammation and immune reaction. These properties are attractive in many situations including acute hemorrhage. Gelfoam is the most ubiquitously used example of this kind of particle. While Gelfoam is resorbed by the body, it is unclear how quickly this happens with reports of 3 days to 4 months being published in animal or human studies.[9] Furthermore, weather the vessels recanalize or undergo neovascular remodeling is also unclear. There are also numerous resorbable particles being studied given the advantages that are inherent to this material.[10]

Permanent particles are so termed because the materials are never resorbed by the body. Permanent occlusion is desirable in some settings such as during tumor embolization. One important characteristic of permanent materials

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Table 1 Strengths and weaknesses of the embolic classes

Type of embolic	Strengths	Weaknesses	Further development
Particles	• Flow directed • Easy to deliver	• Can lead to ischemia • Can result in nontarget embolization • Somehow reliant on coagulation cascade	• Radiopaque beads • Drug-eluting beads • New resorbable beads
Liquids	• Powerful embolic • Flow directed • Not reliant on coagulation cascade	• Requires experience • Can "glue" catheter in place • Nontarget embolization	• Improved visualization without beam hardening • Improved solidification properties
Coils	• Low risk of ischemia • High level of operator control	• Reliant on coagulation cascade • Can require multiple to completely occlude • Trackability can be an issue	• Hydrogel coating • Large volumes • Different shapes • Low-profile delivery
Plugs	• Single-device occlusion • Low risk of ischemia • High level of operator control	• Occlusion can take time or require coils as well • Trackability can be an issue • Larger delivery system	• Improved occlusion times • Improved trackability

is that even though they are not resorbed by the body, the vessel can still be recanalized due to natural thrombolysis and phagocytosis of the embolic materials. Within permanent particles, there is further division into spherical and nonspherical particles. Nonspherical particles, such as polyvinyl alcohol (PVA), available commercially as Contour (Boston Scientific, Marlborough, MA), are not perfectly round and therefore not very uniform. Nonspherical PVA has the advantage of being fairly inexpensive but can also clog microcatheters and due to its nonspherical shape, the exact level of arterial occlusion is difficult to predict.[11,12] To combat these shortcomings, spherical particles were developed. Spherical embolics are available in several different materials including PVA (Bead Block and LC beads; Boston Scientific), trisacryl-gelatin (Embosphere; Merit Medical, South Jordan, UT), and polymethylmethacrylate with a coat of polyzene-F (Embozene; Varian Medical, Palo Alto, CA). Spherical particles have been shown to have a more

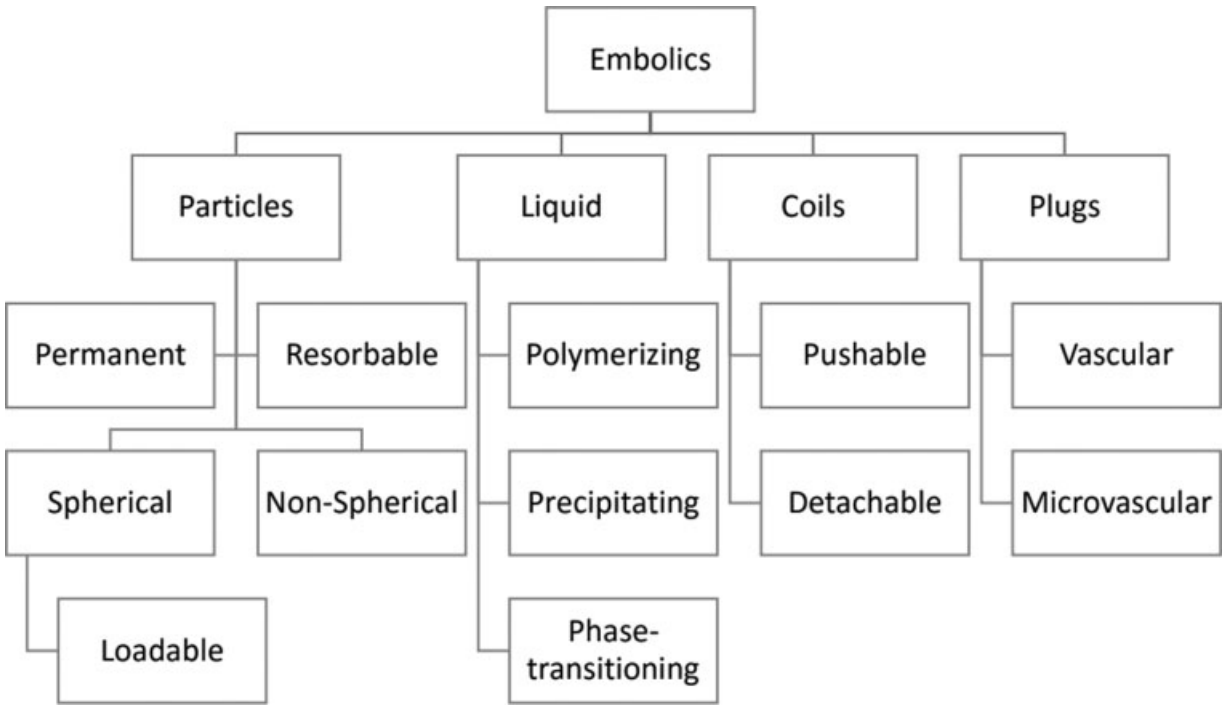

Fig. 1 Various embolic classes and their subdivisions.

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predictable level of arterial occlusion.[13] They also do not result in microcatheter occlusion as frequently. However, these benefits have not always translated to improved clinical outcomes.[14]

Drug-eluting beads (DEBs) are another subgroup of particles which bear mentioning. DEBs are most commonly "loaded" with a drug via an ion exchange mechanism.[15] However, not all drugs are loadable via this mechanism.[16] The beads are delivered in a dehydrated state and the desired drug is loaded in the pharmacy of the institution which plans to use them. There are several available DEBs on the market, including DC Bead (Boston Scientific), HepaSphere™ (Merit Medical), Oncozene™ (Varian Medical), and LifePearl (Terumo Medical, Tokyo, Japan). The benefit of DEBs is that the chemotherapeutic step and embolization step occur simultaneously, and the drug is slowly released decreasing systemic levels.

There are also many other properties of particles which effect the function and are often interrelated. For instance, density affects sedimentation rates, which in turn can affect the frequency of catheter clogging. Other factors such as compressibility and fracture rates also play into the functionality of particles but are beyond the scope of this review. There are many areas of active development in particle embolics. One is the development of radio-opaque particles.[17–19] There is a commercially available radio-opaque particle, LC Bead Lumi™ (Boston Scientific); however, it still requires the addition of contrast to be seen fluoroscopically but is visible on posttreatment computed tomography. New visible particles are in the pipeline. The ideal particle should also be visible during fluoroscopy without requiring any contrast materials. Similarly, new resorbable spherical particles are being developed as well.[18,20,21]

Liquid Embolics

Liquid embolics can function independently of the patient's clotting ability and allow flow-directed treatment of smaller targeted vessels where catheters and coils cannot reach at times. In contrast to particulate or coil embolics that physically obstruct blood flow, liquid embolics can induce embolization via biochemical reactions as well. The most commonly available and used liquid embolic is n-Butyl cyanoacrylate (NBCA) or glue. NBCA is available in several commercially available formulations: Histoacryl® (B/Braun, Tuttlingen, Germany), Trufill® n-BCA (Cordis, Miami Lakes, FL), Neuracryl (Cordis, Warren, NJ), and Glubran (GEM, Viareggio, Italy). Liquid embolics have several different potential mechanisms of action, including polymerizing, precipitating, and phase-transitioning agents.

Polymerizing liquid embolics use initiating agents to polymerize and solidify monomers or micro-monomers, which are in a carrier solution. This can be accomplished in two ways for the purposes of embolization. First, the initiator can be mixed with the monomer solution outside of the body and then delivered. The time to solidification must be known and consistent for this to work and it requires a highly organized and timed delivery, making it less than desirable for clinical use. Another option is to deliver the initiator and the monomer simultaneously through a dual-lumen catheter allowing them to mix and the monomer to solidify after delivery into the target vessel. There are several pipeline products which are polymerizing liquid embolics, including Hydrogel Embolic System (Instylla, Inc., Bedford, MA) and poly(propylene glycol) diacrylate and pentaerythritol tetrakis (3-mercaptopropionate) (PPODA-QT).[22–25]

Precipitating embolic systems use a carrier to dissolve the polymer. When the polymer and dissolvent enter the blood stream, the aqueous conditions lead to precipitation of the polymer chains and it solidifies. This has advantages in that it does not require a dual-lumen catheter or careful timing as the polymerizing agents do; however, disadvantages also exist. For example, the material can be washed away by blood flow leading to nontarget embolization if the polymerization does not occur quickly enough. The dissolving agent must also be nontoxic and preferably avoid alteration of blood flow through vessel spasm. Onyx™ (Medtronic, Dublin, Ireland) is an example of a precipitating agent, which is currently available on the market. Others such as Squid® (Emboflu, Gland, Switzerland), precipitating hydrophobic injectable liquid (PHIL; Terumo Medical), Easyx™ (Antia Therapeutics AG, Berne, Switzerland), and Lava (Black Swan Vascular Inc, Hayward, CA) are in various levels of development and may be available soon.[26–31]

Phase-transitioning agents work by using an external stimulus to transition from liquid to gel. For the purposes of human use, this could be temperature, pH, or salt concentrations in the blood system. There are two products in the pipeline which fall into this group and they are GPX (Fluidx Medical Technology) and PuraMatrix (3D Matrix Co., Tokyo, Japan).[32–35]

While liquid embolics have several benefits, limitations do exist. They are very powerful embolics and as such require a high level of understanding and can lead to significant nontarget embolization or other complications when not used properly. Furthermore, many require mixing with radio-opaque substances, such as lipidol, or shaking if they are reliant on micronized tantalum powder for visibility. Several of the pipeline products are working on the issue of visibility without the need for combination with another substance or shaking. They can also lead to significant artifact on posttreatment CTs or MRIs, another aspect where improvement is the target of pipeline materials.

Coils

Coils have been described in the treatment of several different clinical scenarios and are a commonly utilized embolic material.[36] As such it is not surprising that there are more than 51 different coils with different characteristics and sizes available in the market. When evaluating coils, several aspects should be considered. The authors will start with some intrinsic properties, which must be considered for all coils. First, the coil material is important, as it must be inert, induce thrombosis, and ideally has significant longitudinal, but minimal radial strength.[35–37] It is important to

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remember that coils rely on thrombosis to completely occlude the target vessel and therefore must be thrombogenic.[36–38] Furthermore, the packing density, or how tightly the coil is packed within the target, has been shown to correlate with complete occlusion rates. Therefore, the mechanical cross-sectional packing of the vessel is very important with higher packing rates reducing the risk of delayed recanalization.

An important demarcation between different types of coils is pushable versus detachable. Pushable coils do not have any connection to a wire or other way to retract them, meaning once they enter the catheter or more importantly the patient, they cannot be retracted. Detachable coils have a mechanism which holds them to a wire and therefore can be retracted or "recaptured" until released. Pushable coils have an advantage of typically being more cost-effective per unit, while detachable coils increase the operator's control. However, it is important to note that while each individual pushable coil is less costly, some studies have shown increased number of coils required and time of procedure when using them versus detachable coils, raising the questions of overall procedural savings.[39] Another important concept to understand is softness; increasing softness allows coils to fill the space seamlessly and efficiently without pushing back the delivery system resulting in better loop formation and therefore improved packing density.[40] As mentioned earlier, packing density has been shown to be related to long-term outcomes in some applications such as aneurysm embolization; so, it is an important consideration and typically actively targeted by operators.[41,42] Trackability, which often follows closely with softness, is another area of consideration when choosing coils for certain situations, especially when attempting to deliver along a tortuous course.

Perhaps the most important aspect of any coil is its ability to occlude. Coil technology has developed toward enhancing the ability of occlusion by adding different aspects or changing parameters of the coil, typically aimed at improving thrombogenicity or packing density. Some early generation coils, such as Nester® and Tornado® coils (Cook Medical, Bloomington, IN) which are pushable platinum coils, have nylon fibers which enhance occlusion by triggering blood clot formation to fill the space between the coil pack.[43] This technique has been replicated in detachable coils, such as the Concerto™ coil (Medtronic) as well.[44] Another option is to make coils so soft that they act like "liquid metal," and thus efficiently pack the target space—an example of this is the Ruby® coils family, more precisely the Packing coils (Penumbra Inc, Alameda, CA). Other products, such as the AZUR CX™ Hydrocoil (Terumo Medical), have placed a hydrogel coating on the coils which expands after being delivered to fill-in the space between the platinum coils.[45] The hydrogel, which has a limited expansion at 3 minutes and fully expands by 20 minutes, can take time to occlude the target vessel.

The shape of the coil is also important to understand. Some coils have "memory" and will reform into a given loop, sine wave, or complex 3D shape, while others, such as the packing coil (Penumbra Inc), are relatively amorphous with a goal of completely filling the vessel. Others such as the Ruby® (Penumbra Inc) and the Concerto Versa™ (Medtronic) produce a complex 3D shape, designed to increase packing density. Additional shapes such as straight Hilal™ microcoil (Cook Medical) and ball-shaped sizes have been developed to fill complex targets. To show the range of options, 2 mm × 20 mm up to 20 mm × 300 mm coils are available in the AZUR™ (Terumo Medical) family, and 2 mm × 40 mm up to 20 mm × 500 mm in Concerto™ Helix (Medtronic) family.[46]

Another consideration is anchoring, to allow the coil to begin forming at the desired location. Without anchoring, coils can "run down" the vessel, leading to a nonocclusive coil line. One solution to the need to anchor, but the desire for high packing density, is to have a stiffer tip to help the coil to anchor with a transition to a softer coil for the body—an example is Penumbra POD® coil.[47] Placing coils has at times been thought of as a three-step method, namely, positioning, framing, and packing. As such, some coils have attempted to work around these three steps, such as the earlier-mentioned Medtronic Concerto Versa™ which combines all three different coils into one coil and allows those three steps to be performed with one single coil. Similarly, the AZUR CX™ coil allows both establishing the base and filling the space in one coil.

Coil embolization has several advantages. It is thought of as a permanent occlusion, and the occlusion occurs proximally in the vascular tree and therefore is very efficient in cessation of bleeding without causing ischemia from occlusion of distal capillaries. Additionally, with the newer technology, the coil delivery to challenging points of desired occlusion has become possible, thanks to softer detachable coils that can be delivered via very small microcatheters. Lastly, the versatile options available give the operator the ability to use coils in a variety of different shapes and sizes of vessel pathologies.

Conversely, coils have some limitations as embolics. The beam hardening and scatter artifact from the coil pack can obscure the treated vessel and limit the evaluation by CT scan at follow-up.[48] Similarly, the coil pack can cause susceptibility artifact on MRI at follow-up imaging and limit the evaluation. The dependence on coagulation cascade can limit the effectiveness in patients with coagulation disorders. A large number of coils may also be needed to occlude a target vessel, adding to the cost and time of the procedure. Finally, coil deployment always requires being able to reach the site by the microcatheter and this limits their use in very tortuous or small vessels.

The complex embolization is an area of unmet need in the field of coil embolization. A common scenario is embolization of a branch while maintaining access into further distal branches. In these cases, a dual access is usually needed through a guiding catheter, one for mainlining distal access and one for embolizing a branch vessel. It would be valuable to develop a system for peripheral embolization use that enables the operator to combine all the elements into one system. More research is also needed to reveal the long-term recanalization rate after coil embolization using newer coil models.

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Vascular Plugs

Vascular plugs were created in part to address the issue of having to deliver multiple coils to achieve occlusion. In many ways, they are similar to coils, and they both aim to deliver permanent relatively proximal occlusion of the target vessels. The first plug brought to the market was the Amplatzer™ Vascular Plug (AVP) (Abbott Medical, Chicago, IL).[49] This device comes in four different shapes, although the AVP III is not currently available, but all are made of a nitinol mesh and are detachable, with a micro-coil holding the device to its delivery wire.[49,50] They have been used in several clinical scenarios.[49–52] However, they require fairly large catheters or sheaths to deliver them, making them unusable in many situations.[49] Another issue reported with the AVP is length of time to occlusion or lack of occlusion, necessitating additional coils or embolic materials.

The Microvascular Plug (MVP) (Medtronic) was created to address the issues of deliverability and vessel occlusion seen in the AVP.[44] The MVP can be used in vessels as small as 1.5 mm and delivered in microcatheters with an inner diameter as small as 0.021 in.[53] Like the AVP, it is made of a nitinol frame; however, it uses a polytetrafluroethylene-covering instead of mesh to lead to occlusion.[53,54] It is detachable, via a microscrew, and has been described in several different clinical scenarios.[55,56] The design allows for excellent trackability and deliverability; however, it can also cause migration in high-flow situations.[57]

Because of the potential benefits and continued perception of unmet needs a few plugs are just reaching, or likely to reach the market soon (►**Fig. 2**). These include the Azur Vascular Plug™ (Terumo Medical), Caterpillar (BD, Franklin Lakes, NJ), Lobo vascular occlude (Okami Medical, Aliso Viejo, CA), Hourglass (EMBA Medical, Dublin, IR), and Pillow Occluder (AndraTec, Koblenz, Germany), and IMPEDE (Shape Memory Medical, Santa Clara, CA).[58,59] All these devices come with a membrane or similar mechanism designed to allow faster occlusion.

The Azur plug has the advantage of occluding up to 8 mm vessels through a high-flow Progreat Pro (Terumo Medical) microcatheter. Another plug which is now available, the Caterpillar (BD, Franklin Lakes, NJ), is deliverable through a high-flow microcatheter to occlude up to a 4-mm vessel; however, it needs larger delivery catheters to occlude vessels up to 7 mm. The Hourglass (EMBA Medical) differentiates its self from the market in that it is like a stent that is restrained in the middle with a proximal membrane.[58] The Pillow occluder is a large vascular plug which is 25 mm in length and either 4 or 8 cm in diameter, with delivery through an 8-Fr system. This device has a stent as the framework of its design with a polyurethane mesh within the stent and was designed for occlusion of abdominal and thoracic aortic aneurysms. Finally, IMPEDE (Shape Memory Medical) is a foam-based plug that can expand significantly after contact with blood. Studies have shown cellular infiltration provokes mature connective tissue development within the foam scaffold of IMPEDE device and this improves percent vessel occlusion.[60] The foam is also available with a proximal coil to facilitate anchoring the vessel wall and prevent it from migration. This material is pushable and needs larger guiding catheters for delivery.

As mentioned earlier, vascular plugs have the potential advantage of performing a complete embolization after single device placement, unlike coils which frequently

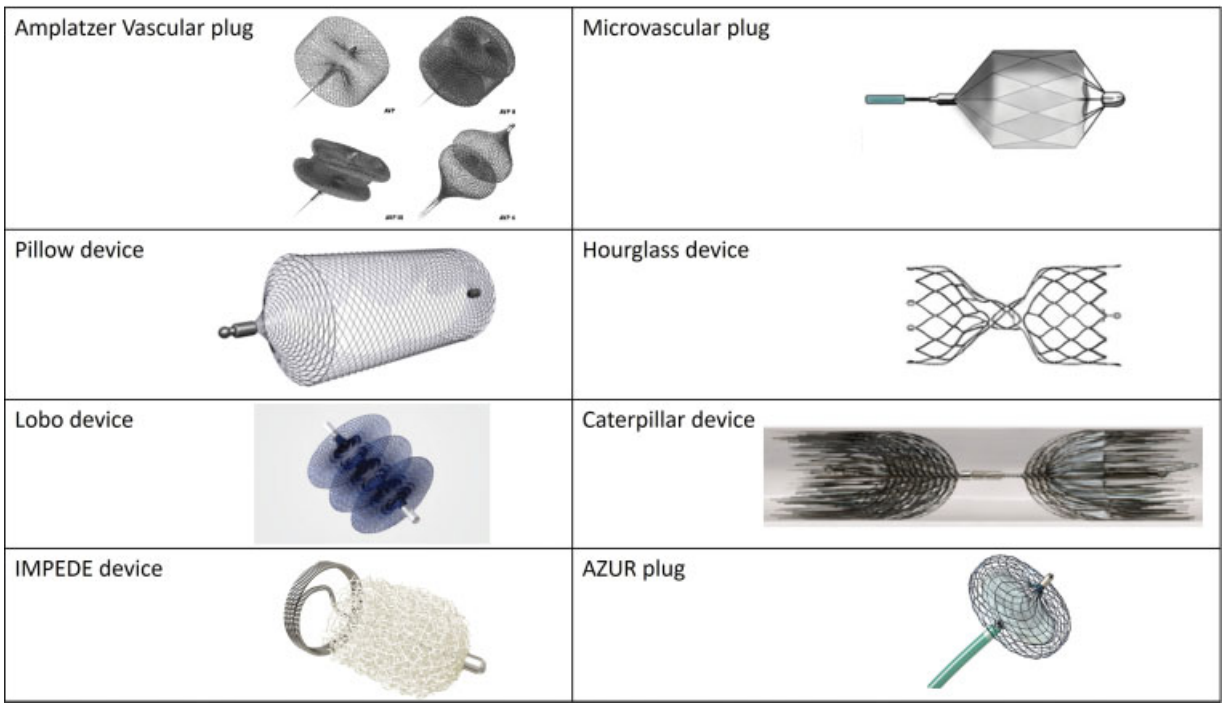

Fig. 2 Various plug devices that are currently available or are in development.

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require several. They are also associated with much less artifact in CT and MR imaging. However, issues such as time to occlusion, the need to add coils to the plug to achieve occlusion, and trackability/deliverability have been raised. While some plugs come with membranes, which attempt to enhance occlusion, they still appear to be reliant on the patient's thrombotic cascade to result in complete occlusion and therefore may be of limited use in those with poor ability to form thrombus.

Conclusion

The number of different embolization materials available to the practicing interventional radiologist is extensive. Furthermore, new devices are being developed and becoming available every year. It is likely that this development will continue in the pursuit of the "ideal" embolic. It is important to understand the various aspects of these devices to correctly select the category and model of device to suit each clinical need.

Conflict of Interest
None declared.

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