Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

HHS Public Access

Author manuscript

*Am J Nephrol*. Author manuscript; available in PMC 2019 August 02.

Published in final edited form as:

*Am J Nephrol*. 2018 ; 48(1): 56–64. doi:10.1159/000491828.

# Effect of anti-hypertensive medication history on arteriovenous fistula maturation outcomes.

**Ke Wang, MD**[1], **Leila R. Zelnick, PhD**[1], **Peter B. Imrey, PhD**[2,3], **Ian H deBoer, MD MS**[1], **Jonathan Himmelfarb, MD**[1], **Michael D Allon, MD**[4], **Alfred K Cheung, MD**[5,7,8], **Laura M Dember, MD**[9,10], **Prabir Roy-Chaudhury, MD**[11,12], **Miguel A. Vazquez, MD**[14], **John W. Kusek, PhD**[15], **Harold I. Feldman, MD**[9,10], **Gerald J. Beck, PhD**[2,3], **Bryan Kestenbaum, MD MS**[1], and **Hemodialysis Fistula Maturation Study Group**

[1]Department of Medicine, Kidney Research Institute, University of Washington, Seattle, Washington [2]Department of Quantitative Health Sciences, Lerner Research Institute, Cleveland Clinic, Cleveland, Ohio [3]Department of Medicine, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, Ohio [4]Division of Nephrology, University of Alabama at Birmingham School of Medicine, Birmingham, Alabama [5]Division of Nephrology and Hypertension, University of Utah School of Medicine, Salt Lake City, Utah [6]Department of Bioengineering, University of Utah School of Medicine, Salt Lake City, Utah [7]Renal Section, Medical Service, Veterans Affairs Salt Lake City Healthcare System, Salt Lake City, Utah [8]Department of Nephrology, The Second Xiangya Hospital, Central South University, Changsha, Hunan, People's Republic of China [9]Renal-Electrolyte and Hypertension, Perelman School of Medicine of the University of Pennsylvania, Philadelphia, Pennsylvania [10]Center for Clinical Epidemiology and Biostatistics and Department of Biostatistics, Epidemiology, and Informatics, Perelman School of Medicine of the University of Pennsylvania, Philadelphia, Pennsylvania [11]Division of Nephrology, University of Arizona Health Sciences and Banner University Medical Center, Tucson, Arizona [12]Medical Service, Southern Arizona Veterans Affairs Healthcare System, Tucson, Arizona [13]Division of Nephrology and Hypertension, University of Utah, Salt Lake City, Utah [14]Division of Nephrology, University of Texas Southwestern Medical Center, Dallas, Texas [15]Division of Kidney, Urologic and Hematologic Diseases, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, Maryland

## Abstract

**Background—**The arteriovenous fistula (AVF) is the preferred vascular access for hemodialysis. However approximately half of AVFs fail to mature. Use of angiotensin converting enzyme inhibitors (ACE-Is), angiotensin receptor blockers (ARBs), and calcium channel blockers (CCBs) exert favorable endothelial effects and may promote AVF maturation. We tested associations of ACE-I and ARBs, CCBs, beta-blockers, and diuretics with maturation of newly created AVFs.

**Corresponding author**: Ke Wang, MD, *Mail:* Kidney Research Institute, Harborview Medical Center, 325 9th Avenue, Box 359606, Seattle, WA 98104; *Phone:* 617-378-8935; *Fax:* 206-744-5087; kewang@uw.edu.

**Conflicts of Interest**: The authors do not report any conflicts of interest.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

**Methods—**We evaluated 602 participants from the Hemodialysis Fistula Maturation Study, a multi-center, prospective cohort study of AVF maturation. We ascertained the use of each medication class within 45 days of AVF creation surgery. We defined maturation outcomes by clinical use within 9 months of surgery or 4 weeks of initiating hemodialysis.

**Results—**Unassisted AVF maturation failure without intervention occurred in 54.0% of participants, and overall AVF maturation failure (with or without intervention) occurred in 30.1%. After covariate adjustment, CCB use was associated with a 25% lower risk of overall AVF maturation failure (95% CI 3%-41% lower), but a non-significant 10% lower risk of unassisted maturation failure (95% CI 23% lower to 5% higher). ACE-I/ARB, beta-blocker and diuretic use were not significantly associated with AVF maturation outcomes. None of the antihypertensive medication classes were associated with changes in AVF diameter or blood flow over 6 weeks following surgery.

**Conclusions—**CCB use may be associated with a lower risk of overall AVF maturation failure. Further studies are needed to determine whether CCBs might play a causal role in improving AVF maturation outcomes

### Keywords

arteriovenous fistula maturation failure; calcium channel blocker; anti-hypertensive medications

## BACKGROUND

Hemodialysis is the most common form of renal replacement therapy in the United States with more than 100,000 Americans initiating maintenance hemodialysis each year.[1] The arteriovenous fistula (AVF) is the preferred method of vascular access due to greater longevity, lower infection rates, and longer survival compared to other access methods.[2] However, approximately one-half of surgically created AVFs fail to mature and no therapies can meaningfully improve AVF maturation outcomes.[3] Identifying modifiable risk factors for AVF maturation failure is an important step toward suggesting new therapeutic interventions.

Angiotensin converting enzyme inhibitors (ACE-I), angiotensin receptor blockers (ARBs), and calcium channel blockers (CCB) are commonly prescribed to hemodialysis patients and may promote AVF maturation through diverse mechanisms. Angiotensin II induces growth factor production and stimulates vascular smooth muscle cell proliferation.[4,5] *In vitro* and animal experimental models of vascular injury have demonstrated that angiotensin blockade halts vascular smooth cell migration and reduces endothelial intimal formation.[6–9] CCBs reduce cellular calcium entry, which mitigates pathologic intracellular calcium overload of end-stage renal disease, increases stable nitric oxide metabolites, and prevents apoptosis.[10,11] Previous studies have reported associations of ACE-I/ARBs and CCBs with greater patency of existing AVFs and arteriovenous grafts (AVGs), but few have investigated associations with primary AVF maturation.[12–15]

We hypothesized that ACE-I/ARB and CCB use would be associated with lower rates of AVF maturation failure. To test this hypothesis, we evaluated associations of ACE-I/ARB

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

and CCB use, at baseline, with clinical AVF outcomes of overall and unassisted maturation in the prospective Hemodialysis Fistula Maturation (HFM) Study. In exploratory analyses we also assessed the associations of beta-blockers and diuretics, two other commonly prescribed antihypertensive medication classes, with clinical maturation outcomes.

## METHODS

### Study Population

The HFM Study enrolled 602 participants, each undergoing creation of a single autogenous upper extremity AVF between 2010 and 2013 at one of seven study sites in the U.S.[16] Study participants were either receiving maintenance dialysis or expected to start dialysis within three months of planned AVF surgery. Exclusion criteria were age less than 18 years or greater than 80 years if not yet on dialysis, inability to provide informed consent, and life expectancy less than nine months. All participants gave written informed consent and Institutional Review Board approval was obtained at each study site.

### Ascertainment of Antihypertensive Medication Use

HFM Study personnel obtained names of all active medications from participants by interview and chart review within 45 days prior to planned AVF surgery. Specific medication dosages and administration schedules were not collected. Moreover, information regarding intravenous medications provided during dialysis was not abstracted. All medications were coded using the World Health Organization (WHO) drug system. We classified antihypertensive medications into one of four mutually exclusive categories: (1) angiotensin converting enzyme inhibitors (ACE-Is) or angiotensin receptor blockers (ARBs), (2) beta-blockers, (3) calcium channel blockers (CCBs), and (4) diuretics. For additional analyses, we further sub-classified ACE-I/ARB separately as ACE-I and ARB, and CCB as dihydropyridine (DHP) and non-dihydropyridine (non-DHP).

### Determination of AVF Maturation Outcomes

We evaluated the HFM Study outcomes of unassisted and overall AVF maturation.[16] Unassisted AVF maturation, the primary HFM Study outcome, was defined as successful clinical use of the AVF for hemodialysis within 9 months of surgical placement, or within 4 weeks of initiating hemodialysis without maturation-enhancing procedures. Successful clinical use entailed the use of the AVF with two needles for at least 75% of hemodialysis sessions during a four week period plus either (1) a mean dialysis blood pump speed greater ≥300 ml/minute for four consecutive sessions, or (2) a measured spKt/V ≥ 1.4 or URR>70% in any session during the four week period, with the above time windows applied to the first of the 4 days that a mean pump speed ≥300 mL/minute, or the first day an spKt/V ≥1.4 or URR >70% is achieved. Overall AVF maturation was identified using the same criteria, but allowing additional ancillary procedures to promote AVF maturation if needed.

### Preoperative and Postoperative Ultrasound Measurements

Centrally trained study sonographers at each clinical site performed preoperative (baseline) ultrasound mapping of arteries and veins in the arm intended for AVF creation. Sonographers obtained subsequent ultrasound images of the surgically created AVF early

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

postoperatively (days 0-3, targeting day 1), and at weeks 2 and 6. All ultrasound measurements were obtained following a standardized HFM protocol that has been previously described.[17] Measurements and imaging data were transmitted to the HFM Ultrasound Core, where a sonographer blinded to the study data evaluated images and measurements for accuracy and adherence to protocol. HFM Study radiologists, also blinded to the study data, then read the images and entered the results into the study database.

## Other Study Variables

HFM Study personnel used patient interviews and medical records to complete standardized forms recording patient demographics, medical histories, dialysis and vascular access histories, and social habits. Such information was updated if more than 45 days elapsed before AVF surgery. Participant demographics and lifestyle factors included age, sex, race, smoking status, and highest education level completed. Comorbid conditions included histories of coronary artery disease (angina, myocardial infarction, coronary artery bypass, or percutaneous coronary revascularization), congestive heart failure (New York Heart Association Class II or greater), and diabetes. HFM Study personnel also collected height, weight, and three resting blood pressures in the non-access arm.

## Statistical Analysis

We tabulated baseline characteristics of HFM Study participants by the use *versus* non-use of each anti-hypertensive medication class. We calculated the unassisted and overall AVF maturation failure proportions for users and non-users and used Poisson regression with robust standard errors to estimate the relative risk of AVF maturation failure associated with use of each antihypertensive medication class. We formulated three covariate adjustment models prior to analyses. The first model adjusted for age, sex, race (black *versus* non-black), and study site. The second model added adjustments for body mass index, history of diabetes and congestive heart failure, dialysis status, AVF location, smoking status, and highest level of education. A third model, viewed as primary, added adjustments for baseline systolic blood pressure and the remaining antihypertensive medication classes to estimate independent associations for each class. We also tested the 2-way, 3-way, and 4-way interactions among the four medication classes with a single omnibus test. We conducted additional analyses to assess separate associations for ACE-Is and ARBs, and for DHP and non-DHP CCBs. For these sensitivity analyses only we excluded participants who were concomitantly on ACE-Is and ARBs (n=14) or DHP and non-DHP CCBs (n=2).

We ascertained ultrasound measurements of AVF flow (mL/min) and draining vein diameter (mm) for each patient during a pre-operative vessel mapping examination, early postoperatively (days 0-3, targeting day 1), week 2, and week 6. We constructed linear mixed models to examine the differences in temporal changes in ultrasound measurement between users and non-users of each antihypertensive class. In each case, the linear mixed model allowed for a random effect of patient, main effects of time modeled continuously and the antihypertensive class of interest, the interaction between these two, and additional covariates as described earlier. Statistical significance of the linear interaction between time and use of the antihypertensive class of interest was taken to be evidence of a difference in the change in AVF diameter or flow between users and non-users.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

For all regression analyses, we used multiple imputation with 10 imputations and chained equations to account for missingness in covariates and AVF outcomes.[18,19] We combined the resulting estimates using Rubin's rules to account for variability in the imputation procedure.[20] A 2-sided p-value of 0.05 was considered significant for all analyses. Analyses were conducted using open-source package R version 3.3.0 (R Foundation, Vienna, Austria)[21] and STATA 11 (College Station, TX).[22] We used the lmer function in the lme4 R package[23] for linear mixed models and the glm function in R for Poisson regression models.

## RESULTS

### Description of the Study Population

Among the 602-person HFM Study cohort, the mean age was 55.1 years; 423 participants (70.2%) were male, 264 (43.8%) were black, and 383 (63.6%) were receiving maintenance dialysis at the time of surgery. Anti-hypertensive medication use was highly prevalent in the HFM Study cohort, with respectively 70 (11.6%), 135 (22.4%), and 365 (60.6%) of participants reporting use of one, two, and 3-4 anti-hypertensive medication classes. The most commonly used anti-hypertensive medication classes were beta-blockers (73.0%), followed by CCBs (65.2%), diuretics (48.5%), and ACE-I/ARBs (47.1%). Baseline characteristics of ACE-I/ARB and CCB users were generally similar to those of non-users of these medications (Table 1). CCB users were more likely to be black (46.6 vs 38.8%) and less likely to be receiving maintenance hemodialysis (59.0 vs 72.2%) compared to non-CCB users. Diuretic and beta-blocker users tended to have more co-morbid conditions compared to non-users (Supplemental Tables 1-2). Users of each antihypertensive class tended to have higher baseline systolic blood pressures compared to non-users (Table 1, Supplemental Tables 1-2).

### Associations with Unassisted AVF Maturation Failure

In the multiply-imputed data, failure to achieve unassisted AVF maturation occurred in an average of 325 HFM Study participants (54.0%). None of the drug classes showed statistically significant association with unassisted maturation failure under any adjustment model (Table 2). More specifically, ACE-I/ARB users had a higher crude incidence of unassisted AVF maturation failure than non-users (57.4 vs 51.5%) and exhibited non-significant 11-14% higher risks of unassisted AVF maturation failure in minimally or fully adjusted models. CCB users had non-significantly lower crude incidence of unassisted AVF maturation failure than non-CCB users (51.4 vs. 59.8%) in minimally or fully adjusted models (Model 3 adjusted relative risk [RR] 0.90; 95% CI 0.77, 1.05; p=0.16). Subgroup comparisons were non-significant, although there was a trend towards lower risk of unassisted AVF maturation failure with non-DHP than with DHP CCBs (Model 3 adjusted RR 0.86; 95% CI 0.63, 1.18; p=0.35).

### Associations with Overall AVF Maturation Failure

213 (35.4%) HFM participants required at least one intervention to promote maturation after AVF creation. Angioplasty was the most common intervention (26.1%), followed by occlusion of accessory vein (6.1%), fistula repositioning (4.2%), and thrombectomy (3.0%). Failure to achieve overall AVF maturation occurred in an average of 181 HFM Study

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

participants (30.1%). Users and non-users of ACE-I/ARB and beta-blocker demonstrated similar unadjusted incidences of overall AVF maturation failure (Table 3). CCB use was associated with a statistically significant 23%-25% lower risk of overall maturation failure after full covariate adjustment in Models 2 and 3 (95% confidence interval 3% to 41% lower; p=0.03, after Model 3 adjustment). Diuretic use was associated with a non-significant 20-29% greater risk of overall maturation failure across all levels of adjustment.

The association of CCB use with lower rates of overall AVF maturation failure was not statistically significantly modified by use *versus* non-use of ACE-I/ARB, beta-blockers, or diuretics (Figure 1; omnibus p-for-interaction = 0.69). There were no statistically significant differences in overall AVF failure comparing ARB use to ACE-I use (Model 3 adjusted RR 0.90; 95% CI 0.60, 1.35; p value=0.61), or non-DHP use to DHP CCB use (Model 3 adjusted RR 0.79; 95% CI 0.45, 1.39; p value=0.41).

### Association with Postoperative AVF Diameter and Flow

Venous diameter and blood flow increased substantially within one day following AVF creation surgery, followed by smaller increases after two and six weeks. Diameter and flow were substantially greater in upper arm AVFs compared to forearm AVFs (Supplemental Figure 1).[17] There were no significant differences in changes in vein diameter (p=0.12) or AVF flow (p=0.96) over time between ACE-I/ARB users and non-users (Supplemental Figure 1), CCB users and non-users (diameter p=0.63, blood flow p=0.35; Supplemental Figure 2), or between users and non-users of beta-blockers (Supplemental Figure 3) and diuretics (Supplemental Figure 4).

## DISCUSSION

In summary, we observed an association of CCB use within 45 days of AVF creation surgery with a lower incidence of overall AVF maturation failure in a prospective cohort study of 602 patients undergoing AVF creation surgery. CCB use was also associated with a numerically lower, but not statistically significantly different, incidence of unassisted AVF maturation failure. In contrast, the use of ACE-I/ARBs and other anti-hypertensive medication classes were not associated with unassisted or overall AVF maturation failure.

To our knowledge, this is only the second study to assess anti-hypertensive medication use in relation to primary AVF maturation. A previous single center study of 97 AVFs also observed higher rate of AVF maturation among CCB users (84%) compared to non-users (46%).[15] Most previous studies have evaluated ACE-Is and CCBs in relation to maintenance of AVF and AVG patency. For example, a retrospective cohort study of hemodialysis patients undergoing angioplasty for access stenosis reported CCB use to be associated with a 32% higher patency rate for AVFs and 25% higher patency rate for AVGs.[12] The Dialysis Outcomes and Practice Patterns (DOPPS) study, which evaluated 900 hemodialysis patients with AVFs and 1944 patients with AVGs, observed associations of CCB use with higher rates of primary AVG patency and ACE-I use with improved secondary AVF patency.[13] Moreover, Chen *et al* reported lower risks of AVF and AVG failure associated with ACE-I/ARB and CCB use in a study of 37,771 AVFs and 4,473 AVGs.[14] These observational data

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

suggest that ACE-I and CCBs may enhance the life span of existing vascular accesses, but do not address possible effects on primary AVF maturation.

Several factors have been suggested to influence AVF maturation. The innate ability of the artery to dilate, as reflected by both flow- and nitroglycerin-mediated dilation, was associated with AVF development on ultrasonography in a prior HFM study.[19] CCBs may promote vasodilation of the arterialized vein post AVF creation. However, we were unable to detect differences in post-surgical trajectories of AVF diameter or flow, assessed by ultrasonography, comparing CCB users to non-users in the present study.

CCBs may also inhibit endothelial neointimal hyperplasia through inhibition of calcium influx via L-type calcium channels, a critical process for vascular smooth muscle cell growth and migration.[24] *In-vitro* models of coronary atherosclerosis have demonstrated dose-dependent inhibitory actions of CCBs on smooth muscle cell proliferation.[25,26] In animal models of vascular injury, the administration of CCB decreased aortic neointimal area.[27,28] In a human trial of patients with concomitant hypertension, diabetes, and coronary artery disease, CCBs reduced the progression of carotid neointimal area more than diuretics, beta-blockers, or ACE-I despite comparable blood pressure reductions.[29] CCBs may also decrease intracellular calcium signaling by inhibiting calcium release from the sarcoplasmic reticulum.[30,31] However, the role of neointimal hyperplasia in AVF maturation is uncertain. Several studies, including the HFM Study, have not established a significant association of preexisting venous hyperplasia with clinical AVF maturation failure.[32–34] On the other hand, post-operative venous stenosis on ultrasound was associated with both unassisted and overall AVF maturation failure.[34] To the extent that AVF maturation may be attributed to neointimal hyperplasia and stenosis, it is plausible that CCB promotes AVF maturation by inhibiting hyperplasia that develops after creation of the AVF.

We observed a non-statistically significant trend toward lower rates of overall AVF maturation failure associated with non-DHP *versus* DHP CCBs. In experimental models, verapamil and diltiazem have been shown to be more potent inhibitors of vascular smooth muscle cell functions compared to nifedipine.[35] Verapamil has also been shown to be a potent inhibitor of platelet aggregation and promoter of endothelial-dependent relaxation of coronary artery bypass graft.[36,37] Observational studies have demonstrated that that CCBs confer mortality benefit in dialysis patients, and a retrospective study suggested lower all-cause and cardiovascular mortality in users of DHP compared to non-DHP.[38–42] DHP and non-DHP CCBs differ in their peripheral and central physiologic effects. DHP CCBs share a common chemical structure derived from pyridine and have known vascular dilatory properties. In comparison, non-DHP CCBs exert more negative chronotropic effects.[43] While DHP CCBs are recommended agents for hypertension treatment in dialysis patients,[44] we advise cautious interpretation of our findings and do not suggest selective prescription of CCBs for the purpose of fistula maturation.

The primary limitation of this study is the potential for confounding-by-indication. It is possible that unmeasured characteristics of CCB users *versus* non-CCB users distorted the observed association with overall AVF maturation failure. The possibility of confounding is moderated to some degree by concurrent evaluation of other anti-hypertensive medication

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

classes, which may be prescribed for similar indications, and by adjustment for known predictors of AVF maturation that were measured using standardized procedures. A second limitation is the possibility of false discovery in the context of multiple testing. CCB use was associated with significant differences in overall AVF maturation failure, but not with unassisted maturation failure, in the context of testing four medication classes, two AVF maturation outcomes, and across multiple adjustment models. Failure to reach statistical significance for unassisted AVF maturation failure may have been due to inadequate study power. However, the possibility of false discovery requires a cautious interpretation and replication of these findings in other studies. Combination effects from the simultaneous use of several antihypertensive classes may have also influenced our results. We have addressed this overlap by adjusting for use of other medication classes in our analyses, although we recognize that we are not powered to conduct individual sub-group analyses. Finally, the HFM Study assessed the use *versus* non-use of medications of interest at a single time point, precluding assessment of dosage or duration of therapy. A causal benefit of CCB also cannot be inferred based on our results.

An important strength of this study is evaluation of primary AVF maturation outcomes within the largest prospective study of AVF maturation conducted to date. The multi-center setting of the HFM Study enhances applicability of our findings beyond the practice patterns of a single clinical site. A second strength is the examination of several anti-hypertensive medication classes in association with AVF outcomes.

## CONCLUSIONS

CCB use was associated with lower risk of overall clinical AVF maturation failure. Further studies are needed to probe potential relevant mechanisms of action. Ultimately, randomized clinical trials are necessary to determine whether CCBs play a causal role in promoting AVF maturation.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgements:

The HFM Study was funded by grants U01DK082218, U01DK082222, U01DK082232, U01DK082236, U01DK082240, U01DK082179, U01DK082189 from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). This study was partially supported by NIDDK grant K24DK103986. The members of the Hemodialysis Fistula Maturation Study Group are as follows: Chair, Steering Committee, University of Pennsylvania: H. Feldman; Clinical Centers, Boston University: L. Dember (principal investigator [PI]), A. Farber, J. Kaufman, L. Stern, P. LeSage, C. Kivork, D. Soares, M. Malikova; University of Alabama: M. Allon (PI), C. Young, M. Taylor, L. Woodard, K. Mangadi; University of Cincinnati: P. Roy-Chaudhury (PI), R. Munda, T. Lee, R. Alloway, M. El-Khatib, T. Canaan, A. Pflum, L. Thieken, B. Campos-Naciff; University of Florida: T. Huber (PI), S. Berceli, M. Jansen, G. McCaslin, Y. Trahan; University of Texas Southwestern: M. Vazquez (PI), W. Vongpatanasin, I. Davidson, C. Hwang, T. Lightfoot, C. Livingston, A. Valencia, B. Dolmatch, A. Fenves, N. Hawkins; University of Utah: A. K. Cheung (PI), L. Kraiss, D. Kinikini, G. Treiman, D. Ihnat, M. Sarfati, Y.T. Shiu, C. Terry, I. Lavasani, M. Maloney, L. Schlotfeldt; University of Washington: J. Himmelfarb (PI), C. Buchanan, C. Clark, C. Crawford, J. Hamlett, J. Kundzins, L. Manahan, J. Wise; Data Coordinating Center, Cleveland Clinic: G. Beck (PI), J. Gassman, T. Greene, P. Imrey, L. Li, J. Alster, M. Li, J. MacKrell, M. Radeva, B.Weiss, K. Wiggins; histology core facility, University of Washington: C. Alpers (PI), K. Hudkins, T. Wietecha; US core facility, University of Alabama at Birmingham: M. Robbin (PI), H. Umphrey, L. Alexander, C. Abts, L. Belt; vascular function core facility, Boston University: J. Vita (PI, deceased), N. Hamburg (PI). M. Duess, A. Levit; National

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) biosample repository, Fisher BioServices: H. Higgins, S. Ke, O. Mandaci, C. Snell; NIDDK DNA repository, Fred Hutchinson Cancer Research Center: J. Gravley, S. Behnken, R. Mortensen; External Expert Panel: G. Chertow (Chair), A. Besarab, K. Brayman, M. Diener-West, D. Harrison, L. Inker, T. Louis, W. McClellan, J. Rubin; NIDDK: J. Kusek, R. Star. We thank the patients for their participation in the HFM Study. We acknowledge Lin Belt, Carl Abts and Lauren Alexander for their invaluable expertise at the HFM Ultrasound Core. This ancillary study was funded by grant R01 DK094891-01.

*Funding:* this work was supported by R01DK094891 granted to Dr. Kestenbaum.

## LIST OF ABBREVIATIONS

| | |
|---|---|
| **ACE-I** | angiotensin converting enzyme inhibitor |
| **ARB** | angiotensin receptor blocker |
| **AVF** | arteriovenous fistula |
| **AVG** | arteriovenous grafts |
| **CCB** | calcium channel blocker |
| **DHP** | dihydropyridine |
| **HFM** | Hemodialysis Fistula Maturation |
| **spKt/V** | single-pooled Kt/V |
| **URR** | urea reduction ratio |

## REFERENCES

1. Saran R, Li Y, Robinson B, et al. US Renal Data System 2014 Annual Data Report: Epidemiology of Kidney Disease in the United States. American journal of kidney diseases : the official journal of the National Kidney Foundation. 2015;66(1 Suppl 1):Svii, S1–305. [PubMed: 26111994]
2. Polkinghorne KR, McDonald SP, Atkins RC, Kerr PG. Vascular access and all-cause mortality: a propensity score analysis. Journal of the American Society of Nephrology : JASN. 2004;15(2):477–486. [PubMed: 14747396]
3. Allon M, Robbin ML. Increasing arteriovenous fistulas in hemodialysis patients: problems and solutions. Kidney Int. 2002;62(4):1109–1124. [PubMed: 12234281]
4. Gibbons GH, Dzau VJ. The emerging concept of vascular remodeling. The New England journal of medicine. 1994;330(20):1431–1438. [PubMed: 8159199]
5. Daemen MJ, Lombardi DM, Bosman FT, Schwartz SM. Angiotensin II induces smooth muscle cell proliferation in the normal and injured rat arterial wall. Circulation research. 1991;68(2):450–456. [PubMed: 1991349]
6. Powell JS, Clozel JP, Muller RK, et al. Inhibitors of angiotensin-converting enzyme prevent myointimal proliferation after vascular injury. Science (New York, NY). 1989;245(4914):186–188.
7. Prescott MF, Webb RL, Reidy MA. Angiotensin-converting enzyme inhibitor versus angiotensin II, AT1 receptor antagonist. Effects on smooth muscle cell migration and proliferation after balloon catheter injury. The American journal of pathology. 1991;139(6):1291–1296. [PubMed: 1750504]
8. Liu SQ. Focal expression of angiotensin II type 1 receptor and smooth muscle cell proliferation in the neointima of experimental vein grafts: relation to eddy blood flow. Arteriosclerosis, thrombosis, and vascular biology. 1999;19(11):2630–2639.
9. Wong J, Rauhoft C, Dilley RJ, Agrotis A, Jennings GL, Bobik A. Angiotensin-converting enzyme inhibition abolishes medial smooth muscle PDGF-AB biosynthesis and attenuates cell proliferation

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

in injured carotid arteries: relationships to neointima formation. Circulation. 1997;96(5):1631–1640. [PubMed: 9315558]

10. Xie L, Clunn GF, Lymn JS, Hughes AD. Role of intracellular calcium ([Ca2+]i) and tyrosine phosphorylation in adhesion of cultured vascular smooth muscle cells to fibrinogen. Cardiovascular research. 1998;39(2):475–484. [PubMed: 9798532]
11. Scherberich A, Campos-Toimil M, Ronde P, Takeda K, Beretz A. Migration of human vascular smooth muscle cells involves serum-dependent repeated cytosolic calcium transients. Journal of cell science. 2000;113(Pt 4):653–662. [PubMed: 10652258]
12. Doi S, Masaki T, Shigemoto K, Harada S, Yorioka N. Calcium channel antagonists reduce restenosis after percutaneous transluminal angioplasty of an arteriovenous fistula in hemodialysis patients. Therapeutic apheresis and dialysis : official peer-reviewed journal of the International Society for Apheresis, the Japanese Society for Apheresis, the Japanese Society for Dialysis Therapy. 2008;12(3):232–236.
13. Saran R, Dykstra DM, Wolfe RA, Gillespie B, Held PJ, Young EW. Association between vascular access failure and the use of specific drugs: the Dialysis Outcomes and Practice Patterns Study (DOPPS). American journal of kidney diseases : the official journal of the National Kidney Foundation. 2002;40(6):1255–1263. [PubMed: 12460045]
14. Chen FA, Chien CC, Chen YW, Wu YT, Lin CC. Angiotensin Converting-Enzyme Inhibitors, Angiotensin Receptor Blockers, and Calcium Channel Blockers Are Associated with Prolonged Vascular Access Patency in Uremic Patients Undergoing Hemodialysis. PloS one. 2016;11(11):e0166362. [PubMed: 27832203]
15. Bashar K, Zafar A, Elsheikh S, et al. Predictive parameters of arteriovenous fistula functional maturation in a population of patients with end-stage renal disease. PloS one. 2015;10(3):e0119958. [PubMed: 25768440]
16. Dember LM, Imrey PB, Beck GJ, et al. Objectives and design of the hemodialysis fistula maturation study. American journal of kidney diseases : the official journal of the National Kidney Foundation. 2014;63(1):104–112. [PubMed: 23992885]
17. Robbin ML, Greene T, Cheung AK, et al. Arteriovenous Fistula Development in the First 6 Weeks after Creation. Radiology. 2016;279(2):620–629. [PubMed: 26694050]
18. Royston P: Multiple imputation of missing values. Stata J 4:227–241, 2004
19. Allon M, Greene T, Dember LM, et al. Association between Preoperative Vascular Function and Postoperative Arteriovenous Fistula Development. Journal of the American Society of Nephrology : JASN. 2016;27(12):3788–3795. [PubMed: 27160404]
20. Rubin D: Multiple Imputation for Nonresponse in Surveys, New York: Wiley, 1987
21. R Core Team: R: A language and environment for statistical computing. Foundation for Statistical Computing, Vienna, Austria URL https://www.R-project.org/, 2017
22. StataCorp: Stata Statistical Software: Release 11. College Station, TX: StataCorp LP, 2009
23. Bates DMM, Bolker BM, Walker SC. Fitting linear mixed-effects models using lme4. J Stat Softw. 2015(67: 1–48).
24. Clunn GF, Sever PS, Hughes AD. Calcium channel regulation in vascular smooth muscle cells: synergistic effects of statins and calcium channel blockers. International journal of cardiology. 2010;139(1):2–6. [PubMed: 19523699]
25. Yang Z, Noll G, Luscher TF. Calcium antagonists differently inhibit proliferation of human coronary smooth muscle cells in response to pulsatile stretch and platelet-derived growth factor. Circulation. 1993;88(3):832–836. [PubMed: 8353912]
26. Voisard R, Koschnick S, Baur R, et al. High-dose diltiazem prevents migration and proliferation of vascular smooth muscle cells in various in-vitro models of human coronary restenosis. Coronary artery disease. 1997;8(3–4):189–201. [PubMed: 9237030]
27. Cristofori P, Crivellente F, Campagnola M, et al. Reduced progression of atherosclerosis in apolipoprotein E-deficient mice treated with lacidipine is associated with a decreased susceptibility of low-density lipoprotein to oxidation. International journal of experimental pathology. 2004;85(2):105–114. [PubMed: 15154916]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript


28. Jackson CL, Bush RC, Bowyer DE. Inhibitory effect of calcium antagonists on balloon catheter-induced arterial smooth muscle cell proliferation and lesion size. Atherosclerosis. 1988;69(2-3): 115–122. [PubMed: 3348836]
29. Wang JG, Staessen JA, Li Y, et al. Carotid intima-media thickness and antihypertensive treatment: a meta-analysis of randomized controlled trials. Stroke. 2006;37(7):1933–1940. [PubMed: 16763185]
30. Brozovich FV, Nicholson CJ, Degen CV, Gao YZ, Aggarwal M, Morgan KG. Mechanisms of Vascular Smooth Muscle Contraction and the Basis for Pharmacologic Treatment of Smooth Muscle Disorders. Pharmacological reviews. 2016;68(2):476–532. [PubMed: 27037223]
31. Valdivia HH, Valdivia C, Ma J, Coronado R. Direct binding of verapamil to the ryanodine receptor channel of sarcoplasmic reticulum. Biophysical journal. 1990;58(2):471–481. [PubMed: 2169916]
32. Tabbara M, Duque JC, Martinez L, et al. Pre-existing and Postoperative Intimal Hyperplasia and Arteriovenous Fistula Outcomes. American journal of kidney diseases : the official journal of the National Kidney Foundation. 2016;68(3):455–464. [PubMed: 27012909]
33. Allon M, Robbin ML, Young CJ, et al. Preoperative venous intimal hyperplasia, postoperative arteriovenous fistula stenosis, and clinical fistula outcomes. Clinical journal of the American Society of Nephrology : CJASN. 2013;8(10):1750–1755. [PubMed: 23813559]
34. Cheung AK, Imrey PB, Alpers CE, et al. Intimal Hyperplasia, Stenosis, and Arteriovenous Fistula Maturation Failure in the Hemodialysis Fistula Maturation Study. Journal of the American Society of Nephrology : JASN. 2017;28(10):3005–3013. [PubMed: 28710091]
35. Block LH, Emmons LR, Vogt E, Sachinidis A, Vetter W, Hoppe J. Ca2+-channel blockers inhibit the action of recombinant platelet-derived growth factor in vascular smooth muscle cells. Proceedings of the National Academy of Sciences of the United States of America. 1989;86(7): 2388–2392. [PubMed: 2928338]
36. L LL, Lam JY, Hung J, Waters D. Oral verapamil inhibits platelet thrombus formation in humans. Circulation. 1994;89(2):630–634. [PubMed: 8313551]
37. He GW. Verapamil plus nitroglycerin solution maximally preserves endothelial function of the radial artery: comparison with papaverine solution. The Journal of thoracic and cardiovascular surgery. 1998;115(6):1321–1327. [PubMed: 9628674]
38. Kestenbaum B, Gillen DL, Sherrard DJ, Seliger S, Ball A, Stehman-Breen C. Calcium channel blocker use and mortality among patients with end-stage renal disease. Kidney Int. 2002;61(6): 2157–2164. [PubMed: 12028456]
39. Ishani A, Herzog CA, Collins AJ, Foley RN. Cardiac medications and their association with cardiovascular events in incident dialysis patients: cause or effect? Kidney Int. 2004;65(3):1017–1025. [PubMed: 14871422]
40. Griffith TF, Chua BS, Allen AS, Klassen PS, Reddan DN, Szczech LA. Characteristics of treated hypertension in incident hemodialysis and peritoneal dialysis patients. American journal of kidney diseases : the official journal of the National Kidney Foundation. 2003;42(6):1260–1269. [PubMed: 14655199]
41. Wetmore JB, Shireman TI. The ABCs of cardioprotection in dialysis patients: a systematic review. American journal of kidney diseases : the official journal of the National Kidney Foundation. 2009;53(3):457–466. [PubMed: 19022545]
42. Wetmore JB, Mahnken JD, Phadnis MA, Ellerbeck EF, Shireman TI. Relationship between calcium channel blocker class and mortality in dialysis. Pharmacoepidemiology and drug safety. 2015;24(12):1249–1258. [PubMed: 26371369]
43. Elliott WJ, Ram CV. Calcium channel blockers. Journal of clinical hypertension (Greenwich, Conn). 2011;13(9):687–689.
44. Georgianos PI, Agarwal R. Pharmacotherapy of Hypertension in Chronic Dialysis Patients. Clinical journal of the American Society of Nephrology : CJASN. 2016;11(11):2062–2075. [PubMed: 27797886]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

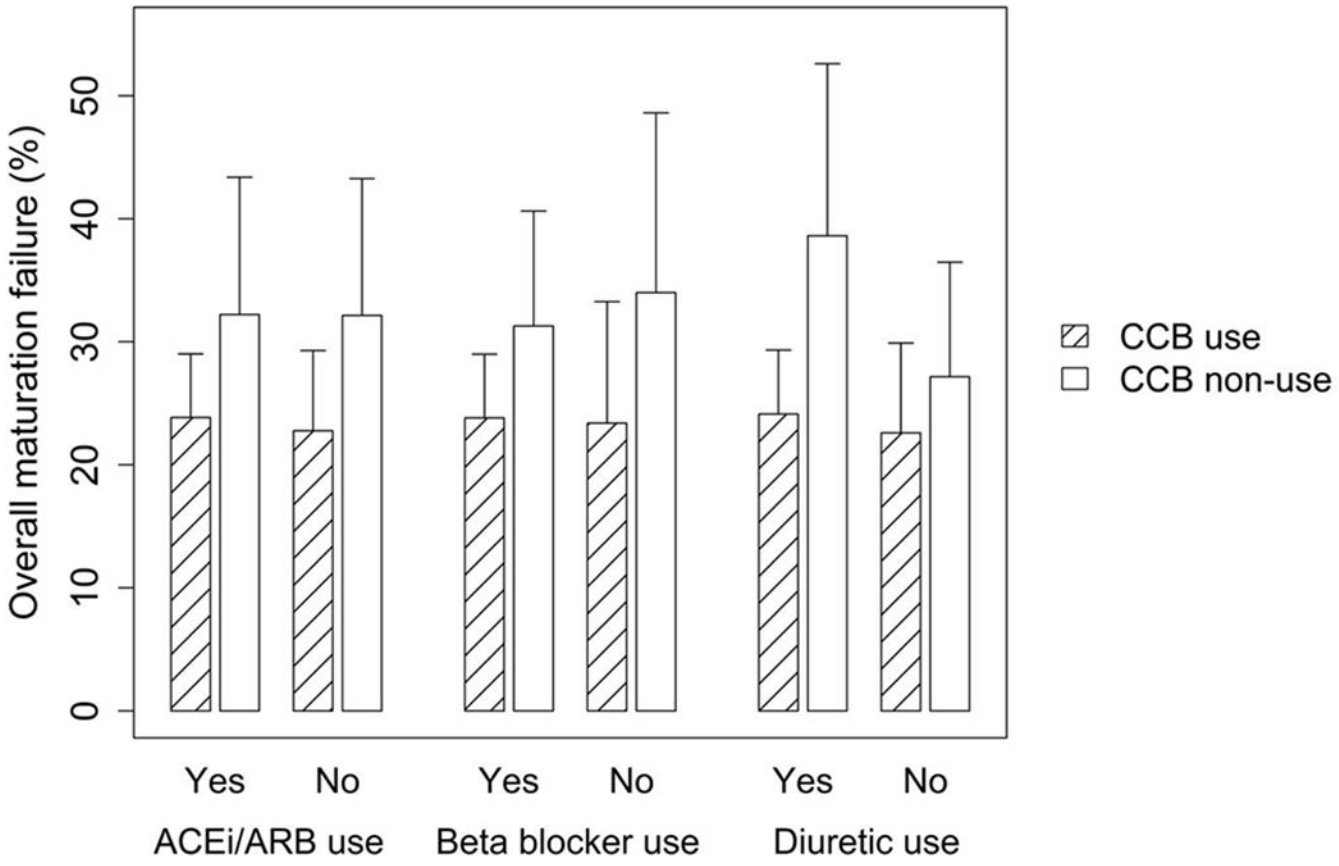


**Figure 1. Overall maturation failure rates of CCB users and non-users stratified by the use of other antihypertensive medications.**

Bar graph comparing overall AVF maturation failure rates of CCB users and non-users (y-axis) stratified by use and non-use of ACE-I/ARB, beta-blocker, and diuretic (x-axis). Overall maturation failure rates are adjusted for Model 3 covariates and obtained using Poisson model that allowed for interaction between CCB and other antihypertensive classes. Error bars delineate upper limit of 95% confidence interval.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

**Table 1.**

Baseline characteristics by ACE-I/ARB and CCB use.

| | ACE-I/ARB use | | CCB use | |
|---|---|---|---|---|
| | **Yes** | **No** | **Yes** | **No** |
| | **(N=284)** | **(N=318)** | **(N=393)** | **(N=209)** |
| Age (years) | 54.5 ±12.9 | 55.6 ±13.8 | 55.2 ±13.0 | 54.8 ±14.1 |
| Male sex | 197 (69.4) | 226 (71.1) | 280 (71.2) | 143 (68.4) |
| Race/ethnicity | | | | |
| White | 131 (46.1) | 152 (47.8) | 178 (45.3) | 105 (50.2) |
| Black | 128 (45.1) | 136 (42.8) | 183 (46.6) | 81 (38.8) |
| Other | 25 (8.8) | 30 (9.4) | 32 (8.1) | 23 (11.0) |
| Education[1] | | | | |
| No high school diploma | 87 (30.6) | 74 (23.3) | 107 (27.2) | 54 (25.8) |
| High school diploma | 79 (27.8) | 84 (26.4) | 112 (28.5) | 51 (24.4) |
| Post-secondary education | 107 (37.7) | 153 (48.1) | 163 (41.5) | 97 (46.4) |
| Smoking[2] | | | | |
| Current | 45 (16.0) | 60 (19.0) | 72 (18.3) | 33 (15.8) |
| Former | 103 (36.5) | 117 (37.1) | 146 (37.2) | 74 (35.4) |
| Never | 134 (47.5) | 138 (43.8) | 170 (43.3) | 102 (48.8) |
| Maintenance dialysis | 179 (63.0) | 204 (64.2) | 232 (59.0) | 151 (72.2) |
| History of diabetes | 173 (60.9) | 180 (56.6) | 236 (60.1) | 117 (56.0) |
| Prevalent cardiovascular disease | 140 (49.3) | 150 (47.2) | 190 (48.3) | 100 (47.8) |
| History of congestive heart failure | 80 (28.2) | 85 (26.7) | 102 (26.0) | 63 (30.1) |
| Body mass index (kg/m$^2$) | 30.8 ± 7.8 | 30.0 ± 7.4 | 30.5 ± 7.5 | 30.1 ± 7.8 |
| Systolic blood pressure (mmHg) | 153.7 ± 24.7 | 149.0 ± 22.9 | 153.5 ± 23.2 | 146.9 ± 24.4 |
| Estimated GFR (mL/min/1.73m$^2$)* | 14.1 ± 4.7 | 13.5 ± 4.9 | 13.5 ± 4.6 | 14.5 ± 5.2 |
| AVF location | | | | |
| Forearm | 75 (26.4) | 68 (21.4) | 91 (23.2) | 52 (24.9) |
| Upper arm | 209 (73.6) | 250 (78.6) | 302 (76.8) | 157 (75.1) |
| Antihypertensive medication use | | | | |
| No antihypertensive medications | 0 (0.0) | 32 (10.1) | 0 (0) | 32 (15.3) |
| ACE-I/ARB | 284 (100.0) | 0 (0.0) | 183 (46.6) | 101 (48.3) |
| Beta-blockers | 219 (77.1) | 221 (69.5) | 301 (76.6) | 139 (66.5) |
| CCB | 183 (64.4) | 210 (66.0) | 393 (100) | 0 (0) |
| Diuretics | 141 (49.6) | 151 (47.5) | 215 (54.7) | 77 (36.8) |

Values in the table expressed as mean ± standard deviation or number (percent).

GFR=glomerular filtration rate

[1]Education data missing for 18 participants

[2]Smoking status missing for 5 participants

*Excludes participants on dialysis

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

**Table 2.**

Associations of antihypertensive medication use with unassisted AVF failure.

| | Number of participants | Number of failures (%) | Relative risk (95% confidence interval) | | |
|---|---|---|---|---|---|
| | | | Model 1 | Model 2 | Model 3 |
| ACE-I/ARBs | | | | | |
| No | 318 | 164 (51.5) | 1.0 (Reference) | 1.0 (Reference) | 1.0 (Reference) |
| Yes | 284 | 163 (57.4) | 1.14 (0.99, 1.32) | 1.11 (0.96, 1.29) | 1.11 (0.96, 1.29) |
| P-value | | | 0.07 | 0.15 | 0.16 |
| Beta-blockers | | | | | |
| No | 162 | 90 (55.5) | 1.0 (Reference) | 1.0 (Reference) | 1.0 (Reference) |
| Yes | 440 | 237 (53.8) | 1.01 (0.86, 1.19) | 0.97 (0.82, 1.14) | 0.96 (0.81, 1.14) |
| P-value | | | 0.88 | 0.71 | 0.68 |
| CCBs | | | | | |
| No | 209 | 125 (59.8) | 1.0 (Reference) | 1.0 (Reference) | 1.0 (Reference) |
| Yes | 393 | 202 (51.4) | 0.90 (0.77, 1.05) | 0.90 (0.77, 1.04) | 0.90 (0.77, 1.05) |
| P-value | | | 0.17 | 0.16 | 0.16 |
| Diuretics | | | | | |
| No | 310 | 165 (53.2) | 1.0 (Reference) | 1.0 (Reference) | 1.0 (Reference) |
| Yes | 292 | 162 (55.4) | 1.06 (0.92, 1.23) | 1.00 (0.85, 1.18) | 1.02 (0.86, 1.20) |
| P-value | | | 0.41 | 0.98 | 0.82 |

Model 1 adjusted for age, gender, race/ethnicity (black vs non-black) and study site.

Model 2 adds adjustment for body mass index, diabetes, dialysis status, AVF location, education, smoking, and history of congestive heart failure.

Model 3 adds adjustment for other anti-hypertensive medication classes and systolic blood pressure.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

**Table 3.**

Associations of antihypertensive medication use with overall AVF failure.

| | Number of participants | Number of failures (%) | Relative risk (95% confidence interval) | | |
|---|---|---|---|---|---|
| | | | Model 1 | Model 2 | Model 3 |
| ACE-I/ARBs | | | | | |
| No | 318 | 94 (29.5) | 1.0 (Reference) | 1.0 (Reference) | 1.0 (Reference) |
| Yes | 284 | 89 (31.3) | 1.10 (0.86, 1.41) | 1.08 (0.84, 1.38) | 1.07 (0.84, 1.37) |
| P-value | | | 0.44 | 0.56 | 0.59 |
| Beta-blockers | | | | | |
| No | 162 | 49 (30.2) | 1.0 (Reference) | 1.0 (Reference) | 1.0 (Reference) |
| Yes | 440 | 134 (30.4) | 1.08 (0.82, 1.43) | 1.00 (0.75, 1.32) | 0.97 (0.73, 1.29) |
| P-value | | | 0.58 | 0.98 | 0.83 |
| CCBs | | | | | |
| No | 209 | 74 (35.4) | 1.0 (Reference) | 1.0 (Reference) | 1.0 (Reference) |
| Yes | 393 | 109 (27.7) | 0.80 (0.62, 1.02) | 0.77 (0.60, 0.99) | 0.75 (0.59, 0.97) |
| P-value | | | 0.07 | 0.04 | 0.03 |
| Diuretics | | | | | |
| No | 310 | 84 (27.1) | 1.0 (Reference) | 1.0 (Reference) | 1.0 (Reference) |
| Yes | 292 | 99 (33.9) | 1.29 (1.00, 1.67) | 1.20 (0.90, 1.60) | 1.26 (0.94, 1.69) |
| P-value | | | 0.05 | 0.20 | 0.12 |

Model 1 adjusted for age, gender, race/ethnicity (black vs non-black), and study site.

Model 2 adds adjustment for body mass index, diabetes, dialysis status, AVF location, education, smoking, and history of congestive heart failure.

Model 3 adds adjustment for other anti-hypertensive medication classes and systolic blood pressure.