

## **Predictors of Arterio-Venous Fistula Failure: A post-hoc analysis of the FAVOURED Study**

Yong Pey See<sup>1,3</sup>, Yeoungjee Cho<sup>1,2,11</sup>, Elaine M Pascoe<sup>2,11</sup>, Alan Cass<sup>4</sup>, Ashley Irish<sup>5,6</sup>, David Voss<sup>7</sup>, Kevan R Polkinghorne<sup>8</sup>, Lai Seong Hooi<sup>9</sup>, Loke-Meng Ong<sup>10</sup>, Peta-Anne Paul-Brent<sup>2,11</sup>, Peter G Kerr<sup>8</sup>, Trevor A Mori<sup>6</sup>, Carmel M Hawley<sup>1,2,11</sup>, David W Johnson<sup>1,2,11</sup>, and Andrea K Viecelli<sup>1,2,11</sup>, on Behalf of the Omega 3 Fatty Acids (Fish Oils) and Aspirin in Vascular Access Outcomes in Renal Disease (FAVOURED) Study Collaborative Group\*

<sup>1</sup>Department of Nephrology, Princess Alexandra Hospital, Brisbane, Australia; <sup>2</sup>Australasian Kidney Trial Network, School of Medicine, University of Queensland, Brisbane, Australia;

<sup>3</sup>Department of Renal Medicine, Tan Tock Seng Hospital, Singapore; <sup>4</sup>Menzies School of Health Research, Charles Darwin University, Darwin, Australia; <sup>5</sup>Department of Nephrology, Fiona Stanley Hospital, Perth, Australia; <sup>6</sup>Medical School, University of Western Australia, Perth, Australia; <sup>7</sup>Middlemore Renal Department, Counties-Manukau Health, Auckland, New Zealand; <sup>8</sup>Department of Nephrology, Monash Medical Centre, Melbourne, Australia;

<sup>9</sup>Department of Medicine and Hemodialysis Unit, Hospital Sultanah Aminah, Johor Bahru, Malaysia; <sup>10</sup>Department of Nephrology, Penang Hospital, Georgetown, Malaysia;

<sup>11</sup>Translational Research Institute, Brisbane, Australia;

### **Corresponding author:**

Dr Andrea Viecelli, MD, FRACP, PhD  
Department of Nephrology  
Princess Alexandra Hospital  
Level 2, ARTS Building  
199 Ipswich Road, Woolloongabba, QLD 4102, Australia  
Phone: +61 7 3176 5080  
Fax: +61 7 3176 5480  
Email: [andrea.viecelli@health.qld.gov.au](mailto:andrea.viecelli@health.qld.gov.au)

## **ABSTRACT**

### **Background**

An autologous arteriovenous fistula (AVF) is the preferred hemodialysis vascular access but successful creation is hampered by high rates of AVF failure. This study aimed to evaluate patient and surgical factors associated with AVF failure to improve vascular access selection and outcomes.

### **Methods**

This is a post-hoc analysis of all participants of FAVOURED, a multi-center, double-blind, multinational, randomized placebo-controlled trial evaluating the effect of fish oil and/or aspirin in preventing AVF failure in patients receiving hemodialysis. The primary outcome of AVF failure was a composite of fistula thrombosis and/or abandonment and/or cannulation failure at 12 months post AVF creation and secondary outcomes included individual outcome components. Patient data (demographics, comorbidities, medications and laboratory data) and surgical factors (surgical expertise, anesthetic, intraoperative heparin use) were examined using multivariable logistic regression analyses to evaluate associations with AVF failure.

### **Results**

Of 536 participants, 253 patients (47%) experienced AVF failure during the study period. The mean age was  $55 \pm 14.4$  years, 64% were male, 45% were diabetic and 4% had peripheral vascular disease. Factors associated with AVF failure included female sex (odds ratio [OR] 1.79, 95% confidence interval [CI] 1.20-2.68), lower diastolic blood pressure (OR for higher DBP 0.85, 95% CI 0.74-0.99), presence of central venous catheter (OR 1.49, 95% CI 1.02-2.20,  $p=0.04$ ) and aspirin requirement (OR 1.60, 95% CI 1.00-2.56).

### **Conclusions**

Female sex, requirement for aspirin therapy, requiring hemodialysis via a central venous catheter and lower diastolic blood pressure were factors associated with higher odds of AVF failure. These associations have potential implications for vascular access planning and warrant further studies.

## INTRODUCTION

An autologous arteriovenous fistula (AVF) is the vascular access of choice<sup>1-4</sup> for most patients requiring hemodialysis due to improved longevity once successfully established, lower associated mortality<sup>5</sup> and lower health costs<sup>6</sup> compared to an arteriovenous graft or central venous catheter. These long-term benefits are however hampered by exceedingly high rates of early AVF failure due to thrombosis and maturation failure affecting up to 60% of patients<sup>7,8</sup>. It is thus not surprising that vascular access function is one of the most critically important outcomes for patients on hemodialysis and their caregivers<sup>9</sup>.

Previous studies have identified delayed nephrology care<sup>10,11</sup>, smaller arterial<sup>12-13</sup> and venous<sup>12,13,15,16</sup> calibre on sonographic evaluation and demographic factors such as older age and female sex<sup>11,15,17-19</sup> to be associated with AVF failure while greater surgical experience and use of regional anesthesia<sup>21-26</sup> were associated with better AVF outcomes. Unfortunately, many of these studies have shown inconsistent and conflicting outcomes likely driven by differences in study populations, sample size and methodology as well as substantial heterogeneity of outcome definitions<sup>7</sup>. Scoring systems incorporating multiple factors have been used to improve predictive scoring for AVF failure; although showing promise<sup>27</sup> they have not been shown to consistently predict vascular access outcomes when applied to different study populations<sup>10</sup>. Furthermore, few studies have evaluated potentially modifiable predictors such as surgical expertise or anesthetic technique in different study populations including Australian and New Zealand cohorts<sup>28-29</sup>.

This post-hoc analysis of the randomized controlled FAVOURED study conducted in Australia, New Zealand, Malaysia and United Kingdom was therefore performed to identify

potentially modifiable pre- and perioperative patient and surgical factors associated with AVF failure, defined as a clinically relevant composite outcome of thrombosis, abandonment and/or failure to cannulate within one year of AVF creation in patients requiring hemodialysis.

## **METHODS**

The FAVOURED trial was a multicenter, double-blind randomized, placebo-controlled trial conducted in 35 hemodialysis centers in Australia, New Zealand, Malaysia and United Kingdom investigating the effect of fish oil supplementation or aspirin on preventing AVF failure amongst patients recruited between August 2008 and February 2014. The trial was registered with the Australia and New Zealand Clinical Trial Registry (ACTRN12607000569404). The original 2 by 2 factorial design was amended in June 2011 to allow patients who required ongoing aspirin therapy to be randomized to fish oil or matching placebo but continue open-label aspirin use when deemed medically required<sup>30</sup>. The FAVOURED trial had obtained local Human Research Ethics Committees in all participating centres prior to trial commencement.

Adult patients aged  $\geq 19$  years with stage 4 or 5 chronic kidney disease receiving or expected to receive hemodialysis within 12 months and scheduled for AVF creation were eligible for the study. Patients with significant bleeding risk or contraindication to use of the study agents were excluded. A detailed description of the study protocol has been published previously<sup>31</sup>.

Patient-related factors collected at baseline prior to AVF creation included demographic data (i.e. sex, age, region of recruitment [Australia, New Zealand and UK collectively referred as ANZ versus Malaysia]), clinical information (i.e. body mass index [BMI], waist-hip ratio, baseline blood pressure [BP] taken as per local practices, smoking history, cause of end-stage kidney disease [ESKD], presence of diabetes mellitus [DM], hypertension, peripheral vascular disease [PVD], ischemic heart disease [IHD], cerebrovascular disease status, presence of central venous catheter [CVC] and medications such as statins, erythropoiesis stimulating agents [ESA], calcium channel blockers [CCB], beta-blockers, aspirin and fish oil) and relevant blood investigations (i.e. full blood count [FBC], coagulation profile [INR, APTT], serum calcium, phosphate, parathyroid hormone [PTH], low density lipoprotein cholesterol [LDL-C] and glycated haemoglobin [HbA1c]) at the time of AVF creation. Recorded surgical factors included the type of anesthesia used (i.e. general, regional or local), intra-operative heparin use, surgical expertise defined by level of training (i.e. trainee such as resident and registrar versus consultant) and type of AVF created (i.e. radiocephalic [RC], brachiocephalic [BC], brachio basilic [BB] and others).

The primary outcome of AVF failure was a composite of fistula thrombosis and/or abandonment and/or cannulation failure at 12 months. Thrombosis was defined as the absence of a thrill or bruit by clinical examination and/or requirement of rescue intervention (medical thrombolysis or surgical thrombectomy). Abandonment was defined as permanent abandonment of the study AVF including unsalvageable thrombosis of the study AVF, imaging showing that the study AVF was unusable or not amenable to any intervention for its improvement, insertion of another dialysis access (new AVF, AVG, CVC or peritoneal dialysis access) or ligation of the study AVF. Cannulation failure was defined as failure to

successfully cannulate the study AVF during 8 or more of 12 consecutive hemodialysis sessions during the cannulation assessment period (Table S1).

## **STATISTICAL ANALYSIS**

Baseline characteristics are presented as frequency (percentage), mean ( $\pm$  standard deviation) or median (interquartile range), as appropriate. Differences between patients with and without AVF failure were analyzed using the independent student t-test or Mann-Whitney U test for continuous variables according to data distribution.  $\chi^2$  test and Fisher's exact test were performed for categorical variables, as appropriate.

Associations between factors and the composite outcome of AVF failure were examined by univariable and multivariable logistic regression. All patient factors that were found to be associated with AVF failure on univariable logistic regression with p-values < 0.2 were included in a multivariable logistic regression in Model 1. Diabetes mellitus was pre-specified for inclusion in Model 1 due to its clinical importance regardless of p-value on univariable logistic regression<sup>32</sup>. Similarly, the use of study agents (open-label aspirin, randomized aspirin or matching placebo and fish oil or matching placebo) was included in Model 1 as these agents were randomized interventions from the original FAVOURED trial. Surgical factors associated with AVF failure on univariable analysis (p < 0.2) or pre-specified for inclusion due to its clinical importance (i.e. type of anesthesia, surgical expertise)<sup>25</sup> were then included to patient factors in Model 1 to derive Model 2. Factors with more than 5% missing data were excluded from multivariable logistic regression. On preliminary analysis, sex-specific differences in diastolic BP (DBP) and site of AVF created were observed and therefore interactions between DBP and gender as well as site of AVF and gender on AVF

failures were examined. Model fit was evaluated using the Hosmer-Lemeshow test and diagnostic accuracy was tested by the area under the operating characteristic curve (AUC). Subsequently, Model 2 was applied to determine factors associated with individual cause specific components of AVF failure (i.e. AVF thrombosis, abandonment and failure to cannulate at 12 months). P values <0.05 were considered statistically significant. Statistical analyzes were performed with Stata version 14.1 (Stata Corporation, College Station, Texas, USA).

## **RESULTS**

### **Study participants**

All 536 participants randomized and analyzed in the original FAVOURED study were included in this present study<sup>31</sup>. Amongst those recruited, 334 participants were enrolled from Australia (62%), 144 from Malaysia (27%), 49 from New Zealand (9%), and 9 from United Kingdom (2%). The baseline characteristics for participants with and without AVF failure are shown in Table 1. More than 5% missing data were present for laboratory parameters including HbA1c, LDL-C, INR, APTT and PTH levels.

### **Predictors of AVF failure**

AVF failure occurred in 253 participants (47%); 109 participants experienced at least one episode of AVF thrombosis, 121 participants had AVF abandonment and 212 participants experienced cannulation failure. On univariable logistic regression, female sex, older age, non-Malaysian region of recruitment, absence of hypertension, lower DBP and mean arterial pressure, higher parathyroid hormone level and open labelled (i.e. medically required) aspirin use were statistically significantly associated with increased odds of AVF failure (Table 2). Surgical expertise, type of anesthesia used, intra-operative anticoagulation use or the type of AVF created were not associated with AVF failure on univariable logistic regression.



Multivariable logistic regression of patient factors including female sex, age, region of recruitment, DBP, presence of DM, presence of PVD, presence of CVC, hemoglobin levels, use of CCB, randomization to aspirin and fish oil, was performed in Model 1. Diastolic blood pressure was chosen over history of hypertension and mean arterial pressure for inclusion into Model 1 as it is biologically plausible and most strongly associated statistically on univariable logistic regression. Female sex (adjusted OR 1.60, 95% CI 1.10-2.32), presence of CVC (adjusted OR 1.53, 95% CI 1.05-2.23) and open labelled aspirin use (adjusted OR 1.59, 95% CI 1.00-2.53) were associated with increased odds of AVF failure (Table 2). In contrast, every 10mmHg increase in DBP (adjusted OR 0.84, 95% CI 0.73-0.97) and Malaysian region of recruitment (adjusted OR 0.60, 95% CI 0.38-0.95 compared to ANZ) were associated with lower odds of AVF failure (Table 2).

When surgical factors (surgical expertise, type of AVF created and use of local versus general or regional anesthesia) were added (Model 2), Malaysian region of recruitment was no longer associated with lower AVF failure (adjusted OR 0.66, 95% CI 0.34-1.25). Female sex (adjusted OR 1.79, 95% CI 1.20-2.68), DBP (adjusted OR 0.85, 95% CI 0.74-0.99), presence of CVC (adjusted OR 1.49, 95% CI 1.02-2.20) and open labelled use of aspirin (adjusted OR 1.60, 95% CI 1.00-2.56) remained associated with AVF failure. None of the other surgical factors were associated with AVF failure in Model 2. The Hosmer-Lemeshow goodness of fit were 6 ( $p=0.65$ ) and 8.26 ( $p=0.41$ ) for Model 1 and 2 respectively. Furthermore, the addition of surgical factors did not improve the prediction of AVF failure (AUC 0.67 compared to 0.65 for Model 1,  $p=0.08$ ).

Amongst the factors identified to be associated with AVF failure, diastolic blood pressure was potentially modifiable. An inverse relationship was observed between DBP and AVF failure that remained unchanged on multivariable analysis when factors used in Model 2 were added (Figure 1). The probability of AVF failure was greater than 50% with diastolic pressure of 80 mmHg and lower (Figure 1). There was similar trend towards greater probability of AVF failure with decreasing mean arterial pressure (Figure S1) and to a lesser extent with systolic BP (Figure S2). On the other hand, an association between higher pulse pressure and higher probability of AVF failure was observed (Figure S3).

Female participants had on average lower DBP ( $79.6 \pm 13.0$  mmHg) at baseline compared to males ( $82.4 \pm 13.5$  mmHg,  $p=0.02$ ) (Table S2), but no significant interaction between blood pressure and sex was observed ( $p=0.79$ ). It was also noted that female patients had more upper arm AVFs created (62%) compared to only 29% (Table S3) in males but no significant interaction between AVF site and sex was observed (OR 1.20, 0.57-2.55  $p=0.10$ ).

### **Predictors of the individual components of AVF failure**

The factors associated with the individual outcomes of AVF thrombosis, abandonment and cannulation failure were different (Table 3). Female sex was associated with increased odds of AVF abandonment (adjusted OR 2.02, 95% CI 1.27-3.20) and cannulation failure (adjusted OR 1.74, 95% CI 1.16-2.61) but not AVF thrombosis. The presence of PVD was associated with increased odds of AVF abandonment (adjusted OR 3.24, 95% CI 1.31-7.98). The presence of CVC, lower DBP and non-Malaysian region of recruitment were associated with higher odds of cannulation failure (adjusted OR [CVC] 1.66, 95% CI 1.11-2.46, [DBP] 0.80, 95% CI 0.68-0.93, [Region of recruitment] 0.50 95% CI 0.26-0.98, respectively). BC-

AVF were less likely to be abandoned compared to RC AVF (adjusted OR 0.48, 95% CI 0.29-0.81) while BB-AVF were more likely to fail cannulation compared to RC-AVF (adjusted OR 2.24, 95% CI 1.07-4.53).

## **DISCUSSION**

This post-hoc analysis of a large multinational, multicentre, randomized controlled trial demonstrated that AVF failure was independently associated with female sex, lower diastolic pressure, presence of CVC and medically required use of aspirin. Potentially modifiable surgery-related factors including surgical expertise, anesthesia and AVF type were not associated with AVF failure. Factors associated with individual components of AVF failure differed. Female sex, presence of PVD and type of AVF created were associated with AVF abandonment while low diastolic blood pressure, presence of central venous catheter and non-Malaysia region of recruitment were additional risk factors for cannulation failure.

The association between female sex and higher risk of AVF failure has been reported previously<sup>12,19,20,33</sup>, however the biological process underpinning this observation remains uncertain. While there is commonly held belief that females have smaller vessel calibre and therefore are at increased risk of AVF failure, a retrospective sonographic evaluation of vessel size in 192 patients did not find consistent differences in vascular calibre between the two sexes<sup>34</sup>. In this study, females were twofold more likely to have their AVF created in their upper limb compared to their male counterparts. This may reflect physicians' preference for upper arm AVF in females to avoid inadequate vessel size. Unfortunately, there was no mandatory sonographic assessment of participants' vessels in the FAVOURED trial to further explore this hypothesis. Although female participants in the FAVOURED study exhibited

lower diastolic blood pressure, no significant interaction was observed to account for additional risk attributable to sex. Despite the increased risk of AVF failure in females, careful selection and preparation of female patients considered suitable for AVF surgery with thorough physical examination and pre-operative sonographic examination of venous access may further improve outcomes<sup>16,35</sup>.

Earlier studies suggested that tight control of systolic, diastolic and/or mean arterial pressures pre-operatively was associated with increased odds of AVF thrombosis<sup>36,37</sup> and early primary AVF failure<sup>38,39</sup>. Pandey et al studied 224 patients prospectively and reported that patients with early AVF failure had lower diastolic blood pressure of 88.4 mmHg compared to 91.2mmHg in those with AVF success<sup>39</sup>. Similarly, a retrospective review of 1051 patients found patients with early primary failure had lower diastolic pressure of 79.7mmHg compared to 83.1mmHg in those with AVF success<sup>38</sup>. In the present study, lower diastolic blood pressure and mean arterial pressure pre-surgery were associated with an increased risk of AVF failure with an AVF failure exceeding 50% at a diastolic blood pressure of 80 mmHg or lower. Higher pulse pressure, a potential measure of decreased vessel compliance, was observed to be associated with higher odds of AVF failure but this was not statistically significant. After the creation of AVF, intra-dialytic hypotension has also been associated with a higher risk of AVF thrombosis<sup>40</sup>. Lower diastolic pressure may lead to venous stasis thereby predisposing to early AVF thrombosis and may also reflect reduced vascular compliance associated with a wider pulse pressure, both impairing vascular remodelling and maturation<sup>41</sup>. These findings suggest that maintaining a higher perioperative diastolic blood pressure may be a modifiable factor to improve AVF outcomes. However, prospective randomized controlled studies are required to establish causality and recommend an optimal

blood pressure target taking into consideration the overall perioperative risk profile and anticipated benefits.

The finding of an increased risk of AVF failure in patients with a CVC in this study is consistent with that reported in the Dialysis Outcomes and Practice Patterns Study<sup>42-44</sup>. This increased risk may be related to potential hemodynamic effects and central vein stenosis associated with ipsilateral catheter placement<sup>45</sup>. In addition, CVC predispose patients to blood stream infection and hospitalization<sup>46</sup> which could indirectly predispose to AVF failure via hypotension and the inflammatory response. However, CVC use may be a surrogate of patients referred late to a nephrology service, a known predictor of AVF failure<sup>11,44</sup> or other unadjusted confounders.

Whilst the FAVOURED study demonstrated that neither aspirin nor fish oil use was protective against AVF failure<sup>31</sup>, this post hoc analysis did find that patients who were required to continue on open-label aspirin for clinical indications were more likely to experience AVF failure. Although cardiovascular disease such as IHD and PVD were not associated with AVF outcomes, it is possible that open-label aspirin use identified patients with more severe cardiovascular disease that was not adequately adjusted for in multivariable logistic regression.

Another finding of the present study was that different factors were associated with individual components of AVF failure. While female sex was associated with overall poorer AVF outcomes, the presence of PVD was the predominant predictor of AVF abandonment. Participants with PVD may be at increased risk of steal syndrome or identify a population

with more diffuse atherosclerosis, which might limit intervention to promote maturation and prevent AVF abandonment. While the AVF location was not significantly associated with an increased risk of the composite outcome of AVF failure ( $p=0.06$ ), it was associated with an increased risk of cannulation failure ( $p=0.04$ ); Specifically, brachiobasilic AVFs were less likely to be successfully cannulated compared to radiocephalic AVFs. However, it remains unclear whether this is a statistical type 1 error given the number of comparisons and small sample size. Alternatively, the observed association may have been due to the fact that brachiobasilic vessels tend to be deeper and technically more challenging to cannulate. It is also possible that other unadjusted factors including prior history of AVF failure as a predictor of future AVF failure<sup>47,48</sup> maybe driving this association.

Despite selection of a comprehensive list of factors that might predict AVF failure, the overall diagnostic accuracy of the complete model was modest with an AUC of 0.67. It is possible that the predictive ability of the model could be further improved by including other pre- and post-operative measures, such as pre-operative arterial and venous vessel size and adherence with vascular access surveillance and management protocols, which were not investigated in this study<sup>16,21</sup>. Sonographic evaluation of artery and venous calibre has been associated with better selection of vessels suitable for AVF creation<sup>12,13,15,16</sup>. Although, post-operative care, such as dedicated protocolised surveillance to detect early AVF dysfunction<sup>21</sup>, has yielded mixed results with respect to preventing AVF failure in studies, it is possible that this may improve model prediction in the present study. While prediction models for AVF success are helpful, their accuracy is limited by the complexity of the process to establish a successful AVF. In particular, some practice-related factors of interest such as surgical and cannulation expertise and techniques are difficult to standardize and assess consistently across different studies and settings, thereby limiting the accuracy of prediction models.

Beyond having a successful AVF, there should also be consideration of alternatives to AVF such as arterio-venous graft<sup>49</sup>, alternative dialysis such as peritoneal dialysis and even long-term tunnelled dialysis catheter depending on patient's preferences, prior access history, expected life expectancy, anticipated dialysis start and course of kidney replacement<sup>3</sup>.

The strengths of this study included the use of a well-characterized study population from a randomized controlled trial, ensuring standardized and accurate collection of patient and surgical variables. A systematic and methodical approach was also taken in the analysis. However, several limitations exist, including the limited number of participants and events, insufficient granularity of data (such as severity of comorbidities, location of the CVC in relation to the AVF, history of previous failed vascular access, indication of AVF abandonment or standardized pre-operative sonographic assessment of vessel size and quality), lack of standardized blood pressure assessment and data missingness that potentially introduced informative censoring bias. Furthermore, country-specific variation in practice patterns and expertise (e.g. surgical expertise measured as number of AVF creations as compared to phase of surgical training in this study or cannulation skills) were unavailable to better determine potentially modifiable predictors of AVF failure. This hypothesis is supported by the observation of lower risk of AVF failure amongst participants recruited in Malaysia compared to Australia, New Zealand and United Kingdom on univariable logistic regression which was no longer evident when adjusting for surgical factors in Model 2. Lastly, the trial population was younger with less PVD compared to the general hemodialysis population which could limit the generalizability of the result.

## **CONCLUSION:**

Failure of newly created AVF is a major barrier to the successful establishment of hemodialysis access and occurred in almost 50% of study participants. Female sex, low diastolic blood pressure, the need for aspirin therapy and central venous catheter dependence were associated with an increased risk of AVF failure. Avoidance of peri-operative hypotension and central venous catheters at the time of AVF creation may help improve AVF outcomes and warrants further study.

## **DISCLOSURES**

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*The FAVOURED Study Collaborative Group* comprises the Trial Steering Committee: Chen Au Peh, Elaine Beller, Alan Cass, Sharan Dogra, David Gracey, Elvie Haluszkiewicz, Carmel Hawley, Lai-Seong Hooi, Colin Hutchison, Ashley Irish, Peter Kerr, Amanda Mather, Stephen

McDonald, Chris McIntyre, Trevor Mori, Elaine Pascoe, Kevan Polkinghorne, Amanda Robertson, Johan Rosman, David Voss.

The Data and Safety Monitoring Board: Andrew Tonkin, Andrew Forbes, Adeera Levin, David C. Wheeler.

***The Investigators:*** Krishna Karpe, Patricia Johnson, Martin Gallagher, Jenny Burman, Alistair Gillies, Leanne Garvey, Michael Suranyi, Belinda Yip, Grant Luxton, Debbie Pugh, Kathleen McNamara, Bruce Cooper, Cheryl Macadam, Kate Wyburn, Samantha Hand, Meg Jardine, Anne Heath, Dakshinamurthy Divi, Tammy Schmidt, Andrew Bofinger, Leanne Glancy, David Mudge, Amanda Coburn, Sree Krishna Venuthurpali, Elizabeth Coroneos, Suzi Hanna, George Kan, Vicki Hartig, Karen Katil, Meg Hockley, Peter Mount, Pascal Bisscheroux, Maree Ross-Smith, Rob McGinley, Anthony Perkins, Kevan Polkinghorne, Mechelle Seneviratne, Eugenie Pedagogos, Connie Karchimkus, Solomon Menahem, Suzanne Douglas, Vicki Levidiotis, Debra Broomfield, Jason Bennier, Paolo Ferrari, Ulrich Steinweadel, Ashley Irish, Maria Martin, Monika Chang, Sharan Dogra, Susan Pellicano, Helen Herson, Ravindran Visvanathan, Norlida Omar, Zanariah Arsat, Loke-Meng Ong, Ah-Heong Ang, Sukeri Mohamad, Najhah Md Nawi, Anita Bhajan Manocha, Norhaniza Bt Adom, Lai-Seong Hooi, Wen Jiun Liu, Mohd Rais Bin Periman, Norisham Bin Mohd Dom, Zawawi Nordin, Suhaizan Bt Mohd Rasidi, Indralingam Vaithilingam, Ramli Zaraee, Lim Soo Kun, Tiviyah Sinniah, John Schollum, Liz Berry, David Voss, Penelope Eadie, Chris McIntyre, Marie Appleby.

***The AKTN Executive Committee Members:*** Neil Boudville, Alan Cass, Carmel Hawley, Meg Jardine, David Johnson, Vlado Perkovic.

***The AKTN Project Management Team:*** Carmel Hawley, David Johnson, Alicia Morrish, Elaine Pascoe, Peta-Anne Paul-Brent, Donna Reidlinger, Liza Vergara. Elaine Beller, Sunil Badve, Anish Scaria, Stephane Heritier.

The complete list of contributing institutions is included as a supplemental appendix.

### **Author Contributions**

YP See: Formal analysis; Methodology; Project administration; Writing - original draft; Writing - review and editing

Y Cho: Formal analysis; Supervision; Writing - original draft; Writing - review and editing

E Pascoe: Data curation; Formal analysis; Methodology; Supervision; Writing - original draft; Writing - review and editing

A Cass: Writing - review and editing

D Voss: Writing - review and editing

L-S Hooi: Writing - review and editing

L Ong: Writing - review and editing

PA Paul-Brent: Data curation; Project administration; Writing - review and editing

P Kerr: Writing - review and editing

T Mori: Writing - review and editing

C Hawley: Conceptualization; Formal analysis; Methodology; Supervision; Writing - original draft; Writing - review and editing

D Johnson: Conceptualization; Methodology; Supervision; Writing - original draft; Writing - review and editing

A Irish: Writing - review and editing

K Polkinghorne: Writing - review and editing

A Viecelli: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Supervision; Writing - original draft; Writing - review and editing

### **Supplementary Material**

**Appendix:** Omega 3 Fatty Acids (Fish Oils) and Aspirin in Vascular Access Outcomes in Renal Disease (FAVOURED) Study Collaborative Group

**Table S1.** Cannulation Assessment Periods

**Table S2.** Baseline blood pressure profile according to gender

**Table S3.** Site of AVF created according to gender

**Figure S1.** Proportion of arteriovenous fistula failure (composite outcome of arteriovenous fistula abandonment, thrombosis and failure to cannulate) with change in mean arterial pressure.

**Figure S2.** Proportion of arteriovenous fistula failure (composite outcome of arteriovenous fistula abandonment, thrombosis and failure to cannulate) with change in systolic blood pressure.

**Figure S3.** Proportion of arteriovenous fistula failure (composite outcome of arteriovenous fistula abandonment, thrombosis and failure to cannulate) with change in pulse pressure.

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## TABLES

**Table 1.** Baseline characteristics of the study population.

Parameter	All participants (n=536)	Patients without AVF failure <sup>^</sup> (n=283)	Patients with AVF failure <sup>^</sup> (n=253)	p- value
Female, n (%)	194 (36)	89 (32)	105 (42)	0.02
Age (years)	55.0 ± 14.4	53.6 ± 14.3	56.5 ± 14.4	0.02
Ethnicity, n (%)				0.25
-Caucasoid	289 (54)	143 (51)	146 (58)	
-Asians	169 (32)	101 (36)	68 (27)	
-Aboriginal and Torres Strait Islander	21 (4)	9 (3)	12 (5)	
-Maori and Pacific Islander	38 (7)	20 (7)	18 (7)	
-Others	19 (4)	10 (4)	9 (4)	
Region of recruitment, n (%)				0.01
- Australia/NZ/UK	392 (73)	193 (68)	199 (79)	
- Malaysia	144 (27)	90 (32)	54 (21)	
Cause of ESKD, n (%)				0.90
- Diabetes Mellitus	202 (38)	104 (37)	98 (39)	
- Glomerulonephritis	72 (13)	40 (14)	32 (13)	
- Hypertension	71 (13)	40 (14)	31 (12)	
- Polycystic	40 (8)	23 (8)	17 (7)	
- Reflux	26 (5)	14 (5)	12 (5)	
- Others	125 (23)	62 (22)	63 (25)	
BMI	27.2 (23.4-32.0)	27.1 (23.9-31.7)	27.5 (23.0-32.5)	0.83
Comorbidity, n (%)				
-Hypertension	475 (89)	259 (92)	216 (85)	0.03
-DM	243 (45)	132 (47)	111 (44)	0.52
-IHD	53 (10)	24 (9)	29 (12)	0.25
-CCF	21 (4)	12 (4)	9 (4)	0.68
-PVD	23 (4)	8 (3)	15 (6)	0.08
-CVD	17 (3)	11 (4)	6 (2)	0.32
-Composite of IHD, CVD and PVD	79 (15)	38 (13)	41(16)	0.37
Baseline blood pressure (mmHg)				
-SBP	146.1 ± 23.0	147.2 ± 21.9	144.9 ± 24.2	0.25
-DBP	81.4 ± 13.4	83.1 ±12.9	79.5 ± 13.6	<0.01
-MAP	103.0 ± 14.4	104.5 ± 13.6	101.3 ± 15.0	0.01
-PP	64.1 ± 20.0	64.1 ± 19.6	65.4 ± 20.5	0.45
HbA1c (%) *	6.2 ± 1.4	6.3 ±1.5	6.2 ± 1.3	0.25
LDL-C (mmol/L) *	2.4 (1.8-3.1)	2.6 (1.9-3.3)	2.3 (1.7-3.1)	0.07
Smoking, n (%)				0.68
- never	264 (49)	137 (48)	127 (50)	
- current or previous	272 (51)	146 (52)	126 (50)	
Current or previous history of KRT, n (%)	268 (50)	139 (49)	129 (51)	0.63
Presence of central venous catheter, n (%)	218 (41)	107 (38)	111 (44)	0.15
Serum Albumin (g/L)	36 (32-40)	37 (33-41)	36 (32-40)	0.22
PTH (pmol/L) *	28 (16.1-45.3)	30.2 (16.6-50.8)	26.6 (15.2-40.8)	0.05
INR*	1(1.0-1.1)	1(0.9-1.1)	1(1-1.1)	0.58
APTT*	30.1(27-34)	31(27.7-35)	30 (27-34)	0.09

Hemoglobin (g/L)	108.2 ±18.6	106.8 ±17.7	109.7 ±19.5	0.08
Platelets	233 (191-288)	233(193-289)	233(191-287)	0.83
Medications, n (%)				
- Statin	275 (51)	148 (52)	127 (50)	0.63
- ESA,	253 (47)	139 (49)	114 (45)	0.35
- Beta-blockers	247 (46)	135 (48)	112 (44)	0.43
- ACE-I /ARB	224 (42)	117 (41)	107 (42)	0.82
- CCB	299 (56)	167 (59)	132 (52)	0.11
Surgeons, n (%)				0.43
-Consultants	419 (78)	225 (80)	194 (77)	
-Registrars/Residents	117 (22)	58 (21)	59 (23)	
Type of anesthesia, n (%)				
-Local	211 (40)	122 (43)	89 (36)	0.08
-Regional/General anesthesia	322 (60)	161 (57)	161 (64)	
AVF created, n (%)				0.08
- Radiocephalic	312 (58)	168 (59)	144 (57)	
- Brachiocephalic	180 (34)	99 (35)	81 (32)	
- Brachiobasilic	37 (7)	12 (4)	25 (10)	
- Others	7 (1)	4 (1)	3 (1)	
Intra-operative heparin, n (%)	352 (66)	184 (65)	168 (67)	0.73
Randomization to aspirin, n (%)	194 (36)			
- Randomized to placebo	194 (36)	107 (38)	87 (34)	0.04
- Randomized to aspirin	148 (28)	111 (39)	83 (33)	
- Open label aspirin		65 (23)	83 (33)	
Randomization to Fish Oil, n (%)	270 (50)	142 (50)	128 (51)	0.92

# Continuous variables are presented in means ( $\pm$  standard deviation) if normally distributed and median (interquartile range) if non-normal distribution.

^ AVF failure is defined as composite of AVF thrombosis and/or failure to cannulate and/or abandonment of AVF within 12 months of AVF creation

\* Variables with more than 5% missing data

Abbreviations: NZ- New Zealand; UK- United Kingdom; ESKD – end-stage kidney disease; BMI – body mass index; DM- diabetes mellitus; IHD- ischemic heart disease; CCF - congestive cardiac failure; CVD - cerebrovascular disease; GN – glomerulonephritis; SBP- systolic blood pressure; DBP -diastolic blood pressure; MAP – mean arterial pressure; PP – pulse pressure; KRT – Kidney replacement therapy; LDL-C – low-density lipoprotein; PTH - parathyroid hormone; PVD - peripheral vascular disease; INR- international normalized ratio; APTT- activated partial thromboplastin time; ESA – erythropoietin stimulating agent; ACE-I/ARB- angiotensin converting enzyme inhibitor/ angiotensin receptor blocker; CCB- calcium channel blocker; AVF – arteriovenous fistula

Independent student t-test and Mann-Whitney U test performed for continuous variable when appropriate. Chi-squared test and Fischer-exact test performed for categorical variables when appropriate

**Table 2.** Logistic Regression of patient and surgical factors associated with arterio-venous fistula failure.

Parameter	Univariable Odds Ratio (95% CI)	P-value	Model 1^ Odds Ratio (95% CI)	P-value	Model 2* Odds Ratio (95% CI)	P-value
Female	1.54 (1.09-2.20)	0.02	1.60 (1.10-2.32)	0.01	1.79 (1.20-2.68)	<0.01
Age (per 10 years)	1.15 (1.02-1.29)	0.02	1.06 (0.92-1.21)	0.42	1.06 (0.92-1.22)	0.41
Ethnicity						
-Caucasoid	Ref	0.25	-	-	-	-
-Asians	0.66 (0.45-0.97)					
-Aboriginal and Torres Strait Islander	1.31(0.53-3.19)					
-Maori and Pacific Islander	0.88 (0.45-1.74)					
-Others	0.88 (0.35-2.23)					
Region ^						
- Australia/NZ/UK	Ref	0.01	Ref	0.03	Ref	0.20
- Malaysia	0.58 (0.39-0.86)		0.60 (0.38-0.95)		0.66 (0.34-1.25)	
Cause of ESKD						
- DM	Ref	0.90	-	-	-	-
- GN	0.85 (0.49-1.46)					
- Hypertension	0.82 (0.48-1.42)					
- APKD	0.78 (0.40-1.56)					
- Reflux	0.91 (0.40-2.06)					
- Others	1.08 (0.69-1.68)					
BMI	1.01 (0.99-1.04)	0.33	-	-	-	-
Hypertension	0.54 (0.31-0.93)	0.03	-	-	-	-
DM	0.89 (0.64-1.26)	0.52	0.81 (0.55-1.20)	0.29	0.85 (0.57-1.27)	0.42
IHD	1.40 (0.79-2.47)	0.25	-	-	-	-
PVD	2.17 (0.90-5.20)	0.08	1.78 (0.70-4.53)	0.23	1.87 (0.74-4.78)	0.19
CCF	0.83 (0.35-2.01)	0.68	-	-	-	-
Cerebrovascular disease	0.60 (0.22-1.65)	0.32	-	-	-	-
Composite of IHD, CVD and PVD	1.25 (0.77-2.01)	0.37	-	-	-	-
SBP (per 10 mmHg)	0.96 (0.89-1.03)	0.25	-	-	-	-
DBP (per 10 mmHg)	0.81 (0.71-0.93)	<0.01	0.84 (0.73-0.97)	0.02	0.85 (0.74-0.99)	0.04
MAP (per 10 mmHg)	0.85 (0.76-0.96)	0.01	-	-	-	-

PP (per 10 mmHg)	1.03 (0.95-1.13)	0.45	-	-	-	-
HbA1c (%) <sup>#</sup>	0.93 (0.82-1.05)	0.25	-	-	-	-
LDL-C (mmol/L) <sup>#</sup>	0.86 (0.72-1.01)	0.07	-	-	-	-
Smoking						
- Never smoker	Ref	0.68	-	-	-	-
- Current or former smoking	0.93 (0.66-1.31)					
Current or previous history of kidney replacement therapy	0.92 (0.65-1.29)	0.63	-	-	-	-
Presence of central venous catheter	1.29 (0.91-1.82)	0.15	1.53 (1.05-2.23)	0.03	1.49 (1.02-2.20)	0.04
Serum Albumin (g/L)	0.98 (0.96-1.01)	0.22	-	-	-	-
PTH (pmol/L) <sup>#</sup>	0.99 (0.99-0.99)	0.03	-	-	-	-
INR <sup>#</sup>	1.13 (0.57-2.26)	0.73	-	-	-	-
APTT <sup>#</sup>	0.99 (0.98-1.01)	0.40	-	-	-	-
Hemoglobin (g/L)	1.01 (1.00-1.02)	0.08	1.01 (0.99-1.02)	0.27	1.01 (0.99-1.02)	0.30
Platelets	1.00 (0.99-1.00)	0.85	-	-	-	-
Statin use	0.92 (0.65-1.29)	0.63				
ESA use	0.85 (0.60-1.19)	0.35				
Beta-blocker use	0.87 (0.62-1.22)	0.47				
ACE-I /ARB use	1.04 (0.74-1.47)	0.82				
CCB use	0.76 (0.54-1.07)	0.11	0.86 (0.60-1.25)	0.44	0.84 (0.58-1.22)	0.35
Surgeons						
-Trainees	Ref	0.43	-	-	Ref	0.66
-Consultant	0.85 (0.56-1.28)				0.91 (0.59-1.40)	
Anesthesia						
- Regional/General anesthesia	Ref				Ref	
- Local	0.73 (0.51-1.04)	0.08	-	-	0.93 (0.54-1.63)	0.81
Intra-operative heparin	1.07 (0.74-1.52)	0.73	-	-	-	-
AVF type						
-Radiocephalic	Ref	0.10	-	-	Ref	0.06
-Brachiocephalic	0.95 (0.66-1.38)				0.76 (0.50-1.16)	
-Bachiobasilic	2.43 (1.18-5.01)				2.24 (1.10-5.05)	
-Others	0.88 (0.19-3.97)				0.75 (0.15-3.71)	

Randomization to aspirin	Ref	0.04	Ref	0.05	Ref	0.03
- Randomized to placebo	0.92 (0.62-1.37)		0.89 (0.59-1.35)		0.85 (0.55-1.29)	
- Randomized to aspirin	1.57 (1.02-2.42)		1.59 (1.00-2.53)		1.60 (1.00-2.56)	
- Open label aspirin						
Randomization to fish oil use	1.02 (0.72-1.43)	0.92	1.05 (0.73-1.49)	0.80	1.09 (0.76-1.56)	0.64

^ Model 1: Multivariable logistic regression using patient factors with p<0.2 on univariable logistic analysis and less than 5% missing data inclusive of diabetes mellitus, randomization to aspirin and fish oil forced in, patient factors included are female, age, diastolic blood pressure, region, presence of peripheral vascular disease, presence of central venous catheter, use of calcium channel blocker and hemoglobin levels.

\* Model 2: Multivariable logistic regression using Model 1 with addition of surgical related factors such as surgeons, type of anesthesia use and type of AVF created.

^ Australia, New Zealand, United Kingdom region of recruitment was grouped when compared to Malaysian region of recruitment in this analysis.

# Variables with more than 5% missing data

Single imputation for missing values of individual outcome components was performed and described in detail in the primary outcome analysis <sup>31</sup>

Abbreviations: NZ- New Zealand; UK- United Kingdom; ESKD – end-stage kidney disease; BMI – body mass index; DM- diabetes mellitus; IHD- ischemic heart disease; CCF- congestive cardiac failure; PVD-peripheral vascular disease; CVD- cerebrovascular disease; GN – glomerulonephritis; SBP- systolic blood pressure; DBP-diastolic blood pressure; MAP- mean arterial pressure; PP – pulse pressure; LDL-C – low-density lipoprotein; PTH- parathyroid hormone; INR- international normalized ratio; APTT- activated partial thromboplastin time; ESA – erythropoietin stimulating agent; ACE-I/ARB- angiotensin converting enzyme inhibitor and receptor blocker; CCB- calcium channel blocker; AVF – arteriovenous fistula



**Table 3** Multivariable logistic regression analysis of patient and surgical factors for individual outcome components including AVF abandonment, thrombosis and cannulation failure at 12 months.

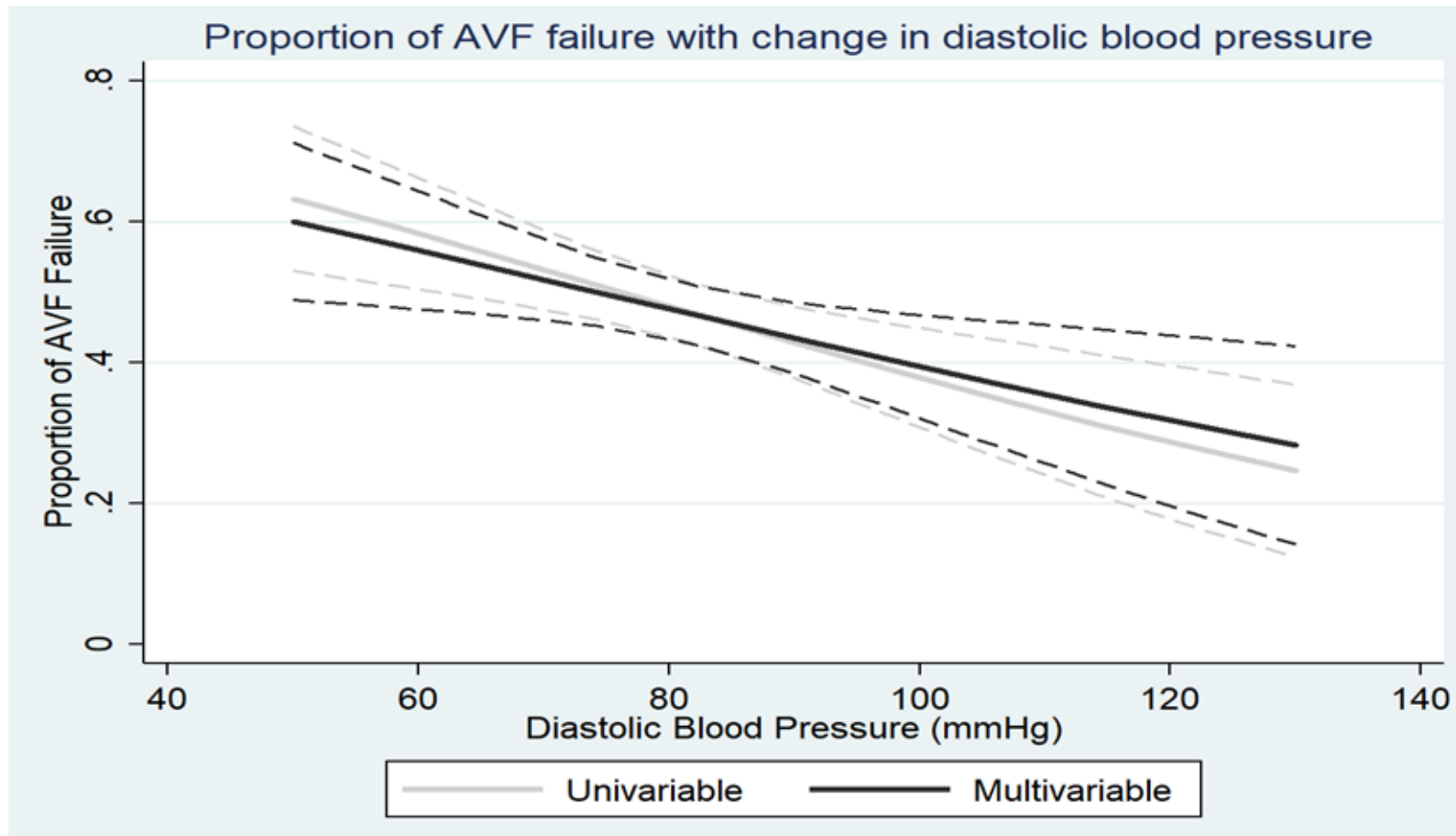
Parameter	Abandonment	p-value	Thrombosis	p-value	Failure to Cannulate	p-value
Participants with event	121		109		212	
Female sex	2.02 (1.27-3.20)	<0.01	1.16 (0.72-1.89)	0.54	1.74 (1.16-2.61)	0.01
Age (per 10 years)	1.01 (0.86-1.19)	0.89	0.92 (0.77-1.08)	0.30	1.12 (0.97-1.29)	0.12
Diastolic pressure (per 10 mmHg)	0.91 (0.76-1.08)	0.27	0.90 (0.75-1.07)	0.23	0.80 (0.68-0.93)	0.01
Region ^						
- Australia/NZ/UK	Ref		Ref		Ref	
- Malaysia	1.18 (0.56-2.47)	0.66	1.30 (0.57-2.97)	0.54	0.50 (0.26-0.98)	0.04
Diabetes mellitus	0.87 (0.54-1.39)	0.55	0.70 (0.43-1.14)	0.15	0.92 (0.61-1.38)	0.69
Presence of PVD	3.24 (1.31-7.98)	0.01	2.46 (0.95-6.35)	0.06	0.92 (0.37-2.27)	0.85
Presence of central venous catheter	1.03 (0.65-1.61)	0.91	0.77 (0.48-1.24)	0.27	1.66 (1.11-2.46)	0.01
Use of CCB	0.91 (0.58-1.42)	0.67	0.84 (0.53-1.32)	0.45	0.88 (0.60-1.29)	0.51
Hemoglobin	1.00 (0.99-1.01)	0.98	1.00 (0.99-1.02)	0.58	1.00 (0.99-1.01)	0.48
Randomization to aspirin						
- Randomized to placebo	Ref	0.16	Ref0.99 (0.58-1.68)	0.26	Ref	0.44
- Randomized to aspirin	0.71 (0.42-1.18)		1.50 (0.86- 2.63)		0.93 (0.60-1.43)	
- Open label aspirin	1.19 (0.70-2.02)				1.26 (0.78-2.03)	
Randomization to fish oil use	1.00 (0.65-1.52)	1.00	0.86 (0.56-1.33)	0.50	1.13 (0.78-1.63)	0.53
AVF type						
- Radiocephalic	Ref	0.05	Ref	0.23	Ref	0.04
- Brachiocephalic	0.48 (0.29-0.81)		0.60 (0.35-1.02)		0.71 (0.46-1.10)	
- Brachiobasilic	0.95 (0.41-2.19)		0.56 (0.21-1.53)		2.24 (1.07-4.72)	
- Others	1.20 (0.20-7.15)		0.66 (0.07-5.82)		0.89(0.18-4.53)	
Surgeons						
- Registrar/Residents	Ref		Ref		Ref	
- Consultant	0.85 (0.52-1.41)	0.54	0.65 (0.40-1.08)	0.10	1.08 (0.69-1.69)	0.72
Anesthesia						
- Regional/General anesthesia	Ref		Ref		Ref	
- Local	1.30 (0.69-2.45)	0.42	0.78 (0.39-1.55)	0.48	1.08 (0.62-1.88)	0.80

Single imputation for missing values of individual outcome components was performed and described in detail in the primary outcome analysis <sup>31</sup>

^ Australia, New Zealand, United Kingdom region of recruitment was grouped when compared to Malaysian region of recruitment in this analysis.

Abbreviations: NZ- New Zealand; UK- United Kingdom; PVD – peripheral vascular disease; CCB – calcium channel blocker; RC- radiocephalic; BC-brachiocephalic; BB- Brachiobasilic; AVF – arteriovenous fistula

**Figure 1.** Proportion of arteriovenous fistula failure (composite outcome of arteriovenous fistula abandonment, thrombosis and failure to cannulate) with change in diastolic blood pressure.



The light grey line reflects an almost inverse linear relationship between diastolic blood pressure and proportion of AVF failure on univariable logistic regression and the dashed grey line represent the 95% confidence interval at each diastolic blood pressure level. The black line shows a similar relationship between diastolic blood pressure and proportion of AVF failure on multivariable analysis adjusted for female sex, age, region of recruitment, presence of diabetes, presence of peripheral vascular disease, presence of central venous catheter, use of calcium channel blockers, haemoglobin levels, randomization to aspirin, randomization to fish oil, type of AVF created, surgical expertise and type of anesthesia use added and the dotted black line representing the 95% confidence interval.