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REVIEW

Antithrombogenic peripherally inserted central catheters: overview of efficacy and safety

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ABSTRACT

Introduction: Thrombotic complications associated with peripherally inserted central catheters (PICCs) are common, as most synthetic materials when placed in the presence of serum often result in platelet activation, fibrin deposition, thrombotic occlusion, and potentially embolization. A current innovation focus has been the development of antithrombogenic catheter materials, including hydrophilic and hydrophobic surfaces. These are being incorporated into PICCs in an attempt to prevent the normal thrombotic cascade leading to patient harm.

Areas covered: This review focuses on the laboratory efficacy and clinical effectiveness of antithrombogenic PICCs to prevent PICC-associated thrombosis, as well as their efficiency and safety. This synthesis was informed by a systematic identification of published and unpublished laboratory and clinical studies evaluating these technologies.

Expert commentary: A range of PICCs have been developed with antithrombogenic claims, using varying technologies. However, to date, there is no peer-reviewed laboratory research describing the individual PICCs' effectiveness. Despite promising early clinical trials, adequately powered trials to establish efficacy, effectiveness, efficiency, and safety of all of the individual products have not yet been undertaken.

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1. Overview of the market

Secure and reliable venous access is a cornerstone in the care of hospitalized and critically ill patients [1]. As care transitions occur with greater frequency, the need for safe access to also continue in the ambulatory setting has been increasingly recognized [2]. As such, the demand and market for devices that provide reliable and prolonged venous access has always been strong.

Central venous access (i.e., insertion of a vascular catheter such that the tip terminates in a deep vein of the neck, chest, or abdomen) is a key component of venous access. Both hospitalized and critically ill patients are often in need of central venous access for indications that range from hemodynamic monitoring, difficult venous access, and long-term intravenous therapy such as antibiotics or chemotherapy. A variety of central venous catheters (CVCs) to achieve such access are available, each with their own risks and benefits. Over the past two decades, peripherally inserted central catheters (PICCs) have emerged as one of the most often clinically used devices for achieving central venous access [3]. Several properties of PICCs have allowed them to emerge as the leading choice in the market. First, PICCs are unique in that they are inserted in peripheral veins of the upper extremities in adults; thus, they avoid the risks associated with insertion of CVCs including injury to the vessels of the neck or chest and pneumothorax. Second, growth in the number of vascular access teams that comprise largely of nurse specialists who receive additional training to place these devices has made PICCs more accessible [4]. Third, because PICCs can be placed at a patient's bedside, they have become more convenient for patients and providers. Finally, as reimbursement and policies encouraging shorter lengths of hospital stay have emerged, PICCs serve as an ideal transition device from the hospital to the outpatient setting. It is therefore little surprise that PICCs are the market leader when it comes to venous access devices, especially the CVC segment.

However, it is important to recognize that PICCs are not without their own risks [3,5]. In a systematic review and meta-analysis of the literature, PICCs were found to be associated with 2.5× greater risk of thrombosis than CVCs [6]. Similarly, endoluminal routes of infection coupled with longer dwell times have led to the finding that rates of bloodstream infection with PICCs parallel those of CVCs, especially in critically ill and cancer populations [7]. Additionally, a number of other important complications including migration, dislodgement, and catheter occlusion have been associated with these devices – often at rates exceeding other CVCs [8,9]. Thus,

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a key and unmet need in the market – and for PICC design – is the development of new and safer technologies that safeguard against these risks by incorporating novel designs, materials, and insertion techniques. In addition, as PICCs begin to populate more outpatient settings, attention to human factors including more active patients and the ergonomics of device insertion, care, and maintenance have become a more central focus of research.

1.1. Basic materials and design

PICCs have evolved substantially since their introduction in the 1970s by Verne Hoshal and Millie Lawson [10]. Key changes include improvement in catheter material, design, and configuration. The first-generation PICCs were made of silicone-based polymers – thought to be more durable and dependable than non-silicone rubbers. However, this was not the case and silicone PICCs exhibited many problems including rupture of the catheter wall and local reactions along the vessel wall. These local reactions – ranging from mild irritation to phlebitis – often led to premature device removal and painful complications for patients [11]. In the early 1980s, polyurethane-based materials were introduced as a means to reduce these complications. However, first-generation polyurethane devices were associated with many of these same complications including phlebitis and venous irritation. Third-generation polyurethane materials (currently used in most PICCs) have provided the optimal blend of patient acceptance and durability. These materials, in turn, can also withstand high-pressure injections – leading to the term 'POWER PICCs' being used for devices compatible with radiographic injectors, for example [12].

In addition, PICC design has included valves built into the device in an effort to reduce occlusion. These valves serve as one- or two-way portals designed to reduce reflux of blood from the catheter tip back into the lumen as a means to prevent occlusion. Valve technology has continued to improve, but meaningful changes to clinical outcomes remain elusive. In a randomized controlled trial (RCT), no changes in device longevity or occlusion rates were observed when three different valve types were compared head to head [13]. Future research into valve technology, and engineering models that test reflux prevention strategies are needed. Another improvement in PICCs relates to the configuration of the devices. PICCs are now available in single, double, triple, and quadruple lumen devices. These diverse options allow for greater flexibility and clinical versatility, but may also increase risk of complications. Increasing number of lumens and catheter size, for example, are well-recognized predictors of PICC-related complications [14,15]. Conversely, efforts to reduce the number of lumens has led to improvements in complications, including bloodstream infection [16–18].

1.2. What are the unmet needs of the currently available technology/devices?

Improvements in catheter materials is the new frontier of PICC science. Newer materials that aim to prevent infection and thrombosis have been introduced, with early data suggesting potentially important clinical benefits related to these devices. For example, in a systematic review, PICCs coated or impregnated with antiseptic materials such as chlorhexidine and minocycline–rifampin were found to be associated with lower rates of infection than non-coated devices [19]. While outcomes related to thrombosis are not known, it is plausible that materials designed to impair coagulation or prevent platelet activation might have similar benefits. Such properties would be welcomed in patients at high risk of deep vein thrombosis – such as critically ill and cancer populations.

The aim of this review is to provide a concise review of the design, basic technology, clinical use, and future potential of antithrombogenic coatings and materials, how they are being used on PICCs, and the data available to support their efficacy to improve patient and health-care service outcomes.

2. Introduction to the device

2.1. How the device works

There are four common methods for introducing antithrombogenic properties to catheters, namely (a) use of hydrophilic surfaces; (b) use of hydrophobic surfaces; (c) 'biological' surfaces; and (d) added drugs. A hydrophilic surface – usually obtained by grafting a hydrophilic polymer to the surface – aims to reduce protein adsorption by creating a water-solvated surface layer which proteins will not bind to [20]. In contrast, a hydrophobic surface (or polymer, such as Teflon FEP) will rapidly absorb proteins due to hydrophobic interactions with proteins; however, there is the potential to selectively bind proteins that have antithrombogenic properties (such as albumin) [20]. The 'biological' approach entails coating the surface of the PICC with a particular protein that may reduce thrombosis (e.g., albumin) and reduce the nonspecific protein absorption that happens on a synthetic surface. Finally, use of drugs (e.g., chlorhexidine) on polyurethane surfaces has been shown to reduce thrombosis in an animal model and is another strategy to help prevent PICC complications [21].

These strategies, by no means, are all encompassing. Other approaches being studied include zwitterionic materials, pyrolytic carbon, heparin, slippery liquid-infused porous surfaces, and micropatterning [22]. Yet, despite the wealth of active interest and research in this area, there is a scarcity of new devices on the market. The gap between interests and device availability is likely explained by the extremely high costs associated with bringing a new device to market. As well, many of the coating, drug, or biological approaches offer what appear to be only incremental improvements on existing products. Justifying the investment in developing and bringing these devices to market can thus be difficult for most companies.

One example of a device that is relatively new to the market is HydroPICC™ (Access Vascular; Bedford), a PICC intended for long-term use. HydroPICC is an example of a hydrophilic coating approach using a polymer, in this case polyvinyl alcohol (PVA). Preclinical testing data from tests of the HydroPICC properties were sourced from one patent application [23]. Details contained within this application indicate

that heparinized bovine blood was pumped through an *in vitro* flow loop (200 mL/min in a 0.35-in diameter PVC tube) and heated to 98°F for 120 min. Devices within the flow loop were assessed after 45 and 120 min for thrombus accumulation. Radiolabeled platelets were included in the circulating blood and the platelets adhered to the device were quantified by gamma counting. Percent platelet adherence was calculated relative to the average total adherence observed across all test conditions (so that data are expressed for each device type relative to the average result). The results showed fewer platelet accumulation for the PVA HydroPICC compared to a commercially available polyurethane PICC, although this was a relative and not absolute measure. It remains unclear why the authors did not quantify absolute platelet adhesion in each condition, and is perhaps related to limitations of this method. It should be noted that the parameter reported was specific to platelet adhesion, not thrombus formation, as indicated in the source. Thus, the clinical relevance of this *in vitro* finding is not clear. An important limitation of this study was the inclusion of heparinized blood within the circulation loop which would inhibit coagulation; therefore, the results are not generalizable to the *in vivo* situation, except, perhaps in heparinized patients. As so further laboratory studies could be found for evaluation, the overall confidence in the manufacturer's claim – at this stage – is low.

While the most common approaches to creating antithrombogenic surfaces overwhelmingly use coating techniques, the BioFlo® PICC from AngioDynamics Inc. (Queensbury, NY) takes the approach of adding a small amount of polymer/macromolecule additive to polyurethane/carbothane® during the extrusion molding manufacturing process to add hydrophobic properties to the PICC [24]. The additive is a recently patented polymer called 'Endexo' which is a surface-modifying macromolecule consisting of a polyurethane molecular chain incorporating fluorine atoms at the chain ends [25]. Because Endexo consists of mostly polyurethane, it can be mixed with other polyurethanes used in catheter devices during the extrusion molding process without leading to phase separation of the Endexo and hence, homogeneous distribution of the Endexo throughout the catheter material is ensured. Fluorine-containing polymers are known to be surface active – meaning the hydrophobic fluorine-rich chain ends of Endexo will naturally migrate to any surface of the PICC, thereby creating a homogeneous hydrophobic surface. Importantly, the homogeneity in the Endexo distribution means it will be present in the surface of the polymer regardless of imperfections or defects in the catheter. This is an important distinction compared with surface modifications which are prone to gaps in the surface treatment due to processing, defects due to handling (e.g., flexing, especially during flushing) or degradation over time that can lead to non-specific protein adsorption and initiate the cascade of cellular responses cumulating in thrombosis. Since Endexo is an additive and not a surface coating it can easily be used in existing catheter manufacturing processes without any retooling of machinery or additional process steps making it an easily implemented technology.

In comparison to the HydroPICC, the BioFlo® PICC has a hydrophobic surface, which is expected to repel water, blood plasma, and formed elements [24,26]. However, this property is likely to encourage protein deposition and retention due to hydrophobic interactions. The antithrombogenic mechanism is presumably similar to that of other hydrophobic surfaces, whereby the retention of albumin is favored over thrombogenic proteins (e.g., fibrinogen, fibronectin, and vitronectin). This coating of albumin can allow the surface to exhibit antithrombogenic properties. While comparatively more preclinical data have been used to support BioFlo PICC claims, none of these data have been published in peer-reviewed journals. Unverified claims include experiments utilizing an *ex vivo* flow loop and *in vivo* experiments in sheep and rabbits [26]. Similar to previous manufacturers, BioFlo PICCs were suspended in bovine blood, within a flow loop for a period of PICC hours, which was maintained at physiological temperature. The adherence of radiolabelled platelets were assessed on the surface of various PICCs as a surrogate marker of thrombogenicity, with a claim of substantially reduced platelet adhesion, compared to competitor polyurethane PICCs. Subsequently, using an ovine model of bilateral PICC placement, BioFlo and comparator heparin-coated polyurethane devices were inserted, and the external catheter investigated after 14 and 31 days at necropsy. Observation suggested similar resistance to thrombosis, in comparison to the heparin-coated device. BioFlo and polyurethane PICCs were then placed in the jugular veins of rabbits, to assess immuno-compatibility. Complement, fibrinogen, activated thromboplastin time, and total protein were assessed. No differences in any of these parameters were determined after 14 or 31 days between animals with different PICCs. Although these data are suggestive of general biocompatibility (e.g., in terms of no impact on coagulation), limited assessment of complement activation does not adequately allow for a conclusion that the device has no effect on immune function/activation [26]. Given the substantial amount of time since this device/formulation came to market, it remains unclear why these findings have not been published. The lack of peer-reviewed data and detailed methods provided in marketing materials results in the overall confidence of the manufacturers claim being low.

Ultimately, peer-review and publication of laboratory-based investigations, which are then used to market devices, are critical to ensure that appropriate experimental design, experimental conduct and data reporting/statistical analysis is performed. Such reporting would also allow for claims to be independently verified. The absence of detailed published works, unfortunately only casts doubt upon manufacturers' claims and does not allow for a sound rationale for clinical trials to be established. Manufacturers must consider sharing nonproprietary data in order to better evaluate the promise of this strategy.

2.2. Cost-effectiveness

An estimation of the cost-effectiveness of antithrombotic PICCs is not yet available. Each antithrombotic PICC is associated with increased direct purchasing costs, in comparison to polyurethane PICCs [27,28]. In order to reach cost-effectiveness, antithrombotic PICCs need to demonstrate a reduction in PICC-associated occlusion and thrombosis, and

the costs associated with its sequelae of these events (such as premature catheter removal, replacement of a device, treatment costs related to complications). Multiple authors and studies have highlighted the significant costs associated with PICC-associated thrombosis [14,29,30], including treatment delays, increased length of stay, and thrombosis intervention. Australian [31] and US [18] studies have found the attributable increase in length of hospitalization to be ~4–5 days and the attributable cost to be US$12,317–15,973. Thus, antithrombotic PICC manufacturers must provide convincing economic data to suggest that use of their devices is not only better for patient outcomes, but also economically. To date, no such data are available.

3. Clinical profile and post-marketing findings

3.1. Phase I, II, and III data

3.1.1. Systematic identification of clinical literature

A systematic search of published literature was undertaken across Ovid MEDLINE (1950–August 2018), Ovid EMBASE (1980–August 2018); EBSCOhost CINAHL (1982–August 2018), and Cochrane Central Register of Controlled Trials (August 2018 issue).

Medical Subject Headings (MeSH) were developed in collaboration with a health-care librarian and were 'Catheterization, Peripheral', with additional search terms of "(catheter near impregnat*); (catheter* near coat*); (catheter* near bond*); and (anti thrombogenic). Searches were performed without year restrictions and not limited to human studies. Gray literature was identified through contact with product manufacturers.

Through independent searching, four published studies were identified; however, one study was later excluded as the trial evaluated an older version PICC, without antithrombogenic materials incorporated [32]. Additional information and studies (n = 3) were provided by product manufacturers. These studies are summarized in Table 1 [4,27,28,33–35].

To date, all published clinical studies have evaluated the efficacy of the BioFlo® antithrombogenic PICC (AngioDynamics Inc.), in comparison to traditional polyurethane PICCs, to reduce PICC-associated thrombosis, promote PICC function and assess patient safety. The safety of the BioFlo PICC, including mortality, has been demonstrated in all clinical trials. A recent Australian pediatric, pilot RCT [28] (n = 150) comparing BioFlo with a standard polyurethane PICC (Cook™ [Cook Medical]) demonstrated a nonsignificant reduction in PICC-associated venous thrombosis (BioFlo 3% [2/72] vs. Cook 8% [5/74]), and PICC failure (BioFlo 11% [8/72] vs. Cook 22% [16/74]. An unpublished, unfunded, quasi-experimental Canadian clinical evaluation of the BioFlo PICC reported a 60% reduction in occlusion and PICC-associated thrombosis (n = 193), in comparison to a plain polyurethane power-injectable PICC [33]. Another Canadian retrospective cohort study [4] reported a low proportion of PICC-associated thrombosis (2.1%) and occlusion requiring thrombolytic therapy (11.4%). Other clinical evaluations in the United Kingdom [34,35] found similar results.

Comparatively, a retrospective cohort study found no significant difference in the need for thrombolysis (i.e., alteplase administration) in BioFlo PICCs, when compared with polyurethane PowerPICCs® (Bard, Murray Hill, NJ) [27]. Overall, while the product and technology show promise, high quality, adequate statistically powered research evaluating BioFlo PICCs to reduce thrombotic complications associated with PICCs has not yet been undertaken.

4. Alternative

Alternative catheter materials have been developed for use in PICCs and other types of vascular access devices, and are currently being clinically used in an attempt to prevent catheter-associated thrombosis and other forms of catheter complication, including infection and occlusion. Heparin coating and impregnation has been trialled in other forms of CVCs, most commonly in the intensive care setting. A Cochrane Review [36] involving pediatric patients concluded that there was no difference in the risk of catheter-related thrombosis when comparing heparin-bonded to nonbonded catheters (low quality evidence, two studies, n = 287, risk ratio [RiR] 0.34, 95% confidence interval [CI] 0.01–7.68). Since then a large, multisite three-arm RCT [37] evaluated the efficacy of heparin-coated and antibiotic-impregnated catheters in the same pediatric population and catheter types. With 1485 children recruited, the study concluded there was no effect of impregnated (antibiotic or heparin) catheters compared with standard CVCs (hazard ratio [HR] for time to bloodstream infection 0.71, 95% CI 0.37–1.34). However, secondary analyses showed that antibiotic CVCs were better than standard CVCs (HR 0.43, 95% CI 0.20–0.96) and heparin CVCs (HR 0.42, 95% CI 0.19–0.93), but heparin did not differ from standard CVCs (HR 1.04, 95% CI 0.53–2.03). A reduction in catheter-associated thrombosis between heparin-coated catheters and other catheter types was not observed (HR 0.88; 95% CI 0.68–1.14).

Antibiotic (e.g., minocycline–rifampicin) and antiseptic (e.g., chlorhexidine–silver sulphadiazine) catheter impregnation has been well studied in other (non-PICC) catheter types, with a recent Cochrane Review [38] concluding there was high quality evidence that antimicrobial (non-PICC) catheters significantly reduced catheter-associated bloodstream infection risk (RR 0.62; 95% CI 0.52–0.74, n = 10,405, 42 RCTs). These catheters are now often used in intensive care settings to prevent significant harm in this vulnerable group. Similarly, antimicrobial PICC coatings have been developed aiming to reduce catheter-associated bloodstream infections, including PICCs impregnated with chlorhexidine gluconate (CHG), a cationic biguanide that provides rapid antisepsis because of its broad spectrum of germicidal activity against most catheter-associated bloodstream infection-causing pathogens [39]. However, the weight of evidence to support the use of CHG in PICCs is minimal, as the population requiring PICCs, in comparison to other catheters, and the clinical settings of use, differ significantly. For example, in a systematic review [19], CHG and minocycline–rifampin-coated PICCs were associated with a reduction in bloodstream infection compared to non-coated catheters (relative risk [ReR], 0.29; 95% CI, 0.10–0.78). However, most studies included were conducted in trauma and burn intensive care units, where the risk of infection is substantially elevated.

Table 1. Summary of studies evaluating antithrombogenic PICCs.

Author (year)	Reference	Method	Population	PICCs tested	Results: thrombosis	Results: other complications
Kleidon, Ullman (2018)	[28]	Pilot, randomized controlled trial	Hospitalized pediatric patients (n = 150)	(1) Cook™; polyurethane power-injectable (Cook Medical, Bloomington, IN); with clamp (2) BioFlo®; antithrombogenic polyurethane, power-injectable (AngioDynamics Inc., Queensbury, NY) with proximal valve	PICC-associated venous thrombosis: (1) 5/74 (7%) (2) 2/72 (3%)	PICC failure: (catheter-associated bloodstream infection, local infection, venous thrombosis, occlusion, PICC fracture or PICC dislodgement at PICC removal): (1) 16/74 (22%) (2) 8/72 (11%) PICC complications during treatment (1) 25/74 (34%) (2) 11/72 (15%)
McDiarmid, Scrivens (2017)	[4]	Retrospective cohort	Outpatient-managed adults (n = 656)	(1) BioFlo®; antithrombogenic polyurethane, power-injectable (AngioDynamics Inc., Queensbury) with proximal valve	PICC-associated venous thrombosis: (1) 14/656 (2.1%)	PICC occlusion requiring thrombolytic agent (1) 75/656 (11.4%)
Musial, Hamad (2016)	[27]	Retrospective cohort	Adult patients undergoing treatment for cancer (n = 299)	(1) Polyurethane PowerPICCs® (Bard, Murray Hill, NJ) with clamp (2) BioFlo PICC®; antithrombogenic polyurethane, power-injectable (Interface Biologics Inc, Toronto ON/AngioDynamics Inc., Queensbury with clamp	N/A	PICC occlusion requiring thrombolytic agent (1) 71/157 (45.2%) (2) 54/145 (37.2%)
Hill (2017)	[33]	Quasi-experimental, clinical evaluation	Hospitalized adult patients (n = 183)	(1) Power PICC Solo 2®; polyurethane power-injectable; (Bard, Murray Hill); with proximal valve (2) BioFlo®; antithrombogenic polyurethane, power-injectable (AngioDynamics Inc., Queensbury) with proximal valve	PICC-associated venous thrombosis: (1) 5/60 (8.3%) (2) 2/133 (1.5%)	PICC occlusion (complete and partial) (1) 53/60 (88%) (2) 37/133 (28%)
Pain (2018)	[34]	Retrospective cohort	Not described (n = 852)	(1) "Non-valved PICCs": brand and type not reported (2) BioFlo®; antithrombogenic polyurethane, power-injectable (AngioDynamics Inc., Queensbury) with proximal valve	PICC-associated venous thrombosis: (1) 3/286 (1.0%) (2) 2/566 (0.3%)	PICC occlusion: (1) 75/286 (26.2%) (2) 15/566 (2.6%)
Simcock (2018)	[35]	Quasi-experimental, clinical evaluation	Patients with sarcoma (n = undisclosed) with retrospective control	(1) Xcela ® PICC (AngioDynamics Inc., Queensbury) (2) BioFlo®; antithrombogenic polyurethane, power-injectable (AngioDynamics Inc., Queensbury) with proximal valve	PICC-associated venous thrombosis: (1) 13% (2) 6%	

PICC = peripherally inserted central catheter.

Manufacturer funded, laboratory studies also suggest CHG coating has a role in the prevention of thrombosis development, with *in vivo* ovine models with CHG catheters demonstrating a significant reduction in fibrin sheath development after 30 days *in situ*, in comparison to uncoated catheters (median 0.05 g [CHG] vs. 0.7 g [uncoated] [40]). The potential benefit of CHG coating on PICC surfaces has to also be balanced against the possibility of selecting for CHG resistance in common colonizing organisms such as *Staphylococcus aureus*. CHG is frequently used for skin decontamination prior to sterile surgical procedures and for decolonization of patients with recurrent methicillin-resistant *S. aureus* skin infections [41]. Furthermore, genes which encode CHG resistance may be colocated on mobile genetic elements (such as plasmids or transposons) with other multidrug resistance determinants in gram-positive and gram-negative bacteria [42]. This raises the possibility that exposure to CHG may inadvertently select other resistance determinants and compromise antibiotic therapy for nosocomial pathogens.

5. How the technology fits into the field of medical devices

5.1. Device status

Antithrombogenic PICCs are an emerging technology, with device approval variable between manufacturer and product. The BioFlo® PICC, by AngioDynamics Inc., is indicated for short- or long-term peripheral access to the central venous system for intravenous therapy, including but not limited to the administration of fluids, medications and nutrients; the sampling of blood; and for power injection of contrast media. The non-valved PICCs are also indicated for central venous pressure monitoring. They are registered in the US, Europe, Australia, New Zealand, Canada, and Brazil. The HydroPICC® by Access Vascular has the same indications for use, but currently has approval only in the US. Other applications of these antithrombogenic material technologies may be under development.

5.2. Conclusion

PICCs are a common medical device and an important component of modern health care, but complications are rife. Almost all synthetic materials when placed in the presence of serum will absorb a multitude of different proteins to the surface within less than a second. These absorbed proteins then set off a cascade of events including thrombus deposition, embolization, and thrombotic occlusion. As demonstrated in other vascular access catheters, innovations in PICC materials, including the development of antithrombogenic materials, are an opportunity to reduce this preventable harm to patients, and improve efficiencies in health care. However, thrombosis is a natural injury response that prevents bleeding, bacterial ingress and helps to encourage wound healing. If there is reduced thrombosis at the site of insertion, it is possible that this may result in an increased risk of bleeding into the tissue and extravasation.

This technology is novel and potentially lifesaving, and early trials have indicated safety. However independent, sufficiently powered RCTs are necessary to ascertain efficacy. Adoption of new technologies without evidence, including economic, may increase expenditure without increased value, or cause unintended adverse events. At present, practitioners and policy makers face PICC decision-making in an evidence vacuum.

6. Expert commentary

With around 30% of PICCs developing serious complications, there is little doubt that improvements in technologies are needed, especially for high risk patients [43]. Patients with PICCs need these devices to dwell for extended periods, in both hospital and outpatient settings, necessitating an optimal material that can reside within, and interact with, the blood vessel while causing minimal undesirable side effects. Just as antimicrobial catheters provided an option to reduce infection risk [19], the emergence of antithrombogenic PICCs offers promise to now significantly reduce thrombosis and occlusion. From a scientific view point, it appears biologically plausible that this benefit could be realized, but there is little human data as yet to be convincing.

An important barrier to uptake of such new devices is lack of persuasive data from well-designed observational studies or large randomized clinical trials. For antithrombogenic PICCs, some smaller trials have been completed, but all have tested one product type. Although, substantial research and development funds are invested by private companies in the premarket development of new products, once regulatory approval is attained, the investment generally switches focus to marketing and sales. At first glance this appears logical, given regulatory bodies in the USA and EU do not require evidence of efficacy for registration for class II devices, which include PICCs [44]. This is in contrast to pharmaceuticals which require human clinical trial data for registration. However, given the known lag time of health sciences from innovation to consistent adoption is typically 17 years [45], and the current evidence-based health-care paradigm, early and convincing published RCTs could assure efficacy which would speed adoption. In addition, as new devices are typically more expensive than older products, clinical trial data are needed to demonstrate cost-effectiveness, which would further convince health-care institutions to invest in new products.

PICCs are an important part of the overall vascular access market which was globally valued at $4 billion in 2017 and the market for PICCs continues to grow [46]. There is likely a place for antithrombogenic PICCs in many patients; however, health-care institutions may not find an impetus to move toward these devices if they remain unaware of the high rate of complications associated with PICCs they currently use. In some notable exceptions, health institutions have developed their own PICC quality registry, regularly benchmarking of complication rates within and between facilities, and over time, in their own system have led to realization that innovation is needed [47]. Where established, these have been able to identify internal complication rates, as well assess the

success of changes in PICC types for example of reduced use of triple lumen devices, that was associated with reduced thrombosis rates [17]. External commercial registries are also available (cvadregistry.com).

The benefit promised by anti-thombogenic PICCs will need to withstand other factors that impact on thrombus development. Factors such as patient (e.g., prior thrombosis, cancer, critical illness), device (e.g., lumen number, tip location, catheter-to-vessel ratio), and provider (e.g., inserter experience, number of attempts) all contribute to the development of PICC-associated thrombosis [3,14]. Starting with insertion, variability in inserter technique and competence using the steel needle introducer can mean more or less vessel damage may occur at the outset. This is in addition to patients who may already be coagulopathic or with existing vessel frailty or damage. If the distal catheter tip is positioned outside of the distal superior vena cava or cavoatrial junction, there is a further increased risk for thrombosis [48]. During the weeks or months of dwell ahead, factors such as the catheter/vessel ratio, and the activity level of the patient will subject the vessel wall to repeated and ongoing physical contact with the catheter. It remains to be seen whether PICC material advancements can withstand these important sources of thrombus development. Finally, it may be that not all thrombus associated with PICCs is unwanted. The role of non-symptomatic thrombosis remains unclear clinically, and this may even have some protective effect against other unwanted adverse events, such as vessel wall rupture or insertion site irritation.

7. Five-year view

A thorough, high quality clinical evaluation of antithrombogenic catheter materials to prevent PICC-associated harm, including thrombosis, is necessary, prior to wider application of this emerging technology. Once efficacy is understood, then a clearer picture of the role and cost-effectiveness of antithrombogenic catheter materials in health services will be available. If antithrombogenic PICCs are effective, there are many potential applications of antithrombogenic materials to other thrombosis-prone medical devices, including renal dialysis catheters and tubing, and peripheral vascular access devices. This is likely to make a significant impact on health service provision, resulting in a reduction in treatment delays and costs.

Lacking from the current antithrombogenic material technology is the incorporation of an antimicrobial element within the material. While the prevention of thrombotic accumulation and development on catheters is clinically important, due to the severity of sequelae associated with bloodstream infection, many clinicians will elect to prioritize an antimicrobial PICC or other vascular access catheter. A dual-action material, effective at preventing both thrombosis and infection development, would be of considerable value.

The role of PICCs in health care is changing. Over the next 5 years, we are likely to see a maturing in the use of PICCs, to incorporate the change in patient illness severity, chronic morbidities, and inpatient vs. outpatient model of services. The availability of catheter materials that improves reliability of these devices, and the prevention of patient harm, is essential.

Key issues

- PICCs play an important role in health-care provision; however, thrombotic and infective complications are common, especially in patients with hematological and oncological conditions.
- Previous PICC evolutions in PICC materials, from silicone to types of polyurethane, have demonstrated reductions in procedural complications and vessel irritation.
- Antithrombogenic PICC materials to prevent thrombotic development and attachment show promise in industry-sponsored laboratory studies and small clinical trials and evaluations.
- Further post-market evaluation of these devices is necessary to ascertain efficacy and efficiency.

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Dr Ullman conceptualized and designed the study, drafted the initial manuscript, and approved the final manuscript as submitted. Drs Bulmer, Dargaville, Rickard, and Chopra contributed to the writing of the review and reviewed content prior to submission. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Declaration of interest

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