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Kidney biopsy: Challenges with peri-procedural management

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ABSTRACT

Native kidney biopsies are high-risk for bleeding complications due to the vascularity of the kidney and the inability to compress the biopsy site within a deep retroperitoneal location. Recommended parameters to minimize bleeding risk include a platelet count above $100 \times 10^9/L$, hemoglobin above 10 g/dL, systolic blood pressure <140 mm Hg, and minimizing the number of biopsy cores. In this paper we present patient cases to discuss management of other factors pertinent to kidney biopsy planning including interruption of anticoagulation, treatment of anxiety which can elevate blood pressure, and use of Doppler. Undiagnosed chronic kidney disease can affect triaging of tissue to light, immunofluorescence and electron microscopy, as sclerosed glomeruli are difficult to visualize in fresh cores. It is recommended to have a back-up retrieval protocol in place to obtain immunofluorescence and electron microscopy results, in the event that only limited kidney tissue was acquired for light histology. A collaborative effort between nephrology, interventional radiology and pathology is essential to optimize the diagnostic yield while minimizing bleeding risk with kidney biopsies. Of paramount importance is physician judgment of whether there is an acceptable balance of benefits/risks to proceed with a kidney biopsy.

Implication for health policy/practice/research/medical education:

Factors that influence bleeding risk with native kidney biopsies include thrombocytopenia, anemia, hypertension, anticoagulation therapy and repeated sampling if glomeruli are difficult to visualize in tissue cores. Centers should have a back-up retrieval protocol in place to obtain immunofluorescence and electron microscopy results, in the event that only limited kidney tissue was acquired for light histology.

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Introduction

Ultrasound-guided percutaneous kidney biopsy is the standard of care for obtaining diagnostic tissue during evaluation of proteinuria, microscopic hematuria, renal manifestations of systemic disease, transplant rejection, and unexplained kidney dysfunction (1,2). Native kidney

biopsies are high-risk for bleeding complications due to the vascularity of the kidney and inability to compress the biopsy site within a deep retroperitoneal location (3). Patients with kidney disease often have uremia-associated platelet dysfunction, hypertension, and inflammatory states which further increase bleeding risk (3). A widely-

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cited meta-analysis of 9474 ultrasound-guided native kidney biopsies performed with automated biopsy devices reported the following rates of major complications: blood transfusion (0.9%), angiographic intervention (0.6%), nephrectomy (0.01%), bladder obstruction (0.3%) and death (0.02%) (4). A more recent meta-analysis of 118 064 biopsies noted similar rates for blood transfusion (1.6%), angiographic or surgical intervention (0.3%) and death (0.06%) (5).

Established criteria during the planning steps for native kidney biopsies include; 1) imaging confirmation of non-atrophic kidneys with adequate cortex, 2) platelet count $>100 \times 10^9/L$, 3) hemoglobin $>10 \text{ g/dL}$, 4) systolic blood pressure $<140 \text{ mm Hg}$, 5) use of 16-gauge needle (not 14-gauge) and limiting to a maximum of 5 passes, 6) exclusion of kidney infection (1,6,7). In this paper, we describe a case series and discuss additional strategies to limit bleeding risk with percutaneous kidney biopsies.

Case 1

A 32-year-old male with lupus nephritis, antiphospholipid syndrome with a history of pulmonary emboli and left lower extremity deep venous thrombus requiring lifelong anticoagulation therapy had two prior uneventful kidney biopsies. The latter biopsy had revealed class 3+5 lupus nephritis with cellular crescents in 3 out of 14 glomeruli for which he was treated with steroids and monthly cyclophosphamide infusion. He was then lost to follow up.

He was admitted to the hospital 8 months later with worsening of shortness of breath and lower extremity edema present for 4 days. Labs confirmed acute kidney injury and 2.3 g/d proteinuria. The patient was empirically started on pulse steroids and cyclophosphamide. A decision was made to perform a biopsy to determine lupus nephritis activity and degree of fibrosis to guide therapy (8). The left kidney biopsy demonstrated class 4+5 lupus nephritis with focal active cellular crescents, focal old fibrous crescents, and mild interstitial fibrosis and tubular atrophy. Post-biopsy ultrasound showed a small sub-capsular hematoma and hemoglobin was stable at 9.8 g/dL. At 48 hours after the biopsy, anticoagulation with warfarin and bridging enoxaparin was resumed. The patient was discharged home 72 hours post-biopsy.

Four days after discharge the patient returned to the hospital with worsening left flank pain that radiated down his left leg. He was found to be severely anemic and was transfused six units of packed red blood cells. Imaging showed a large retroperitoneal hematoma requiring embolization of the left renal artery. Management of anemia was complicated by the presence of multiple autoantibodies leading to hemolysis of transfused blood cells.

Case 1 discussion

This case highlights the complexity of the timing for resuming anticoagulation after kidney biopsy when a patient is at high thrombosis risk especially in the context of antiphospholipid syndrome and previous thromboembolic disease. To minimize bleeding risk, withholding anticoagulation for 7 days post biopsy is preferred. However, when the patient is at high risk for thrombotic events, resuming anticoagulation after 48-72 hours may be warranted. Inpatient monitoring for up to 7 days post-biopsy is not cost-effective. A potential strategy is to resume bridging anticoagulation at 48-72 hours, such as enoxaparin injections, and to perform follow-up ultrasound imaging of the biopsied kidney at 7 days prior to resuming oral anticoagulation. Management of peri-procedural anticoagulation and antiplatelet agents is summarized in Table 1.

Of note, a hematoma visualized on post-biopsy imaging is not useful to predict significant acute anemia requiring blood transfusion (positive predictive value of only 7%) (7). Paradoxically, although the antiphospholipid syndrome is a pro-thrombotic state, it is associated with higher risk of bleeding after kidney biopsy, especially if there is concurrent thrombotic microangiopathy and intimal hyperplasia (9). Percutaneous kidney biopsy is contraindicated if anticoagulation cannot be safely interrupted, e.g., in the setting of an acute pulmonary embolus or recent placement of coronary drug-eluting stent. In this scenario, and in cases of uncorrectable clotting disorder, the trans-jugular biopsy is an option in centers with experienced operators. The complication rate is similar to that of percutaneous biopsies (10), with the added risk of contrast-induced acute kidney injury (~8%) (11).

Cases 2-4

These next cases highlight the risk of bleeding in the setting of advanced kidney fibrosis that was not obvious on pre-biopsy imaging. In the first case, a 77-year-old male with stage 3 chronic kidney disease, type 2 diabetes mellitus, hypertension and abrupt worsening of proteinuria underwent right native kidney biopsy. Post-biopsy imaging demonstrated a 6-7 cm sub-capsular hematoma as well as a blood clot in the bladder. Hemoglobin trended down from 11 to 9 g/dL and stabilized; the patient did not require blood transfusion nor surgical intervention. The biopsy reported severe arteriosclerosis with focal segmental glomerulosclerosis, diffuse global glomerulosclerosis and extensive interstitial fibrosis/tubular atrophy (60%). One year later, the patient continues to be followed closely in the outpatient chronic kidney disease clinic with optimization of diabetes mellitus and hypertension management.

In the second case, a 20-year-old male had known dense

Table 1. Management of anticoagulation and antiplatelet medications to minimize bleeding with kidney biopsy; recommendations differ between native and transplant biopsies (deep retroperitoneal versus superficial location, thus lower bleeding risk with transplant biopsies)

Medication	When to discontinue medication prior to kidney biopsy	Blood test prior to biopsy	When to resume medication after kidney biopsy
Subcutaneous heparin and low molecular weight heparins (dalteparin, enoxaparin)	Evening prior to biopsy (i.e., skip 2 doses prior to biopsy)	N/A	
Heparin infusion	24 hours	aPTT or anti-factor Xa level on morning of biopsy*	7 days is preferred; can restart at 48-72 hours once confirmed no significant retroperitoneal hematoma on surveillance ultrasound imaging
Warfarin	5 days	INR 12-24 hours prior to biopsy	
Factor Xa inhibitors (apixaban, edoxaban, rivaroxaban)	<ul style="list-style-type: none"> • CrCl >50 mL/min: 2 days • CrCl <50 mL/min: 3 days 	N/A	
Direct thrombin inhibitor (dabigatran)	<ul style="list-style-type: none"> • CrCl >50 mL/min: 3 days • CrCl <50 mL/min: 5 days 	N/A	
Antiplatelet agents (aspirin, cilostazol, clopidogrel, dipyridamole, prasugrel, ticagrelor, non-steroidal anti-inflammatory drugs)	<ul style="list-style-type: none"> • Native kidney biopsy: 10 days • Transplant biopsy: 7 days (or 5 days if urgent biopsy) 	Platelet function test 12-24 hours prior to biopsy	<ul style="list-style-type: none"> • Native kidney biopsy: 7 days (can be 48-72 hours depending on clinical scenario) • Transplant biopsy: 48 hours

aPTT: activated partial thromboplastin time; CrCl: creatinine clearance; INR: international normalized ratio; N/A: not applicable.

* Anti-factor Xa level should be undetectable prior to biopsy. Measurement of anti-factor Xa to document absence of heparin or low molecular weight heparin effect is recommended in the presence of autoantibodies such as lupus anticoagulant, which can falsely elevate aPTT.

deposit disease from two prior kidney biopsies. Ultrasound reported normal kidney sizes 12.5 cm bilaterally with normal cortical echogenicity. Due to increasing proteinuria and a creatinine uptrend from 2.1 to 3.5 mg/dL over a 4-month period, the patient underwent a left native kidney biopsy. Follow up renal ultrasound showed a 9 cm perinephric hematoma. The patient's hemoglobin remained stable at 9 g/dL for 24 hours and repeat imaging showed no change in the hematoma; no blood transfusion or intervention was needed. The biopsy reported dense deposit disease with membranoproliferative glomerulonephritis, diffuse glomerulosclerosis with evidence of acute tubular necrosis, and extensive interstitial fibrosis/tubular atrophy (>80%). There were IgG kappa glomerular and tubulointerstitial deposits consistent with eculizumab deposition. The patient had progressive kidney disease and transitioned to dialysis 9 months later.

The third case was a 31-year-old female who had not seen a doctor for several years. She presented with an elevated creatinine of 14 mg/dL, hypertensive urgency and sub-nephrotic proteinuria. She was initiated on hemodialysis for volume management and was transfused one unit of packed red blood cells for a hemoglobin of 7.5 g/dL. A left native kidney biopsy demonstrated advanced IgA nephropathy with diffuse mesangial and endocapillary proliferation, diffuse global glomerulosclerosis (70%) and extensive interstitial fibrosis/tubular atrophy (>70%). Post-biopsy perinephric bleeding necessitated repeat blood transfusions and embolization of the left renal artery. The

patient remained dialysis-dependent.

Cases 2-4 discussion

These patients had a shared finding of advanced kidney fibrosis, which makes it difficult for the physician or pathology technician to visualize glomeruli in the fresh tissue cores (Figure 1). Under a dissecting microscope or magnifying glass; typically, 2-3 glomeruli are assigned each to immunofluorescence and electron microscopy and the majority of glomeruli are reserved for light microscopy. Usually 15-20 glomeruli would be a recommended adequate sample for light microscopy analysis (6). Two 1.5- to 2-cm-long cores of tissue sampled with a 16-gauge needle would typically yield sufficient glomeruli for light, immunofluorescence and electron microscopy (3,6).

When glomeruli are not easily visualized in the setting of fibrosis and glomerulosclerosis, this may prompt additional passes with the biopsy needle with an increased risk of bleeding (6). Each of the cases described above had four cores obtained. Of note, published reports have not found a statistically significant correlation between degree of fibrosis, glomerulosclerosis, or number of passes, with bleeding risk (4,7,12). However, there is an inherent risk of inadvertently damaging an arcuate or interlobular artery with each needle pass.

Important to note from case #4 is that low pre-biopsy hemoglobin predicts high-risk for bleeding (1,6,7), with the Boston Kidney Biopsy Cohort reporting an odds ratio of 13.6 (95% confidence interval 5.4-34.1) for post

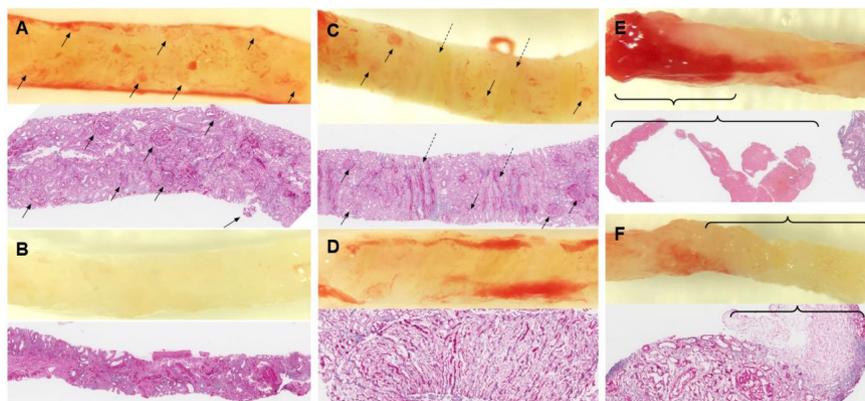


Figure 1. Comparison of fresh tissue cores with histologic sections. (A) Non-scarred cortex with easily identifiable glomeruli (arrows). (B) Scarred cortex with difficult to identify glomeruli. (C) Non-scarred cortex with easily identifiable glomeruli (arrows) and medullary rays (dotted arrows). (D) Medullary tissue without visible glomeruli. (E) Obscuring blood clot (brackets). (F) Renal capsule and perinephric soft tissue (bracket). A-D and F histology images are periodic acid Schiff stained sections; E is H&E stained section.

biopsy transfusion requirement if baseline hemoglobin was <10 versus ≥ 10 g/dL (7). The patient in case #4 was transfused one unit of blood pre-procedure; there are no evidence-based guidelines on whether transfusion to a specific target hemoglobin reduces bleeding risk.

It is thus important to analyze for markers of chronic kidney disease, which may indicate the possibility of advanced kidney fibrosis. Considerations include smaller kidney sizes than expected for body size, elevated parathyroid hormone, hyperphosphatemia or anemia. These cases can be particularly challenging when a patient presents with nephrotic proteinuria, elevated creatinine, and unknown baseline kidney function. In centers where the nephrologist is not performing the kidney biopsy, communication with the interventional radiology and pathology teams is essential so they are aware that the tissue may yield sclerosed glomeruli, and to not proceed with additional passes if there is high confidence that cortex was obtained.

Desmopressin (dose of 0.3 $\mu\text{g}/\text{kg}$) administered 30-60 min before biopsy has been suggested in patients with azotemia (blood urea nitrogen >50 mg/dL) to ameliorate platelet dysfunction. A randomized study of 162 adults demonstrated fewer (13.7% versus 31%) and smaller ultrasound-detected hematomas in patients using desmopressin versus placebo; there was no effect on transfusion requirements and no serious adverse events (13). However, this study enrolled patients with serum creatinine level ≤ 1.5 mg/dL and/or estimated glomerular filtration rate ≥ 60 mL/min/1.73 m² and normal coagulation parameters (13), thus the utility of desmopressin in high-risk patients with more severe azotemia is unclear.

Case 5

A 47-year-old female presented for an outpatient native

kidney biopsy. The patient endorsed compliance with antihypertensive medications including lisinopril 40 mg daily, amlodipine 10 mg daily and furosemide 20 mg daily; home blood pressure has been averaging 128/70. She had significant anxiety in anticipation of the biopsy procedure. Blood pressure measured in the pre-procedural suite was 150/75 mm Hg and remained elevated on recheck, thus the biopsy was cancelled.

Case 5 discussion

Blood pressure control is essential when performing a native kidney biopsy, with experts recommending a threshold <149/90 mm Hg (1, 10). A retrospective study of 293 patients reported a 10-fold increase in major complications (requirement for transfusion or intervention) when systolic blood pressure was >140 mm Hg or diastolic blood pressure was >90 mm Hg (14). Blood pressure optimization can be complex if it is related to worsening kidney function or anxiety, and may require hospital admission prior to the biopsy for close monitoring and escalation of blood pressure medications. If there is a component of significant anxiety causing a blood pressure spike, a one-time dose of the short-acting oral benzodiazepine alprazolam 1 mg can be prescribed to be taken 1-2 hours before the kidney biopsy.

Following a kidney biopsy, a persistently elevated blood pressure should prompt imaging to evaluate for a subcapsular hematoma and potential pape kidney (6).

Case 6

A 55-year-old male with a kidney transplant underwent an allograft biopsy to evaluate gradual rise in creatinine. The biopsy showed mild mesangial sclerosis and arteriosclerosis, with secondary focal segmental glomerulosclerosis with no evidence of rejection. However, sampling of several arcuate to interlobar sized arteries was noted on the biopsy

specimen. The patient's creatinine increased from 2.1 to 3.2 mg/dL post kidney biopsy. Due to a persistently elevated serum creatinine, another biopsy was performed 2 weeks later, which showed evidence of infarction suggestive of segmental vascular compromise, possibly due to injury to arcuate or inter-lobar arteries sustained in the first biopsy (Figure 2).

Case 6 discussion

The complication rate with transplant biopsies is lower than with native kidney biopsies (15). The allograft kidney, being superficial, is easier to image during biopsy and allows more effective application of manual pressure at the biopsy site after the procedure. At our center, the kidney transplant biopsy protocol requires a less restrictive blood pressure target (systolic <150 mm Hg instead of <140 mm Hg) and a shorter duration of withholding antiplatelet agents (Table 1). The case described highlights the inherent risk of injury to arcuate or interlobular arteries with kidney biopsies. The use of Doppler to visualize and avoid areas of higher vascular blood-flow during ultrasound-guided biopsy is imperative to minimize this risk (16).

During the procedure, if Doppler detects perinephric bleeding or an arteriovenous fistula the biopsy procedure is terminated, and close monitoring is warranted to ensure that bleeding is controlled. If limited core(s) were obtained and there is uncertainty about glomeruli yield (e.g., glomeruli obscured by overlying blood, or glomeruli are sclerosed and difficult to visualize, see Figure 1) the tissue can be placed in the buffered formaldehyde fixative for light microscopy. Most pathology centers have salvage protocols to retrieve tissue from the light microscopy fixative or paraffin block, to reprocess for immunofluorescence and electron microscopy. However, these salvage techniques are sub-optimal for the diagnosis

of certain conditions including anti-glomerular basement membrane disease, pediatric nephrotic syndrome or hereditary nephropathy. Electron microscopic studies reprocessed from paraffin-embedded tissue are not reliable for assessment of glomerular basement membrane thickness and often show poor preservation of endothelial cells and podocyte foot processes (17). In terms of immunofluorescence, studies can be performed on paraffin embedded tissue following an antigen retrieval step (e.g., pronase digestion) but are significantly less sensitive for the detection of C3 glomerulopathy, bacterial infection associated glomerulonephritis, primary membranous nephropathy, and anti-glomerular basement membrane nephritis as well as slightly less sensitive for IgA nephropathy, lupus nephritis, AL-amyloidosis, and monoclonal immunoglobulin deposition disease (18).

Conclusion

With standardization of imaging-guided kidney biopsy using automated devices, the focus has shifted to defining best practice for peri-biopsy management [Box 1 and see detailed Up-to-date section on "The kidney biopsy" (10)]. Attention to platelet count and blood pressure control is paramount. Anticoagulation and antiplatelet agents should not be resumed for at least 7 days, to decrease the risk of an expanding hematoma. If the medications are restarted sooner, close imaging surveillance of the biopsy site and/or hemoglobin checks are warranted. Communication between the nephrologist, interventional radiologist and pathologist with regards to potential underlying chronic kidney disease can help to minimize the acquisition of multiple biopsy cores. Lastly, nephrology fellow training in the planning of kidney biopsies is important. Some leaders in the field have questioned whether competence in performing kidney biopsies should remain a requirement of nephrology fellowship programs, since reimbursement

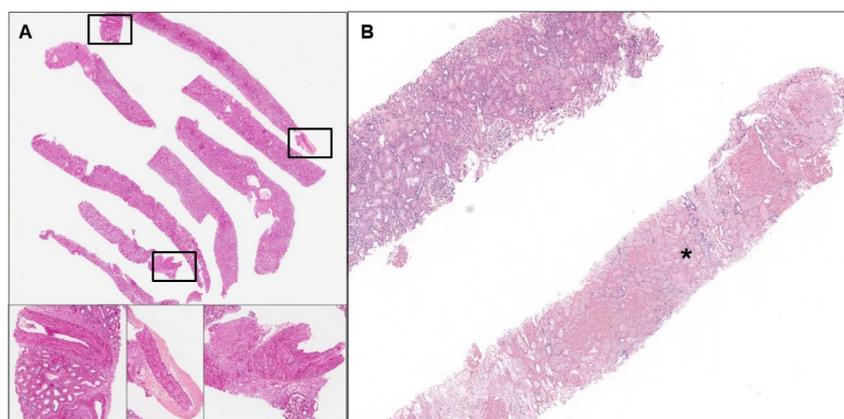


Figure 2. Evidence of vascular injury from kidney biopsy. (A) First kidney allograft biopsy with >5 passes included sampling of large arcuate to interlobar sized arteries. Inset boxes are magnifications of large arteries. (B) Follow up biopsy ~2 weeks later with 40% cortical infarction (*infarcted tissue core).

Box 1. Recommended safety practices for kidney biopsy

Criteria

1. Evaluate indication for kidney biopsy and discuss benefits and harms with the patient.
2. Imaging confirmation of non-atrophic kidneys with adequate cortex.
3. Systolic blood pressure < 140 mm Hg (for transplant biopsy < 150 mm Hg).

Contraindications

1. Kidney infection.
2. Altered mental status impairing patient's ability to cooperate for a safe biopsy.
3. Solitary kidney may be a relative contraindication for native kidney biopsy.

Medications

1. If blood urea nitrogen >50 mg/dL: consider desmopressin 0.3 mcg/kg IV to be given over 10 minutes within 1 hour prior to biopsy.
2. Hold diuretics and insulin on the morning of the biopsy.
3. Take all blood pressure medications the day of the procedure
4. Anticoagulation and antiplatelet agents – see Table 1.

Labs

1. Labs including hemoglobin, platelet count, coagulation panel and basic metabolic panel should be performed within 3-5 days of the biopsy.^a
2. If platelet count <100 × 10⁹/L, consider platelets transfusion pre-biopsy.
3. If hemoglobin <10 g/dL consider packed red blood cells transfusion pre-biopsy.
4. Consider anti-factor Xa level or platelet function test if indicated, see Table 1.
5. For native kidney biopsy: consider type & screen on the

procedure day, prior to biopsy, to minimize delays in blood transfusion if significant bleeding occurs.

During biopsy

1. If patient has significant anticipatory anxiety which may contribute to hypertension, consider giving a one-time dose of the short-acting oral benzodiazepine alprazolam 1 mg at 1-2 hours before the kidney biopsy (does not interfere with moderate sedation).
2. Use ultrasound or computed tomography guidance. If ultrasound is used, utilize Doppler to visualize and avoid areas of higher vascular blood-flow.
3. Use spring loaded automated biopsy device, 16-gauge or 18-gauge needle preferred. Do not use 14-gauge needles.
4. Limit to a maximum of 5 passes (typically 2-3 cores are taken).
5. Physician or pathology technician reviews each core with a dissecting microscope and the procedure is stopped as soon as adequate glomeruli are obtained.

Post-biopsy monitoring

1. Strict bedrest for 4-6 hours after biopsy.
2. Recheck hemoglobin and ultrasound of biopsy site approximately 4 hours after biopsy to ensure stability.
3. High-risk patients, including those with bleeding diatheses or were on anticoagulation, should be hospitalized for observation with a follow up hemoglobin and biopsy site ultrasound next morning.
4. No heavy lifting or vigorous exercise for 1-2 weeks after the biopsy.

^a Bleeding time can be considered; utility in kidney biopsy planning is debated (10).

and time constraints have largely shifted this procedure to interventional radiologists (19). At minimum, fellows need to be engaged in the peri-procedural management and be required to observe kidney biopsies during their training, to fully appreciate the indications, contraindications and potential complications. This training experience is imperative to develop clinical judgment when deciding if there is an acceptable risk/benefit ratio to proceed with a kidney biopsy.

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Authors' contribution

LN and WLL were responsible for the concept and design, and drafted the original manuscript. SS and JEZ generated the original figures for the manuscript. JLT and

LL revisited the manuscript and critically evaluated the intellectual contents. All authors participated in preparing the final draft of the manuscript, revised the manuscript and critically evaluated the intellectual contents. All authors have read and approved the content of the manuscript and confirmed the accuracy or integrity of any part of the work.

Conflicts of interest

WL Lau has received honoraria and/or support from American Heart Association, Fresenius, Hub Therapeutics, Roche, Sanofi, and ZS Pharma. JE Zuckerman is a paid consultant for Leica Biosystems. The other authors declare no conflict of interest.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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