Article: https://www.kireports.org/article/S2468-0249(24)01917-X/fulltext

🌠Tweetorial Alert 🌠

1/
Hey #NephTwitter!
Welcome to a 🆕 #tweetorial #xtorial brought to you by @KIReports.

2/
Our author is Melvin @MChanMD (pediatric nephrologist)
Our topic: The role of angiopoetins in kidney diseases

#MedTwitter #nephtwitter @ISNkidneycare #XTwitter

3/
There are no conflicts of interest. Please also check out #KIReportsCommunity educational #blogposts lead by @sophia_kidney at https://www.kireportscommunity.org/. FOLLOW US at @KIReports for more expert #MedEd in #kidneydisease. #FOAMed @MedTweetorials

4/ Let's start with a review on angiopoetin (Ang)
💡Ang-1 binds to Tie receptors inducing angiogenesis and stabilization of endothelial cells.
💡During inflammation, Ang-2 can disrupt the endothelium by inducing remodeling and increasing sensitivity to cytokines.

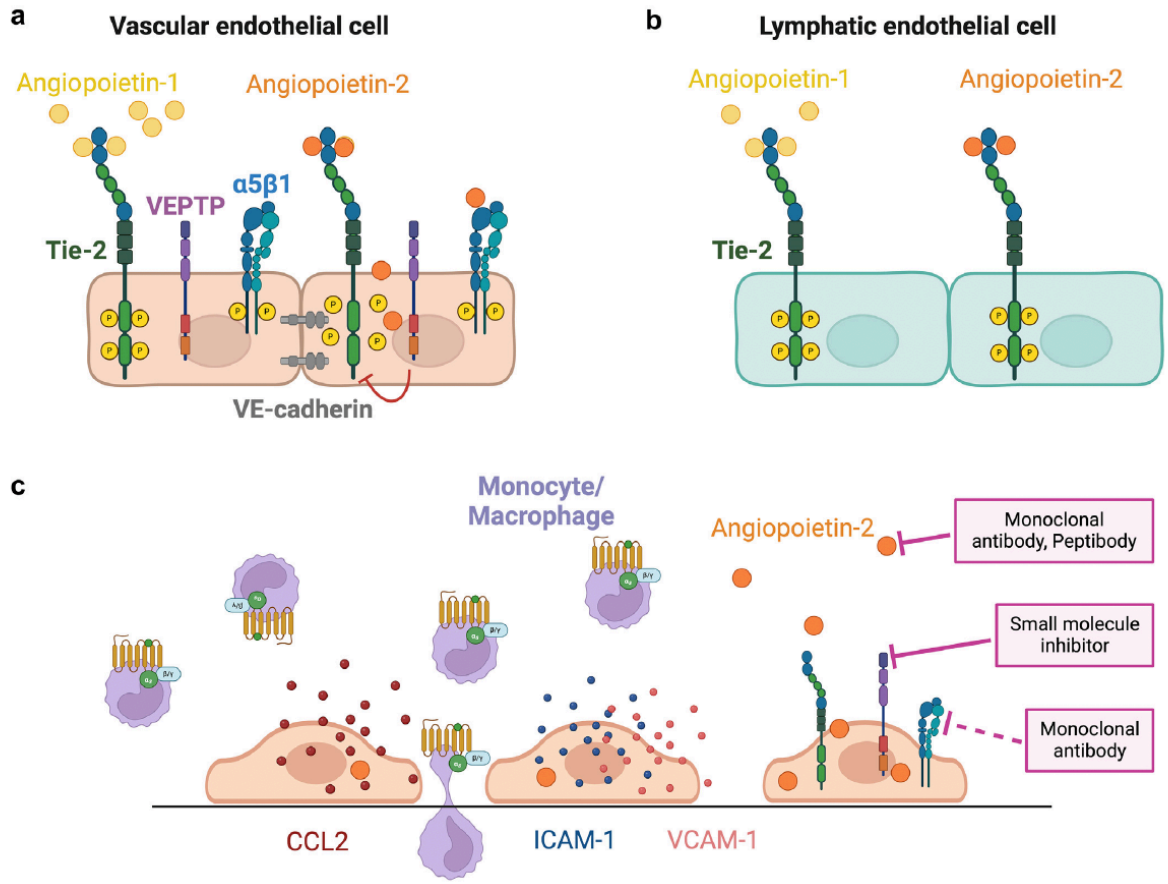


Figure 1. Scheme of angiopoietin-2 signaling and potential therapeutic targets in kidney diseases. Dysregulated angiopoietin-2 signaling is implicated in the pathogenesis of clinical scenarios, including acute kidney injury, acute kidney disease, chronic kidney disease, and other systemic conditions, such as sepsis, acute respiratory distress syndrome, cardiovascular disease, hepatic failure, and diabetes mellitus. This figure illustrates the relevant signaling pathways and potential therapeutic interventions targeting angiopoietin-2, vascular endothelial protein tyrosine phosphatase (VEPTP), and β1 integrin in kidney diseases. (a) Angiopoietin-2 signaling in vascular endothelial cells. Tie-2 is a receptor tyrosine kinase found in endothelial cells and some hematopoietic stem cells, consists of an extracellular domain for ligand binding, a transmembrane domain, and a cytoplasmic carboxy-terminal tyrosine kinase domain.[17,18] The ectodomain contains 3 Ig domains, 3 epidermal growth factor (EGF) repeats, and 3 fibronectin type III repeats, mediating angiopoietins binding. In vascular endothelial cells, angiopoietin-1 induces Tie-2 phosphorylation, which is antagonized by angiopoietin-2. This antagonistic activity is regulated by the Tie-2 phosphatase, VEPTP. In addition, angiopoietin-2 influences cell-cell junctions and endothelial cell integrity through Tie-2-independent mechanisms. Integrins are αβ heterodimeric receptors, and angiopoietin-2 has been shown to activate β1 integrin, leading to endothelial destabilization. (b) Angiopoietin-2 signaling in lymphatic endothelial cells. In the absence of VEPTP, angiopoietin-2 functions as an agonist of the Tie-2 receptor in lymphatic endothelial cells. (c) Endothelial cell activation and inflammation mediated by angiopoietin-2. The proinflammatory effects of angiopoietin-2 depend on the presence of various cytokines, such as vascular endothelial growth factor and tumor necrosis factor-α. Under the influence of these cytokines, angiopoietin-2 mediates the expression of adhesion molecules intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) in endothelial cells, promoting monocyte/macrophage infiltration. In addition, angiopoietin-2-sensitized endothelial cells increase the expression of chemokines, such as chemokine C-C motif ligand 2 (CCL2), further facilitating monocyte/macrophage infiltration. Clinical trials targeting angiopoietin-2, through direct inhibition of angiopoietin-2 or indirect inhibition of VEPTP or β1 integrin, represent a promising approach for therapeutic intervention. VE-cadherin, vascular endothelial cadherin.

5/ Given the important roles of Ang and the endothelium, let's do a deeper dive by reviewing a recent @KIReports article: Exploring Angiopoietin-2: Clinical Insights and Experimental Perspectives in Kidney Diseases by Luo et al.

https://www.kireports.org/article/S2468-0249(24)01917-X/fulltext

6/
Here is a great summary on all the outstanding research in this field:

Table 1. Diseases associated with disturbed angiopoietins/Tie-2 signaling

	angiopietin-1[a]	angiopietin-2	angiopietin-2/1 ratio	soluble Tie-2
Acute kidney injury in associated clinical conditions				
Critical illness	Lower[19,20]	Higher[19-22]	Higher[19-21]	Lower[20]
AMI	No difference[23]	Higher[23]		No difference[23]
Post-cardiac surgery	No difference[24]	Higher[24,25]		No difference[24]
COVID-19	No difference[26]	Higher[26]	No difference[26]	
Liver cirrhosis		Higher (mortality, AKIN stage, need for RRT)[27]		
Chronic kidney disease and outcomes				
Kidney outcome		Higher[13,28-30]	Higher[13]	
CV disease	Lower[31]	Higher[31-35]	Higher[31]	
mortality		Higher[13,35-37]		
Albuminuria				
		Higher[38-42]		

AKIN, Acute Kidney Injury Network; AMI, acute myocardial infarction; COVID-19, coronavirus disease 2019; CV, cardiovascular; RRT, renal replacement therapy.
[a]Plasma or serum angiogenic growth factors were measured by enzyme-linked immunosorbent assay.

7/With acute kidney injury (AKI)!
⚡Ang-2 levels correlate well with severity of sepsis, acute respiratory distress syndrome, acute myocardial infarctions, and post-cardiac surgeries.
⚡Levels are predictive of increased risk for 🪦in decompensated liver cirrhosis and AKI.

8/ What about chronic kidney disease (CKD)?
🫘Higher levels have also been associated with CKD progression and initiation of dialysis.

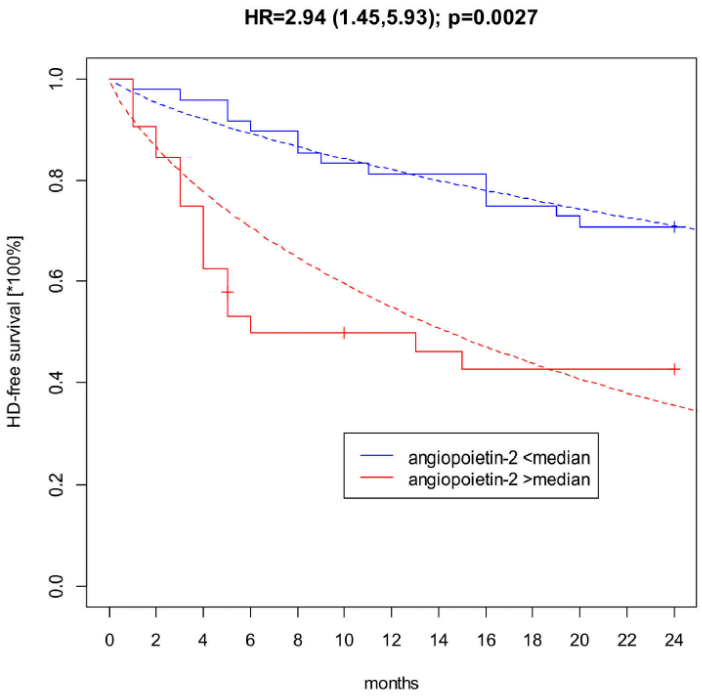


Figure 2. Kaplan-Meier survival curves for high vs. low Angiopoietin-2 concentrations. A high level of angiopoietin-2 (red line; >median 3.15 ng/mL) is indicative of dialysis initiation within two years. Low level of angiopoetin-2 (blue line; below median) is indicates a better prognosis.

https://pmc.ncbi.nlm.nih.gov/articles/PMC10298020/

9/What about cardiac-kidney-metabolic (CKM)?
👉Higher Ang-2 levels correlate with dysfunction, specifically ⬆️left ventricular mass index & left ventricular hypertrophy, vascular abnormalities including coronary artery disease, peripheral artery disease, & arterial stiffness.

10/ How about albuminuria?
🧂 Endothelial dysfunction can lead to increased vascular permeability and glomerular albumin leakage.
🧂 Elevated Ang-2 levels are associated with new onset microalbuminuria in both type 1 and type 2 diabetes.

11/ Do SGLT2 inhibitors affect Ang-2 levels?
📢Use of SGLT2 inhibitors appear to decrease Ang-2 levels in a post-hoc analysis of CREDENCE and primary outcome (initiation of dialysis, doubling of creatinine, or cardiorenal death).

https://journals.lww.com/cjasn/fulltext/2024/04000/associations_of_angiopoietin_2_and_vascular.6.aspx

	Placebo (EVENT/N)	Canagliflozin (EVENT/N)	HR (95% CI)	p	Interaction P-value
Primary Outcome					
Angiopoietin 2, Baseline					0.03
Q1	38/321	19/321	0.47 (0.27 to 0.82)	0.008	
Q2	43/331	29/310	0.69 (0.43 to 1.11)	0.13	
Q3	53/319	36/332	0.65 (0.43 to 0.99)	0.05	
Q4	56/300	63/341	0.98 (0.68 to 1.41)	0.92	
VEGF-A, Baseline					0.41
Q1	50/305	33/341	0.58 (0.37 to 0.90)	0.09	
Q2	51/332	45/314	0.89 (0.60 to 1.34)	0.13	
Q3	43/316	32/330	0.69 (0.44 to 1.10)	0.03	
Q4	47/327	40/319	0.85 (0.56 to 1.30)	0.78	
Heart failure hospitalization/cardiovascular death					
Angiopoietin 2, Baseline					0.9
Q1	19/321	15/321	0.77 (0.39 to 1.52)	0.46	
Q2	27/331	18/310	0.70 (0.38 to 1.26)	0.23	
Q3	32/319	24/322	0.73 (0.43 to 1.24)	0.25	
Q4	60/300	51/341	0.71 (0.49 to 1.03)	0.07	
VEGF-A, Baseline					0.47
Q1	32/305	28/341	0.78 (0.47 to 1.30)	0.35	
Q2	37/332	31/314	0.85 (0.53 to 1.37)	0.5	
Q3	34/316	27/330	0.74 (0.44 to 1.22)	0.24	
Q4	36/327	22/319	0.61 (0.36 to 1.04)	0.07	

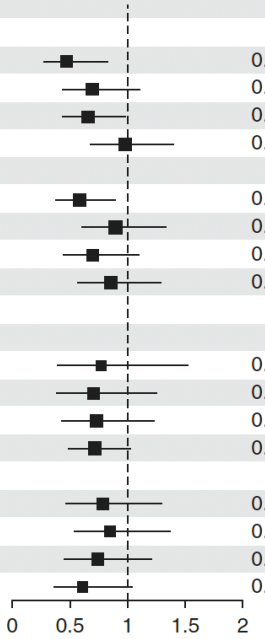
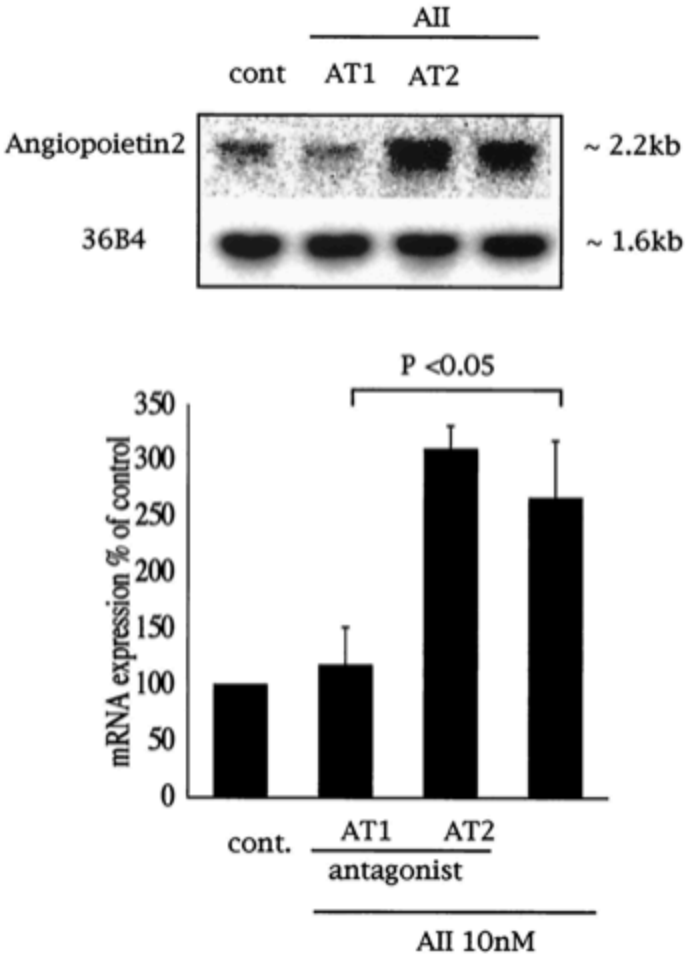


Figure 1. Efficacy of canagliflozin in lowering risk of primary composite outcome and heart failure or cardiovascular death across angiopoietin 2 and VEGF-A. Treatment-by-angiopoietin 2 interaction was present for primary composite outcome; canagliflozin was at a more effective level against the study primary composite outcome among patients with lower angiopoietin 2. CI, confidence interval; HR, hazard ratio; VEGF-A, vascular endothelial growth factor-A. Figure 1 can be viewed in color online at www.cjasn.org.

12/Does angiotensin II (All) affect Ang-2 levels?

🥊In animal studies, All increased Ang-2 levels through both type 1 and type 2 receptors.

🥊Blockade of type 1 receptors with losartan blunted mRNA expression of Ang-2 levels.



Effect of AT1 and AT2 antagonists on AII-stimulated Ang2 mRNA expression. BRECs were pretreated with losartan or PD123319 for 15 min followed by stimulation of 10 nmol/l AII for 4 h. The AT1 antagonist completely blocked AII-induced Ang2 mRNA expression. Representative blots are shown (top panel). Results are expressed as a percentage of the uninhibited controls (n = 3) (bottom panel).

https://diabetesjournals.org/diabetes/article/50/4/867/10970/Angiotensin-II-Induces-Expression-of-the-Tie2

13/ Clinical Implications

🧠Higher Ang-2 levels have been associated with worse cardiovascular, hepatic, and renal outcomes.

🧠The benefits of ACE/ARB and SGLT2 inhibitors may, in part, be due to blunting of the effects of Ang-2

14/ Now, let's see if you learned something!

How does Ang-2 affect blood vessels during inflammation?

A. Stabilizes it
B. Augment Ang-1
C. Cause remodeling
D. None of the above

15/ The answer is C by inducing remodeling. One more question.

What is one biomarker of new onset microalbuminuria in Type 1 and 2 diabetics?

A. Ang-1
B. Ang-2
C. Tie-2
D. VEG-F

16/ The answer is B: Ang-2. Please share this #tweetorial with your followers and friends! Thanks to @MChanMD for authoring & @Brian_rifkin, @sophia_kidney for great feedback!
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