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Vascular Access Type, Inflammatory Markers, and Mortality in Incident Hemodialysis Patients: The Choices for Healthy Outcomes in Caring for End-Stage Renal Disease (CHOICE) Study

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Abstract

Background—Few reports have shown an association between access type and inflammatory markers in a longitudinal cohort. We investigated the role of access type on serial inflammatory markers and the role of inflammatory markers in mediating the association of access type and the risk of mortality in a prospective study of incident dialysis patients.

Study Design—Cohort study, post-hoc analysis of Choices for Healthy Outcomes in Caring for ESRD (CHOICE) Study.

Setting & Participants—In 583 participants, inflammation was assessed by measuring serum C-reactive protein (CRP) and interleukin 6 (IL-6) after access placement and at multiple time

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Contributions: Research idea and study design: TB, SJK, TS, NRP; data acquisition: NRP, JC, BA; data analysis/interpretation: TB, SJK, TS; statistical analysis: TB; supervision or mentorship: NRP, TS. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved. TB and NRP take responsibility that this study has been reported honestly, accurately, and transparently; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

Supplementary Material

Table S1: Baseline characteristics of incident HD patients who were included and excluded.
Item S1: Supplementary methods regarding mixed-effects pattern mixture model.
Note: The supplementary material accompanying this article (doi:_____) is available at www.ajkd.org

points during 3 years' follow-up. Type of access was categorized as central venous catheter (CVC), arteriovenous graft (AVG), and arteriovenous fistula (AVF) and changes over time were recorded.

Predictor—Access type, age, gender, race, body mass index, diabetes, cardiovascular disease, serum albumin.

Outcomes—CRP, IL-6, and mortality

Measurements—We used mixed-effects pattern mixture (MEPM) models to study the association between access type and repeated measures of inflammation and survival analysis to investigate the association of access type and mortality, adjusting for predictors.

Results—In a MEPM model, compared to AVF, the presence of a CVC and an AVG were associated with 62% (p=0.02) and 30% (p=0.05) increase in the average CRP levels, respectively. Cox proportional hazards model yielded non-significant associations of CVC and AVG use (vs. AVF) with the risk of mortality when adjusted for inflammatory markers. Higher levels of CRP were associated with increased risk of CVC failure than lower levels of CRP.

Limitations—CRP, IL-6 measurements not performed for all hemodialysis patients.

Conclusions—CVCs, compared to AVFs, are associated with a greater state of inflammation in incident hemodialysis patients and the association of catheter use and mortality may be mediated by access-induced inflammation. Our findings support recommendations for the early removal or avoidance of CVC placements.

Keywords

Cox proportional hazard model; C-reactive protein (CRP); interleukin 6 (IL-6); hemodialysis; mixed effects model; vascular access type; access failure; inflammation; central venous catheter (CVC); biomarker; access patency; end-stage renal disease (ESRD)

The long-term hemodialysis population is greatly burdened by vascular access complications. In incident hemodialysis patients, the access type at initiation of hemodialysis has been associated with different outcomes. The National Kidney Foundation-Dialysis Outcomes Quality Initiative (NKF-KDOQI) clinical practice guideline for vascular access recommends the use of arteriovenous (AV) accesses for hemodialysis and to avoid the use of a central venous catheter (CVC).[1] Among AV accesses, an arteriovenous fistula (AVF) provides better outcomes when compared with an arteriovenous graft (AVG).[2]

Vascular access for hemodialysis through a CVC is associated with an increased risk of acute infection, thrombosis, septicemia, central venous stenosis, shorter access survival, and inadequate dialysis.[1,3–7] Central venous catheters are particularly associated with increased rates of infection, such as bacteremia, endocarditis, and osteomyelitis versus other access types.[8] In addition to the type of access, there are other causes that can induce inflammation in dialysis patients. Prior literature has shown evidence of a clotted, non-functioning AVG being a frequent harbinger of infection.[9,10] Further, the existence of a failed allograft is associated with predictors of poor outcomes in patients receiving dialysis. These

abnormalities might be explained by inadequate predialysis care but could also indicate chronic inflammation, which is a major mortality risk factor in the dialysis population.[11,12]

Access type can change over time in individual patients, but the majority of studies on access and outcomes base access type assignment on a cross-sectional ascertainment at one point in time.[13–16] Previous observational studies have noted a high prevalence of inflammation in patients using a catheter as an access for dialysis.[17] There are limited data on long-term serial changes in inflammatory markers and their relationship to the access type in hemodialysis patients, and the contribution of access type to the inflammatory status of hemodialysis patients is not well described.[18,19] Moreover, studies have shown a higher risk of mortality associated with catheter use. The question of whether mortality due to catheter use could be mediated by inflammation has not been addressed in previous studies. In addition, some studies have identified C-reactive protein (CRP) as a risk factor for development of access thrombosis.[20,21] Thrombosis due to disproportionate intimal hyperplasia causes, by far, most AVF failure.[22] Based on these observations, we hypothesized that the CRP levels may be associated with access type failure. To address these issues, we studied i) the association between access type and inflammation assessed by CRP and interleukin 6 (IL-6); ii) whether the inflammatory markers mediate the association of access type with risk of mortality; and iii) the association of access patency by inflammatory markers, in well characterized cohort of incident hemodialysis patients.

Methods

Study Design and Population

The study participants were dialysis patients who participated in the Choices for Healthy Outcomes in Caring for ESRD (CHOICE) Study. The CHOICE Study is a national, prospective cohort study of incident hemodialysis and peritoneal dialysis patients with the goal of investigating treatment choices (i.e modality), dialysis dose and outcomes of dialysis care. A total of 1,041 dialysis patients were recruited from across the United States from October 1995 through June 1998 at a median of 45 days after the initiation of dialysis therapy. These patients were aged 18 years or older, initiating outpatient dialysis, provided informed consent, spoke English or Spanish, and were without previous history of kidney transplantation. Study participants were enrolled from 81 dialysis clinics associated with Dialysis Clinic, Inc (DCI, Nashville, TN), New Haven CAPD (New Haven, CT), and St. Raphael's Hospital (New Haven, CT). A specimen bank was established for the DCI participants of the CHOICE Study. Non-fasting, pre-dialysis blood specimens were centrifuged at 2500–3000 rpm for 15 minutes within 30–45 minutes of blood collection. Separated and refrigerated specimens were then mailed overnight on ice to the DCI Central Laboratory until they were thawed (1 thaw cycle) for analysis. Each blood collection was aliquoted into multiple vials and stored at −80°C.[23]

The present study includes participants treated with hemodialysis as their initial renal replacement modality with three dialysis treatments in a week and who had access information available (N=739). Of these, serum samples were available for 604 (81.7%) participants. Markers of inflammation (CRP and IL-6) were measured for 583 participants with available serum in the specimen bank within a median of 4.8 (interquartile range, 3.6–

8.1) months from initiation of dialysis, and then subsequently during the first 3 years of dialysis within an average interval between two successive measurements of 4 months. The specimens were not collected at the time of fistula creation or catheter insertion. We accounted for changes in access type over time and the corresponding access type was determined for each available period of cytokine measurement.

Exposure Assessment

The primary exposure of interest was the type of stable access (i.e. CVC, AVG, or AVF) being used at the time inflammatory markers were measured. A stable access implied that the same access was in use for at least 30 days prior to blood testing.

Measurement of Inflammatory Markers

Serum high-sensitivity CRP, an acute-phase protein, was measured by using a colorimetric competitive enzyme-linked immunosorbent assay (ELISA; coefficient of variation of 8.9%). The central proinflammatory cytokine IL-6 was measured in serum by an ultrasensitive ELISA method (coefficient of variation of 7%).

Mortality Ascertainment

The observation period for each participant began at enrollment and continued until Dec 31, 2004. Mortality events were ascertained from clinic reports, medical records, and Center for Medicare & Medicaid Services. The participants who underwent kidney transplantation or no longer had access information available were censored.

Evaluation of Access Patency

Access information was obtained through review of discharge summaries, dialysis flow sheets, and dialysis clinic progress notes, as described elsewhere.[24] Permanent access failure was defined as the need for a surgical intervention to replace poorly or non-functioning fistula or graft. Catheter failure was defined as the need for placement of another catheter.

Other Covariates

Other potential confounders included age, gender, race (self-reported, categorized as African-American, White or other), history of diabetes, history of peripheral vascular disease, history of cardiovascular disease, smoking history (current, past or never), body-mass index, serum albumin, and comorbidity. Comorbidity was assessed at baseline using the Index of Coexistent Disease (ICED), which is a validated 4-level scale of comorbidity that incorporates measures of both disease severity and physical impairment.[25] The ICED scores were categorized as mild (0 or 1), moderate (2), or severe (3). These covariates were measured at baseline and were not time-varying.

Statistical Analyses

The characteristics of patients using each type of access at initiation of hemodialysis were compared using one-way ANOVA for continuous variables and χ^2 tests for categorical variables. Baseline characteristics among patients included in the study were compared to those who were excluded.

The association of access type and level of inflammation determined by CRP and IL-6 was investigated using mixed-effects pattern mixture (MEPM) models for repeated measures[26], with adjustment for the potential covariates. The MEPM model used the indicator variable for death as the missing pattern. The adjusted models take into account every cytokine measurement and the corresponding access type for each available period. To explore the effect of time-varying access type associated with changes of CRP and IL-6 levels, we adjusted the model for previous CRP and IL-6 levels. Both CRP and IL-6 were log-transformed for the analysis due to their right skewed distribution. In terms of percent change, the expected percent increase in the geometric mean of the outcome variable is $100*(e^{\beta 1} - 1)$ percent for a 1-unit increase in the independent variable while all other variables in the model are held constant (see Item S1, available as online supplementary material).

Stratified analysis by the access type was carried out to examine the effect of time (number of days) after access placement on level of inflammatory markers in patients who had complete measures of CRP and IL-6 at least until 6 months. Mixed models were used to derive the percent changes in the inflammatory markers over time associated with the baseline access. The reference category considered for this analysis was >180 days, since the inflammation state was highest within 6 months of the access insertion in the hemodialysis patients.

The association of access type and mortality was investigated using multivariable Cox proportional hazards model, with the access type in use treated as a time-dependent variable. These analyses included each access used for at least one dialysis session. Survival time was calculated from the date of first use of the access to the date of death, loss to follow-up, or the last observation date.

Cumulative probability curves using Kaplan Meier plots were constructed to examine the association of CRP levels with patency of the CVC within the first year from the initiation of dialysis. We used Cox proportional hazard models to assess the strength of associations between varying levels of CRP and access failure. The proportionality assumption was tested using Schoenfeld residuals.

We conducted additional analyses using generalized estimating equations with dichotomous responses to relate the odds of changing from a catheter to an AVF to changes in CRP levels during the preceding 6 months, controlling for baseline covariates.

Sensitivity analyses were performed to test the robustness of our findings on patients with minimal comorbidity (ICED score, 0 or 1) to minimize confounding by comorbid disease status.

In all analyses, the possibility of confounding by dialysis clinic was controlled with fixed-effects modeling, clustered on clinic, which accounted for within-clinic correlation and between-clinic differences in outcomes.[27] All analyses were performed using SAS 9.3 (SAS Institute Inc. Cary, NC).

Results

Study Participants

A total of 583 incident hemodialysis patients were included. The remaining 156 excluded patients were similar to included patients in terms of their socio-demographic and clinical characteristics (see Table S1). Median follow-up for our study population was 3.0 years (range, 4 months to 9.5 years). The baseline patient demographic and laboratory data are provided in Table 1. The number of patients in each access group was as follows: AVF, 159 (27.3%); AVG, 235 (40.3%); CVC, 189 (32.4%). Those in the AVF group were more likely to be younger, male, and have less comorbidity when compared with the AVG and CVC groups. There were no other significant between-group differences in baseline demographics and laboratory values.

Since we did not have the information on the cause for failure of the access during the study period, we considered a sub-cohort of patients in whom dialysis was initiated using their initial access. After 3 months of follow-up, the mean levels of CRP and IL-6 after 3 months were 17.1 mg/L and 16.1 pg/mL in the CVC group, 15.1 mg/L and 10.9 pg/mL in the AVG group, and 10.4 mg/L and 6.8 pg/mL in the AVF, respectively. We further followed this subcohort to 8 months and estimated the mean levels of the inflammatory markers. Mean levels of CRP and IL-6 were 15.8 mg/L and 11.6 pg/mL in the CVC group, 14.2 mg/L and 10.1 pg/mL in the AVG group, and 10.2 mg/L and 7.9 pg/mL in the AVF group, respectively.

Association of Vascular Access and Inflammatory Markers

In multivariable analyses, the difference in average CRP levels across time was 62% higher in the CVC ($p=0.02$) than the AVF group (Table 2). An AVG compared to an AVF showed a 30% increase in average CRP levels ($p=0.05$). We did not observe any statistically significant difference in average IL-6 levels across time between CVC and AVF and an AVG and AVF. Furthermore, there was a 24% decrease in average CRP levels between CVC and AVF survivors while the average CRP levels were 39% higher for AVG compared to AVF survivors ($P>0.05$ for all values). Although the average IL-6 levels were higher for both CVC and AVG survivors than AVF survivors, the association was not statistically significant ($P=0.3$ and 0.2, respectively).

During the study, change from a CVC to an AVF after at least 6 months of dialysis with a CVC occurred on 46 occasions. We observed a significant decrease in the CRP levels when there was a change from a CVC to an AVF (odds ratio, 1.43; 95% confidence interval [CI], 1.15–1.68).

Stratified analysis showed that CRP levels decreased over time in cases of AVF with the highest inflammatory state 30 days after access placement when compared with the markers over 180 days, but did not reach statistical significance (Figure 1). There was a decrease in IL-6 levels over time as well, which did not reach statistical significance when compared with the markers over 180 days (Figure 2). On the other hand, an increase in CRP levels within 60 days was observed after CVC placement when compared with markers over 180

days (p=0.02). We again did not observe any significant change in the levels of IL-6 over time in patients with CVCs.

Effect of Inflammatory Markers on Risk of Mortality by Access Type

Both CVC and AVG use remained associated with higher mortality after adjustment for the potential confounders such as age, gender, race, peripheral vascular disease, cardiovascular disease, diabetes, body mass index, ICED score, smoking status, and timing of first referral to a nephrologist (Table 3). On further adjustment for the inflammatory markers of CRP and IL-6, the hazard ratio for the association of CVC or AVG use and mortality was attenuated and did not reach statistical significance (hazard ratios of 1.27 [95% CI, 0.92–1.83; P=0.07] and 1.17 [95% CI, 0.60–1.83; P=0.07], respectively; Table 3).

Association of Access Patency by Inflammatory Markers

Among patients who had a CVC as the primary access type from initiation of dialysis, the cumulative probability plot illustrates that the highest tertile of CRP showed greater catheter failure rate than the lowest tertile of CRP (p=0.03, Figure 3). Table 4 shows higher levels of CRP were associated with increased risk of CVC failure than lower levels of CRP, while no significant association was observed between the varying levels of CRP and arteriovenous access failure.

Sensitivity Analyses

After restricting the cohort to patients with an ICED score of 0 or 1 (n=170) to reduce confounding by comorbid disease status, we found significant difference in the average CRP levels in the CVC compared to the AVF groups (percent change, 29.9%; p=0.05). The average CRP levels across time were 9.8% lower when an AVG was compared to an AVF (p=0.4). We did not observe any significant difference in the average IL-6 levels both in the CVC (percent change, 4.8%; p=0.2) and AVG (percent change, 3.1%; p=0.15) groups compared to the AVF group.

Discussion

In this study, we found that CVCs in comparison to AVFs displayed greater states of inflammation as determined by 62% higher average CRP levels in patients who died than who survived. More inflammation was also associated with a 79% higher risk of CVC failure and the association of access type with mortality weakened when adjusted for inflammatory markers.

Our study corroborated the findings of previous studies[28] that CVCs in comparison to fistulas have a greater state of inflammation defined by CRP levels in incident hemodialysis patients. This was further strengthened by our findings on the association of the inflammatory state after access insertion. We observed a transient state of inflammation with initial fistula insertion which weakened with time. Catheter insertion was associated with a heightened state of inflammation which persisted even after 60 days from insertion.

We further investigated the association of change in CRP levels with change in type of access during the preceding 6-month interval. We observed that change from a CVC to an AVF was associated with decreased levels of CRP compared with patients who used CVCs at both times. Thus, this finding that change in CRP levels is associated with change in access type adds additional support to the body of the observational evidence suggesting that the catheter itself contributes to an increase in inflammatory markers in hemodialysis patients.

Hemodialysis patients frequently have increased levels of inflammatory markers, which then predict increased risk of death or cardiovascular events.[29] Available evidence suggests that CRP is an objective measure of a patient's inflammatory state and that it accurately reflects generation of pro-inflammatory cytokines, such as IL-6 and tumor necrosis factor α. Recent literature suggests that CVC use for dialysis access is associated with serological and cellular indices of inflammatory reaction.[18,19] Moreover, a graded mortality risk, from both cardiovascular and infectious disease, according to access type, has been shown by large studies, and CVC use has been associated with the worst outcomes.[13–15] Some of these studies were based on longitudinal follow-up data.[30] In our study, we again found the use of a catheter to be associated with a high risk of death, an association that remained even after adjustment for several potential confounders (eg, timing of nephrology referral) and after accounting for changes in access type with time. However, on adjustment for the inflammatory markers of CRP and IL-6, we observed a loss of significance in the association of access type and mortality. These results suggest that the association between access type and mortality may also be indirect, as access type has been shown to be associated with increased inflammatory markers that may relate to the risk of death.[5,28,31] It is possible that the presence of vascular access–induced inflammation may contribute to the excess mortality reported in patients using catheters and AVGs in the first months of hemodialysis. The significant direct relationship between CRP level and the likelihood of catheter use that we observed appears to support such a mechanism.

Access failure is a key cause of morbidity in hemodialysis patients.[7] Previous studies have identified numerous risk factors for fistula failure; however they do not account for all of the variation in the AVF failures.[32] In a retrospective analysis, Chou *et al*.[33] identified CRP as an independent risk factor for fistula thrombosis. These investigators suggested that CRP strongly predicts access thrombosis events in long-term hemodialysis patients, possibly because CRP is a marker of intimal hyperplasia in AVF. Notably, although we detected a high inflammatory state 30 days after placement of AVF in the hemodialysis patients, the presence of the highest levels of CRP versus the lowest levels was not predictive of AV access failure, thus potentially resulting in less detrimental effects on survival as compared to that of a catheter. It appears that the greater inflammation observed in the patients with an AVF was transient and the patients perhaps had a prolonged time without thrombosis. However, the loss of catheter patency in hemodialysis patients may be a direct result of the significant state of inflammation that is observed after catheter insertion.

Our findings support the emphasis on early fistula placement and removal of CVCs in incident hemodialysis patients. Our results are in agreement with the findings from the US Renal Data System from 1995 to 1997 in incident patients older than 67 years, where a 70%

higher risk for 1-year mortality was found for patients who initially used a catheter and a 16% higher risk for those who initially used an AVG, when compared with an AVF.[15] The use of fistulas may be particularly beneficial with respect to decreasing the risk of inflammation. Our findings are also in agreement with previous observations of increased infection associated with catheter use. For patients in whom a catheter must be placed for hemodialysis, preventing infection is crucial for lowering mortality.

Our study adds to the previous reports that show an association between access type and inflammatory markers in a longitudinal cohort study with repeated measures of inflammation. The prospective collection of data and the national multi-center design, whereby characteristics were similar to the US dialysis population,[34] also resulted in a well-characterized, generalizable cohort of dialysis patients.

This study has some limitations that deserve mention. Not all hemodialysis patients had CRP and IL-6 measurements performed, thus introducing the potential for selection bias. However, there was no significant difference in the socio-demographic and clinical characteristics in the participants whom we included in our study and those excluded. Since this cohort was recruited from 1995 to 1998, it may not be sufficiently contemporary to allow us to make appropriate inferences about dialysis patients today. We lacked measures of other inflammatory markers, thus residual confounding could have limited our inferences. However, our sensitivity analysis on the restricted sub-cohort of the healthiest patients corroborated our previous findings. We also did not have information about whether a patient with an AVF still had a catheter in situ. This would bias against the fistula.

In summary, this study of incident hemodialysis patients revealed that the use of a CVC for access, when compared to an AVF, was significantly associated with the presence of an inflammatory state, as evidenced by elevations in CRP and IL-6. Although we found a significant association between catheter use and the risk of mortality, statistical significance was lost after adjusting the model for the inflammatory markers. These results suggest that the association of catheter use and mortality may be indirect, and it is possible that this association is mediated through access-induced inflammation. Evidence-based clinical practice guidelines recommend that hemodialysis catheter use should be restricted to only patients who have no other options for vascular access. Our results support this recommendation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. National Kidney Foundation: NKF-DOQI clinical practice guidelines for vascular access. National Kidney Foundation-Dialysis Outcomes Quality Initiative. Am J Kidney Dis. 1997; 30(4 Suppl 3):S150–S191. [PubMed: 9339150]
2. Allon M, Robbin ML. Increasing arteriovenous fistulas in hemodialysis patients: problems and solutions. Kidney Int. 2002; 62:1109–1124. [PubMed: 12234281]
3. Churchill DN, Taylor DW, Cook RJ, et al. Canadian Hemodialysis Morbidity Study. Am J Kidney Dis. 1992; 19:214–234. [PubMed: 1553966]
4. Twardowski ZJ. Percutaneous blood access for hemodialysis. Semin Dial. 1995; 8:175–186.
5. Powe NR, Jaar B, Furth SL. Septicaemia in dialysis patients: Incidence, risk factors, and prognosis. Kidney Int. 1999; 55:1081–1090. [PubMed: 10027947]
6. Hernandez D, Diaz F, Rufino M, et al. Subclavian vascular access stenosis in dialysis patients: Natural history and risk factors. J Am Soc Nephrol. 1998; 9:1507–1510. [PubMed: 9697674]
7. Feldman HI, Kobrin S, Wasserstein A. Hemodialysis vascular access morbidity. J Am Soc Nephrol. 1996; 7:523–535. [PubMed: 8724885]
8. Nassar GM, Ayus JC. Infectious complications of the hemodialysis access. Kidney Int. 2001; 60:1–13. [PubMed: 11422731]
9. Nassar GM, Fishbane S, Ayus JC. Occult infection of old nonfunctioning arteriovenous grafts: a novel cause of erythropoietin resistance and chronic inflammation in hemodialysis patients. Kidney Int Suppl. 2002; 80:49–54. [PubMed: 11982813]
10. Ayus JC, Sheikh-Hamad D. Silent Infection in Clotted Hemodialysis Access Grafts. J Am Soc Nephrol. 1998; 9:1314–1317. [PubMed: 9644644]
11. Ayus JC, Achinger SG, Lee S, Sayegh MH, Go AS. Transplant Nephrectomy Improves Survival following a Failed Renal Allograft. J Am Soc Nephrol. 2010; 21:374–380. [PubMed: 19875809]
12. Ayus JC, Achinger SG. Editorial Focus: Transplant Nephrectomy: At the Peril of Dialysis Patients: Ignoring the Failed Transplant. Seminars in Dialysis. 2005; 18(3):180–184. [PubMed: 15934958]
13. Dhingra RK, Young EW, Hulbert-Shearon TE, Leavey SF, Port FK. Type of vascular access and mortality in U.S. hemodialysis patients. Kidney Int. 2001; 60:1443–1451. [PubMed: 11576358]
14. Pastan S, Soucie JM, McClellan WM. Vascular access and increased risk of death among hemodialysis patients. Kidney Int. 2002; 62:620–626. [PubMed: 12110026]
15. Xue JL, Dahl D, Ebben JP, Collins AJ. The association of initial hemodialysis access type with mortality outcomes in elderly medicare ESRD patients. Am J Kidney Dis. 2003; 42:1013–1019. [PubMed: 14582045]
16. Polkinghorne KR, McDonald SP, Atkins RC, Kerr PG. Vascular access and all-cause mortality: A propensity score analysis. J Am Soc Nephrol. 2004; 15:477–486. [PubMed: 14747396]
17. Wystrychowski G, Kitzler TM, Thijssen S, Usvyat L, Kotanko P, Levin NW. Impact of switch of vascular access type on key clinical and laboratory parameters in chronic hemodialysis patients. Nephrol Dial Transplant. 2009; 24:2194–2200. [PubMed: 19228757]
18. Sachdeva M, Kovalchuk O, Bitzer M, Mokrzycki MH. Vascular access type and changes in inflammatory markers in incident dialysis patients: a pilot study. J Vasc Access. 2009; 10(3):174–179. [PubMed: 19670170]
19. Coli L, Donati G, Cappucilli ML, et al. Role of the hemodialysis vascular access type in inflammation status and monocyte activation. Int J Artif Organs. 2011; 34(6):481–488. [PubMed: 21725929]
20. Schillinger M, Exner M, Sabeti S, et al. Excessive carotid in-stent neointimal formation predicts late cardiovascular events. J Endovasc Ther. 2004; 11:229–239. [PubMed: 15174911]

21. Hashimoto H, Kitagawa K, Hougaku H, Etani H, Hori M. Realtionship between C-reactive protein and progression of early carotid atherosclerosis in hypertensive subjects. Stroke. 2004; 35:1625–1630. [PubMed: 15155971]
22. de Graaf R, Dammers R, Vainas T, Hoeks AP, Tordoir JH. Detection of cell-cycle regulators in failed arteriovenous fistulas for hemodialysis. Nephrol Dial Transplant. 2003; 18:814–818. [PubMed: 12637654]
23. Lewis MR, Callas PW, Jenny NS, Tracy RP. Longitudinal stability of coagulation, fibrinolysis, and inflammation factors in stored plasma samples. Thromb Haemost. 2001; 86:1495–1500. [PubMed: 11776319]
24. Astor BC, Eustace JA, Powe NR, et al. Timing of nephrologist referral and arteriovenous access use: the CHOICE Study. Am J Kidney Dis. 2001; 38:494–501. [PubMed: 11532680]
25. Athienites NV, Miskulin DC, Fernandez G, et al. Comorbidity assessment in hemodialysis and peritoneal dialysis using the index of coexistent disease. Semin Dial. 2000; 13:320–326. [PubMed: 11014695]
26. Hedeker D, Gibbons RD. Application of Random-Effects Pattern Mixture Models for Missing Data in Longitudinal Studies. Psychological Methods. 1997; 2(1):64–78.
27. Breslow NE, Day NE. *Statistical methods in cancer research*. Volume I: The analysis of case-control studies. IARC Sci Publ . 1980; 32:5–338. [PubMed: 7216345]
28. Goldstein SL, Ikizler TA, Zappitelli M, Silverstein DM, Ayus JC. Non-infected hemodialysis catheters are associated with increased inflammation compared to arteriovenous fistulas. Kidney Int. 2009; 76(10):1063–1069. [PubMed: 19675528]
29. Arici M, Walls J. End-stage renal disease, atherosclerosis, and cardiovascular mortality: Is C-reactive protein the missing link? Kidney Int. 2001; 9:407–414. [PubMed: 11168922]
30. Astor BC, Eustace JA, Powe NR, Klag MJ, Fink NE, Coresh J. for the CHOICE Study. Type of Vascular Access and Survival among Incident Hemodialysis Patients: The Choices for Healthy Outcomes in Caring for ESRD (CHOICE) Study. JASN. 2005; 16:1449–1455. [PubMed: 15788468]
31. Jaar BG, Hermann JA, Furth SL, Briggs W, Powe NR. Septicemia in diabetic hemodialysis patients: Comparison of incidence, risk factors, and mortality with non-diabetic hemodialysis patients. Am J Kidney Dis. 2000; 35:282–292. [PubMed: 10676728]
32. Lin CC, Yang WC. Prognostic factors influencing the patency of hemodialysis vascular access: literature review and novel therapeutic modality by far infrared therapy. J Clin Med Assoc. 2009; 72:109–116.
33. Chou CY, Kuo HL, Yung YF, Liu YL, Huang CC. C-reactive protein predicts vascular access thrombosis in hemodialysis patients. Blood Purificat. 2006; 24:342–346.
34. Liu Y, Coresh J, Eustace JA, et al. Association between cholesterol level and mortality in dialysis patients: Role of inflammation and malnutrition. JAMA. 2004; 291:451–459. [PubMed: 14747502]

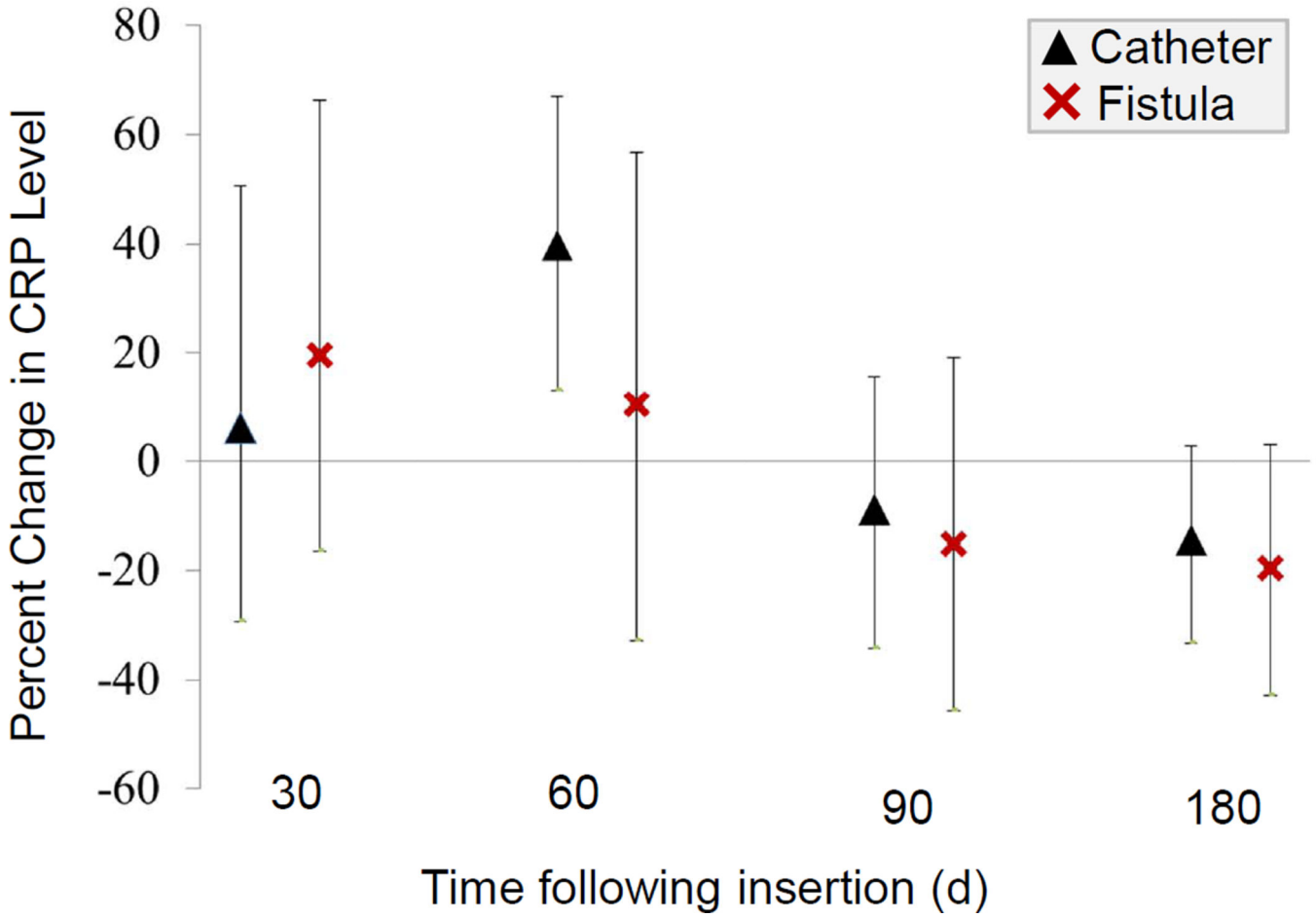

Figure 1.

Percent Change associated with C-Reactive Protein at time following insertion of central venous catheter and arteriovenous fistula. Upper and lower limits of the lines at each time point represent 95% confidence intervals.

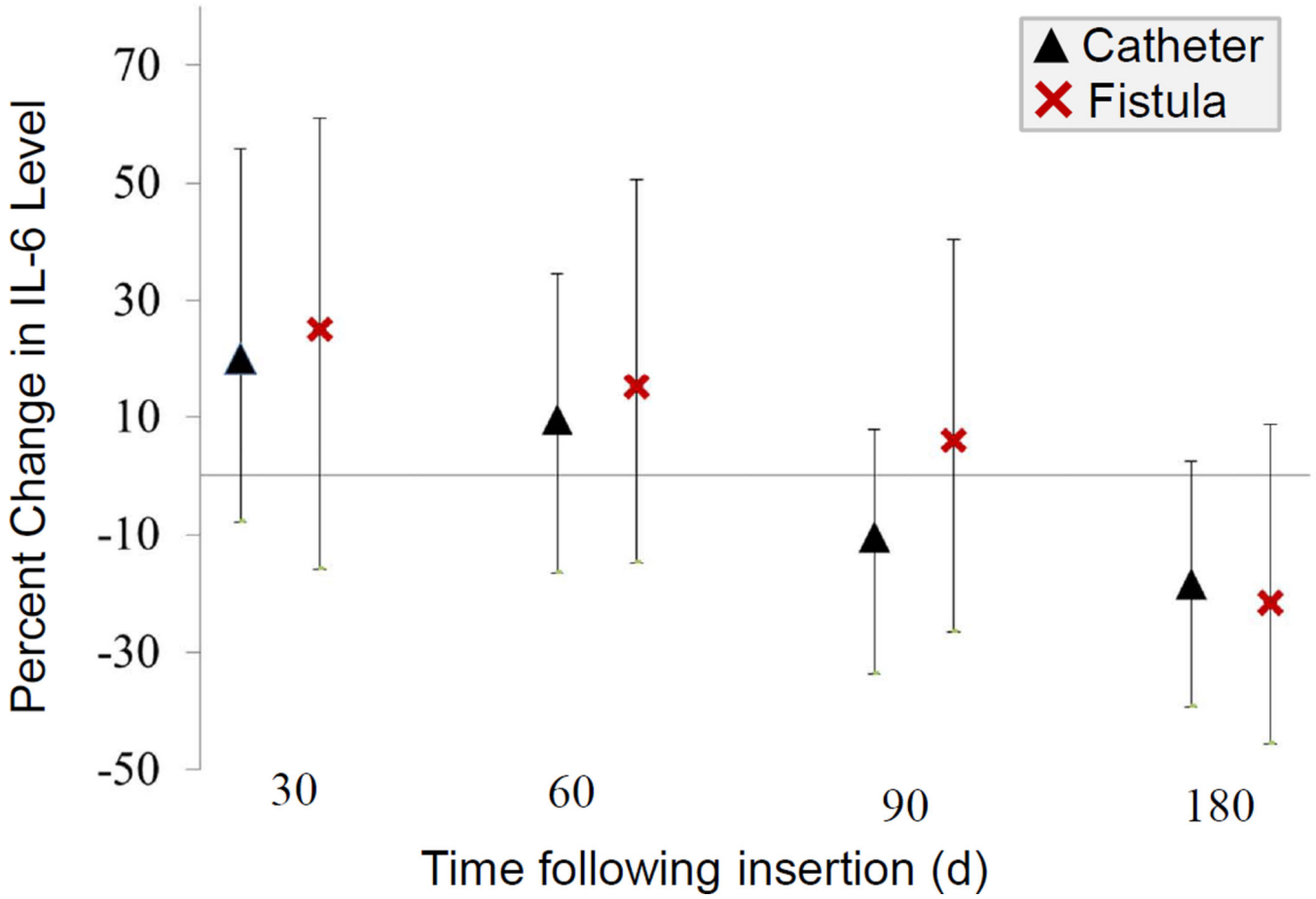

Figure 2.
Percent Change associated with interleukin-6 at time following insertion of central venous catheter and arteriovenous fistula. Upper and lower limits of the lines at each time point represent 95% confidence intervals.

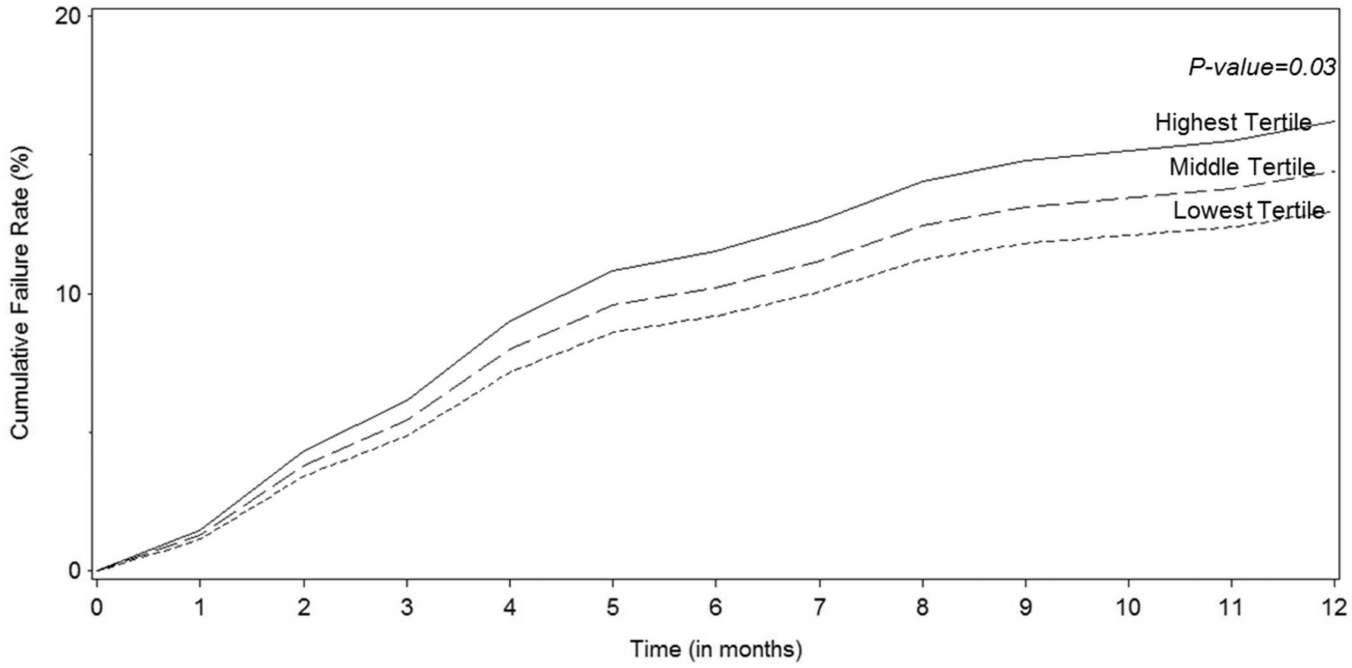

Figure 3.

Cumulative probability curve for central venous catheter failure rate in patients with varying CRP levels within the first year from dialysis initiation.

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Table 1

Baseline Characteristics of incident hemodialysis patients stratified by vascular access type

Characteristic	Total (N=583)	CVC (n=189)	AVG (n=235)	AVF (n=159)	p#
Age at enrollment (y)	58.7±14.6	57.9 ±15.2	60.7 ±13.7	56.6 ±14.7	0.02
Female sex	44.8	43.2	55.9	37.8	<0.001
Race/ethnicity					0.06
African American	30.1	28.3	40.4	24.4	
White	65.3	66.8	57.8	68.9	
Other	4.6	4.9	1.83	6.7	
BMI (kg/m^2)	27.5±7.1	26.6 ±7.1	28.5 ±7.5	27.2 ±6.0	0.07
Smoking					0.09
Current Use	16.6	20.6	12.1	15.7	
Past Use	42.5	41.7	48.2	42.6	
Never	40.9	37.7	39.7	41.7	
Diabetes	55.4	55.6	60.4	47.8	0.4
PVD	26.6	26.0	32.1	21.1	0.7
CVD	48.0	47.2	46.8	48.9	0.3
ICED score					<0.001
0 – 1	29.2	24.9	25.7	44.8	
2	38.1	39.7	38.6	33.6	
3	32.8	35.4	35.7	21.6	
Serum albumin (g/dL)	3.7 [3.4–3.9]	3.7 [3.4–3.9]	3.6 [3.4–3.8]	3.8 [3.5–4.0]	0.04
CRP (mg/L)	7.3 [3.0–16.9]	8.1 [3.1–18.7]	6.6 [3.5–14.1]	6.5 [2.2–16.2]	0.1
IL-6 (pg/mL)	6.1 [3.6–10.8]	6.2 [3.7–11.4]	6.0 [3.8–9.9]	5.7 [2.9–10.4]	0.07

Note: Unless otherwise indicated, values for categorical variables are given as percentages; values for continuous variables are given as mean ± standard deviation or median [interquartile range].

AVG, arteriovenous graft; AVF, arteriovenous fistula; BMI, body mass index; CVC, central venous catheter; CVD, cardiovascular disease; PVD, peripheral vascular disease; CRP, C-reactive protein; IL-6, Interleukin 6, ICED, Index of Co-existent Disease.

#By ANOVA or chi-square test

Table 2

Difference in average percent change of CRP and IL-6 levels in mixed-effect pattern mixture model

Access type	CRP (mg/L)		IL-6 (pg/mL)	
	% Change (95% CI)	P	% Change (95% CI)	P
Central venous catheter	+61.6 (4.1 to 182.9)	0.02	−10.5 (−30.4 to 9.40)	0.2
Arteriovenous graft	+29.6 (−1.2 to 60.2)	0.05	−12.1 (−29.8 to 6.44)	0.2
Arteriovenous fistula	0 (reference)		0 (reference)	

Note: n=583. Adjusted for age, gender, race, presence of diabetes, history of cardiovascular disease, history of peripheral vascular disease, body mass index, Index of Coexistent Disease score, smoking status, serum albumin.

CRP, C-reactive protein; CI, confidence interval; IL-6, interleukin 6

Table 3

Unadjusted and adjusted relative hazard of mortality, by type of vascular access

	CVC	AVG	AVF
Unadjusted	1.76 (1.52–2.04)	1.40 (0.61–1.90)	1.00 (reference)
Model 1[a]	1.62 (1.39–1.87)	1.37 (0.80–1.90)	1.00 (reference)
Model 2[b]	1.46 (1.21–1.77)	1.29 (0.70–1.83)	1.00 (reference)
Model 3[c]	1.27 (0.92–1.63)	1.17 (0.60–1.83)	1.00 (reference)

Note: n=583. Values shown as hazard ratio (95% confidence interval).

[a] Adjusted for age, gender, and race.

[b] Adjusted for variables in model 1 plus presence of diabetes, history of cardiovascular disease, history of peripheral vascular disease, body mass index, Index of Coexistent Disease score, smoking status, serum albumin, and timing of referral to a nephrologist.

[c] Adjusted for variables in model 2 plus inflammatory markers of C-reactive protein and interleukin 6.

AVG, arteriovenous graft; AVF, arteriovenous fistula; CVC, Central venous catheter;

Table 4

Relative hazard associated with access failure by CRP tertile

Vascular access type	Unadjusted HR (95% CI)			Adjusted HR* (95% CI)		
	Lowest: 0.2 – 4.1 mg/L	Middle: 4.1–14.8 mg/L	Highest: 14.8–84.4 mg/L	Lowest:0.2–4.1 mg/L	Middle: 4.1–14.8 mg/L	Highest: 14.8–84.4 mg/L
Central venous catheter	1.00 (reference)	1.32 (1.08–1.95)	1.92 (1.28–2.90)	1.00 (reference)	1.22 (1.02–1.79)	1.79 (1.19–2.18)
Arteriovenous access**	1.00 (reference)	1.44 (0.34–2.10)	1.65 (0.13–2.22)	1.00 (reference)	1.27 (0.30–2.16)	1.36 (0.21–2.38)

*Adjusted for age, gender, race, presence of diabetes, history of cardiovascular disease, history of peripheral vascular disease, body mass index, Index of Coexistent Disease score, smoking status, and serum albumin.

**Fistula and graft.

CI, confidence interval; CRP, C-reactive protein; HR, hazard ratio