

# Novel Concepts in Childhood Hypertension

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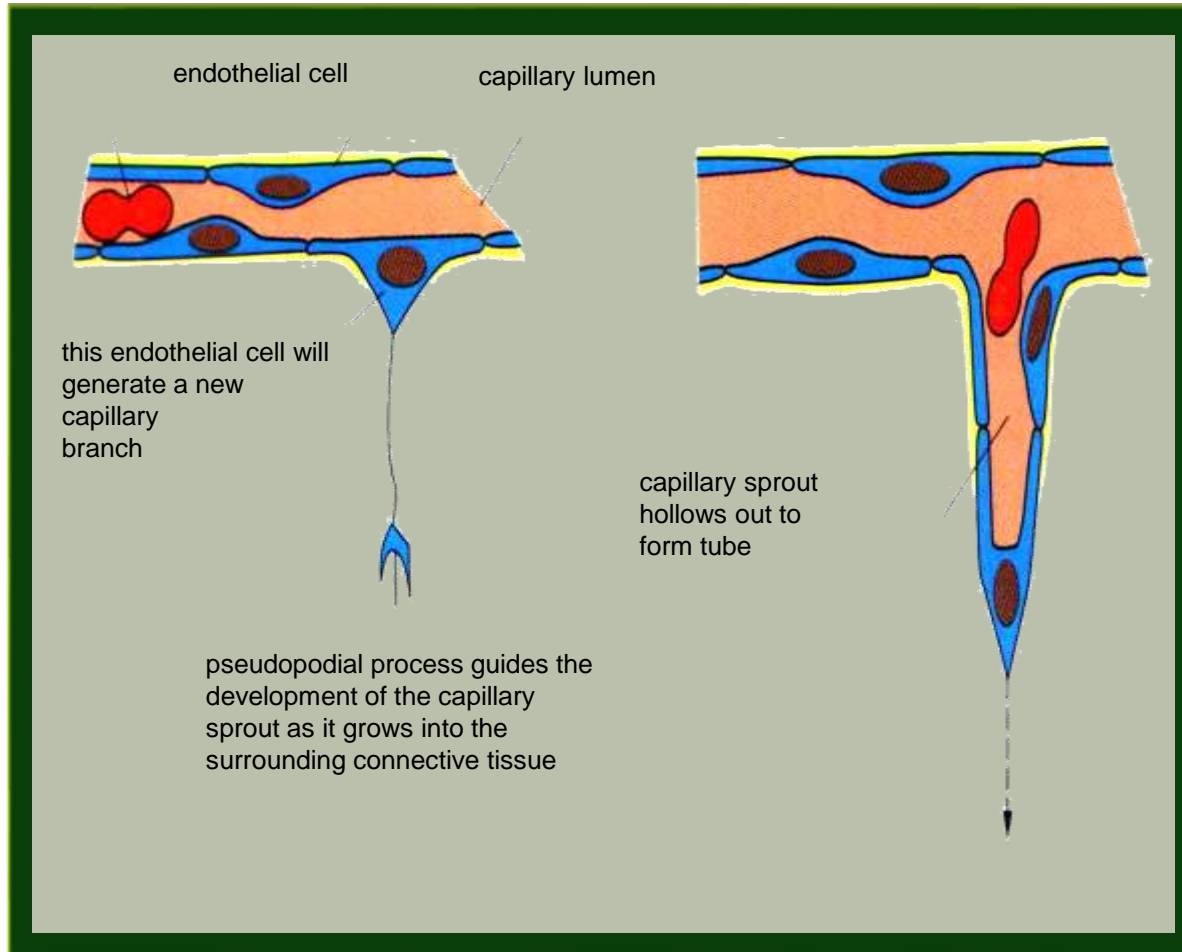
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# Novelty Topics

- **Management of hypertension in children on new generation chemotherapy**
  - **Mechanisms of bevacizumab mediate hypertension**
  - **Implications for models of vascular control**
- **Blood pressure and cardiovascular risk management with new generation therapy of diabetes mellitus**
  - **Use of SGLT2 inhibitor medications**
- **Short tour of a large pheo cohort**



# Angiogenesis: The Basics

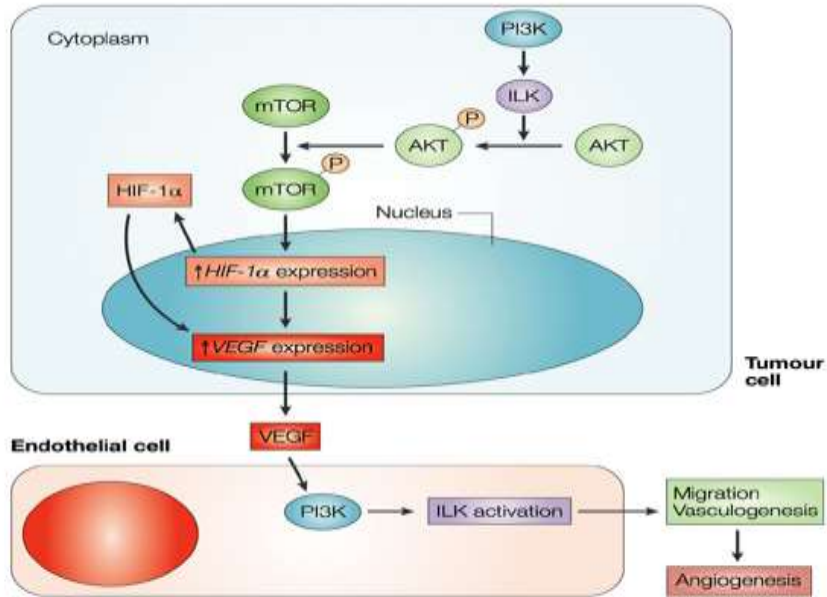


## Effectors:

- VEGF
- VEGF-R
- HIF
- HO
- >20 other GFs



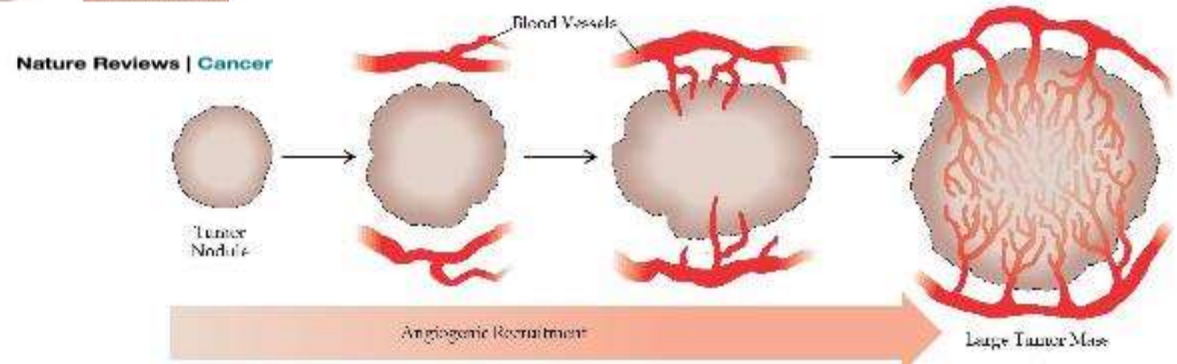
# Angiogenesis and Solid Tumors



**1971:** Proposed as a therapy by Folkman

**1999:** First therapeutic agent tested in humans

**2017:** 26 agents on the market



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# Normal and Disordered Angiogenesis

## Normal Angiogenesis

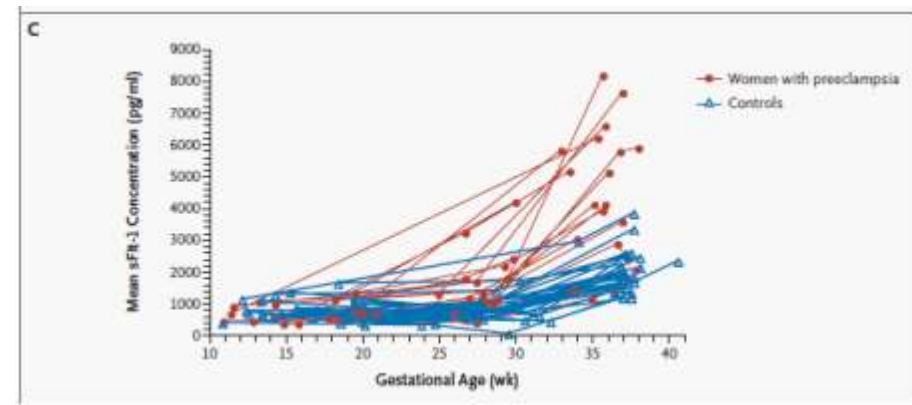
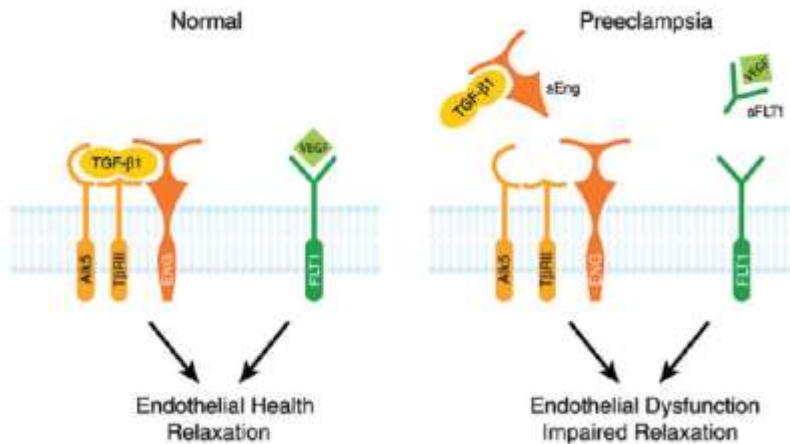
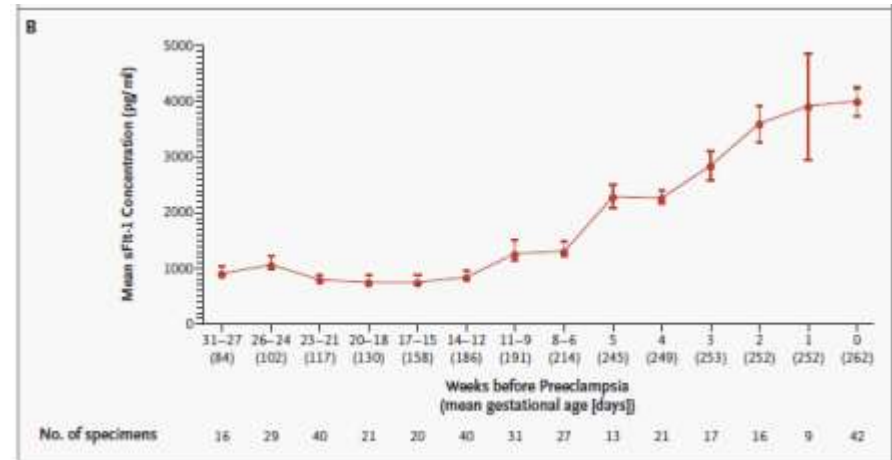
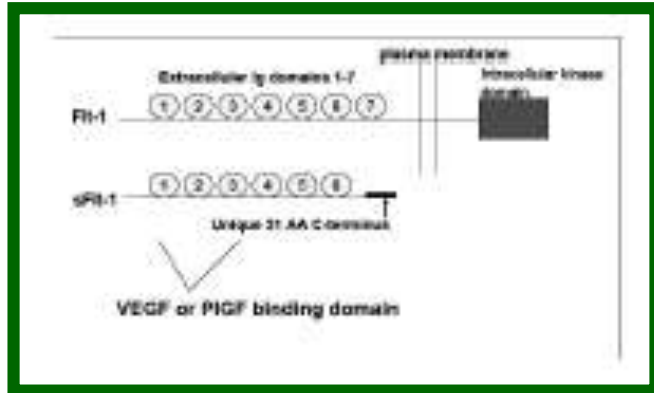
- Growth
- Vessel development
- Wound healing
- Maintenance of capillaries
- Podocyte stability
- ?? Endothelial function

## Disrupted angiogenesis

- Non-healing
- Edema
- Nephrosis
- Hypertension
- Pre-eclampsia

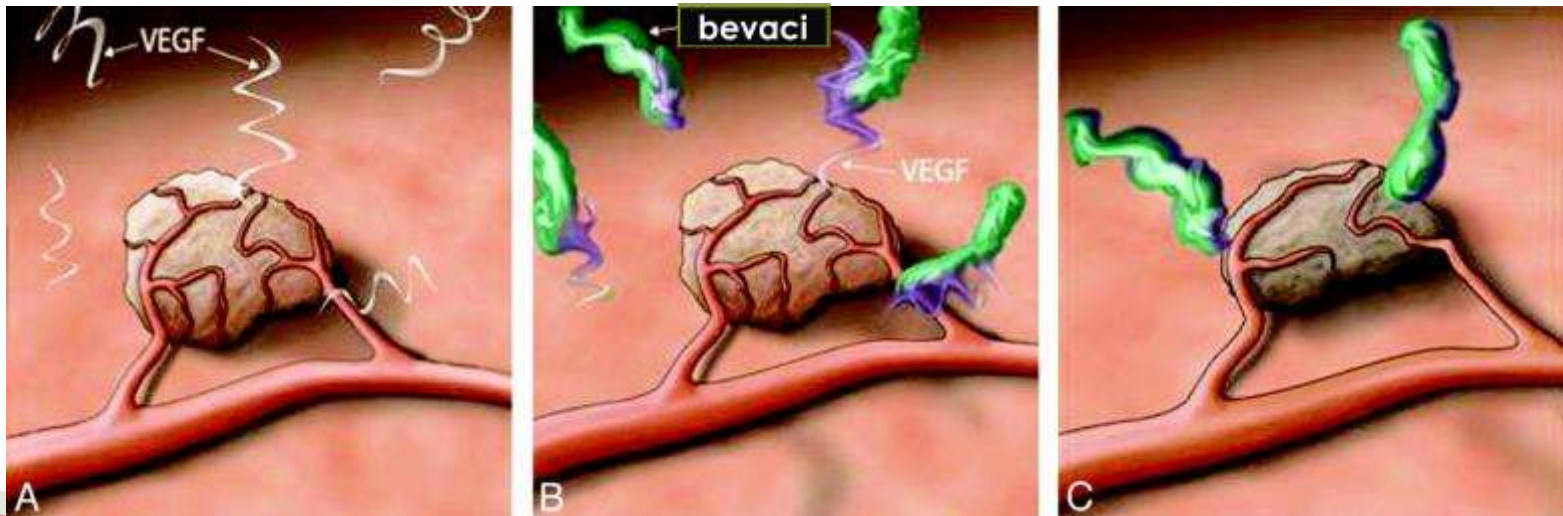


# Mechanism of Pre-eclampsia



# Mechanism of bevacizumab

- **Monoclonal antibody to VEGF to destabilize tumor angiogenesis**
- **Refractory solid tumors, especially in CNS and metastatic colon**
- **94 children received at UAB in 2017**
- **Estimate >100,000 children currently being treated worldwide**



# Complications of antiangiogenic therapy

- **Hypertension: 60-80%**
- **Hospitalized for hypertensive emergency: 8-12%**
- **Proteinuria: 25-40%**
- **Nephrotic Syndrome 10-15%**





# Mechanisms of bevacizumab hypertension

- **Destabilizes endothelium resulting in impaired endothelium mediated vasodilation**
- **Blocks induction of eNOS by VEGF worsening endothelial dysfunction**
- **Induction of ET-1**
- **Podocyte derived VEGF is an autocrine stabilizer of glomerular capillaries – likely relevant to proteinuria**



# Mechanism based management of anti-angiogenic hypertension

- **Infusion of VEGF or PIGF**
  - Counterproductive considering tumor therapy
- **Enoxaparin which increases renal clearance of sFLT**
  - Might be useful for BP but unclear impact on anti-tumor efficacy or bleeding risk
- **Induction of eNOS with arginine**
  - Has potential but has not been tested in clinical trials
- **CO exposure – induces VEGF through HIF and HO**
  - Poor idea in many ways
- **ET-1 antagonism (ambrisartan)**
  - Likely good approach but drugs not readily available or tested in kids



# Experience based therapy

- **Amlodipine (calcium channel blockade)**
  - Recommended 1<sup>st</sup> line therapy based on use in pre-eclampsia. Sufficient in 50-80%
- **Carvedilol (beta blocker)**
  - Beta blockers shown to blunt maternal sFLT rise in pre-eclampsia literature.
  - Sufficient monotherapy 30-40%, so used as 2<sup>nd</sup> agent
- **Losartan (Angiotensin receptor blocker)**
  - Many recipients of bevacizumab have pre-existing renal injury and additional renin mediated hypertension or proteinuria
  - Not tested as monotherapy, used 2<sup>nd</sup> or 3<sup>rd</sup> agent
- **Lisinopril (Angiotensin Converting Enzyme Inhibitor)**
  - Same issues as ARB



# Recommendations

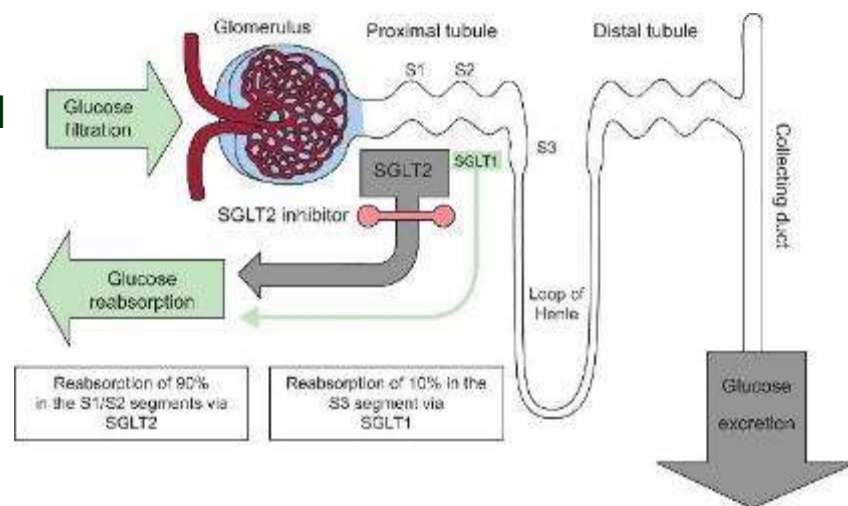
- **Patients receiving anti-angiogenic tumor therapy require close monitoring of BP**
- **Aggressive BP management is required to mitigate morbidity**
- **Therapy**
  - **Calcium Channel Blocker (amlodipine)**
  - **Beta Blocker (carvedilol or atenolol)**
  - **Angiotensin Receptor Blocker (losartan)**



# Sweet New Medication?

## SGLT2 inhibitors

- Inhibits a Na Glucose transport protein resulting in increased glucosuria
- Used for adjunct therapy for Diabetes Mellitus
- Results in HBA1c improvement of 0.5-1.0% at 12mo
- Concerns regarding polyuria, dehydration and UTIs but not seen in clinical trials
- Initial Large Clinical Trials also showed
  - Improved CV survival
  - Improved BP
  - Decreased CKD Progression
  - Weight loss



# SGLT2 Inhibitors - CV Outcomes

Impact of  
SGLT2i

REDUCED:

- HGBA1c
- Hypertension
- Renin-angiotensin activation
- Serum uric acid
- Vascular remodeling / Inflammation
- Decline of GFR

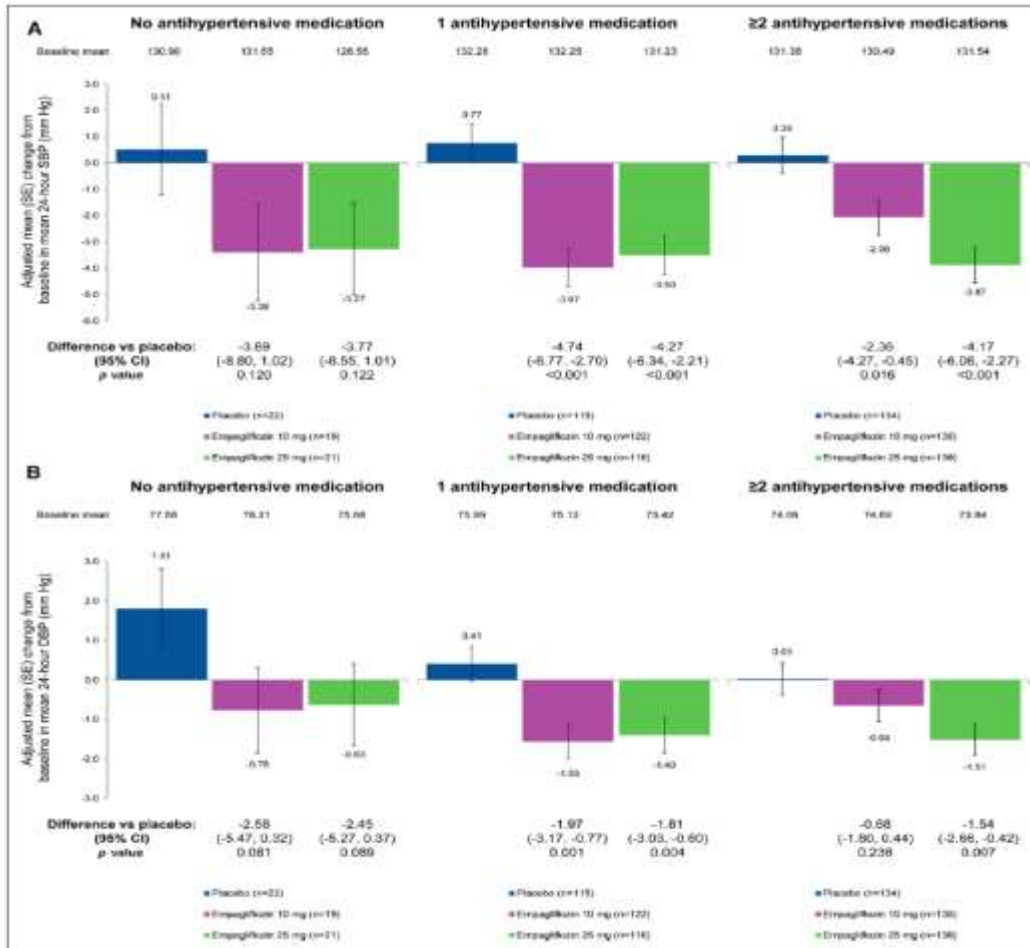
Cardiac  
Work  
reduced

- Preload and afterload reduced
- LVEDP reduced
- Lower cardiac oxygen demand

CV death  
HF  
hospitalization  
reduced



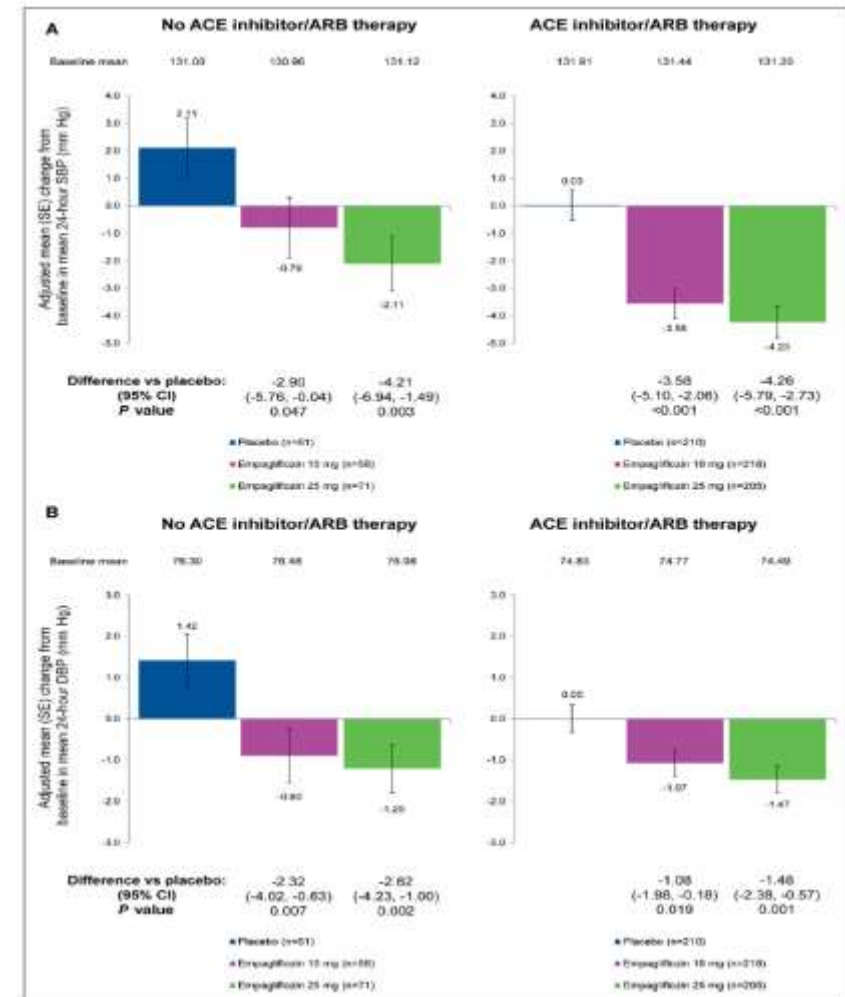
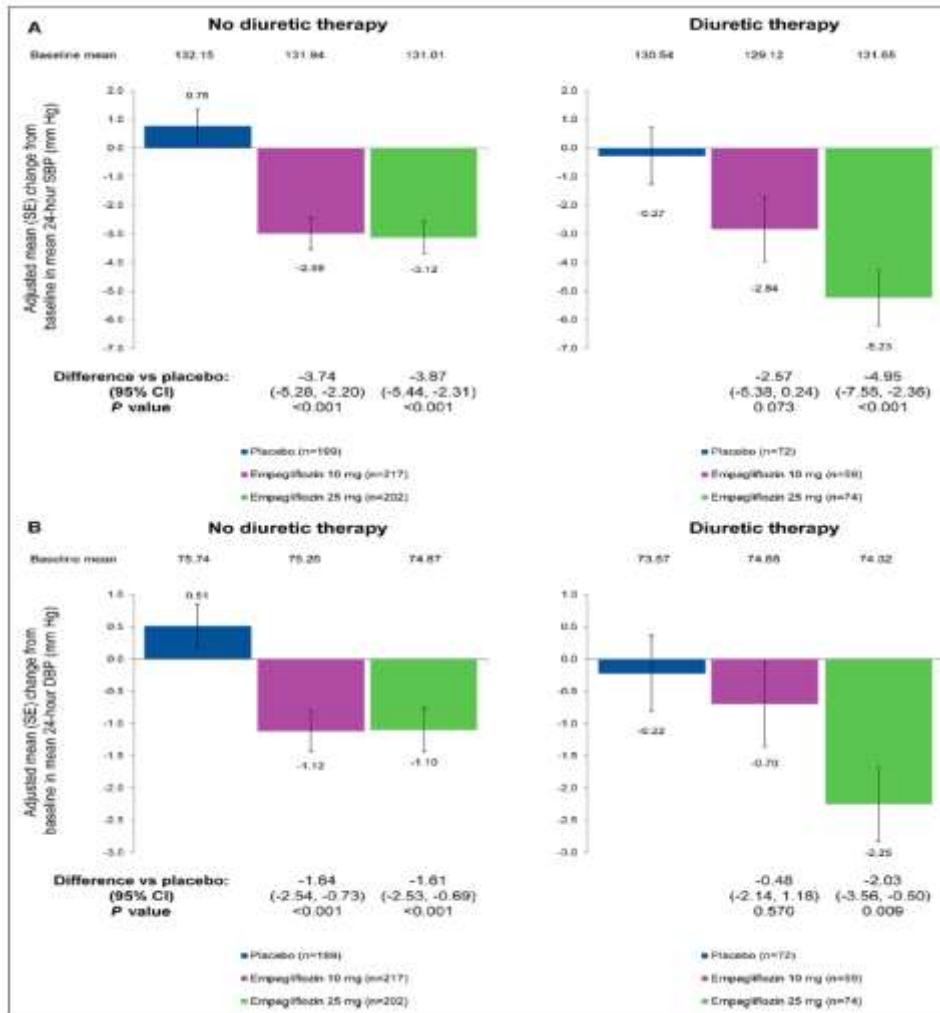
# Empagliflozin lowers BP



- All Type 2 Diabetics, 823 patients randomized to placebo, 10mg, 25mg
- BP endpoint ABPM
- Maximal BP effect seen with lower dose range of SGLT2i
- BP effects do not correlate with HgbA1c
- SBP and DBP reduction observed
- Effect seen in patients on no, 1, or multiple BP medications



# Empagliflozin effects additive to diuretics and ACEi medications

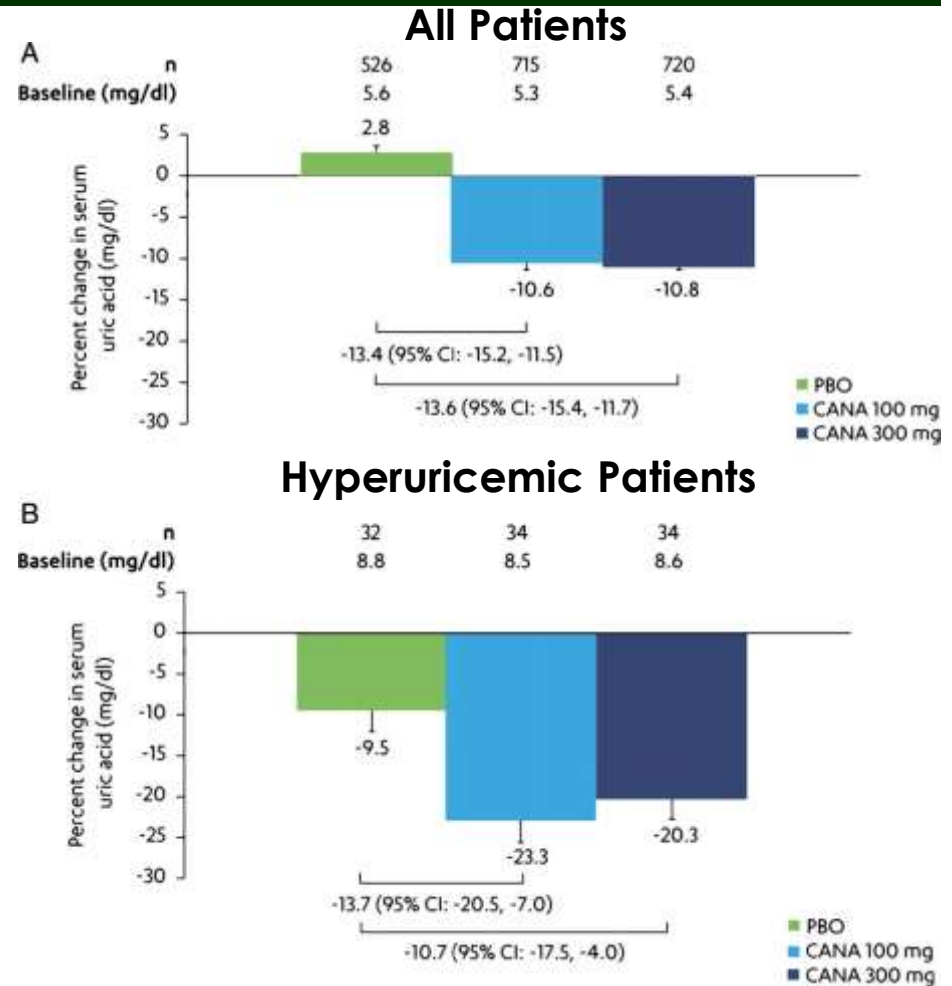




# Canagliflozin Reduces Serum Uric Acid in Patients with T2DM

(MJ. Davies, 2015)

- **Serum uric acid levels reduced by ~ 13%** in all patients and in a patient subset with hyperuricemia (uric acid  $\geq$  8 mg/dL)
- **Pooled data from 4 Phase 3 trials with CANA** (100 or 300 mg) for 26 weeks
- **Mechanisms by which SGLT2Is reduce serum uric acid** may involve the renal SLC2A9 (GLUT9) transporter (Caulfield 2008) and reduced hyperinsulinemia (Facchini 1991)



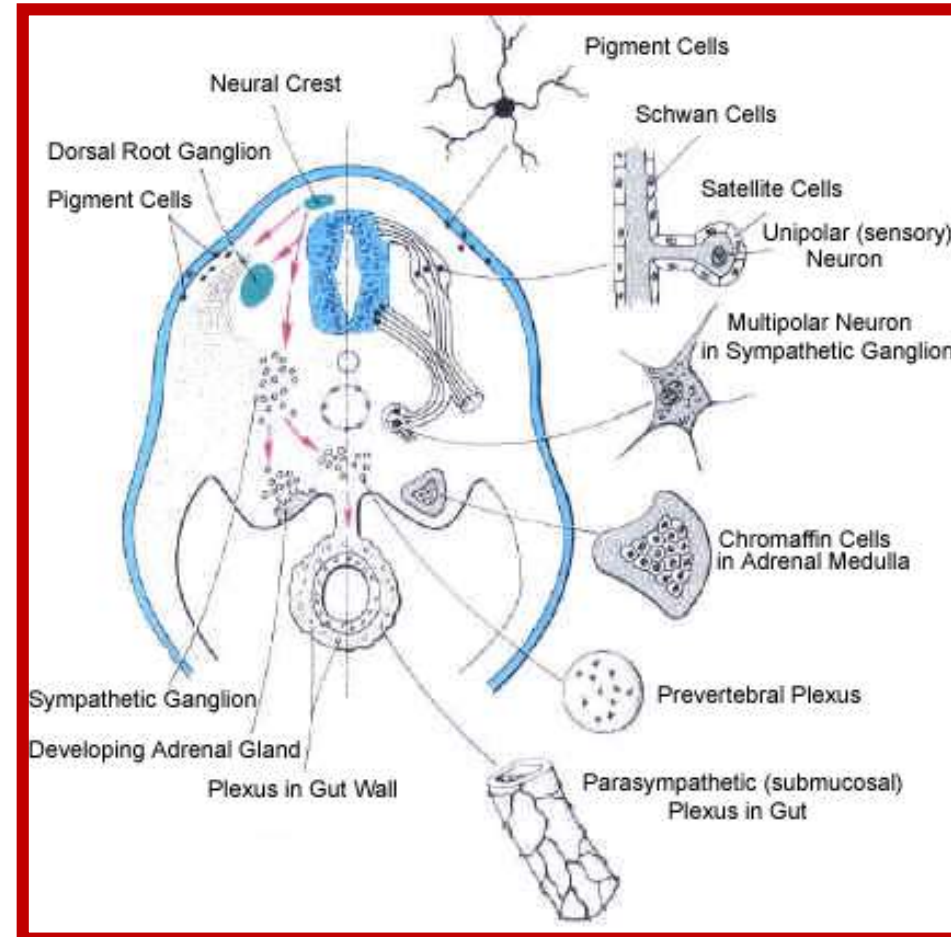
# SGLT2i in pediatrics

- **Nothing to report**
- **In light of BP data and CKD progression data, pediatric trials are needed**
- **Currently very expensive**



# Pheochromocytomas

- Pheochromocytoma = adrenal location
- Paraganglioma = anywhere else
- Tumor of neural crest cell origin



# Pheo/Para Cohort

- **1999-2017**
  - **34 patients**
    - **4 sib pairs**
    - **1 with mom**
  - **45 episodes of tumors**
    - **8 patients with 1 recurrence**
    - **1 with 3**
  - **59 tumors**
- **Demographics**
  - **Male 19 (59%)**
  - **Age 13.6yr (8mo-18yr)**
    - **- Relapse 15.2yr**
    - **+ Relapse 10.2yr**
  - **Race**
    - **White 17 (53%)**
    - **Black 8 (25%)**
    - **Hispanic 5 (16%)**
    - **Asian 2 (6%)**



# Presenting Complaints

"Typical Symptoms"	
<b>Hypertension</b>	<b>90.3%</b>
Palpitations	25.8%
Diaphoresis	9.6%
Flushing	3.2%
<b>Freq Headache</b>	<b>51.6%</b>
<b>Anxiety</b>	<b>67.7%</b>
Weight loss	19.3%
<b>Fatigue</b>	<b>67.7%</b>

Atypical Symptoms	
Vomiting (exercise)	19.3%
Abdominal Pain	22.5%
Constipation	12.9%
Diarrhea	25.8%
<b>Chest Pain</b>	<b>35.5%</b>
Hiccoughs	9.6%
Hallucinations	12.9%
Tremor	16.1%
Weight Gain	12.9%
Syncope with voiding	6.4%

**Note: All 11 recurrences were asymptomatic, identified on screening**



# Presenting Complications

- **Target organ damage**
  - **Left Ventricular Hypertrophy 61.2%**
  - **Retinal lesions 32.2%**
- **Comorbid Diagnoses**
  - **Migraine 45.2%**
  - **Cyclic vomiting 12.9%**
  - **Irritable Bowel Syndrome 32.2%**
  - **Psychiatric:**
    - **Anxiety 51.6%**
    - **Hallucinations 6.4%**
    - **Depression 25.8%**



# Diagnostics: Laboratory Evaluation

Test	Sensitivity	Specificity
<b>Plasma MN+NME</b>	<b>95%</b>	<b>99%</b>
Plasma NE+Epi	91%	62%
Plasma VMA+HMA	58%	62%
Urine MN+NMN	98%	95%
Urine NE+Epi	97%	84%
Urine VMA+HMA	41%	29%
<b>Chromagranin A</b>	<b>89%</b>	<b>96%</b>

Havekes et al *Pediatr Nephrol* 2009; 24:943  
Zuber et al. *Eur J Clin Invest* 2014; 44: 365

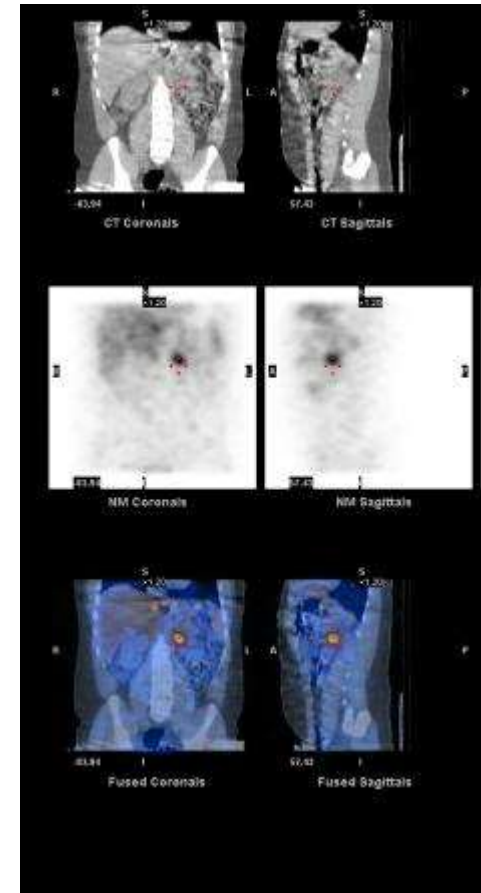


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# Diagnostics: Imaging

- **US: poor sensitivity in small tumors**
- **MRI thought to be more sensitive for small tumors than CT – both may miss small multiples**
- **$^{123}\text{I}$ -MIBG 83-95% sensitive, risk of false negative for small, extra-adrenal**
- **Fusion imaging**
- **Functional PETs**
  - **$^{18}\text{F}$ -FDA: risk of false positive because of strong adrenal uptake. +in DA secretors missed by MIBG**
  - **$^{18}\text{F}$ -FDG: superior for metastatic and SDHb but higher risk of false positive than MIBG**





# Tumor Locations: 45 cases, 59 tumors

<b>Adrenal</b>	<b>33</b>
Right Adrenal	12
Left Adrenal	19
Bilateral	2
Para-aortic	17
Mesentary	4
Bladder Wall	2
Bowel Wall	1
Chest wall	1
Lung (mets)	1
<b>Cases with multiple tumors</b>	<b>7 (15.5%)</b>



# Genetics

Gene	Published Prevalence	Cohort Prevalence
SDHa	rare	0
SDHb	8-45%	35.4%
SDHc	0-9%	3.2%
SDHd	6-29%	16.1%
VHL	0-52%	25.8%
RET (MEN2)	4-32%	3.2%
NF-1	0-10%	3.2%
Other: SDHAF2, TMEM127, MAX, HIF2A, KIF1B, PHD1, PHD2, FH, HRAS, BAP1, MEN1	0-8%	0
Unknown	10-70%	9.6%



# Blockade

- **Our protocol**
  - **Phenoxybenzamine escalating does x2 wks**
  - **Addition of Metyrosine for second week**
  - **Propranolol if needed for tachycardia**
  - **Volume expansion with Na/water intake**
  
- **Other protocols**
  - **Amlodipine**
  - **Phenoxybenzamine alone**
  - **Phenoxybenzamine then Propranolol**



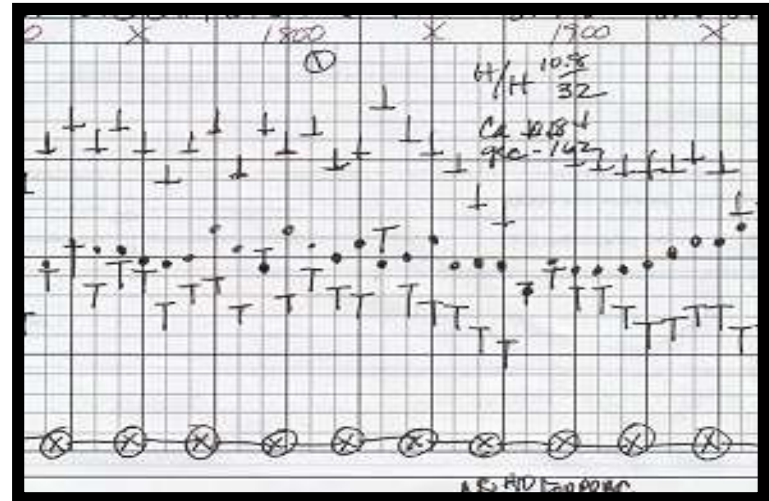
# Pre-Op Targets

- **Resting BP consistently <50<sup>th</sup> %ile**
- **Mild to moderate orthostatic symptoms**
- **Moderate to severe nasal congestion**
- **Moderate to severe fatigue**
- **Volume expansion: >10% weight gain**
- **Admit 1-2 days pre-op for final medication titration and IVF**



# Blockade Results

- **Protocols complications**
  - Amlodipine 2/2
  - Phenoxy alone 2/3
  - Phenoxy/Propranolol 3/6
  - Phenoxy/Metyr 0/34
- **Post Op**
  - Significant risk of hypotension
  - Mitigated by volume expansion
  - May need Vasopressin infusion
  - Short acting medications
  - Polyuria is common
  - Hyponatremia is common
  - Screen for adrenal insufficiency



# Conclusions

- **Hopefully this met the definition of “Novel”**
- **Anti-angiogenic cancer chemotherapy will be providing us a lot of patients in the near future**
- **SGLT2i inhibitors hold promise in diabetics with hypertension but must to studied in children**
- **Pheos aren’t so difficult**

