



Resuscitative endovascular balloon occlusion of the aorta: promise, practice, and progress?

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Purpose of review

Resuscitative endovascular balloon occlusion of the aorta (REBOA) is a minimally invasive damage control procedure for life-threatening abdominal or pelvic haemorrhage. The purpose of this review is to summarize the current understanding and experience with REBOA, outline potential future applications of this technology, and highlight priority areas for further research.

Recent findings

REBOA is a feasible method of achieving temporary aortic occlusion and can be performed rapidly, with a high degree of success, in the emergency setting (including at the scene of injury) by appropriately trained clinicians. The procedure supports central perfusion, controls noncompressible haemorrhage, and may improve survival in certain profoundly shocked patient groups; but is also associated with significant risks, including ischaemic tissue damage and procedural complications. Evolutions of this strategy are being explored, with promising proof-of-concept studies in the fields of partial aortic occlusion and the combination of REBOA with extracorporeal support.

Summary

Noncompressible torso haemorrhage is the leading cause of preventable trauma deaths. The majority of these deaths occur soon after injury, often before any opportunity for definitive haemorrhage control. For a meaningful reduction in trauma mortality, novel methods of rapid haemorrhage control are required.

Keywords

bleeding, haemorrhage, resuscitation, resuscitative endovascular balloon occlusion of the aorta, trauma

INTRODUCTION

Injury is a global public health problem, responsible for one in 10 deaths, and the leading cause of life years lost [1,2]. One in three of these deaths is the direct result of uncontrolled bleeding [3]. In many cases, the injuries are repairable, and prompt haemorrhage control would have prevented death [3,4]. However, even in well-organized trauma systems, there is an inevitable delay between injury and the ability to stop bleeding. The majority of preventable deaths occur during this vulnerable period, often before the injured patient reaches a hospital, and before any opportunity for definitive surgical haemostasis [3,5,6^{*}]. There is therefore a pressing need for early interventions that can temporarily control bleeding until definitive haemostasis is achieved [6^{*},7].

This renewed understanding of the pivotal role of early haemorrhage control on outcome has driven recent advances in trauma resuscitation. Most notable are the advances that have been made in the treatment of extremity (compressible) haemorrhage [8]. Prior to definitive haemostasis,

temporary tourniquets and novel haemostatic dressings are simple and effective adjuncts to stop bleeding that cannot be controlled by direct pressure [9]. Trauma systems that prioritize early access to these interventions have all but eliminated deaths from extremity haemorrhage [4].

Uncontrolled (noncompressible) bleeding from injuries in the chest, abdomen, or pelvis is now the predominant cause of preventable deaths in mature trauma systems [4,10]. These injuries require surgery or angio-embolization, and as yet, there has been minimal progress developing temporizing

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KEY POINTS

- Exsanguinating haemorrhage is the leading cause of preventable death after injury, and current trauma resuscitation practice is often too slow to cope.
- To improve trauma outcomes, innovative methods of controlling exsanguinating haemorrhage soon after injury are needed.
- REBOA is a promising method of achieving rapid haemorrhage control and can be performed early, in the emergency setting.
- REBOA can cause harm, and the widespread use is restrained by limited evidence of benefit, unclear indications, inadequate technology, and difficulties training and maintaining procedural competence.

interventions that can prevent exsanguination before definitive haemostasis is achieved.

For a meaningful reduction in trauma mortality, novel methods of rapid haemorrhage control are required [3,6[†]]. Resuscitative endovascular balloon occlusion of the aorta (REBOA) is an endovascular damage control procedure that may have an important role in the temporary control of life-threatening noncompressible bleeding. This review will summarize the current understanding and experience with REBOA, and highlights priority areas for further research.

PROMISE

Temporary control of bleeding with proximal vascular occlusion is a fundamental principle of surgery and the key initial step in many damage control surgery interventions [11]. For noncompressible bleeding, proximal vascular control requires surgical exposure of the relevant blood vessels. This is the rate-limiting step that impedes effective resuscitation. REBOA offers a minimally invasive method of occluding the aorta proximal to an injury, potentially allowing effective resuscitation to be achieved before surgical intervention and definitive haemostasis is possible.

REBOA is not new. The technique was pioneered in the 1950s [12], during the Korean War, at a time when surgeons were first attempting vascular injury repair, and endovascular therapy was at its inception [13]. Although effective at restoring blood pressure and temporarily controlling exsanguinating haemorrhage, the intervention was not evaluated further and not adopted into routine trauma care. This was likely because of the lack of endovascular technology and infrastructure to support its use at

the time. By the Vietnam War, interest had shifted to Military Anti-Shock Trousers and emergency thoracotomy with direct aortic occlusion, as the preferred methods to rapidly control exsanguinating torso haemorrhage in the prehospital and in-hospital settings, respectively [14,15]. Neither were effective in patients with uncontrolled subdiaphragmatic haemorrhage, which led some investigators to reevaluate the role of REBOA as an adjunct to resuscitation [16,17]. Once again, these studies showed that REBOA was a feasible method of achieving aortic occlusion, restoring vital organ perfusion, and controlling exsanguinating haemorrhage. Approximately one quarter of moribund patients resuscitated using REBOA in these historic studies survived (Table 1). Nonetheless, thoracotomy remained the preferred method to achieve proximal aortic control in exsanguinating patients with circulatory collapse [18].

The past two decades have seen major advances in endovascular technology. Balloon occlusion is now an established endovascular haemorrhage control technique and an important component of the effective management of other causes of life-threatening, noncompressible haemorrhage, such as ruptured abdominal aortic aneurysms [19].

This improved technology, together with the recent burden of potentially preventable military deaths from noncompressible haemorrhage, has once again renewed interest in the role of REBOA for trauma resuscitation [20]. Over the past few years, the US Army Institute for Surgical Research has produced a considerable body of translational research into the role of REBOA as an adjunct to damage control resuscitation. Using large animal models, they have demonstrated that REBOA is a feasible method of achieving proximal aortic occlusion, resulting in significantly improved central perfusion, and effectively controlling distal haemorrhage, in otherwise lethal haemorrhagic shock [21–25]. In addition, they have shown that REBOA is at least as effective as thoracotomy with direct aortic occlusion at supporting central perfusion during severe shock, but with significantly less physiological disturbance [21]. Animal studies also suggest that REBOA may significantly improve survival from uncontrolled haemorrhage [26,27] and that the procedure can be accurately performed in the emergency setting, without the need for fluoroscopic guidance [24–26].

Recent clinical studies corroborate these translational research findings. Only a few, small, civilian observational studies have been published (Table 1), but these studies affirm that REBOA is a feasible method of achieving aortic occlusion in the emergency setting, and suggest it can be performed with a

Table 1. Clinical observational studies describing survival after resuscitative endovascular balloon occlusion of the aorta for trauma

Author	REBOA indication	Overall			Zone I			Zone III		
		n	S	%	n	S	%	n	S	%
Historic observational studies										
Hughes (1954)	Abdominal haemorrhage with PEA despite massive blood transfusion	2	0	0	2	0	0	–	–	–
Low (1986)	Exsanguinating haemorrhage with refractory shock ^a	15	2	13.3	15	2	13.3	–	–	–
Gupta (1989)	Penetrating abdominal injury with refractory shock ^a	21	7	33.3	21	7	33.3	–	–	–
Total:		38	9	23.7	38	9	23.7	–	–	–
Contemporary observational studies										
Martinelli (2010)	Pelvic haemorrhage with refractory shock ^a	13	6	46.2	–	–	–	13	6	46.2
Brenner (2013)	Abdominal/pelvic haemorrhage with refractory shock ^a	6	4	66.6	4	3	75.0	2	1	50.0
Ogura (2015)	Abdominal solid organ injury with haemodynamic instability ^b	7	6	85.7	7	6	85.7	–	–	–
Moore (2015)	Noncompressible torso haemorrhage with refractory shock ^a	24	9	37.5	19	6	31.6	5	3	60.0
Saito (2015)	Abdominal/pelvic haemorrhage with refractory shock ^a	24	7	29.2	24	7	29.2	–	–	–
Irahara (2015)	Abdominal/pelvic haemorrhage with shock (SBP<90 mmHg or SI>1.0)	14	5	35.7	–	–	–	–	–	–
Tsurukiri (2016)	Haemorrhagic shock (SBP<90 mmHg or SI>1.0)	16	6	37.5	12	3	25.0	4	3	75.0
DuBose (2016)	Unclear	46	13	28.3	–	–	–	–	–	–
Teeter (2016)	Unclear	33	14	42.4	33	14	42.4	–	–	–
Total:		183	70	38.3	99	39	39.4	24	13	54.2
Trauma registry studies										
Norii (2015) ^c	Unclear	452	109	24.1	–	–	–	–	–	–
Inoue (2016) ^c	Unclear	625	239	38.2	–	–	–	–	–	–

n, sample size; PEA, pulseless electrical activity; REBOA, resuscitative endovascular balloon occlusion of the aorta; S, survival; SBP, systolic blood pressure; SI, shock index.

^aHaemorrhagic shock unresponsive to standard trauma resuscitation with impending cardiac arrest.

^bUndefined.

^cThe study population described by Inoue *et al.* is from the same trauma registry and includes all REBOA cases from the Norii *et al.* study.

high degree of success by nonexpert interventionists [28,29[■],30,31,32[■]]. In addition, it seems that the procedural time to achieve aortic occlusion is comparable with thoracotomy [33,34[■]] and REBOA may enable earlier aortic occlusion, possibly even at the scene of injury [30,33].

These clinical studies consistently demonstrate significant improvements in central perfusion in patients with life-threatening haemorrhagic shock [28,30,31,32[■],34[■],35[■],36], and although not directly comparable, there is a marked difference in the observed survival of moribund patients with subdiaphragmatic exsanguination when REBOA is used for temporary haemorrhage control (38%, Table 1) compared with when thoracotomy with direct aortic occlusion is used (< 10%) [29[■],37[■],38[■]].

Certain injury characteristics seem to be associated with better outcomes. For example, for a similar degree of haemorrhagic shock, survival seems better in patients with pelvic haemorrhage amenable to zone III REBOA compared with bleeding necessitating zone I REBOA (Table 1), and also following penetrating trauma as compared with blunt [34[■]].

Overall, REBOA appears to be a potential alternative to direct aortic occlusion in exsanguinating patients and offers a number of theoretical advantages. In addition to being less invasive, REBOA may allow rapid and earlier control of non-compressible abdominal and pelvic haemorrhage, avoid morbidity associated with more invasive damage control surgery procedures (e.g., resuscitative thoracotomy and preperitoneal pelvic packing),

decrease blood loss and blood transfusion requirements, minimize hypothermia, and improve survival following particular injury patterns [39,40].

PRACTICE

Despite its promise, only a few enthusiast centres worldwide have implemented REBOA into clinical practice. The possible reasons are worth considering. First, REBOA has not yet been systematically evaluated, and there is a lack of high-quality evidence to support its widespread use. Indications as to which patient groups are likely to benefit, or come to harm, are unclear [41[■],42]. Although many clinicians may appreciate the potential benefit, they may have justifiable uncertainty in implementing the procedure prematurely [41[■]]. Second, although REBOA may temporarily control bleeding, this comes at the expense of distal ischaemia, an additional time-critical problem [43[■]]. Hospitals that do not have established trauma systems that ensure rapid access to definitive haemorrhage control, and thus timely balloon deflation, are likely to be reluctant to implement REBOA because of the risks of iatrogenic harm. Conversely, mature trauma centres, with prompt access to definitive haemorrhage control, may argue that there is little need for REBOA in these systems. Third, the lack of bespoke REBOA equipment makes the procedure unnecessarily complex, and potentially increases risk [24,32[■]]. These constraints are also likely to have influenced uptake. Finally, few centres will have clinicians experienced with REBOA, and the procedure is required relatively infrequently [44–46]. For example, it is estimated that around 200 patients per year ($\approx 0.5\%$ of all moderate to major injuries) in England and Wales may benefit from REBOA, with the busiest Major Trauma Centres predicted to see only 16 of these patients per year [44]. This poses a tremendous challenge to train REBOA operators, maintain procedural competence, and integrate the procedure into standard trauma resuscitation protocols. Despite this, some institutions have established effective training and quality assurance programmes [47,48].

Although the exact population that may benefit from REBOA is not yet clearly defined, recent clinical experience suggests that patients with blunt or penetrating injuries to the abdomen or pelvis and haemorrhagic shock with imminent circulatory collapse that is unresponsive to standard trauma resuscitation are most likely to benefit from REBOA [28,29[■],30,36]. Patients with a thoracic source of bleeding are unlikely to benefit, indeed REBOA may be harmful in these situations as it may exacerbate bleeding [41[■],46]. Direct haemorrhage control

Table 2. Procedural steps involved in resuscitative endovascular balloon occlusion of the aorta. Adapted from Stannard *et al.* With permission from [20]

Step	Description
1.	Arterial access
2.	Balloon positioning
3.	Balloon inflation
4.	Balloon deflation
5.	Sheath removal

via thoracotomy may be a more appropriate immediate intervention in these cases [41[■]]. REBOA's role in the management of traumatic (hypovolaemic) cardiac arrest is unclear. Until more robust evidence is available, patient selection will require astute clinical judgement along with an individualized risk: benefit assessment. In addition, outcomes should be carefully reviewed to inform best practice.

REBOA involves five distinct steps (Table 2) [20]. Although the procedure may appear straightforward – using a Seldinger technique, a compliant balloon catheter is inserted into the aorta via the common femoral artery (CFA) and inflated – the first step (CFA access) can be technically challenging in the profoundly shocked patient. This step, which can be performed percutaneously (under ultrasound guidance) or surgically via a femoral cut-down, is key to REBOA and often responsible for the majority of procedural time [6[■],18]. Apart from the degree of shock, a number of additional factors are also likely to influence the difficulty and duration of this step. These include the method used (percutaneous or open), operator experience, and patient factors such as age, obesity, and arterial anatomy. Indeed, failed arterial access seems to be more common using a percutaneous technique, and in patients who are elderly, obese, or in cardiac arrest [16,31]. It is unclear how much time arterial access may require, but it is an important consideration, as prolonged attempts may delay definitive haemorrhage control and negate any potential benefit from the procedure.

Once arterial access is achieved, the remainder of the procedure is relatively straightforward and balloon occlusion can be accomplished within minutes [33,34[■],48]. Consequently, some experts suggest early placement of a femoral arterial line in haemodynamically unstable patients, as this not only enables pressure monitoring to guide decision-making, but also simplifies REBOA should patient deterioration occur at any stage prior to definitive haemostasis being achieved [49].

Accurate balloon positioning is essential to minimize complications. Two aortic zones are targeted for occlusion: zone I (above the coeliac artery but below the left subclavian artery) for an abdominal source of bleeding, and zone III (above the aortic bifurcation but below the abdominal visceral vessels) for isolated pelvic bleeding [20]. A number of methods for positioning a REBOA balloon in adults have been described. Real-time fluoroscopic guidance is definitive but not often practical in the emergency setting. Surface anatomy is more convenient, and may offer a sufficiently reliable method of estimating insertion depths with an adequate margin of safety [50]. The direct distance between the mid-sternum and femoral puncture site (2 cm below mid-inguinal point) is suggested for zone I REBOA [50], and the distance between the umbilicus and femoral puncture site is suggested for zone III REBOA [51]. Torso height (distance between the jugular notch and pubic symphysis) can also be used to reliably predict insertion depth for zones I and III REBOA [52]. An additional method for zone III REBOA, using predetermined insertion depths derived from computed tomographic morphometric data, involves inserting a low-surface-area balloon to a depth of

40 cm, then following inflation, allowing the balloon to migrate distally until it occludes the aortic bifurcation [53,54]. If immediately available, plain X-ray can be used to confirm approximate balloon positioning by comparing radio-opaque catheter markings with vertebral levels (zone I: T4–L1 and zone III: L2–L4) [34].

The primary limitation of REBOA is the distal ischaemia it produces, as this determines the duration that the aorta can be safely occluded [43]. Although a short duration of ischaemia is fully reversible, there is a threshold where permanent ischaemic damage will occur. Adverse effects include renal failure, liver failure, intestinal ischaemia, paraplegia from spinal cord ischaemia, limb ischaemia, multiorgan dysfunction, and death. There is a direct relationship between the duration of occlusion and the magnitude of ischaemia-related harm [55]. However, the maximum duration of safe occlusion is unclear, and will likely depend on the level occluded. Animal models suggest 60 min as a tolerable duration for zone I REBOA, with 90 min resulting in organ damage that was still survivable [23,24]. In human studies, there is a clear correlation between survival and short occlusion time (Table 3) with only two survivors with

Table 3. Duration of aortic occlusion in survivors and nonsurvivors treated with resuscitative endovascular balloon occlusion of the aorta

Author	N	Duration of occlusion (minutes)		P-value
		Survivors	Nonsurvivors	
Historic observational studies				
Hughes (1954)	2	–	Not reported	–
Low (1986)	15	30	Not reported	–
Gupta (1989)	21	Not reported	Not reported	–
Contemporary observational studies				
Martinelli (2010)	13	46 (Range: 30–70)	91 (Range: 45–135)	0.026
Brenner (2013)	6	39 (Range: 12–70)	51 (Range: 36–65)	0.67
Ogura (2015)	7	80 (Range: 33–150)	No deflation	–
Moore (2015)	24	Not reported	Not reported	–
Saito (2015)	24	21 (Range: 13–26)	35 (Range: 28–35)	0.05
Irahara (2015)	14	46 (SE: 15)	224 (SE: 52)	0.002
Tsurukiri (2016)	16	55 (Range: 40–70)	93 (Range: 57–135)	0.02
DuBose (2016)	46	20 ^b	20 ^b	–
Teeter (2016)	33	49 (Range: 28–92) ^a	80 (Range: 42–114)	0.23
Trauma registry studies				
Norii (2015) ^c	452	Not reported	Not reported	–
Inoue (2016) ^c	625	Not reported	Not reported	–

n, sample size; SE, standard error.

^aIncludes period of partial REBOA.

^bDuration of occlusion for survivors and nonsurvivors.

^cThe study population described by Inoue *et al.* is from the same trauma registry and includes all REBOA cases from the Norii *et al.* study.

Table 4. Morbidity and mortality reported in observational studies of resuscitative endovascular balloon occlusion of the aorta for trauma

Author	n	Mortality	REBOA-related complications	
			Ischaemia/reperfusion	Procedural
Historic observational studies				
Hughes (1954)	2	2	–	–
Low (1986)	15	13	MOF (1)	Failed arterial access (6)
Gupta (1989)	21	14	MOF (1)	Femoral artery thrombosis (1)
Contemporary observational studies				
Martinelli (2010)	13	7	None	Femoral artery thrombosis (1)
Brenner (2013)	6	2	None	None
Ogura (2015)	7	1	None	None
Moore (2015)	24	15	None	None
Saito (2015)	24	17	AKI (6); MOF (9); limb ischaemia (2)	Vascular injury (1)
Irahara (2015)	14	9	Not reported	Not reported
Tsurukiri (2016)	16	10	ARDS (1)	Failed arterial access (3)
DuBose (2016)	46	33	AKI (2); MOF (2)	Pseudoaneurysm (1); Distal embolism (2)
Teeter (2016)	33	19	None	None
Trauma registry studies				
Norii (2015) ^a	452	343	Not reported	Not reported
Inoue (2016) ^a	625	386	Not reported	Not reported

AKI, acute kidney injury; ARDS, acute respiratory distress syndrome; MOF, multiple organ failure; n, sample size; REBOA, resuscitative endovascular balloon occlusion of the aorta.

^aThe study population described by Inoue *et al.* is from the same trauma registry and includes all REBOA cases from the Norii *et al.* study.

occlusion times over 90 min described [40]. It is therefore imperative that once a REBOA balloon is inflated, the overriding goal should be rapid haemorrhage control and balloon deflation [36].

Balloon deflation can cause **profound haemodynamic instability**, secondary to a combination of sudden afterload reduction, hypovolaemia, ischaemia-reperfusion injury, hyperkalaemia, hypocalcaemia, and acidaemia [20,43[■]]. These sequelae should be anticipated and prepared for, prior to coordinated balloon deflation.

In addition to ischaemic morbidity, a number of procedure-related complications have also been described (Table 4). These include **femoral artery thrombosis**, distal **emboli**, iatrogenic vascular injury, **pseudoaneurysm**, limb amputation, and balloon rupture [34[■],42]. Many of these complications are related to arterial access and may be **more common** following insertion of the **large femoral sheaths** that are required for **current REBOA catheters** [32[■]].

Practical application of REBOA is constrained by the short duration that the aorta can be safely occluded. Currently, a few specialist trauma centres use REBOA to prevent exsanguination during

damage control procedures and inherent treatment delays, such as procedural preparation and transfers between hospital locations (e.g., emergency department, operating room, and interventional radiology suite) [28,29[■],34[■],36,45]. REBOA has also been used within a well-developed urban trauma system to prevent exsanguination during transfer from the scene of injury to a specialist trauma centre [53[■]]. More widespread use in less well-organized trauma systems, more rural prehospital systems, or to facilitate secondary transfers to specialist trauma centres may not be possible within the time constraints of the current technique and therefore risk significant harm [56]. But modifications of this technique may expand the role of REBOA in the future [57[■]].

Internationally, there is variability in which group of clinicians performs the procedure and no clear guidance, or evidence, as to who is best placed to deliver this resuscitation strategy. Ultimately, competent clinicians who are immediately available are required. The most appropriate clinician may therefore depend on the configuration of the individual trauma system or institution.

Introducing a procedure like REBOA therefore requires a robust clinical governance structure,

supported by all related specialities (emergency medicine, trauma and vascular surgery, anaesthesia, interventional radiology, and intensive care medicine), to ensure safe, effective implementation and quality control. Established, efficient, and rehearsed systems with clear protocols are necessary to minimize occlusion times and the risk of iatrogenic harm. Although REBOA offers potential as a temporizing haemorrhage control intervention, it is important to note that it is not a substitute for, but rather an adjunct to, excellent trauma resuscitation and definitive haemostasis.

PROGRESS

A bespoke 7Fr REBOA catheter for zones I and III aortic occlusion was launched in 2016 [24]. This catheter may simplify REBOA and reduce the risk associated with larger sheaths [24,32[■]]. In addition, the catheter allows invasive blood pressure monitoring to guide management.

Partial REBOA (P-REBOA), a technique that allows titrated and controlled blood flow distal to the site of occlusion, is an emerging strategy that aims to prolong the safe duration of aortic occlusion by limiting distal ischaemia, while still maintaining the afterload augmentation and haemorrhage control benefits of complete REBOA [57[■]]. This strategy may extend REBOA's utility, and appears to be feasible in animal models [27,58[■]]. Translational experience suggests that an initial period of complete REBOA, to allow resuscitation and clot stabilization, followed by P-REBOA and the reinstatement of low volume distal flow may be a practical approach [57[■],58[■]]. However, manual manipulation of balloon volume to targeted blood pressures is likely to be challenging, as even small changes in balloon diameter will result in large changes in flow past the balloon (Poiseuille's law) [43[■]]. Endovascular variable aortic control is being investigated as a means of achieving P-REBOA while using an automated device to control distal flow based on the patient's physiology [59].

REBOA may also be a stepping-stone to novel resuscitation strategies for traumatic cardiac arrest. Currently, injuries that result in hypovolaemic cardiac arrest have a dismal prognosis, and REBOA alone is unlikely to have any impact in this population [60]. Selective aortic arch perfusion (SAAP) aims to combine proximal REBOA with active perfusion of the aortic arch, allowing oxygenation of the brain and myocardium, thereby supporting a return of spontaneous circulation [61[■]]. The addition of central venous access may allow partial extra corporeal membrane oxygenation (ECMO) if required. In the future, it is likely that a paradigm of

resuscitation strategies stemming from femoral arterial access will become available. It can be envisaged that trauma teams could decide to perform, or progress in series, through femoral arterial access, REBOA, P-REBOA, SAAP, ECMO, and even emergency preservation resuscitation using deep hypothermic circulatory arrest, to create a window of opportunity for damage control surgery, prior to instituting cardiopulmonary bypass and rewarming [62]. Early access to these interventions will create considerable challenges for future trauma systems, especially if they are to be delivered in the prehospital setting, but the rewards may be substantial – improving the outcome of a major global disease.

CONCLUSION

With REBOA technology, awareness and demand growing, it is likely that the procedure will be implemented without formal evaluation, fulfilling 'Buxton's Law', where 'it is always too early [for rigorous evaluation] until, unfortunately, it's suddenly too late' [63]. Therefore, there is an urgent need for a formal evaluation of the safety, feasibility, effectiveness, and cost-effectiveness of REBOA. A multicentre randomized controlled trial is currently being designed in the United Kingdom, and a multicentre prospective observational study (AORTA) is collecting data in the United States [34[■]]. These studies aim to address many of the existing knowledge gaps.

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- of special interest
- of outstanding interest

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