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Reduction of Arterial Stiffness After Kidney Transplantation: A Systematic Review and Meta-Analysis

Aboubacar Sidibé, MSc; Catherine Fortier, MSc; Marie-Pier Desjardins, BSc; Hervé Tchala Vignon Zomahoun, PhD; Amélie Boutin, PhD; Fabrice Mac-Way, MD; Sacha De Serres, MD-MSc; Mohsen Agharazii, MD

***Background*—**End-stage kidney disease is associated with increased arterial stiffness. Although correction of uremia by kidney transplantation (KTx) could improve arterial stiffness, results from clinical studies are unclear partly due to small sample sizes.

***Method and Results*—**We conducted a systematic review and meta-analysis of before-after design studies performed in adult KTx patients with available measures of arterial stiffness parameters (pulse wave velocity [PWV], central pulse pressure [PP], and augmentation index) before and at any time post-KTx. Mean difference of post- and pre-KTx values of different outcomes were estimated using a random effect model with 95% confidence interval. To deal with repetition of measurement within a study, only 1 period of measurement was considered per study by analysis. Twelve studies were included in meta-analysis, where a significant decrease of overall PWV by 1.20 m/s (95% CI 0.67-1.73, I^2=72%), central PWV by 1.20 m/s (95% CI 0.16-2.25, I^2=83%), peripheral PWV by 1.17 m/s (95% CI 0.17-2.17, I^2=79%), and brachial-ankle PWV by 1.21 m/s (95% CI 0.66-1.75, I^2=0%) was observed. Central PP (reported in 4 studies) decreased by 4.75 mm Hg (95% CI 0.78–10.28, I^2=50%). Augmentation index (reported in 7 studies) decreased by 10.5% (95% CI 6.9-14.1, I^2=64%). A meta-regression analysis showed that the timing of assessment post-KTx was the major source of the residual variance.

***Conclusions*—**This meta-analysis suggests a reduction of the overall arterial stiffness in patients with end-stage kidney disease after KTx. **(*J Am Heart Assoc*. 2017;6:e007235. DOI: 10.1161/JAHA.117.007235.)**

Key Words: arterial stiffness • augmentation index • kidney • pulse pressure • pulse wave velocity • transplantation

Patients with chronic kidney disease (CKD) have a higher risk of cardiovascular disease compared with the general population, even after adjustment for traditional cardiovascular disease risk factors.[1-3] Arterial stiffness, a nontraditional cardiovascular disease risk factor, has been proposed to explain part of this excess cardiovascular risk.[4,5] Indeed, it has been reported in systematic review and meta-analysis that a raise in aortic PWV by 1 m/s increases the total cardiovascular events, cardiovascular mortality, and all-cause mortality risk, adjusted for age, sex, and other risk factors, by 14%, 15%, and 15%, respectively.[6] Although the risk of cardiovascular disease is attenuated after kidney transplantation (KTx)[7], the impact of KTx on arterial stiffness still remains unknown, mainly due to small-sample studies.[8,9]

Structural alterations in the media of the aortic wall result in increased stiffness, raised pulse pressure (PP) and myocardial workload, and reduced coronary perfusion.[10] These structural abnormalities may occur through various phenomena including breaks in elastin lamellae, crosslinks of the elastin network, fibrosis, inflammation, and medial calcification.[11-18] However, it is not clear whether any single intervention in CKD patients can enhance the complex nature of the CKD-related vascular remodeling. Because successful KTx may restore kidney function and improve a number of metabolic disorders involved in arterial stiffness[19,20], the reduction of arterial stiffness after KTx is plausible. Therefore, we conducted a systematic review and meta-analysis to study the impact of KTx on arterial stiffness as measured by pulse wave velocity (PWV) and its central hemodynamic effects on central pulse pressure (PP) and augmentation index (AIx).

From the CHU de Québec Research Center, L'Hôtel-Dieu de Québec Hospital, Québec, Canada (A.S., C.F., M.-P.D., F.M.-W., S.D.S., M.A.); Division of Nephrology, Faculty and Department of Medicine, Université Laval, Québec, Canada (A.S., C.F., M.-P.D., F.M.-W., S.D.S., M.A.); Department of Social and Preventive Medicine, Faculty of Medicine, Université Laval, Québec, Canada (A.S., A.B.); CHU de Québec Research Center, Université Laval, Saint François d'Assise Hospital, Québec, Canada (H.T.V.Z.); Quebec SPOR-SUPPORT Unit, Québec, Québec, Canada (H.T.V.Z.).

Correspondence to: Mohsen Agharazii, MD, CHU de Québec Research Center, L'Hôtel-Dieu de Québec Hospital, 10 McMahon, Québec City (Québec), Université Laval, G1R 2J6 Canada. E-mail: Mohsen.Agharazii@crchudequebec.ulaval.ca

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Clinical Perspective

What Is New?

- This meta-analysis shows that in patients with end-stage kidney disease, there is a reduction of arterial stiffness after a successful kidney transplantation.
- Part of this reduction is related to changes in mean arterial pressure and the timing of vascular assessment after kidney transplantation.

What Are the Clinical Implications?

- The improvement of cardiovascular risk after kidney transplantation could partly be explained by the improvement of arterial stiffness.

Methods

Study Design

We conducted a systematic review based on methodological recommendations from the *Cochrane Handbook for Systematic Reviews of Interventions*[21], on a registered protocol in Prospero (CRD42016045383) and reported according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement.[22]

Eligibility Criteria

We included in our systematic review before-after design studies conducted in adult (age ≥18) end-stage kidney disease patients who underwent KTx with functioning graft and with repeated measurements of arterial stiffness parameters. The outcomes of interest were arterial stiffness parameters including PWV (the clinical gold standard) and other indirect parameters such as central PP and increased wave reflection as measured by AIx[11] (see Table 1 for details on population, intervention, comparators, and outcome).

Information Sources and Search Strategy

We performed a search using electronic databases (Medline, Cochrane Library, Embase, and the Web of Science) from their inception until January 2016. The search strategy is based on keywords related to the intervention (renal transplantation and synonyms) and the outcomes (arterial stiffness, its parameters, and their synonyms). A search strategy was first set for PubMed/Medline and Embase and then adapted to Cochrane Library and the Web of Science with no restriction. The search strategy established for PubMed/Medline is shown in Table 2. We then hand searched additional references from the reference lists of relevant articles and in gray literature (Google Scholar, thesis repositories including Thesis portal Canada, EtHOS, DART-Europe E-Thesis Portal, the National Library of Australia's Trove, and ProQuest Dissertations & Theses Global).

Table 1. Structured Question

Terms of PICO	Definition of Terms
Population	Adult end-stage kidney disease patients with functioning graft
Intervention	Kidney transplantation
Comparator	Pre-KTx status (hemodialysis, peritoneal dialysis, not yet on dialysis)
Outcomes	Primary outcome: PWV (any type) Secondary outcomes: central pulse pressure and augmentation index
Study design	Before and after design studies

KTx indicates kidney transplant; PICO, population, intervention, comparator, outcome; PWV, pulse wave velocity.

Study Selection and Data Management

After removing duplicates of identified records from our search strategies using EndNote (version x7.2.1, Thomson Reuters, New York, 1988-2014), 2 independent reviewers (A.S. and C.F.) screened each study by title and abstract using standardized and pilot-tested screening forms. Full text was also screened when title and abstract were not enough for inclusion of a study in the review under the eligibility criteria described above.

Data Extraction and Risk of Bias Assessment

Data of included studies were then independently extracted using a standardized and pilot-tested data extraction form. In each step discrepancies between the 2 reviewers were resolved through consensus or with the involvement of a third reviewer (M.P.D.), as required. Extracted data included information on the study, characteristics of the study population and intervention, pre-KTx therapies, and arterial stiffness parameters from eligible studies.

Two authors (A.S. and M.P.D.) assessed the quality (risk of bias) in included studies with a tool developed by the National Health Institute to assess the quality in before-after design studies.[23] Likewise, we assessed conflicts of interest using information on the source of funding for each study.

Data Synthesis

We analyzed and summarized the study data with Review Manager Software (Revman, Computer program, Version 5.3, The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark, 2014). To assess the association

Table 2. Search Strategy for PubMed/Medline

Terms of PICOS	Terms and Synonyms	Connection
Intervention (Kidney transplantation and synonyms)	1. "Kidney Transplantation" [mesh] or 2. (("Kidney" [TIAB] or "Renal" [TIAB]) and ("transplantation*" [TIAB] or "grafting*" [TIAB] or "replacement therap*" [tiab]))	3. =1 OR 2
Outcomes (arterial stiffness parameters)	4. "Vascular Stiffness" [mesh] or 5. (("vascular" [TIAB] or "arterial" [TIAB] or "aortic" [TIAB]) AND ("Stiffness*" [TIAB])) or 6. "Pulse Wave Analysis" [mesh] or 7. (("pulse wave" [tiab] and ("velocit*" [tiab] or "analys*" [tiab])) or 8. "augmentation index" or 9. "AIx" or 10. "pulse pressure"	11. =4 to 10 connected by OR
Combination	12. 3 AND 11	
Extraction of animal studies	13. exp animals/not humans.sh.	
Exclusion of animal studies from the results	14. 12 Not 13	

between KTx and arterial stiffness, we considered the mean difference between arterial stiffness outcomes (PWV [overall, central, peripheral, and brachial-ankle], central PP, and AIx) assessed after KTx and before KTx as effect size. PWV was first analyzed globally regardless of the arterial territory or the period of assessment (overall PWV). Second, we considered a posteriori each arterial territory reported as an outcome: central PWV (composed of carotid-femoral PWV and aorta-femoral PWV), peripheral PWV (composed of carotid-radial PWV and femoral-distal PWV), and brachial-ankle PWV. Two global analyses were performed for each outcome for which more than 2 measurements were performed within a study. Indeed, we included either the earliest measure after the first week (first global analysis) or the latest measure within 1 year (second global analysis). Because we anticipated a potential heterogeneity between the included studies, we estimated the pooled mean difference and its 95% confidence interval using a random-effects model with inverse variance method.[24]

Statistical heterogeneity was assessed using the Higgins I^2 and interpreted as low between 0% and 30%, moderate between 30% and 60%, considerable between 60% and 80%, and substantial from 80% and above.[21,25]

For each outcome of interest, we explored the publication bias using the Begg rank correlation test and the Egger regression as appropriate given the known limitations of these methods[26] using an available macro for SAS.[27] All tests of statistical inference were 2-sided with an α of 5%.

Subgroup Analyses, Meta-Regression, and Sensitivity Analyses

Subgroup analyses were performed for each outcome according to the period of assessment, which was decided in post hoc analysis using the most used period (≤3 months, at 6 months, and at 12 months post-KTx).

A meta-regression was performed in order to quantify the amplitude of influence of some potential factors modifying the effect size estimated in meta-analysis. We considered period of assessment, arterial territory of PWV, and changes in mean arterial pressure (ΔMAP) as independent variables. Each of these independent variables was analyzed alone in a univariate meta-regression. Then, ΔMAP was analyzed in a multivariate meta-regression with period of assessment and/or type of PWV as covariates. All meta-regressions were performed in SAS Version 9.4 (Copyright © 2015, SAS Institute Inc, Cary, NC) using general linear mixed model with random effects.[28] MAP was estimated by the Lian formula (MAP=2/3 DBP+1/3 SBP) in studies that did not report it but for which systolic and diastolic brachial blood pressures were available. Changes in MAP were estimated by computing the absolute difference between the MAP post-KTx and MAP pre-KTx. Sensitivity analyses in meta-analysis were performed by removing studies 1 by 1 to see the impact on the estimated pooled effect size and its statistical heterogeneity. Likewise, sensitivity analyses were performed in meta-regression by removing studies with poor quality (high risk of bias).

Grading of the Evidence

Two reviewers assessed the overall quality of evidence for each outcome using the GRADE tool.[29] Five domains were considered to assess the quality of evidence: quality (risk of bias), inconsistency, indirectness and imprecision, which can be considered serious or very serious, and publication bias, which can be undetected, likely, or very likely. The quality of evidence of observational studies begins low. Although,

grading upward may be warranted if the magnitude of the treatment effect is very large, if there is evidence of a dose-response relation, or if all plausible biases would decrease the magnitude of an apparent treatment effect.[29]

Results

Study Selection and Description of Included Studies

From the 868 citations identified through electronic databases, we included 12 unique studies in meta-analysis (see details in Figure 1), with sample sizes ranging from 18 to 168 observations (9-84 pairs). All studies were quasiexperimental with before-after design study and published in English between 2003 and 2016. Seven studies[8,9,20,30-33] assessed aortic PWV (central), 3 studies[8,9,34] assessed peripheral PWV (carotid-radial or femoral-distal PWV), and 4 studies[35-38] assessed brachial-ankle PWV. Two studies[8,9] assessed both central and peripheral PWV, and 3 studies[20,33,35] used multiple periods of assessment. Central PP was reported in 4 studies[8,9,20,32] and AIx in 7 studies.[8,9,20,31-34] All studies were considered to have a good quality (low risk of bias), except 1 considered as fair quality (moderate risk of bias) and 2[30,34] adjudicated as poor quality (high risk of bias). Tables 3 and 4 show the detailed characteristics of the included studies.

Pulse Wave Velocity

Overall PWV

Analyses of overall PWV regardless of the vascular territory, taking into account either the earliest measure or the latest measure within a study, showed globally a significant reduction by 1.17 m/s (0.64-1.71) and by 1.20 m/s (0.67-1.73), respectively, with considerable heterogeneity (I^2=72; Figures 2 and 3).

Almost all studies were adjudicated to have a good or fair quality, except the study from Keven[30] and that from Covic[34] in which the numbers of participants before and after KTx were different (poor quality). When those studies were excluded in sensitivity analyses, overall PWV remained significantly decreased globally by 1.20 m/s (0.57-1.83, I^2=75%) and 1.23 m/s (0.61-1.85, I^2=75%) for the earliest measure and latest measure within a study, respectively (Table 5). While remaining significantly decreased, the statistical heterogeneity of overall PWV was reduced from considerable to moderate when the study from Kovacs[33] was excluded and to low when the 2 studies from Zoungas[9] and Kovacs[33] were excluded (Table 5).

In subgroup analysis according to the period of assessment post-KTx, overall PWV decreased at ≤3, 6, and 12 months post-KTx, with substantial, low, and considerable heterogeneity, respectively. Although it remained significant in sensitivity analyses, the statistical heterogeneity of overall PWV effect size was reduced to low at 3 months or less and at 12 months post-KTx (Table 6). Publication bias was likely according to Egger regression but unlikely with Begg rank correlation. The overall strength of evidence was considered to be low for overall PWV (Tables 7 and 8).

Central PWV

Analyses of central PWV, considering either the earliest measure or the latest measure within a study, globally showed a significant decrease at any period of assessment (Table 5). Almost all studies were adjudicated to have a good or fair

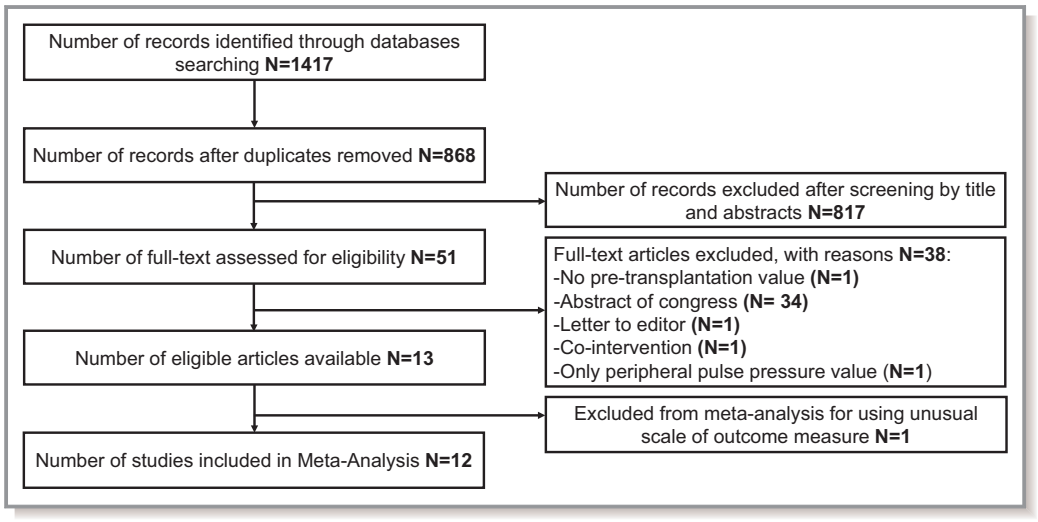

Figure 1. Flow diagram. The figure shows the selection process for the studies included in the meta-analysis.

Table 3. Characteristics of Individual Studies, Population, and Intervention

First Author, Year	Country	Sample Size	Age (y)	Male (%)	Diabetes Mellitus(%)	HTN (%)	CVD (%)	Living Donor (%)	IS (%)	Cr (μmol/L)*	Quality of Study
Covic, 2003[34]	Romania	20	49	50	NR	85	NR	100	100^{C}	NR	Poor
Zoungas, 2004[9]	Australia	36	46±11	75	22	78	11	8	$33^{T}/64^{C}/3^{O}$	143 ± 47^{12Mo}	Good
Keven, 2008[30]	Turkey	28	34±9	68	4	68	NR	71	$29^{C}/71^{T}$	106 ± 27^{12Mo}	Poor
Nishioka, 2008[38]	Japan	9	42±6	78	NR	NR	NR	100	$44^{C}/56^{T}$	124 ± 18^{12Mo}	Good
Ignace, 2011[8]	Canada	52	50±13	71	33	NR	21	12	100^{T}	120 ± 40^{3Mo}	Good
Bachelet-Rousseau, 2011[31]	France	39	56 (49-60)	54	18	92	5	NR	$56^{C}/28^{T}/15^{O}$	$124\ (106\text{-}141)^{6Mo}$	Good
Hornum, 2011[32]	Denmark	40	38±13	70	0	NR	NR	93	$5^{S}/65^{C}/30^{T}/5^{O}$	130 ± 6^{12Mo}	Good
Hotta, 2012[36]	Japan	58	41±12	59	NR	NR	NR	NR	100^{T}	NR	Good
Kaur, 2013[20]	India	23	36±9	96	NR	100	NR	100	100^{T}	66 ± 24^{3Mo} 70 ± 22^{6Mo}	Good
Kovacs, 2013[33]	Hungary	17	46±12	59	NR	NR	NR	NR	NR	$161\pm90^{<1Mo}$	Fair
Kim, 2015[37]	Korea	84	45±12†	54†	NR	NR	6†	NR	$6^{\dagger C}/94^{\dagger T}$	NR	Good
Ro, 2016[35]	Korea	67	46±10	52	NR	NR	NR	NR	95^{T}	106 ± 35^{6Mo} 97 ± 27^{12Mo}	Good

Results are expressed as mean±SD, median [25th-75th], or number. $^{<1Mo}$, <1 month after KTx; ^{12Mo}, 3 months after KTx; ^{6Mo}, 6 months after KTx; C, 12 year after KTx; ^{3Mo}, cyclosporin; Cr, serum creatinine; CVD, cardiovascular disease; HTN, hypertension; IS, immunosuppressive medication; KTx, kidney transplantation; NR, not reported; O, other immunosuppressive medication; S, sirolimus; T, tacrolimus.

*Creatinine values in mg/dL were converted into μmol/L.

†Results are based on n=171.

quality for central PWV except the study from Keven[30], which was adjudicated to have a poor quality because the number of participants before and after KTx were different. When that study was excluded from the sensitivity analysis, the decrease in global central PWV was no longer significant (Table 5). The statistical heterogeneity of central PWV was reduced from substantial to moderate (56% and 53%) after exclusion of the study from Kovacs.[33] However, this reduction was significant

Table 4. Characteristics of Individual Studies by Arterial Stiffness Parameters

First Author, Year	Sample Size	PWV	PP	AIx	Follow-Up (Months)
Covic, 2003[34]*	20	Peripheral	NR	Central	3
Zoungas, 2004[9]	36	Central/Peripheral†	Central§	Central§	12
Keven, 2008[30]	28	Central	NR	NR	12
Nishioka, 2008[38]	9	BA	NR	NR	12
Ignace, 2011[8]	52	Central/Peripheral	Central	Central‖	3
Bachelet-Rousseau, 2011[31]	39	Central	NR	Central§	6
Hornum, 2011[32]	40	Central	Central	Central	12
Hotta, 2012[36]	58	BA	NR	NR	6
Kaur, 2013[20]	23	Central	Central	Central	3, 6
Kovacs, 2013[33]	17	Central‡	Peripheral	Central	<1
Kim, 2015[37]	84	BA	Peripheral	NR	12
Ro, 2016[35]	67	BA	Peripheral	NR	6, 12, 24

Central PWV are carotid-femoral PWV; peripheral PWV are carotid-radial PWV; a central PP and AIx are radial unless indicated otherwise. AIx indicates augmentation index; BA, brachial-ankle PWV; NR, not reported; PP, pulse pressure; PWV, pulse wave velocity.

*Mean arterial stiffness was not reported in the study.

†Femoral-distal PWV.

‡Aortic PWV.

§Carotid site profile.

‖Heart rate–adjusted central augmentation index.

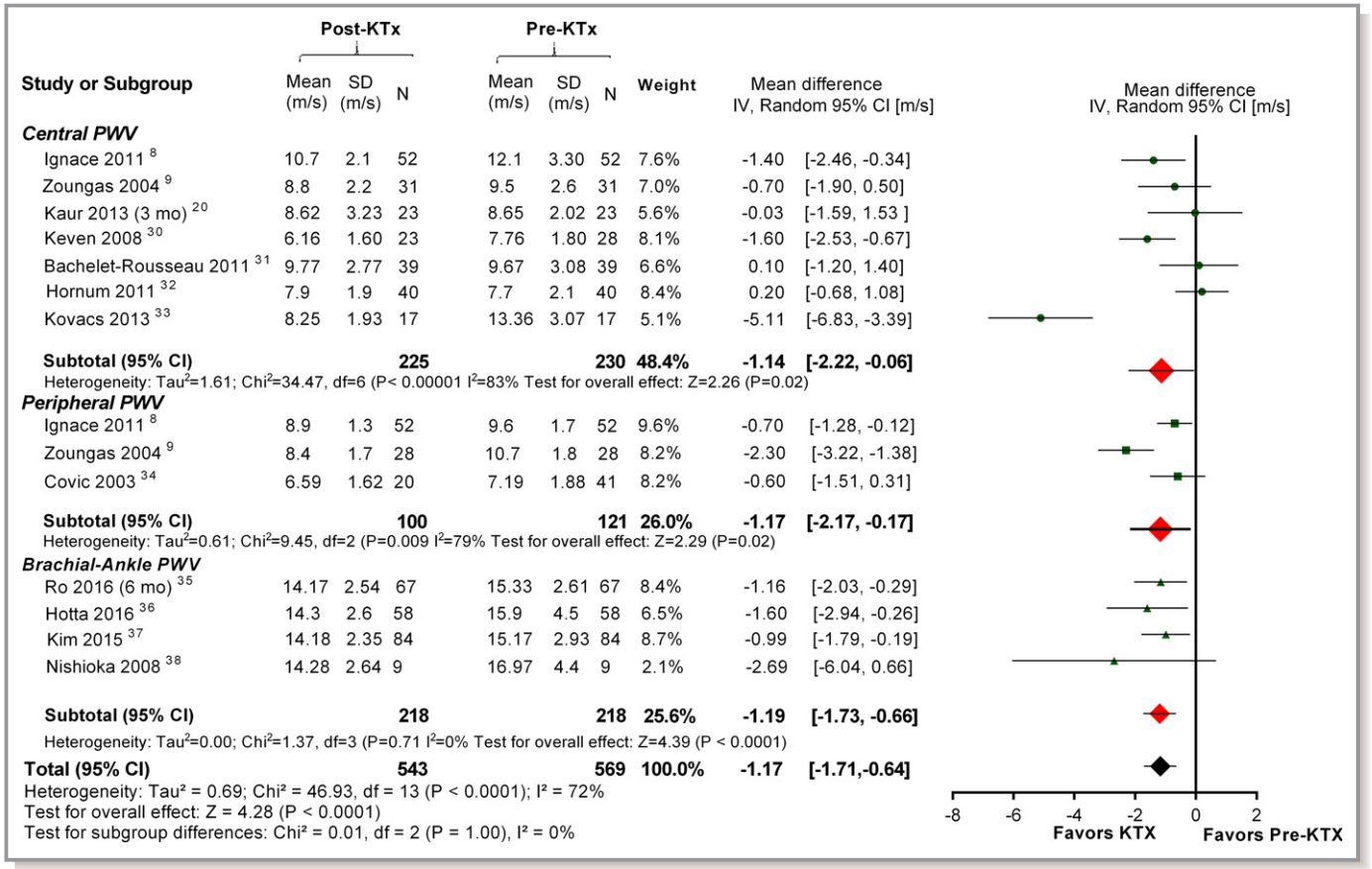

Figure 2. First global analysis of pulse wave velocity. Pulse wave velocity (PWV) is analyzed overall and according to the arterial territory. In the first global analysis, we included the earliest measure reported in studies using multiple measurements (studies from Kaur at 3 months and Ro at 6 months). CI indicates confidence interval; mo, months.

only in regard to the latest measure within a study by 0.68 m/s (0.03-1.34, I^2=53%) (Table 5). Publication bias was likely according to Egger regression but unlikely with Begg rank correlation. The overall strength of evidence was considered as very low for central PWV (Tables 7 and 8).

Peripheral PWV

Only 1 global analysis was performed in peripheral PWV because no studies reported repeated measurements of peripheral PWV. We observed a significant decrease at any period of assessment (Table 5). All studies except that from Covic[34] were adjudicated to have a good quality. When the latter was excluded from the sensitivity analysis, only 2 studies remained, and the reduction was no longer statistically significant (Table 5). Publication bias was unlikely with both tests. The overall strength of evidence was considered very low for peripheral PWV (Tables 7 and 8).

Brachial-Ankle PWV

Analyses of brachial-ankle PWV, considering either the earliest measure or the latest measure within a study, showed globally a significant decrease at any period of assessment with low heterogeneity (Table 5). All studies were adjudicated to have a good quality for brachial-ankle PWV, and publication bias was unlikely according to Egger regression but likely according to Begg correlation. The overall strength of evidence was considered to be low for brachial-ankle PWV (Tables 7 and 8).

Subgroup Analysis of Vascular Territory With Regard to Period of Assessment

Subgroup analyses, although limited due to the small number of studies reporting central PWV (7), peripheral PWV (3), and brachial-ankle PWV (4), were performed according the period of assessment post-KTx and reported in Table 6.

Central Pulse Pressure

Analyses of central PP at any period of assessment, considering either the earliest measure or the latest measure within a study, was not significantly reduced (Table 5). In sensitivity analysis, after exclusion of the study from

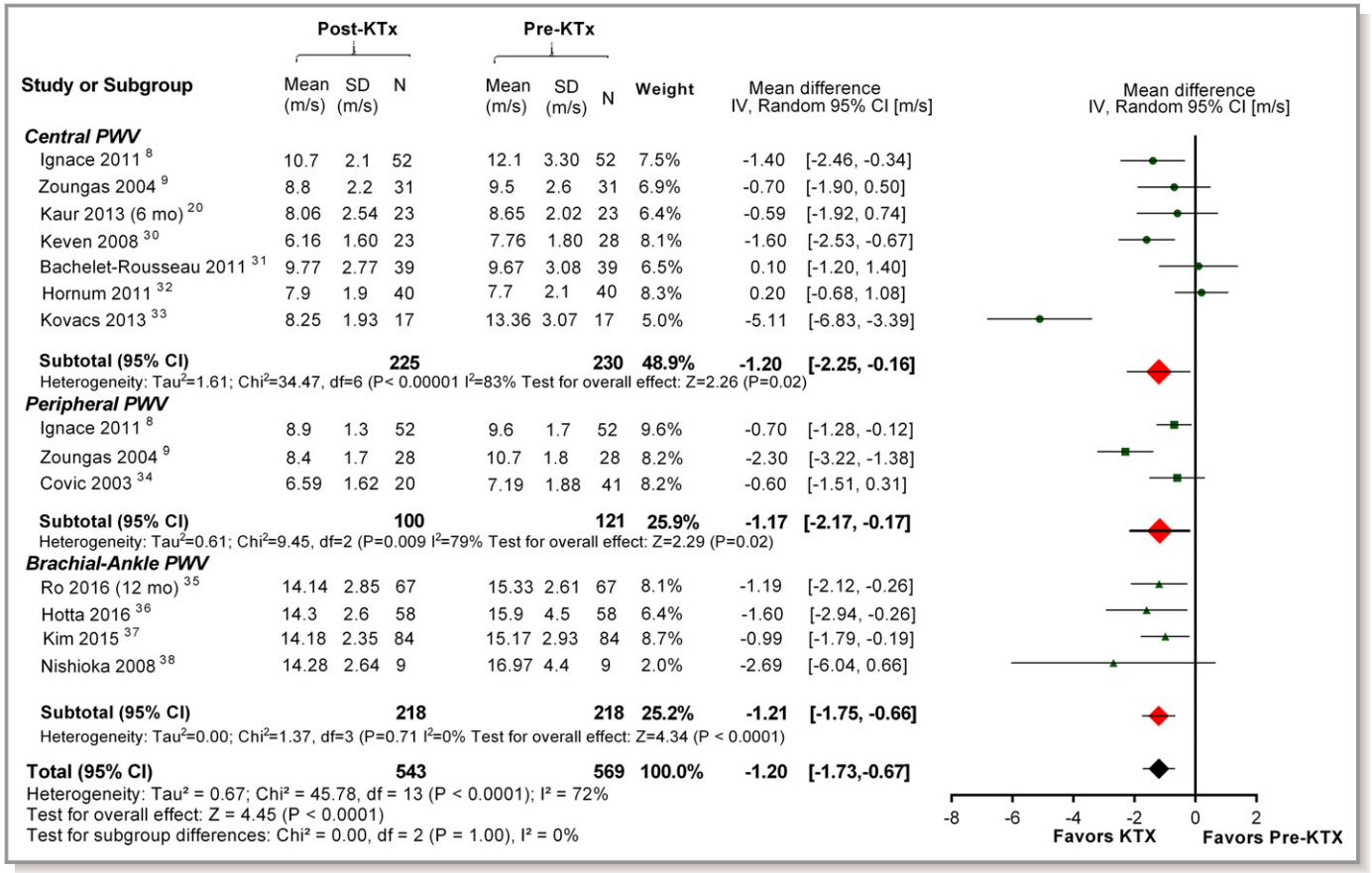

Figure 3. Second global analysis of pulse wave velocity. Pulse wave velocity (PWV) is analyzed overall and according to the arterial territory. In the second global analysis, we included the latest measure reported in studies using multiple measurements (studies from Kaur at 6 months and Ro at 12 months). CI indicates confidence interval; mo, months.

Zoungas[9] in which heart rate had significantly declined after KTx, central PP significantly decreased by 6.0 mm Hg (2.2-9.9, I^2=0%) and 7.0 mm Hg (2.8-11.2, I^2=18%), respectively, when considering the earliest or the latest measure within a study. The statistical heterogeneity was also considerably reduced to low (Table 5).

Subgroup analyses of central PP, although limited by the small number of studies, were performed with regard to the period of assessment post-KTx (Table 6). Publication bias was unlikely according to both tests. All studies were adjudicated to have a good quality for central PP. The overall strength of evidence was considered as very low for central PP (Tables 7 and 8).

Augmentation Index

The AIx at any period of assessment post-KTx, considering either the earliest measure or the latest measure within a study, declined by 10.0% (6.7-13.4, I^2=61%) and 10.5% (6.9-14.1, I^2=64%), respectively (Table 5). All studies were adjudicated to have a good quality for AIx except the study from Covic,[34] which was considered to have poor quality. When the latter was excluded, AIx remained significantly decreased globally (Table 5). Although it remained significantly reduced, the statistical heterogeneity of both global effect sizes of AIx was considerably reduced in sensitivity analysis. Although limited, subgroup analyses were performed according to the period of assessment (Table 6). Publication bias was unlikely according to both tests. The overall strength of evidence was considered as low for AIx (Tables 7 and 8).

Meta-Regression

Pulse Wave Velocity

The between-study variance in PWV was mostly explained by the period of assessment (68% when considering all studies except Covic[34] and 80% when studies from both Covic[34] and Keven[30] were excluded in univariate analysis). The percentage of variance increased to 78% and 87%, respectively, when period of assessment and type of PWV were considered in the same model (Table 9). In univariate meta-regression, only ΔMAP was associated with the effect size of PWV observed.

Table 5. Main and Sensitivity Global Analyses of Arterial Stiffness Outcomes

Outcomes	N (Sample)	Global 1 Mean Difference (95% CI)	I^2	N (Sample)	Global 2 Mean Difference (95% CI)	I^2
Overall PWV	14 (1112)	−1.17 (−1.71 to −0.64)	72%	14 (1112)	−1.20 (−1.73 to −0.67)	72%
	12 (1000)*	−1.20 (−1.83 to −0.57)*	75%*	12 (1000)*	−1.23 (−1.85 to −0.61)*	75%*
	13 (1078)†	−0.95 (−1.36 to −0.54)†	52%†	13 (1078)†	−0.98 (−1.38 to −0.58)	50%†
	12 (1022)‡	−0.82 (−1.17 to −0.47)‡	29%‡	12 (1022)‡	−0.84 (−1.17 to −0.50)‡	25%‡
Central PWV	7 (455)	−1.14 (−2.22 to −0.06)	83%	7 (455)	−1.20 (−2.25 to −0.16)	83%
	6 (404)§	−1.07 (−2.36 to 0.22)§	85%§	6 (404)§	−1.15 (−2.39 to 0.10)§	84%§
	6 (421)†	−0.62 (−1.31 to 0.07)†	56%†	6 (421)†	−0.68 (−1.34 to −0.03)†	53%†
Peripheral PWV	3 (221)	−1.17 (−2.17 to −0.17)	79%	0	NA	NA
	2 (160)‖	−1.46 (−3.03 to 0.11)‖	88%‖	0	NA	NA
Brachial-ankle PWV	4 (436)	−1.19 (−1.73 to −0.66)	0%	4 (436)	−1.21 (−1.75 to −0.66)	0%
Central PP	4 (302)	−4.03 (−8.56 to 0.50)	43%	4 (302)	−4.75 (−10.28 to 0.78)	50%
	3 (230)¶	−6.04 (−9.90 to −2.18)¶	0%¶	3 (230)¶	−7.02 (−11.21 to −2.82)¶	18%¶
AIx	7 (465)	−10.03 (−13.40 to −6.66)	61%	7 (465)	−10.50 (−14.09 to −6.90)	64%
	6 (404)‡	−10.38 (−14.66 to −6.11)‡	67%‡	6 (404)‡	−10.96 (−15.54 to −6.39)‡	70%‡
	6 (431)†	−8.76 (−11.50 to −6.03)†	37%†	6 (431)†	−9.20 (−12.30 to −6.10)†	49%†
	5 (353)#	−9.77 (−12.07 to −7.48)#	0%#	5 (353)#	−10.13 (−12.47 to −7.78)#	0%#

Global 1 is the analysis including the earliest measurement for studies using multiple measurements; Global 2 is the analysis including the latest measurement for studies using multiple measurements. AIx indicates augmentation index; CI, confidence interval; N, number of studies included in analysis; NA, not applicable; PP, pulse pressure; PWV, pulse wave velocity; Sample, number of participants.

*Sensitivity analysis excluding both studies from Keven[30] and Covic[34].

†Sensitivity analysis excluding the study from Kovacs[33].

‡Sensitivity analysis excluding the study from Kovacs[33] and Zoungas[9] (femoral-distal).

§Sensitivity analysis excluding the study from Keven[30].

‖Sensitivity analysis excluding the study from Covic[34].

¶Sensitivity analysis excluding the study from Zoungas[9].

#Sensitivity analysis excluding both studies from Kovacs[33] and Bachelet-Rousseau[31].

In the model including all studies except the 1 from Covic,[34] in which MAP was not available, this association was no longer significant with adjustments for either type of PWV or period of assessment. In the model excluding both studies from Covic[34] and Keven,[30] the association between ΔMAP and the effect size of PWV remained significant when adjusting for the type of PWV but was no longer significant when adjusting for the period of assessment (Figure 4).

Central Pulse Pressure

The between-study residual variance was mostly explained by period of assessment (70%) and ΔMAP (76%) (Table 9). Due to the small number of studies, the association between ΔMAP and the effect size of central PP could not be evaluated.

Augmentation Index

The between-study residual variance was mostly explained by the period of assessment (63%) and did not increase when ΔMAP was added to the same model (Table 9). No association between ΔMAP and the effect size of AIx was observed.

Discussion

In this systematic review we observed a significant decrease in arterial stiffness as measured by PWV and a reduction of wave reflection as measured by AIx in patients with end-stage kidney disease after successful KTx. The decrease in PWV was observed globally as well as in each arterial territory (central, peripheral, and brachial-ankle). Likewise, in subgroup analysis according to the period of assessment, the reduction in overall PWV was significant in all subgroups (≤3, 6, and 12 months post-KTx). The reduction in PWV seems to translate into a lower central PP; however, the reduction in overall central PP was not significant. In subgroup analysis, central PP significantly decreased at ≤3 and 6 months post-KTx but not at 12 months. PP is related to changes in the heart rate, and it is worth mentioning that in the study from Zoungas,[9] the mean heart rate post-KTx declined by 11 beats/min. This explains why the exclusion of the latter study in the sensitivity analysis resulted in a significant reduction in global analysis of central PP. AIx, which is a measure of wave reflection and was more frequently reported, declined significantly. The reduction in AIx was significant at ≤3 and at 12 months post-KTx.

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Table 6. Subgroup and Sensitivity Analyses of Arterial Stiffness Outcomes According to the Period of Assessment

	≤3 Months Post-KTx			6 Months Post-KTx			12 Months Post-KTx		
Outcomes	N (Sample)	Mean Difference (95% CI)	I^2	N (Sample)	Mean Difference (95% CI)	I^2	N (Sample)	Mean Difference (95% CI)	I^2
Overall PWV	5 (349)	−1.43 (−2.61 to −0.24)	84%	4 (374)	−0.86 (−1.53 to −0.19)	24%	7 (569)	−1.16 (−1.83 to 0.48)	66%
	4 (315)*	−0.74 (−1.17 to −0.31)*	0%*	3 (296)†	−1.13 (−1.77 to −0.49)†	0%†	6 (489)‡	−1.41 (−1.92 to −0.91)‡	28%‡
	3 (254)§	−0.79 (−1.34 to −0.24)§	12%§	0	NA	NA	5 (433)‖	−1.18 (−1.64 to −0.72)‖	0%‖
Central PWV	3 (184)	−2.14 (−4.73 to 0.45)	90%	2 (124)	−0.24 (−1.17 to 0.69)	0%	3 (193)	−0.69 (−1.81 to 0.43)	74%
	2 (150)*	−0.84 (−2.16 to 0.48)*	51%*	0	NA	NA	2 (142)¶	−0.15 (−1.01 to 0.71)¶	29%¶
Peripheral PWV	2 (165)	−0.67 (−1.16 to −0.18)	0%	0	NA	NA	1 (56)	−2.30 (−3.22 to −1.38)	NA
Brachial-Ankle PWV	0	NA	NA	2 (250)	−1.29 (−2.02 to −0.56)	0%	3 (186)	−1.13 (−1.72 to −0.53)	0%
Central PP	2 (150)	−6.64 (−11.48 to −1.80)	0%	1 (46)	−11.60 (−18.55 to −4.65)	NA	2 (152)	−1.22 (−9.05 to 6.60)	66%
AIx	3 (184)#	−12.16 (−18.45 to −5.87)#	69%#	2 (124)	−8.06 (−19.07 to 2.95)	85%	2 (142)	−11.79 (−16.36 to 7.23)	0%
	3 (211)*	−9.09 (−11.75 to −6.43)*	0%*	0	NA	NA	0	NA	NA
	2 (150)§	−8.99 (−12.63 to −5.35)§	0%§	0	NA	NA	0	NA	NA

AIx indicates augmentation index; KTx, kidney transplant; N, number of studies included; NA, not applicable; note that I^2=NA when there is only 1 study in a subgroup; PP, pulse pressure; PWV, pulse wave velocity; Sample, number of participants included.

*Sensitivity analysis excluding the study from Kovacs.[33]

†Sensitivity analysis excluding the study from Bachelet-Rousseau[31].

‡Sensitivity analysis excluding the study from Hornum[32].

§Sensitivity analysis excluding studies from both Kovacs[33] and Covic[34].

‖Sensitivity analysis excluding both studies from Hornum[32] and from Zoungas[9] (femoral-distal).

¶Sensitivity analysis excluding the study from Keven[30].

#Sensitivity analysis excluding the study from Covic[34].

Table 7. Test for Publication Bias in the Estimate of Pulse Wave Velocity, Central Pulse Pressure, and Augmentation Index

Parameters	Outcomes	Egger OLS Regression (*P*)	Begg Rank Correlation (Predictor=Variance) (*P*)	Begg Rank Correlation (Predictor=Sample Size) (*P*)
PWV	Overall1	0.002*	0.198	0.492
	Overall2	0.002*	0.232	0.492
	Central1	0.017*	0.160	0.253
	Central2	0.017*	0.160	0.253
	Peripheral	0.515	0.661	0.661
	Brachial-Ankle1	0.187	<0.001*	<0.001*
	Brachial-Ankle2	0.188	<0.001*	<0.001*
Central PP	Global 1	0.359	0.136	1.000
	Global 2	0.258	0.136	1.000
AIx	Global 1	0.072	<0.001*	0.045*
	Global 2	0.077	<0.001*	0.148

Publication bias is assessed by the Egger regression test and the Begg rank correlation. *: Publication bias is likely according to a test when the *P* value is less than 0.05. The number 1 indicates the analysis including the earliest measurement for studies reporting multiple measures. The number 2 indicates the analysis including the latest measurement for studies reporting multiple measures. AIx indicates augmentation index; OLS, Ordinary Least Squares; PP, pulse pressure; PWV, pulse wave velocity; Sample, number of participants included.

Sources of Heterogeneity

Statistical heterogeneity was present in the pooled data, coming from different sources. First, different vascular territories were used to assess PWV. Indeed, 7 studies[8,9,20,30-33] looked at measures of aortic stiffness: the aorta is an elastic capacitive vessel and is more heavily affected with age and pathological conditions such as hypertension, CKD, and diabetes mellitus.[4,10,39-42] Three studies[8,9,34] evaluated medium-sized muscular vascular beds, which are physiologically stiffer and generally less affected by age and pathological conditions.[4,10,39-42] Finally, 4 studies[35-38] looked at brachial-ankle PWV, which gives a general index of overall stiffness. Three studies[20,33,35] performed measurement at different periods post-KTx, and 2 studies[8,9] used multiple sites.

We first performed meta-analyses regardless of the arterial territory and then by considering each arterial territory of PWV as an outcome using a random-effect method. To deal with multiple measurements within a study, we considered in our global analysis the first measure after 1 week (first global analysis) or the latest measure until 1 year (second global analysis). In sensitivity analyses the statistical heterogeneity of the different effect sizes was considerably reduced in overall PWV and central PWV, from considerable to moderate and from substantial to moderate, respectively. But central PWV remained significantly decreased only in the latest period of assessment within a study. Likewise, central PP and AIx significantly decreased in sensitivity analyses, and the statistical heterogeneity of the effect sizes was considerably reduced.

Mean Arterial Pressure, Arterial Stiffness, and Period of Assessment

Vascular remodeling in CKD is complex, and it involves remodeling that is mediated not only through the effects of hypertension but also through mineral disorder–induced vascular calcification,[40] endothelial dysfunction,[43] and alterations of extracellular matrix by uremic toxins such as advanced glycation end products.[44] A successful KTx improves fluid overload and improves the metabolic pathways that are potentially involved in CKD-related vascular stiffness.[7,8] An improvement in arterial stiffness post-KTx does suggest that arterial stiffness is potentially reversible. However, vascular stiffness is also affected by the operating MAP without any changes in the structure of vascular wall (ie, functional stiffness). In this systematic review only 2 studies reported a mean difference of PWV adjusted for MAP.[8,9] It is for this reason that we performed a meta-regression to evaluate the association between changes in MAP (estimated by the Lian formula in 3 studies[30,33,36]) and the effect size of arterial stiffness parameters. A positive association between the effect size of arterial stiffness parameters and changes in MAP suggests that the improvement of arterial stiffness parameters may be related to either functional or structural improvement of vascular wall properties. Although this association was significant in univariate analysis, it was no longer significant after adjustment for the combined effect of the period of measurements and/or type of PWV. The association between changes in MAP and the effect size of central PP could not be evaluated due to a small number of studies, and we did not observe an association between

Table 8. Summary of Grading the Evidence of Findings in PWV, Central PP, and AIx: Kidney Transplantation Compared to Pretransplantation for Reduction of Arterial Stiffness

Intervention: Kidney Transplantation; Comparison: Pretransplantation					
Outcomes	Anticipated Absolute Effects (95% CI)*		No. of Observations (Studies)	Quality of the Evidence (GRADE)	Comments
	Risk Pre-KTx	Risk Post-KTx			
Overall PWV at any period post- KTx	The mean PWV at any period post-KTx was 0 m/s	The mean difference in overall PWV at any period post-KTx was 1.17 m/s lower (1.71 lower to 0.64 lower) Or 1.20 m/s lower (1.73 lower to 0.67 lower)	1112 observations (14 observational studies)	Low	Publication bias was likely according to Egger regression but unlikely with Begg rank correlation. Almost all studies were at good or fair quality for PWV except 2 with poor quality (high risk of bias). The results were consistent in subgroup analysis and when excluding studies with poor quality.
Central PWV at any period post-KTx	The mean PWV at any period post-KTx was 0 m/s	The mean difference in central PWV at any period post-KTx was 1.14 m/s lower (2.22 lower to 0.06 lower) or 1.20 m/s lower (2.25 lower to 0.16 lower)	455 observations (7 observational studies)	Very Low	Publication bias was likely according to Egger regression but unlikely with Begg rank correlation. Almost all studies were at good or fair quality except 1 with poor quality. The results were inconsistent in subgroup analysis and when studies with poor quality were excluded.
Peripheral PWV at any period post-KTx	The mean PWV at any period post-KTx was 0 m/s	The mean difference in peripheral PWV at any period post-KTx was 1.17 m/s lower (2.17 lower to 0.17 lower) or 1.46 m/s lower (3.03 lower to 0.11 upper)	221 observations (3 observational studies) or 160 observations (2 observational studies)	Very Low	Publication bias was unlikely. Almost all studies were at good or fair quality for PWV except 1 with unclear risk of bias. The results were inconsistent when the study with unclear risk of bias was excluded.
Brachial-Ankle PWV at any period post-KTx	The mean PWV at any period post-KTx was 0 m/s	The mean difference in branchial-ankle PWV at any period post-KTx was 1.19 m/s lower (1.73 lower to 0.66 lower) or 1.21 m/s lower (1.75 lower to 0.66 lower)	436 observations (4 observational studies)	Low	All studies were at good or fair quality for PWV. The results were consistent in subgroup analysis; publication bias was likely with both tests.
Central PP at any period post-KTx	The mean central PP at any period post-KTx was 0 mm Hg	The mean difference in central PP at any period post-KTx was 4.03 mm Hg lower (8.56 lower to 0.50 upper) or 4.75 mm Hg lower (10.28 lower to 0.78 lower)	302 observations (4 observational studies)	Very Low	Publication bias was unlikely according to Egger's regression and Begg's rank correlation. All studies were at good or fair quality for central PP. Results were inconsistent in subgroup analysis.
AIx at any period post- KTx	The mean AIx at any period post-KTx was 0%	The mean difference in AIx post-KTx was 10.03% lower (13.40 lower to 6.66 lower) or 10.50% lower (14.09 lower to 6.90 lower)	465 observations (7 observational studies)	Low	Publication bias was unlikely with both tests. Almost all studies were at good or fair quality, except 1 with poor quality. Results were consistent in subgroup analysis and when the study with poor quality was excluded.

GRADE Working Group grades of evidence: high quality, we are very confident that the true effect lies close to that of the estimate of the effect; moderate quality, we are moderately confident in the effect estimate—the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different; low quality, our confidence in the effect estimate is limited—the true effect may be substantially different from the estimate of the effect; very low quality, we have very little confidence in the effect estimate—the true effect is likely to be substantially different from the estimate of effect. AIx indicates augmentation index; CI, confidence interval; KTx, kidney transplant; PP, pulse pressure; PWV, pulse wave velocity.
*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

Table 9. Estimation of Study Residual Variance According to the Arterial Stiffness Parameters

Parameters	PWV		Central PP	AIx
	Model 1	Model 2		
Period of assessment	68%	80%	70%	63%
Type of PWV	1%	3%	. . .	. . .
ΔMAP	1%	37%	76%	1%
Type of PWV+ΔMAP	4%	37%	. . .	. . .
Period of assessment+ΔMAP	53%	79%	NE	62%
Period of assessment+type of PWV	78%	87%	. . .	. . .

AIx indicates augmentation index; Model 1, including all studies except Covic[34]; Model 2, including all studies except Covic[34] and Keven[30]; NE, not estimated; PP, pulse pressure; PWV, pulse wave velocity; Type of PWV, central, peripheral, or brachial-ankle PWV; ΔMAP, mean arterial pressure after transplantation–mean arterial pressure before transplantation.

changes in MAP and the effect size of AIx. In fact, the period of assessment seemed to explain the most important part of the residual variance in PWV, central PP, and AIx. These findings suggest that vascular wall remodeling post-KTx may not follow a homogeneous pattern. Accordingly, it is possible that other factors, such as post-KTx medication or activation of immune system (by HLA mismatching or infection), outweigh the initial improvement of uremia.

Risk of Bias

Risk of bias is a major concern for the internal validity of the results. Almost all studies were adjudicated to have a good (low risk of bias) or fair quality (moderate risk of bias). Indeed, the risk of selection bias was adjudicated as low in all except 2 studies, where it was adjudicated as high due to an important difference between the number of patients in baseline and after KTx.[30,34]

Publication bias was likely for overall PWV, central PWV, brachial-ankle PWV, and AIx. It was unlikely for peripheral PWV and central PP. Finally, the strength of evidence was classified as low for overall PWV, brachial-ankle PWV, and AIx but very low for central PWV, peripheral PWV, and central PP.

Strengths and Limitations

The strengths of this review include the completeness of the search including hand searching of the gray literature and references of relevant citations, the statistical approach including random effect, and the confirmation of the findings in most of the subgroups, the strength of evidence classified as low for overall PWV, brachial-ankle PWV, and AIx.

There are, however, some limitations in the interpretation of the results of this meta-analysis. First, the use of various devices for the assessment of arterial stiffness parameters, kidney source (living or cadaveric), dialysis modality and duration before KTx, the timing of assessment (before and after transplantation), as well as immunosuppressive regimen could all constitute potential sources of heterogeneity. The impact of immunosuppressive drugs, considered as cointervention, could not be explored because little information was provided by the studies. Likewise, the impact of dialysis modality and duration before KTx could not be assessed. Blood pressure was not available for 1 study.[34] Furthermore, the use of the Lian formula to calculate MAP also has its limits when applied to the average of a group's systolic and diastolic

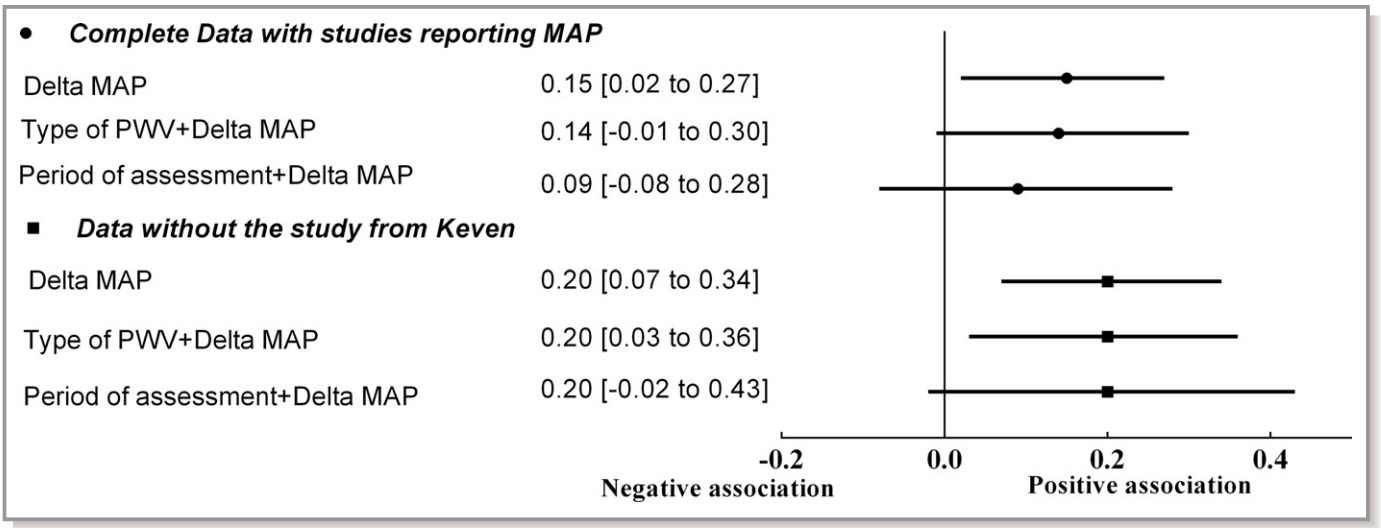

Figure 4. Association between change in mean arterial pressure (ΔMAP) and the effect size of pulse wave velocity (PWV). The figure shows the association between ΔMAP and the effect size of pulse wave velocity analyzed by meta-regression. MAP indicates mean arterial pressure.

blood pressures. The number of included studies could not provide a statistical power necessary to detect all the differences, so some results of meta-regression are at risk of type 2 error. Finally, we could not take into account, in the same model, many sources of heterogeneity in meta-regression by using a random effect for each.

In summary, this study supports the conclusion that CKD-related arterial stiffness may be reversible after a successful KTx. This is an important finding because it gives hope for a potential therapeutic intervention, targeting arterial stiffness in CKD. However, an individual data meta-analysis may be required to perform additional analysis using a more sophisticated approach in determining the blood pressure–independent effect of a regression in arterial stiffness after KTx.[45]

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Disclosures

None.

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