Editor’s Choice – Sex Differences in Response to Administration of Heparin During Non-Cardiac Arterial Procedures

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Objective: Females are more prone to complications during non-cardiac arterial procedures (NCAPs) than males. The current study investigated the difference in the effect of peri-procedural prophylactic heparin in males and females, using the activated clotting time (ACT). This was a retrospective analysis of a prospective multicenter cohort study.

Methods: All patients undergoing elective NCAP using heparin and ACT measurements between January 2016 and March 2020 were included. Two heparin dosage protocols were used: weight-based dosing of 100 IU/kg (international units per kilogram) or a bolus of 5 000 IU. The primary outcome was the anticoagulatory effect of heparin after five minutes, measured by ACT. Secondary outcomes were the effect of heparin after 30 minutes, bleeding complications, and arterial thromboembolic complications (ATECs).

Results: A total of 778 patients were included; 26% were female. After 100 IU/kg (n = 300), females more often reached longer ACT (<200 seconds: 22% vs. 25%, p = .62; 200–250 seconds: 41% vs. 53%, p = .058; 251–280 seconds, 26% vs. 15%, p = .030). The mean ACT after 100 IU/kg heparin was 233 seconds (95% confidence interval [CI] 224 – 243) for females and 226 seconds (95% CI 221 – 231) for males (p = .057). After a bolus of 5 000 IU of heparin (n = 411), females reached significantly higher levels of anticoagulation than males (mean ACT 204 seconds vs. 190 seconds: p ≤ .001; ACT < 200 seconds: 44% vs. 66%; p < .001; ACT 200–250 seconds: 47% vs. 30%, p = .001; ACT 251 – 280 seconds: 7.8% vs. 2.3%, p = .009). Thirty minutes after heparin administration, 58% of all patients had an ACT < 200 seconds. ATECs did not differ between females and males (6.9% vs. 5.1%, p = .33) but bleeding complications were higher in females (27% vs. 16%, p = .001).

Conclusion: Heparin leads to significantly longer ACT in females during NCAP. Further research is needed to investigate whether individually based heparin protocols lead to fewer bleeding complications and lower incidence of ATECs.

Keywords: Activated clotting time, Bleeding, Female, Heparin, Sex, Vascular surgical procedures

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INTRODUCTION

Until now, no distinction has been made between female and male patients during invasive treatment for vascular disease. Increasing evidence, however, shows that treatment outcomes and particularly complications are different between females and males.1–3 A recent cohort study showed that females developed more bleeding complications after invasive treatment for peripheral artery disease.4 Over the past decades it has become clear that there are differences in pharmacokinetics and pharmacodynamics between females and males and that female sex is associated with a higher risk of developing adverse drug reactions.5–8

In open and endovascular non-cardiac arterial procedures (NCAPs) unfractionated heparin (further heparin) is used to prevent arterial thromboembolic complications (ATECs).9,10
Although good studies on heparin use and its benefits or risks are sparse, some studies have shown that myocardial infarction was found to be significantly more frequent in non-heparinised patients than in heparinised patients.\textsuperscript{9,11} Besides heparin’s many benefits, including immediate effect, low cost, and the possibility to quickly reverse its effect, a major disadvantage is the unpredictable effect in the individual patient.\textsuperscript{12–16} The activated clotting time (ACT) can be used to monitor the patient’s peri-procedural (anti) coagulation. Heparin dosing can be adjusted based on ACT measurements to reach a desired level of anticoagulation. Although the optimal target ACT during NCAP has not been determined yet, previous investigations suggest an ACT between 200 and 250 seconds may be preferable.\textsuperscript{17}

Little is known about differences in the effect of heparin in males and females during NCAPs. The aim of this study was to investigate whether there is a difference in the effect of heparin in males and females during NCAPs. The hypothesis was that females might be more sensitive to heparin.

**MATERIAL AND METHODS**

**Study design**

The current study is part of a prospective multicentre cohort study designed to investigate the optimal heparin dose protocol and optimal ACT values during NCAPs. Patients older than 18 years were eligible for inclusion. Exclusion criteria were patients requiring acute intervention, allergy to heparin, history of heparin induced thrombocytopenia, patients who received heparin prior to surgery, a known history of coagulation disorders, or an estimated glomerular filtration rate < 30 mL/min (based on Kidney Disease: Improving Global Outcomes guidelines, 2012).\textsuperscript{18} From January 2016 onwards, this database is being collected for the MANCO trial registered at clinicaltrials.gov (identifier: NCT03426293) and the Dutch Trial Registry (identifier: NTR6973). Collected data are stored in an electronic database using Castor EDC. A case report form was used to gather patient data. The protocol from the MANCO trial was evaluated and approved by the Medical Ethics Committee Noord-Holland. Data were collected from Dijklander hospital, Hoorn; Amsterdam UMC, Amsterdam location VU Medisch Centrum; and Isala hospital, Zwolle. For the current study, patient data were recorded until March 2020. Earlier results of the MANCO study have been published.\textsuperscript{19}

**Heparin protocol**

The effect of a single dose of heparin on the ACT was investigated using two dosing protocols: a standardised bolus of 5 000 IU or 100 IU/kg bodyweight.

**Activated clotting time**

In all participating centres, ACT was measured using the Hemostasis Management System Plus from Medtronic (Medtronic, Minneapolis, MN, USA). High range cartridges were used during all procedures. For every ACT measurement, 3 mL of arterial blood was drawn from the patient. Beforehand, 5 mL of blood was discarded of to prevent contamination of heparin residues. ACT was measured at baseline, five minutes after heparin administration, and every 30 minutes thereafter until the procedure was finished. At the end of surgery, ACT was measured, and protamine was administered at the surgeon’s discretion.

**Heparin effect over time**

To investigate the ongoing effect of heparin in the current study, ACTs five and 30 minutes after heparin administration were compared. For each patient, the absolute difference in seconds between the five minute and 30 minute ACT was calculated, which was defined as ACT drop. The ACT drop might help by predicting whether a patient remains within the therapeutic anticoagulation range after 30 minutes. The median of the ACT drop was reported for the total cohort and per protocol. Based on previous research, an ACT < 200 seconds was defined as underdosed, an ACT between 200 and 250 seconds on target, an ACT between 251 and 280 seconds moderately overdosed, and an ACT > 280 second overdosed. The mean ACT was calculated for both dosing protocols and thereafter compared between males and females.

**The effect of different doses of heparin**

The effect of body weight and body surface area (BSA, IU/m\textsuperscript{2}) on ACT was investigated using the ACT after the heparin dose.\textsuperscript{20} Patients were grouped together based on body weight or BSA, and the dose per bodyweight or BSA was calculated for every patient. Consequently, it was evaluated at which initial heparin dose the majority of patients in each group reached the preferred ACT of 200 — 250 seconds. These analyses were performed in the search for the optimal dosage of heparin for males and females.

**Arterial thromboembolic complications and bleeding complications**

The number of ATECs and bleeding complications were registered up to 30 days after the primary procedure or during the same hospital admission. ATECs included myocardial infarction, cerebrovascular accident, deep venous thrombosis, pulmonary embolism, peripheral embolism, bowel ischaemia, thromboembolic renal insufficiency, athero-embolism, spinal cord ischaemia, and graft thrombosis.

To determine the incidence and severity of bleeding complications, the European Multicentre Study on Coronary Artery Bypass Grafting (E-CABG) registry was used to score and grade intra- and post-operative bleeding.\textsuperscript{21} A bleeding complication is classified as E-CABG grade 0 if 0 — 1 unit of red blood cells (RBCs) is transfused. Grade 1: transfusion of platelets or transfusion of fresh frozen plasma or transfusion of 2 — 4 units of RBCs. Grade 2: transfusion of 5 — 10 units of RBCs or re-operation for bleeding. Grade 3: transfusion of more than 10 units of RBCs. The incidence of ATECs and bleeding complications was investigated for sex differences.
Statistical analyses were performed using SPSS version 25 (Armonk, NY: IBM Corp.). A normality test on eligible data was performed using the Shapiro–Wilk test. Continuous normally distributed variables were expressed as mean ± standard deviation. Skewed variables were expressed as median with interquartile range (IQRs). Categorical variables were expressed as counts and percentage. The independent t test was used to test normally distributed data between groups. The Mann–Whitney U test was used to
test skewed data. Binary data were tested using the chi square test. Multivariable analysis was performed using logistic regression with the variables that had \( p < .20 \) in the univariable analyses. Test results were reported using the \( p \) value. A \( p \) value less than .050 was considered statistically significant. Subjects with missing data were excluded per analysis.

Prior to the retrospective analysis, a power analysis was performed to calculate the required number of patients in each of the groups. The difference between females and males who reach a target ACT of \( > 200 \) seconds was set at 15%. Using an alpha of .05 and a power of .80, the minimum number of patients required per group was 169 (total of 338 patients).

RESULTS
Seven hundred and seventy-eight patients were included in the current study. The cohort consisted of 574 (73%) males, and 204 (26%) females. Patient characteristics and the type of procedures are detailed in Table 1. Females were significantly shorter, weighed less, had a lower body mass index (BMI) and BSA. They underwent open procedures significantly more often. Males underwent an aortic procedure more often, particularly endovascular aneurysm repair. All patients underwent surgery under general anaesthesia. Two hundred and eighteen (28%) patients received a bolus of protamine.

The initial effect of heparin
The results of the measured ACTs are displayed in Figure 1 and Table 2. Seven hundred and eleven patients were enrolled in the 5 000 IU or in the 100 IU/kg dosage group. Sixty-seven patients received a different dose or had no ACT recorded at five minutes. For both male and female patients, less than half reached an ACT of \( 200 – 250 \) seconds (39% and 44% respectively, \( p = .23 \)). Females less often reached an ACT \( < 200 \) seconds (34% vs. 49%, \( p < .001 \)) and more often an ACT of \( 251 – 280 \) seconds (16% vs. 7.5%, \( p < .001 \)). No difference between females and males was found for an ACT of \( > 280 \) seconds, \( p = .49 \).

In the 100 IU/kg group 113 of 214 (53%) males vs. 35 of 86 (41%) females reached an ACT of \( 200 – 250 \) seconds (\( p = .058 \)). Females more often reached an ACT of \( 251 – 280 \) seconds (26% vs. 15%, \( p = .030 \)). Females in this group were more likely to have an ACT > 250 seconds if they were taller (\( p = .037 \)), had a higher weight (\( p = .043 \)), and higher BSA (\( p = .031 \)). A wide variation in ACT values was found for both females and males.

Four hundred and eleven patients received 5 000 IU of heparin and had their ACT measured five minutes after heparin administration. Females reached significantly higher levels of anticoagulation. No difference between females and males was found for patients exceeding an ACT of 280 seconds (\( p = .52 \)). A significant difference was found in mean ACT between females and males (204 seconds, 95% CI 198 – 210, vs. 190 seconds, 95% CI 186 – 193, \( p = .001 \)).

Heparin effect over time
A total of 448 patients had their ACT measured five and 30 minutes after receiving a single dose of heparin. The median ACT drop for these patients was found to be 19 seconds (IQR 29). The median ACT drop for patients enrolled in the 100 IU/kg protocol was 26 seconds (IQR 27), and 13 seconds (IQR 24) for patients in the 5 000 IU protocol. When comparing the results based on sex (132 females vs. 316...
Activated clotting time

Effect of heparin over time, with activated clotting time values presented at 5 minutes after the first heparin administration, with 67 patients having received a different dose or having no ACT recorded at five minutes.

The effect of different doses of heparin

The results of the effect of heparin dose on the five minute ACT are shown in Tables 4 and 5. The heparin dose per bodyweight (kg) or BSA (IU/m²) was calculated for every patient. The highest percentage (56%) of males that reached an ACT of 200 seconds was with a dose between 4 000 and 4 999 IU/m². For females 46% of females reached an ACT of 200 seconds. Ten (3%) patients had an ACT > 200 seconds. After 30 minutes 260 (58%) patients had an ACT < 200 seconds.

Arterial thromboembolic complications and bleeding complications

The combined results of the incidence of ATECs and bleeding complications are displayed in Table 6. No difference was found in the incidence of ATECs between males and females (5.1% vs. 6.9%, p = .33). Because of the low absolute number of ATECs, multivariable analysis was not performed. A total of 143 (18%) bleeding complications occurred in the cohort. When combining all bleeding complications, females developed more bleeding complications than males (27% and 16%, respectively, p = .001), mainly grade 1. Of the patients who developed a bleeding complication, 39% of females and 38% of males had an ACT > 250 seconds, measured at any time during the procedure. Fifty-one (36%) of the patients with a bleeding complication had received protamine. Fifteen (10%) patients underwent re-operation due to bleeding.

Table 2. Activated clotting time five minutes after first heparin administration in 778 patients undergoing non-cardiac arterial procedures between 2016 and 2020 included in this retrospective single centre analysis evaluating differences after heparin administration, by sex and per protocol. Patients were included in this analysis if the activated clotting time (ACT) was recorded at five minutes after the first heparin administration, with 67 patients having received a different dose or having no ACT recorded at five minutes.

| ACT – sec | All protocols | Heparin 5 000 IU | Heparin 100 IU/kg |
|----------|---------------|-----------------|------------------|
|          | Males (n = 535) | Females (n = 188) | p |
|          | Males (n = 309) | Females (n = 102) | p |
|          | Males (n = 214) | Females (n = 86) | p |
| < 200    | 49 (34)       | 66 (44)         | <.001 |
| 200–250  | 39 (44)       | 30 (47)         | .001 |
| 251–280  | 7.5 (16)      | 2.3 (7.8)       | <.001 |
| > 280    | 4.2 (5.9)     | 1.9 (1.0)       | .52 |
| Mean ACT | 204 (217–223) | 190 (186–193)   | <.001 |

Data are presented as % or as mean (95% confidence interval). ACT = activated clotting time.

*p value was calculated using the Mann–Whitney U test.

Table 3. Effect of heparin over time, with activated clotting time values presented at five and 30 minutes after first heparin administration in 778 patients undergoing non-cardiac arterial procedures between 2016 and 2020 included in this retrospective single centre analysis evaluating differences after heparin administration, by sex. Patients were only included in the analysis if the activated clotting time (ACT) was recorded at five minutes and at 30 minutes.

| ACT – sec | Males (n = 316) | Females (n = 132) | Total (n = 448) |
|----------|----------------|------------------|----------------|
|          | 5 min | 30 min | 5 min | 30 min | 5 min | 30 min |
| < 200    | 123 (39) | 194 (61) | 38 (29) | 66 (50) | 161 (36) | 260 (58) |
| 200–250  | 139 (44) | 110 (35) | 63 (48) | 54 (41) | 202 (45) | 164 (37) |
| 251–280  | 34 (11)  | 11 (3.5)  | 24 (18)  | 8 (6.1)  | 58 (13)  | 19 (4.2)  |
| > 280    | 20 (6.5) | 1 (3.2)  | 7 (5.3)  | 4 (3.0)  | 27 (6.0) | 5 (1.1)  |

Variables are shown as count and percentage (%). ACT = activated clotting time.
femorodistal intervention, and protamine. Multivariable analysis of the total patient group showed that when corrected for influencing factors, patients who underwent an open aortic intervention, or who received protamine, had a significantly greater probability of bleeding complications. Patients after carotid intervention or after endovascular aortic intervention had a lower probability of bleeding complications. No significant effects for sex, heparin dosing protocol, or ACT values was found (Supplementary Table S1).

**DISCUSSION**

Female patients reach significantly longer ACTs than male patients after heparin administration in NCAPs. This effect was found for both the weight based dosing protocol of 100 IU/kg heparin and for a standardised bolus of 5 000 IU of heparin. These findings expand on a previous smaller study performed at low cost (cartridges are less than €4 in The Netherlands).

Elimination of heparin is thought to be subject to saturable and non-saturable mechanisms. At low doses, the highly efficient saturable mechanism is mainly responsible for the elimination of heparin. The role of the non-saturable mechanism becomes more relevant when the dose of heparin increases (>100 IU/kg), which leads to an increased heparin half life. In the current study, patients with a higher dose of heparin showed a greater difference in ACT between the five and 30 minute mark. The increase in the ACT drop can be explained by the fact that doses of up to 100 IU/kg are still effectively cleared by both elimination mechanisms. Based on the results of the current study, it seems unlikely that there is a considerable difference in elimination of heparin between males and females, since the ACT drop was equal (19 seconds, IQR 29, and 19 seconds, IQR 31). However, in future research this should be analysed using measurements of plasma heparin levels. Sex differences in response to heparin might be

**Table 4. The effect of heparin dose calculated for body weight in 778 patients undergoing non-cardiac arterial procedures between 2016 and 2020 included in this retrospective single centre analysis evaluating differences after heparin administration, by sex**

| Heparin dose – IU/kg | Sex | n  | ACT – sec |
|----------------------|-----|----|-----------|
|                      |     |    | < 200     | 200–250 | 251–280 | > 280 |
| 40–49                | Males | 9  | 9 (100)   | –       | –       | –     |
|                      | Females | 0  | –         | –       | –       | –     |
| 50–59                | Males | 106 | 80 (75)   | 24 (23) | 1 (0.94) | 1 (0.94) |
|                      | Females | 7  | 4 (57)    | 3 (43)  | –       | –     |
| 60–69                | Males | 109 | 72 (66)   | 34 (31) | 1 (0.92) | 2 (1.8) |
|                      | Females | 26 | 10 (39)   | 13 (50) | 2 (7.7)  | 1 (3.8) |
| 70–79                | Males | 38  | 19 (50)   | 13 (34) | 4 (11)   | 2 (5.3) |
|                      | Females | 27 | 13 (48)   | 13 (48) | 1 (3.7)  | –      |
| 80–89                | Males | 29  | 6 (21)    | 16 (55) | 5 (17)   | 2 (6.9) |
|                      | Females | 27 | 13 (48)   | 13 (48) | 1 (3.7)  | –      |
| 90–99                | Males | 49  | 10 (20)   | 25 (51) | 10 (20)  | 4 (8.2) |
|                      | Females | 23 | 7 (30)    | 10 (44) | 5 (22)   | 1 (4.3) |
| 100–109              | Males | 169 | 43 (25)   | 92 (54) | 22 (13)  | 12 (7.1) |
|                      | Females | 74 | 16 (22)   | 29 (39) | 20 (27)  | 9 (12)  |
| 110–119              | Males | 2   | 1 (50)    | –       | 1 (50)   | –      |
|                      | Females | 3  | 1 (33)    | 2 (66)  | –       | –      |
| >120                 | Males | 1   | –         | –       | –       | 1 (100) |
|                      | Females | 2 | 1 (50)    | –       | 1 (50)   | –      |
| Total                |     | 734 | –         | –       | –       | –      |
| Missing*             |     | 44  | –         | –       | –       | –      |

Data are presented as n (%). ACT = activated clotting time.

* 44 patients had no dose recorded or did not have an ACT measurement after five minutes.
possible, as previous research shows a higher risk of heparin induced thrombocytopenia in females than in males. However, in the current study, no patients developed heparin induced thrombocytopenia. In addition, heparin resistance, the failure to achieve a specified anticoagulation level despite the use of what is considered to be an adequate dose of heparin, is reported in the literature. Until now it has not been known whether heparin resistance is more common in females or males. Moreover, hormonal factors could influence the effect of heparin, as sex related differences in haemostasis have been reported in previous research.

Due to the heterogeneous procedures included in the study, only exploratory analysis was performed on clinical complications. ATECs occurred in 5.1% of males and 6.9% of females. Females suffered from more bleeding complications than males (27% vs. 16%). This difference remained after sub-analysis for open procedures but was not significant after multivariable analysis. Larger studies, containing more homogeneous surgical procedures, need to be performed to investigate the association between sex and complications.

A strength of the current study is that data were collected prospectively, which results in a limited number of missing values. In addition, the data were collected in two general hospitals and one university hospital, so data from a large cohort could be analysed.

A natural limitation of the ACT is that it may be affected by many variables such as hypothermia, platelet count, and

Table 5. The effect of heparin dose calculated for body surface area in 778 patients undergoing non-cardiac arterial procedures between 2016 and 2020 included in this retrospective single centre analysis evaluating differences after heparin administration, by sex

| Heparin dose – IU/m² | Sex     | n    | ACT – sec |
|---------------------|---------|------|-----------|
|                     |         |      | < 200     | 200–250 | 251–280 | > 280 |
| < 2 000             | Males   | 11   | 11 (100)  | –       | –       | –     |
|                     | Females | 1    | –         | 1 (100) | –       | –     |
| 2 000–2 999         | Males   | 282  | 192 (68)  | 79 (28) | 5 (1.8) | 6 (2.1) |
|                     | Females | 70   | 34 (49)   | 32 (46) | 3 (4.3) | 1 (1.4) |
| 3 000–3 999         | Males   | 116  | 29 (25)   | 58 (50) | 20 (17) | 9 (7.8) |
|                     | Females | 94   | 29 (31)   | 41 (44) | 22 (23) | 2 (2.1) |
| 4 000–4 999         | Males   | 122  | 27 (22)   | 68 (56) | 19 (16) | 8 (6.6) |
|                     | Females | 25   | 2 (8.0)   | 10 (40) | 5 (20)  | 8 (32)  |
| > 5000              | Males   | 4    | 1 (25)    | 2 (50)  | –       | 1 (25)  |
|                     | Females | 1    | 1 (100)   | –       | –       | –     |
| Total               |         | 727  |           |         |         |       |
| Missing*            |         | 51   |           |         |         |       |

Data are presented as n (%). ACT = activated clotting time.

* 51 patients had no dose recorded, did not have an ACT measurement after five minutes, or the height or weight was unknown.

Table 6. Incidence of arterial thromboembolic and bleeding complications in 778 patients undergoing non-cardiac arterial procedures between 2016 and 2020 included in this retrospective single centre analysis evaluating differences after heparin administration, by sex

| Arterial thromboembolic complications | Males (n = 574) | Females (n = 204) | p     | Total (n = 778) |
|--------------------------------------|----------------|------------------|------|----------------|
| Graft thrombosis                     | 12 (41)        | 9 (64)           |      | 21 (49)        |
| Pulmonary embolism                   | 1 (3.4)        |                  |      | 1 (2.3)        |
| Myocardial infarction                | 2 (6.9)        | 1 (7.1)          |      | 3 (7.0)        |
| Bowel ischaemia                      | 6 (21)         | 1 (7.1)          |      | 7 (16)         |
| Spinal cord ischaemia                | 2 (6.9)        | 2 (14)           |      | 4 (9.3)        |
| Transient ischaemic attack           | 3 (10)         | 1 (7.1)          |      | 4 (9.3)        |
| Athero-embolus                       | 3 (10)         |                  |      | 3 (7.0)        |
| Total                                | 29 (5.1)       | 14 (6.9)         | .33  | 43 (5.5)       |

| Bleeding complications*              | Males (n = 574) | Females (n = 204) | p     | Total (n = 778) |
|--------------------------------------|----------------|------------------|------|----------------|
| Grade 1                              | 57 (9.9)       | 37 (18)          | .002 | 94 (12)        |
| Grade 2                              | 30 (5.2)       | 16 (7.8)         | .17  | 46 (5.9)       |
| Grade 3                              | 2 (0.35)       | 1 (0.49)         |      | 3 (0.38)       |
| Total                                | 89 (16)        | 54 (27)          | .001 | 143 (18)       |

Variables are presented as n (%).

* Classified using the E-CABG (European Multicentre Study on Coronary Artery Bypass Grafting) registry; Grade 1 = transfusion of platelets OR transfusion of fresh frozen plasma OR octaplas OR transfusion of 2–4 units of red blood counts. Grade 2 = transfusion of 5–10 units of red blood counts OR reoperation for bleeding. Grade 3 = transfusion of > 10 units of red blood counts.
function, ATIII deficiency and time from blood collection to analysis.\textsuperscript{25,34} To reduce the influence of these factors on the ACT, the temperature of patients was maintained as constant as possible during surgery using a convection temperature management system, patients with a low platelet count or platelet dysfunction were excluded from the study, and the time between blood collection and analysis was kept as short as possible.

**Conclusion**

Heparin administration during NCAPs leads to longer ACTs in females than in males. The anticoagulatory effect of heparin proved unpredictable in both males and females, even after body weight or BSA based dosing. Therefore, monitoring of coagulation with ACT seems crucial to ensure the patient has safe and tailor made peri-procedural anticoagulation. Likewise, repeated monitoring of the ACT at least every 30 minutes is necessary because of the large variation in heparin elimination. Future research needs to investigate whether a specific heparin protocol for females leads to safer anticoagulation, and possibly fewer complications.

**CONFLICT OF INTEREST**

None.

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**APPENDIX A. SUPPLEMENTARY DATA**

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejvs.2022.08.005.

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