Introduction

Embolic agents

Embolic agents can be classified into solids, particles and liquids. Solid agents that can be positioned at target site include coils and microcoils, plugs, and balloons. Agents to be released in the bloodstream can be sub-categorized into *particles* and *liquids:* particles can be absorbable or non-absorbable, spherical or non-spherical; liquid agents include cyanoacrylates, gelling solutions, and sclerosing agents (Fig.1). While indications such as varicocele respond well to any kind of treatment, others, such as lower gastrointestinal (GI) bleeding, offer a restricted choice, as the radiologist may have to reach a very distal vessel by using means of a small microcatheter.

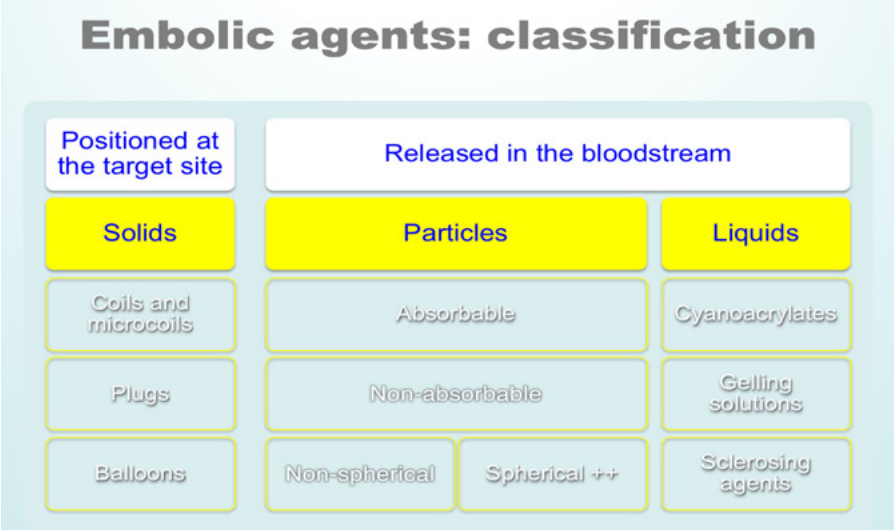

Figure 1

In such cases, liquids are often the best solution, as it may be difficult to properly deploy solid agents, even when it comes to small microcoils (Fig.2). On the contrary, injecting liquid is a viable option in any kind of indication. An interventional radiologist needs to be able to master every tool at their disposal. Gelling solutions or coils can prove efficacious in many cases, however, some indications require a combination of liquid and solid agents or, as this presentation will show, sometimes glue simply represents the best option. The oldest cyanoacrylate for endovascular use is Butyl (NBCA), known as Histoacryl® in Europe and Asia, and Truefill® in the United States. Although Histoacryl® is normally employed in endovascular use, it is never commercially promoted as a product suitable for this kind of environment as it lacks official approval. Truefill® has FDA approval, however, it is only available in the US. The lack of a CE marking is not the only downside to employing Histoacryl®. As one of the most common causes for complications is dried glue causing the microcatheter to stick to the vessel, quick polymerization may increase such risk (Fig.3).

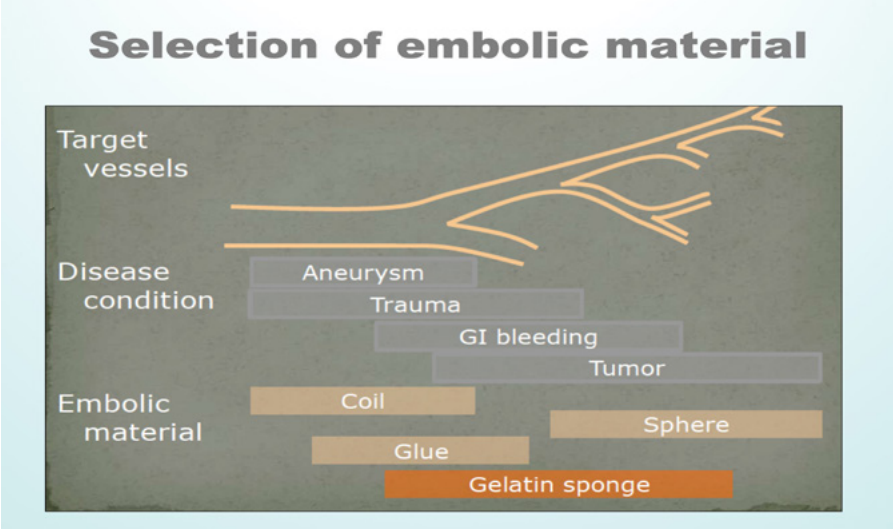

Figure 2

Why Glubran® 2

At this moment in time Glubran®2 (NBCA + Methacryloxy Sulfolane) is the only certified glue for endovascular use in Europe (Fig.4).
The co-monomer allows for better stability and for a spontaneously delayed polymerization time, which makes it less challenging to deploy when compared to Histoacryl® (Fig.5). Another liquid agent is MagicGlue® from Balt, formerly known as Purefill® (Fig.6).
Comparing polymerization time, levels of cytotoxicity and inflammation, and adhesive strength across all available products, Glubran®2 appears to be a perfectly balanced agent in terms of behaviour. It therefore represents a favourable option in many indications.
As costs usually represent a relevant factor, **a great advantage to favoring Glubran®2 is its price**. The price of Ethiodized Oil (Lipiodol®) has been rising consistently over the past 5 years: today, it is about € 250.00 for 10 ml. Since Trufill® comes packaged together with Ethiodized Oil, this may be one

Cyanoacrylates: types and actions

	Methyl (NMCA)	Butyl (NBCA)		Hexyl (NECA)
	Superglue®	NBCA *Histoacryl® Trufill®*	NBCA + CM *Glubran®2*	*MagicGlue®*
CH3 radical	+	++	++	+++
Polymerization time	Very fast	Fast	Intermediate	Low
Cytotoxicity	+++	++	+	+
Inflammation	+++	++	+	+
Adhesive strength	+++	+++	++	+

Used for endovascular purpose

Figure 3

of the reasons for its eccessive cost. A 1 ml vial is about $ 3,000.00, whereas the same amount of Glubran®2 costs about € 100.00. The cost of the mixture may be compared to purchasing a single plug or one detachable microcoil. Onyx® or Squid are about twice the price. Usually, fixing an artery requires 3 to 6 microcoils, whereas a single drop of glue will produce the same results. Another upside is that **Glubran®2 comes in vials of variable capacity (0.25/0.5/1 ml)**. This makes it **quite practical as we do not always need the same amount of product**. While veins require the entire space to be filled, arteries can be occluded by using only a few drops. MagicGlue® from Balt is a "Me too" product in terms of CE marking. This means that no preclinical studies have been made, in fact, the studies from Glubran®2 have been used. The price of this product compares to that of Glubran®2. Glue is used in many fields, not only in interventional radiology but also in surgery. In Europe, it is widely employed in surgical environments, except for France, where the ratio is about 70-30% to interventional radiology.

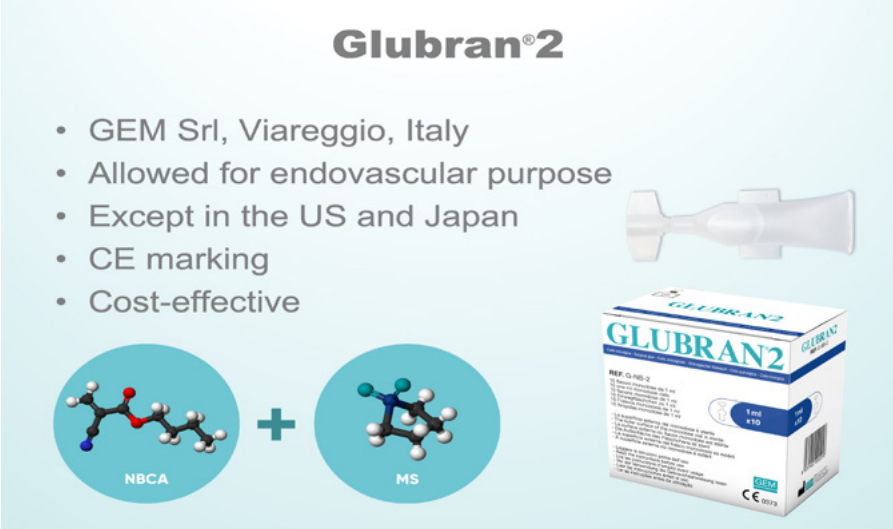

Figure 4

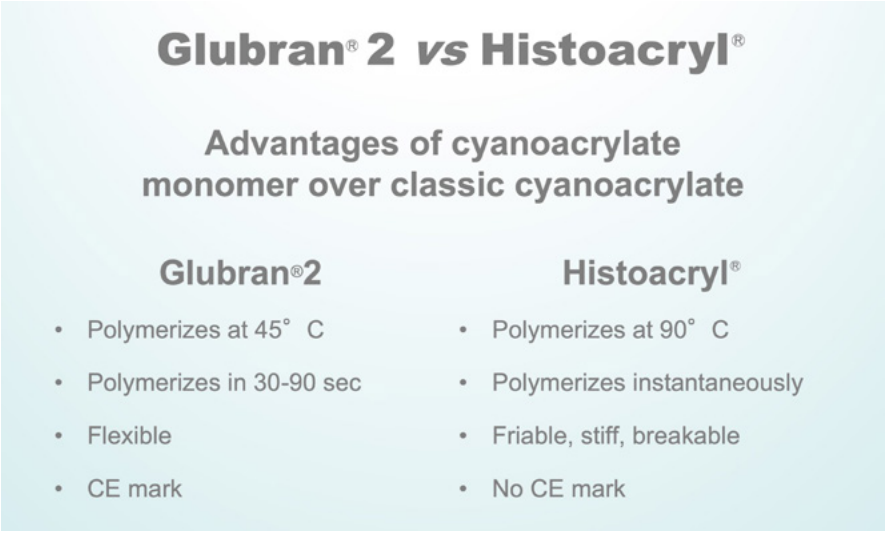

Figure 5

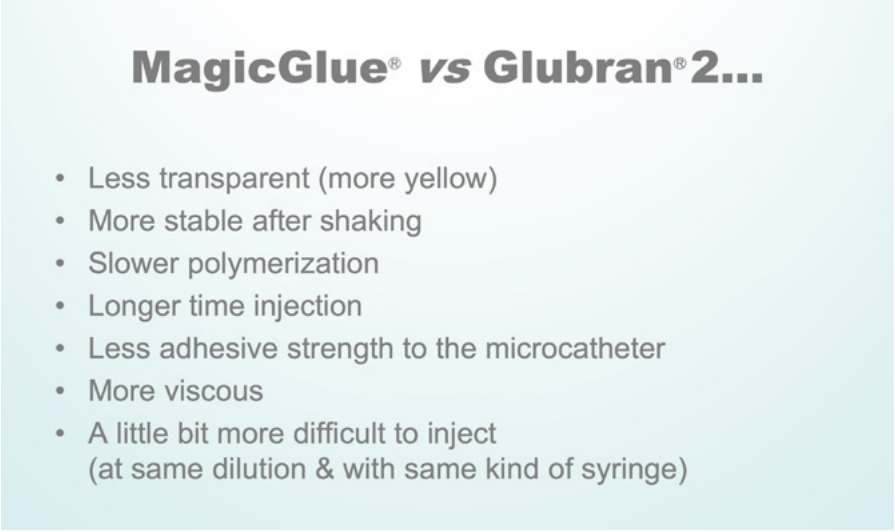

Figure 6

I estimate it is about the opposite in the rest of Europe. MagicGlue® often uses different names depending on the field: in surgery, it is often known as IFABOND, which sounds quite different. Glubran®2, on the other hand, is marketed under the same name in every field. Glubran®2 is transparent, colorless, highly adhesive, and hemostatic (Fig.7).
The fact that the mixture with Ethiodized Oil dissolves polycarbonates might not be of specific interest to interventional radiologists, as we prefer to use different materials, but it is still worth mentioning.
Not only it is an embolic agent, but it is a sclerosant, too, so it can be employed in a variety of indications. It polymerizes in contact with any ion-rich fluid; therefore, it needs to be flushed with a 5% dextrose solution to prevent the blood from refluxing and polymerization from starting inside the catheter. In case of distal embolization such as a tumor, you need to abundantly flush the tumor bed, too, in order to make sure distal embolization is achieved.

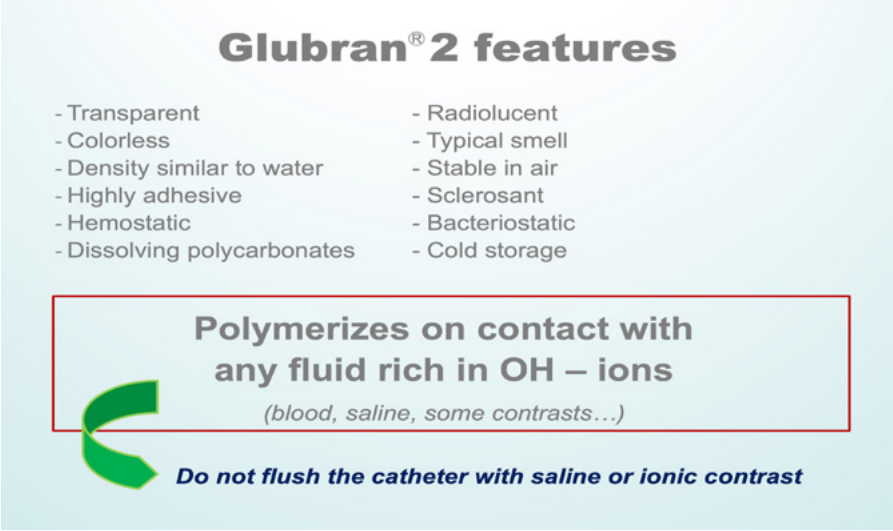

Figure 7

Polymerization of NBCA involves an exothermic reaction that is known to cause pain, even though this mechanism is not clinically obvious. Glubran®2 polymerizes at half the temperature as Histoacryl®, so it causes the patient less pain. Other differences include delayed polymerization, higher flexibility, and official approval. As previously mentioned, the advantages to using Glubran®2 are not limited to cost (Fig.8).

- **A quick embolization also implies less radiations, both for the surgeon and the patient.**
- **This product can be used in a number of indications, with bleeding as perhaps the most suitable.**
- **It is a permanent agent, exceptional when it comes to recanalization. This is not the case with all embolic agents.**
- **The fact that polymerization does not depend on coagulation parameters makes it very interesting in case of bleeding in patients with a coagulation disorder or low levels of platelets.**

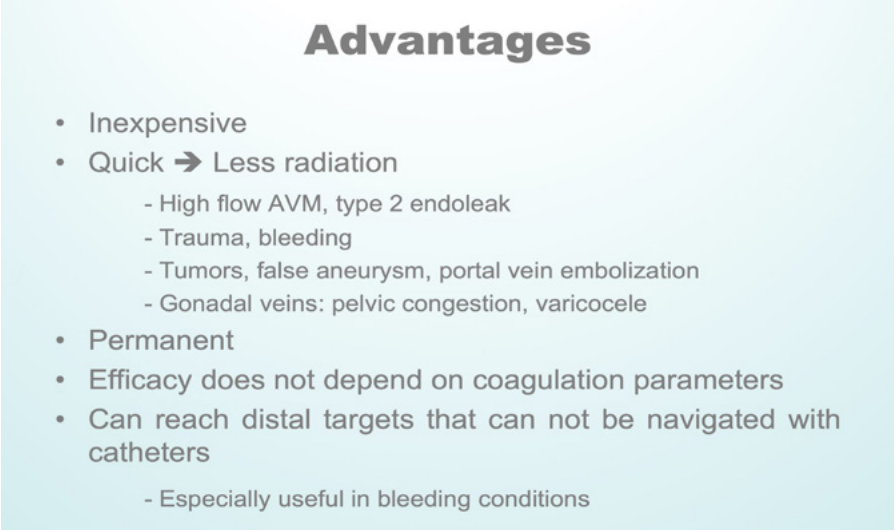

Figure 8

When Glubran® 2 comes into contact with blood, it **never fails to achieve occlusion**. Compared to mechanical agents, this poses a great advantage. In the use of coils, for example, a spontaneous thrombosis needs to be triggered and that can be challenging in patients with coagulation disorders.

- Distal targets are easily accessible even with the smallest microcatheter. In some specific indications, liquids are simply the best option.

When compared to Onyx®, Glubran® 2 is more thrombogenic and quicker to polymerize (Fig.9)[1]. Inflammation rate is also higher. Even though Onyx® may be perceived as safer, as it ensures a more controlled release, in our experience this is not key in any indication. Besides, our concern here is peripheral and visceral application, which is quite different from the neurological area.

As previously mentioned, **Glubran®2 has high adhesive properties, but it still takes a long time for it to stick to the catheter. We have never experienced such an incident**. Onyx®, on the other hand, sometimes needs long breaks between injections, as it often causes immediate reflux.

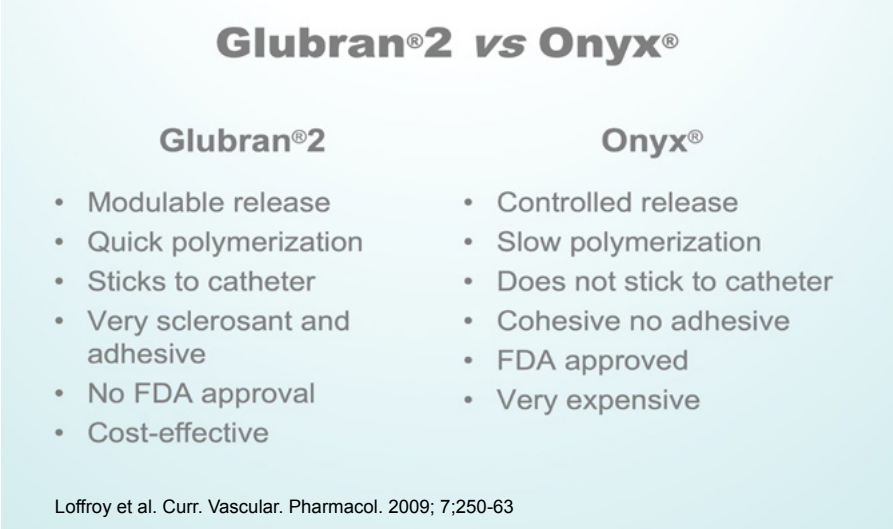

Figure 9

Neuroradiologists may have to wait as long as 45 minutes between injections for a hard cast along the microcatheter to form so that they can push it again into the distal spot. The risk of finding the catheter stuck is quite high in such cases, and this is why there are specific microcatheters with detachable tips, so that the tip can be left in the patient and avoid an undesirable outcome.

Most interventional radiologists see the use of glue as a practice that can lead to multiple complications, chiefly the risk of the catheter sticking to the vessel. During the course of this presentation, some useful advice will be offered towards performing a safe and proper embolization, helping the radiologist to avoid such risk entirely. Generally speaking, **while it may be possible to find the catheter hard to remove, the likelihood of it getting stuck to the point of not being able to remove is non-existent**.

Ischemic risk is also a concern, as many perceive glue as a potentially dangerous agent with high risk of ischemic complications and necrotic lesions. In the past four years, two articles have been published regarding the use of glue in GI bleeding [2,3], showing how cyanoacrylate glue is the most clinically useful embolic agent in treating patients with acute NVIGIB (non-variceal gastrointestinal bleeding), despite the need for a learning curve, especially in cases of coagulopathy.

Despite the bowel being considered as the territory with the highest risk of ischemic complication, we showed that the risk rate is actually lower than with other embolic agents. Microparticles, for example, start from 14 microns in size and, when injected, the risk of ischemic complications is very high. Regardless of the level of dilution, combining Glubran® 2 with Ethiodized Oil makes the mixture highly viscous, which prevents it from reaching the capillaries. A viscous mixture will never become as distal as small microparticles. Non-target embolization caused by reflux is indeed a possibility. Nonetheless, compared to other agents, the upside to employing glue is that it is clearly visible during the procedure. Particles, for instance, are only visible by means of the contrast agent that is added to them.

Although due caution is certainly essential, the endpoint is that cyanoacrylates are easier to handle as they are easier to see.
Besides, as our area of interest is peripheral application, most times a few drops of glue in a non-target vessel will bear no consequences at all, so we can conclude that this kind of complication is not to be considered as such, but rather something we need to be aware of (Fig.10).

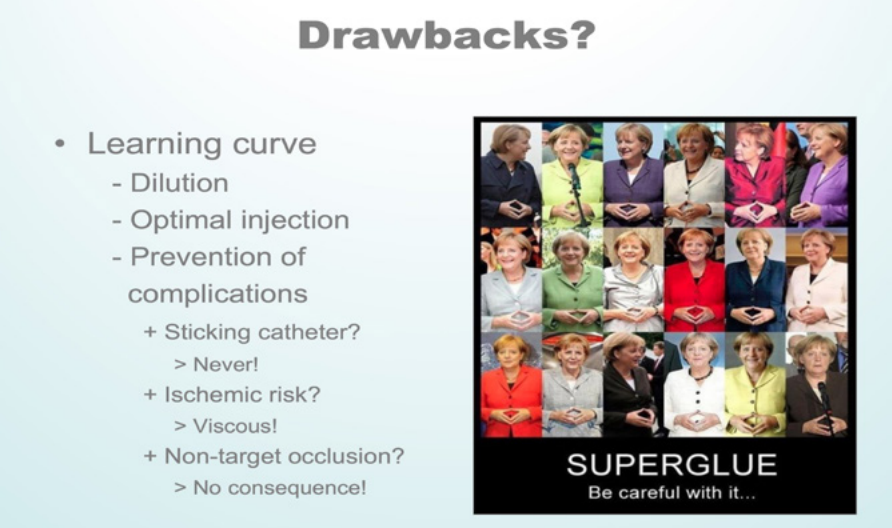

Figure 10