



A worldwide survey on intra-operative antithrombotic strategies during non-cardiac arterial procedures

## **Research protocol**

V2.4, dated 2023-03-30

## Rationale

Optimal anticoagulation is of vital importance to achieve safe and effective non-cardiac arterial procedures (NCAP). Unfractionated heparin is being used for over 70 years in this regard to prevent thrombo-embolic complications (TEC), such as peripheral emboli, graft thrombosis, intestinal ischemia and myocardial infarction.<sup>1,2</sup> However, heparin also increases bleeding risk. Heparin has a non-linear dose response curve and elimination curve, which makes the effect in the individual patient unpredictable.<sup>3,4</sup> These disadvantages could legitimize heparin monitoring strategies during NCAP. The Activated Clotting Time (ACT) can be used to monitor the intra-operative heparin effect, an already widely accepted concept during cardiac surgery.<sup>5,6</sup> But in anticipation of the first randomised trial comparing heparinization strategies during NCAP, high quality evidence on heparin administration and ACT-monitoring is still lacking.<sup>1,7-9</sup> Few guidelines across the world give recommendations about heparin administration, heparin monitoring, and heparin reversal with protamine. However, if recommendations are made, they vary widely across guidelines and are primarily based on observational studies or on no literature at all.<sup>1,10-15</sup> These might lead to substantial differences in local practices worldwide.

A recently performed survey on heparinization strategies in the Netherlands (to be published) showed considerable variation in antithrombotic protocols between hospitals. The majority of hospitals (39/54; 74%) used a single dose of 5 000 IU heparin for all types of NCAP, regardless of the patient characteristics. A minority (28%) monitored the heparin effect by ACT. There was a large variation in ACT target values (180 – 250 seconds or two times the reference value). International antithrombotic strategies during vascular and interventional radiological procedures have been described and indicated that a fixed primary heparin dose of 5000 IU is administered in 90-100% during NCAP.<sup>2,16-18</sup> Also, a previous survey on differences between surgeons in Europe (European Society of Vascular Surgery) and the United States (Society of Vascular Surgery), described that individually calculated heparin doses were used in 39% vs. 56% respectively, instead of a fixed heparin dose. ACT monitoring was used in 43% vs. 80% respectively during CEA.<sup>19</sup>

Optimal antithrombotic strategies during NCAP are of vital importance to minimize TEC, without increasing bleeding risk. High quality evidence is lacking, and therefore might be the cause for a wide variation in the various international guidelines and local protocols worldwide. Previously published overviews showed substantial differences in applied heparinization strategies and heparin monitoring strategies. The current variation in protocols worldwide is however not known, since the previously published overviews are of older date. Also, these overviews describe single countries or limited amount of vascular surgical societies.

Mapping the current practice in antithrombotic strategies worldwide, gives a complete overview. We aim to identify most widely accepted antithrombotic protocols and specify possible international and intercontinental differences in antithrombotic strategies during NCAP. With this extensive overview we aim to identify possible new research targets and the potential need to harmonize protocols or create new protocols between the various hospitals and vascular surgery and interventional radiology societies worldwide.

## Methods

### *Study design*

A comprehensive online survey study. The survey will be accessible via SurveyMonkey: a web-based survey company ([www.surveymonkey.com](http://www.surveymonkey.com)). In order to increase the survey quality and the

international scope, the European Vascular Research Collaborative (EVRC) will be consulted during the survey construction phase and data collection phase.

#### *Survey*

The survey consists of questions on antithrombotic strategies, focussing on unfractionated heparin use, heparin monitoring strategies by ACT and heparin reversal strategies using protamine during NCAP. Questions will be specified for carotid endarterectomy, open abdominal aortic aneurysm repair, EVAR/TEVAR, FEVAR/BEVAR and peripheral arterial surgical interventions. The maximum completion time of the survey will be 15 minutes. The complete survey is added in appendix 1.

#### *Recruiting participants*

Participants in the direct network of the study team and EVRC steering committee will be contacted via E-mail. The invitation E-mail is added in appendix 2. The survey will be directly accessible via the known social platforms. Frequent reminding requests for participation and inclusion updates will be sent via social platforms. Apart from the steering committee of EVRC, representatives from Europe and beyond will be contacted to participate in spreading the survey.

#### *Analysis*

Data will be exported and analysed using the most current version of SPSS (Armonk, NY: IBM corp). Descriptive statistics will be generated. Antithrombotic strategies between different countries, different continents and different international vascular societies will be compared.

#### *Timeframe*

We target to include over 1000 participants into the ACTION-survey. The estimated inclusion period is six months. The targeted inclusion period is March 2023 – September 2023.

### **Ethics and privacy**

General Data Protection Regulation (GDPR) of the European Union is taken into consideration. Participants will be asked to share their contact details. The answers to the survey will be processed under a pseudonym. The identity of participants only will be known to the coordinating researcher (MH) and principal investigator (VJ). The data will be used for research purposes only.

### **Publication policy**

The results of research will be submitted for publication in a peer-reviewed scientific journal. The publication authors will be: Max Hoebink, Liliane Roosendaal, Lan Tran, Arno Wiersema, Vincent Jongkind, ACTION-1 collaborative, EVRC collaborative.

### **Study team**

|                                  |  |
|----------------------------------|--|
| <i>Principal investigator</i>    | Vincent Jongkind<br>Department of Vascular Surgery<br>Amsterdam UMC, location VU University Medical Center<br>De Boelelaan 1117 1081 HV Amsterdam<br>The Netherlands<br>E-Mail: <a href="mailto:v.jongkind@amsterdamumc.nl">v.jongkind@amsterdamumc.nl</a> |
| <i>Coordinating investigator</i> | Max Hoebink<br>Department of Vascular Surgery  |

Amsterdam UMC, location VU University Medical Center  
De Boelelaan 1117 1081 HV Amsterdam  
The Netherlands  
E-mail: [m.hoebink@amsterdamumc.nl](mailto:m.hoebink@amsterdamumc.nl)

*ACTION survey study group*

Arno M. Wiersema  
Vincent Jongkind  
Kak Khee Yeung  
Lan Tran  
Liliane C. Roosendaal  
Max Hoebink

*EVRC collaborative*

Florian Enzmann  
Fabien Lareyre  
Gert Jan de Borst  
Joel Ferreira Sousa  
Lewis Meecham  
Liliana Domingos  
Martin Teraa  
Petar Zlatanovic  
Salome Weiss  
Stefano Ancetti  
Albert Busch  
Bergrós Jóhannesdóttir  
Alexander Gombert  
Katariina Noronen  
Robert Hinchliffe  
Alexandru Predenciuc  
Caroline Caradu  
Panagiotis Doukas  
Leszek Kukulski  
Qasam Ghulam  
Florian Enzmann  
Angelos Karelis  
Maram Darwish  
Mohammad Barbati  
Markvard Møller  
Matt Spreadbury  
Willemien van de Water  
Desiree van den Hondel  
Harm Ebben  
Alexander Croo  
Gilles Uijtterhaegen  
Adina Trusca  
Ryan Gouveia Melo  
Vaiva Dabravolskaite  
Paolo Spath  
Vishal Amlani  
Aoife Kiernan  
Christian Zielasek

*ACTION-1 collaborative*

Mark Koelemay  
Jan Tijssen  
Susan van Dieren  
Jan Blankensteijn  
Sebastian Debus  
Saskia Middeldorp  
Jan Heyligers  
Edo Schubert  
Michel Reijnen  
Hessel Buscher  
Daniël Eefting  
Bram Fioole  
Rutger Hissink  
Rigo Hoencamp  
Rogier Kropman  
Lijckle van der Laan  
Susan Lemson  
Maurice Pierie  
Boudewijn Reichman  
Jan van Schaik  
Peter Schlejen  
Markus Steinbauer  
Joep Teijink  
Edith Willigendael  
Clark Zeebregts  
Xavier Berard  
Pieter Salemans  
Igor Končar  
Marco Virgilio Usai

## References

1. Wiersema, A. M., Jongkind, V., Bruijninx, C. M. A., Reijnen, M. M. P. J., Vos, J. A., Van Delden, O. M., ... & CAPPA study group. (2012). Prophylactic perioperative anti-thrombotics in open and endovascular abdominal aortic aneurysm (AAA) surgery: a systematic review. *European Journal of Vascular and Endovascular Surgery*, 44(4), 359-367.
2. Wiersema, A., Bruijninx, C., Reijnen, M. M. P. J., Vos, J., Van Delden, O., Vahl, A., ... & Moll, F. (2013). Perioperative prophylactic antithrombotic strategies in vascular surgery: current practice in the Netherlands. *The Journal of Cardiovascular Surgery*, 56(1), 119-125.
3. Hirsh, J., & Raschke, R. (2004). Heparin and low-molecular-weight heparin: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest*, 126(3), 188S-203S.
4. Finley, A., & Greenberg, C. (2013). Heparin sensitivity and resistance: management during cardiopulmonary bypass. *Anesthesia & Analgesia*, 116(6), 1210-1222.
5. Nath, F. C., Muller, D. W., Rosenschein, U., Ellis, S. G., & Topol, E. J. (1993). Heparin monitoring during coronary intervention: activated clotting time versus activated partial thromboplastin time. *The Canadian Journal of Cardiology*, 9(9), 797-801.
6. Chew, D. P., Bhatt, D. L., Lincoff, A. M., Moliterno, D. J., Brener, S. J., Wolski, K. E., & Topol, E. J. (2001). Defining the optimal activated clotting time during percutaneous coronary intervention: aggregate results from 6 randomized, controlled trials. *Circulation*, 103(7), 961-966.
7. Wiersema, A. M., Roosendaal, L. C., Koelemaj, M. J., Tijssen, J. G., van Dieren, S., Blankensteijn, J. D., ... & Jongkind, V. (2021). ACTION-1: study protocol for a randomised controlled trial on ACT-guided heparinization during open abdominal aortic aneurysm repair. *Trials*, 22(1), 1-16.
8. Hoebink, M., Roosendaal, L. C., Wiersema, A. M., & Jongkind, V. (2023). ACTION-1: Activated clotting time guided heparinization during open abdominal aortic aneurysm repair, rationale and design of a randomised trial. *European journal of vascular and endovascular surgery: the official journal of the European Society for Vascular Surgery*, S1078-5884.
9. Doganer, O., Wiersema, A. M., Scholtes, V., Blankensteijn, J. D., Yeung, K. K., & Jongkind, V. (2020). No concluding evidence on optimal activated clotting time for non-cardiac arterial procedures. *European Journal of Vascular and Endovascular Surgery*, 59(1), 137-147.
10. Chaikof, E. L., Dalman, R. L., Eskandari, M. K., Jackson, B. M., Lee, W. A., Mansour, M. A., ... & Starnes, B. W. (2018). The Society for Vascular Surgery practice guidelines on the care of patients with an abdominal aortic aneurysm. *Journal of vascular surgery*, 67(1), 2-77.
11. Wanhainen, A., Verzini, F., Van Herzelee, I., Allaire, E., Bown, M., Cohnert, T., ... & Verhagen, H. (2019). Clinical practice guidelines on the management of abdominal aorto-iliac artery aneurysms. *Eur J Vasc Endovasc Surg*, 57(1), 8-93.
12. Björck, M., Koelemay, M., Acosta, S., Goncalves, F. B., Köbel, T., Kolkman, J. J., ... & ESVS Guidelines Committee. (2017). Editor's choice—management of the diseases of mesenteric arteries and veins: clinical practice guidelines of the European Society of Vascular Surgery (ESVS). *European Journal of Vascular and Endovascular Surgery*, 53(4), 460-510.
13. AbuRahma, A. F., Avgerinos, E. D., Chang, R. W., Darling III, R. C., Duncan, A. A., Forbes, T. L., ... & Zhou, W. (2022). Society for Vascular Surgery clinical practice guidelines for management of extracranial cerebrovascular disease. *Journal of Vascular Surgery*, 75(1), 4S-22S.
14. Upchurch Jr, G. R., Escobar, G. A., Azizzadeh, A., Beck, A. W., Conrad, M. F., Matsumura, J. S., ... & Wang, G. J. (2021). Society for Vascular Surgery clinical practice guidelines of

thoracic endovascular aortic repair for descending thoracic aortic aneurysms. *Journal of vascular surgery*, 73(1), 55S-83S.

15. Riambau, V., Böckler, D., Brunkwall, J., Cao, P., Chiesa, R., Coppi, G., ... & ESVS Guidelines Committee. (2017). Editor's choice—management of descending thoracic aorta diseases: clinical practice guidelines of the European Society for Vascular Surgery (ESVS). *European Journal of Vascular and Endovascular Surgery*, 53(1), 4-52.
16. Assadian, A., Senekowitsch, C., Assadian, O., Eidher, U., Hagmüller, G. W., & Knöbl, P. (2005). Antithrombotic strategies in vascular surgery: evidence and practice. *European journal of vascular and endovascular surgery*, 29(5), 516-521.
17. Zaman, S. M., Meiring, P. D. V., Gandhi, M. R., & Gaines, P. A. (1996). The pharmacokinetics and UK usage of heparin in vascular intervention. *Clinical radiology*, 51(2), 113-116.
18. Durran, A. C., & Watts, C. (2012). Current trends in heparin use during arterial vascular interventional radiology. *Cardiovascular and interventional radiology*, 35(6), 1308-1314.
19. Wakefield, T. W., Lindblad, B., Stanley, T. J., Nichol, B. J., Stanley, J. C., Bergqvist, D., ... & Bergentz, S. E. (1994). Heparin and protamine use in peripheral vascular surgery: a comparison between surgeons of the Society for Vascular Surgery and the European Society for Vascular Surgery. *European journal of vascular surgery*, 8(2), 193-198.

## Appendices

### Appendix 1: survey questions

## The ACTION Survey

### Survey about heparin use, heparin monitoring and heparin reversal during non-cardiac arterial procedures (NCAP).

This is a digital survey regarding intra-operative antithrombotic strategies during Non-cardiac Arterial Procedures (NCAP).

With this survey we aim to get detailed insight into the current practice of antithrombotic strategies during NCAP worldwide.

To reach out to you for any additional questions and to analyse any possible geographic trends we ask you to state your name, country of origin, hospital and E-mail address.

Your answers will be processed under a pseudonym. Your personal data will be protected by a password and will only be saved in the database of the Amsterdam University Medical Centre. Your data will be deleted from the database 10 years after publication. The General Data Protection Regulation (GDPR) will be taken into consideration when processing your data

Taking the survey will take approximately 10 minutes.

Thank you for participating in this survey

### Page 1 #Introduction

1. Do you agree with processing the data of this survey, according to the previous statement?
2. What is your profession?
  - a. Vascular surgeon
  - b. Interventional radiologist / angiologist / interventional cardiologist
  - c. Other
3. Which country do you work?
4. Which hospital do you work?
5. What is your E-mail address?

### #Questions per type of procedure (CEA, EVAR/TEVAR, FEVAR/BEVAR, open abdominal aortic repair, peripheral arterial surgical procedures)

### Page 2 #Antithrombotic strategy (fill in per type of procedure)

1. What kind of antithrombotic strategy do you use?
  - a. I do not perform this procedure (go to next procedure)
  - b. I use the same antithrombotic strategy as during ..... (go to next procedure)
  - c. I use a different antithrombotic strategy



**Page 3 #Heparin dose (fill in per type of procedure)**

1. What kind of IV anticoagulant do you administer during the procedure?
  - a. A fixed starting dose of heparin (for example: 5000 IU)
    - i. Explain how many IU .....
  - b. A heparin dose based on actual bodyweight (for example: 100 IU/kg)
    - i. Explain how many IU/kg .....
  - c. A heparin dose based on ideal bodyweight (for example: 100 IU/kg)
    - i. Explain how many IU/kg .....
  - d. I use LMWH instead of unfractionated heparin (go to next procedure)
  - e. I do not use heparin (go to next procedure)
  - f. Other heparin starting dose, please specify ..... (go to next procedure)
2. Do you consider giving additional unfractionated heparin after the starting dose?
  - a. No (go to protamine)
  - b. Yes, a fixed dose according to a standardized protocol (not based on ACT) (go to protamine)
  - c. Yes, a dose based on bodyweight according to a standardized protocol (not based on ACT) (go to protamine)
  - d. Yes, by using a continuous heparin perfusor (with or without ACT)
    - i. Explain how many IU / hour or IU / kg / hour
    - ii. Do you adjust continuous heparin perfusion based on ACT?
      1. Yes
      2. No, based on APTT (go to protamine)
      3. No, please specify ..... (go to protamine)
  - e. Yes, primarily based on ACT
  - f. Yes, primarily based on APTT (go to protamine)
  - g. Yes, a fixed dose primarily based on subjective coagulation status and/or length of surgery (not according to a standardized protocol, not based on ACT) (go to protamine)
  - h. Yes, a dose based on bodyweight primarily based on subjective coagulation status and/or length of surgery (not according to a standardized protocol, not based on ACT) (go to protamine)
  - i. Other, please specify ..... (go to protamine)

**Page 4 #Activated Clotting Time (fill in per type of procedure)**

1. What is your target ACT? (choose 1 of the following options)
  - a. ....seconds (minimal acceptable value)
  - b. ....times the reference value
2. How many minutes after heparin administration do you perform the first ACT measurement?
  - a. .... seconds
3. How many minutes after reaching the target ACT do you measure the ACT again?
  - a. .... seconds
4. How much additional heparin do you administer? (explain how many IU of heparin at which ACT)
  - a. .... heparin (IU of IU/kg) at ACT (sec)
  - b. .... heparin (IU of IU/kg) at ACT (sec)
  - c. .... heparin (IU of IU/kg) at ACT (sec)
5. What is the target ACT at the end of the procedure?

- a. .... seconds (fill in the maximum acceptable ACT value)

**Page 5 #Protamine (fill in per type of procedure)**

1. What is the primary indication to give protamine?
  - a. I do not administer protamine during this type of procedure (go to next procedure)
  - b. Based on subjective intra-operative coagulation status and/or length of surgery (not based on ACT) (go to next procedure)
  - c. Based on the amount of heparin administered (not based on ACT) (go to next procedure)
  - d. Based on ACT at closure
  - e. Other indication (explain): ..... (go to next procedure)

**Page 6 #General questions**

1. Would you like to improve something on your current antithrombotic protocol(s)? (multiple options possible)
  - a. No
  - b. I would like protocol(s) to be more tailored to the individual patient
  - c. I would like to monitor the effect of heparin intra-operatively by ACT
  - d. Other, explain:.....
2. If you measure the ACT, what device do you use to measure the ACT during NCAP?
  - a. I do not monitor the effect of heparin by ACT
  - b. Haemostasis Management System plus (HMS plus, Medtronic®)
  - c. ACT Plus (Medtronic®)
  - d. Hemochron® Signature Elite
  - e. Hemochron® Response
  - f. i-STAT (Abbot®)
  - g. other, please specify:.....

**Page 7 #Additional comments**

1. Do you have any additional comments regarding your antithrombotic strategies during NCAP?
  - a. ....

**Page 8 #Thank you**

We thank you for completing this survey.

Awaiting the first randomised trial regarding ACT guided heparinization during NCAP (ACTION-1, [clinicaltrials.gov: NCT04061798](https://clinicaltrials.gov/ct2/show/study/NCT04061798)) we aim to provide more detailed insight into antithrombotic strategies during NCAP worldwide with this survey.

If you are interested, we invite you to look into our previous work on antithrombotic strategies during NCAP or on the [ACTION-1 website](#).

Sincerely,

On behalf of the European Vascular Research Collaborative (EVRC) and the ACTION-1 research collaborative,

The ACTION study group:

Arno Wiersema, Vincent Jongkind, Kak Khee Yeung, Lan Tran, Liliane Roosendaal, Max Hoebink

*previous research:*

Wiersema AM, Jongkind V, Bruijninx CMA, Reijnen MMPJ, Vos JA, van Delden OM, et al. Prophylactic perioperative anti-thrombotics in open and endovascular abdominal aortic aneurysm (AAA) surgery: A systematic review. *European Journal of Vascular and Endovascular Surgery*. 2012;44:359–367.

Wiersema AM, Jongkind V, Bruijninx C, Reijnen M, Vos JA, van Delden O, et al. Prophylactic intraoperative antithrombotics in open infrainguinal arterial bypass surgery (IABS): a systematic review. *The Journal of Cardiovascular Surgery edizioni minerva medica*. 2014;56:127-143.

Wiersema AM, Bruijninx C, Reijnen M, Vos J, van Delden O, Vahl A, et al. Perioperative prophylactic antithrombotic strategies in vascular surgery: current practice in the Netherlands. *J Cardiovasc Surg (Torino)*. 2015;56:119–125.

Doganer O, Wiersema AM, Scholtes V, Blankensteijn JD, Yeung KK, Jongkind V. No Concluding Evidence on Optimal Activated Clotting Time for Non-cardiac Arterial Procedures. *European Journal of Vascular and Endovascular Surgery*. W.B. Saunders Ltd; 2020;59:137–147.

Doganer O, Jongkind V, Blankensteijn JD, Yeung KK, Wiersema AM. A Standardized Bolus of 5 000 IU of Heparin Does not Lead to Adequate Heparinization during Non-cardiac Arterial Procedures. *Ann Vasc Surg*. 2021;71:280-287.

Doganer O, Wiersema AM, Pierie M, Blankensteijn JD, Yeung KK, Jongkind V. More Effective Anticoagulation During Non-Cardiac Arterial Procedures Using Activated Clotting Time Guided Heparin Administration. *Ann Vasc Surg*. 2021;76:378–388.

Wiersema AM, Roosendaal LC, Koelemay MJW, Tijssen JGP, van Dieren S, Blankensteijn JD, et al. ACTION-1: study protocol for a randomised controlled trial on ACT-guided heparinization during open abdominal aortic aneurysm repair. *Trials*. 2021;22:1-16.

Doganer O, Roosendaal LC, Wiersema AM, Blankensteijn JD, Yeung KK, Jongkind V. Weight Based Heparin Dosage with Activated Clotting Time Monitoring Leads to Adequate and Safe Anticoagulation in Non-Cardiac Arterial Procedures. *Ann Vasc Surg*. 2022;84:327-335

Roosendaal LC, Wiersema AM, Smit JW, Doganer O, Blankensteijn JD, Jongkind V. Editor's Choice – Sex Differences in Response to Administration of Heparin During Non-Cardiac Arterial Procedures. *European Journal of Vascular and Endovascular Surgery*. 2022;64:557–565.

Hoebink M, Roosendaal LC, Wiersema AM, Jongkind V, Koelemay MJW, Tijssen JMM, et al. ACTION-1: Activated clotting time guided heparinization during open abdominal aortic aneurysm repair, rationale and design of a randomised trial. *European Journal of Vascular and Endovascular Surgery*. 2023.

*Appendix 2: invitation E-mail*

*\*attachment: study protocol 'the ACTION survey' V2.4, dated 2023-03-30\**

*Dear colleague,*

*Do you perform non-cardiac arterial procedures (vascular surgery procedures)?*

*On behalf of the European Vascular Research Collaborative (EVRC), and the ACTION-1 research collaborative, we would like to invite you to participate in the 'ACTION-survey': a worldwide survey on antithrombotic strategies during non-cardiac arterial procedures. This survey will take approximately 10 minutes to fill in.*

*The purpose of this survey is to obtain detailed insight into the current practice of antithrombotic strategies during NCAP worldwide, potentially identifying the most accepted antithrombotic strategies, knowledge gaps and new research targets. We hope you agree to participate, and fill in the survey via the link below. Also, we would like to ask you to send the link to your colleague vascular surgeons/interventional radiologists/interventional cardiologists to fill in the survey as well. The attached document is the short study protocol.*

*Please do not hesitate to contact us if you need additional assistance or have any questions.*

*Thank you for taking the time to consider committing to participate in this project.*

*Also, on behalf of the European Vascular Research Collaborative (EVRC) and ACTION-1 research collaborative*

*Sincerely,*

*Max Hoebink  
Liliane Roosendaal  
Lan Tran  
Arno Wiersema  
Kak Khee Yeung  
Vincent Jongkind*

*Department of Vascular Surgery, Amsterdam University Medical Centers, location VU  
De Boelelaan 1117 1081 HV Amsterdam  
The Netherlands  
E-Mail: [m.hoebink@amsterdamumc.nl](mailto:m.hoebink@amsterdamumc.nl)*

<https://www.surveymonkey.com/r/CVQG7MJ>



The ACTION  
survey

Intra-operative  
anticoagulation  
strategies during non-  
cardiac arterial  
procedures

[www.surveymonkey.com](https://www.surveymonkey.com)