

DIRECT RENIN INHIBITOR (DRI) EFFECT ON GFR AND USE IN RENAL ARTERY STENOSIS SCREENING

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Abstract

Objective: A new method using a nuclear camera and a direct renin inhibitor (DRI) to screen for renal artery stenosis (RAS) in hypertensive patients and to measure the otherwise generally DRI increased glomerular filtration rate (GFR).

Methods: Same-day basal and 1 hr post 150-300 mg oral Aliskiren (Tekturna) renography used 10-25 mCi Tc-99m-DTPA intravenous for split GFR with a nonlinear relation of renal activity to GFR corrected for body surface area. Camera sensitivity was corrected using an attenuation coefficient 0.12/cm, with lateral views for simple measure of renal depth.

Results: In 9 of 11 patients Tekturna increased GFR by 10% to 60% ($p < 0.05$). Both patients with either split GFR increased insignificantly by Tekturna had RAS at renal angiography and in one, BP stabilized after renal angioplasty. The only Tekturna side effect was increased BP to 208/104 for < 2 hrs in one RAS case. Decreased GFR expected in affected kidneys from a Goldblatt mechanism may occur with Tekturna; however, we also found RAS when GFR did not significantly increase as it does in normal kidneys, with or without concurrent renin angiotensin aldosterone system (RAAS) inhibition. Inaccurate results typical of captopril renography with concurrent RAAS inhibitor therapy are avoided with Tekturna renography, which has been accurate in clinical follow-up, not only with concurrent angiotensin converting enzyme inhibitors or angiotensin receptor blockers, but also with thiazides and alpha or beta or calcium blockers.

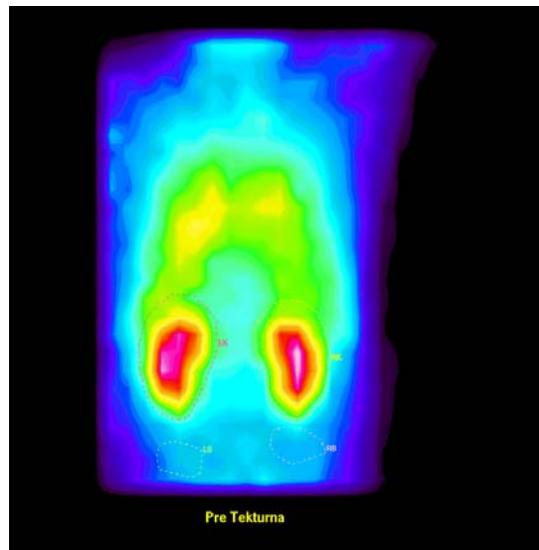
Discussion: Initial studies of DRI show potential for renal protection; however, the potential of captopril renography never materialized, not only due to technical aspects of earlier GFR calculations, but also because of severe and sometimes fatal side effects, especially in patients with RAS. All RAAS inhibitors are contraindicated in pregnancy and may cause hyperkalemia, particularly in diabetics and with combined RAAS inhibitor use. Nonetheless, if the present study results including straight-

forward, reproducible measure of split GFR, as well as only minor side effects are confirmed in further studies, then DRI renography may be widely used in the future.

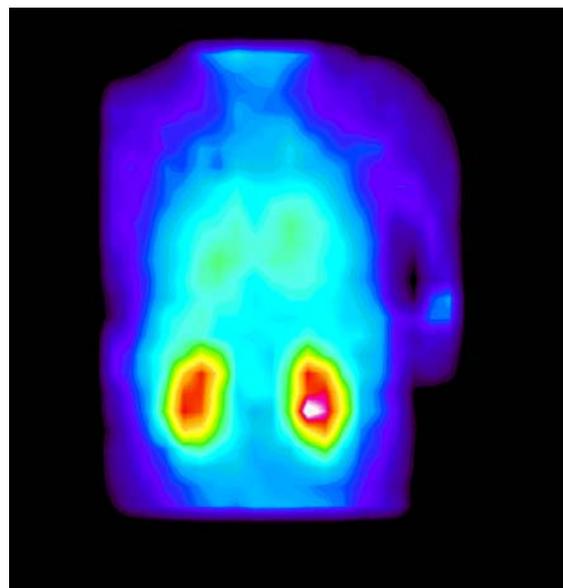
Conclusion: Tekturna, the first widely available DRI, shows promise for nuclear camera based measure of split GFR in a same-day basal and stimulated study, not only for its potential therapeutic increase in GFR; but moreover, in diagnostic screening for the increasing number of patients with RAS.

1

38 year-old type 1 diabetic for 25 years with stage 1 hypertension incompletely controlled on lisinopril (ACE inhibitor) has normal basal GFR of 89 ml/min with symmetrical renal function as shown here using 7.2 mCi Tc-99m-DTPA and a high sensitivity matrix of 32 x 32, which still provides good resolution for GFR analysis. The method is a modification of Li's nonlinear algorithm using the 2 to 3 minute renal activity after bolus injection of the DTPA and depends on measured gamma camera sensitivity and measured renal depths.

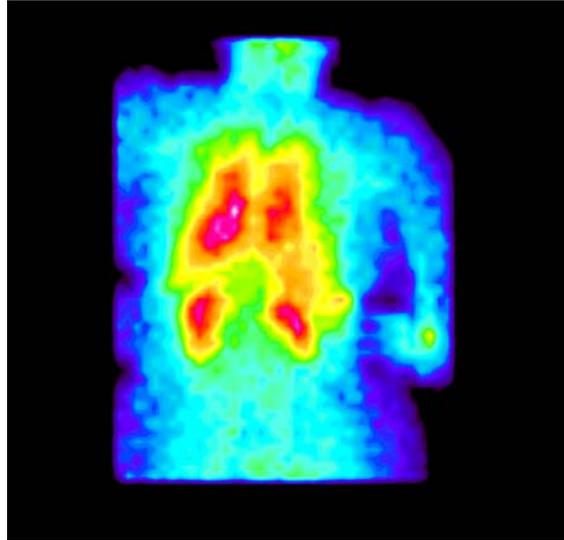


Same hypertensive type 1 diabetic as above, the 2 to 3 minute image post 300 mg Tekturna shown here to demonstrate requirement for subtraction of the right renal pelvis activity, remaining as background from the prior study owing to minor UPJ obstruction. Background is subtracted with a 1 minute image acquired just prior to the study and checked with the dynamic flow images at the beginning of the study. Post Tekturna GFR here was 109 ml/min, a symmetrical (22+-2)% increase over baseline, a normal response more typical of DRI than ACEi.



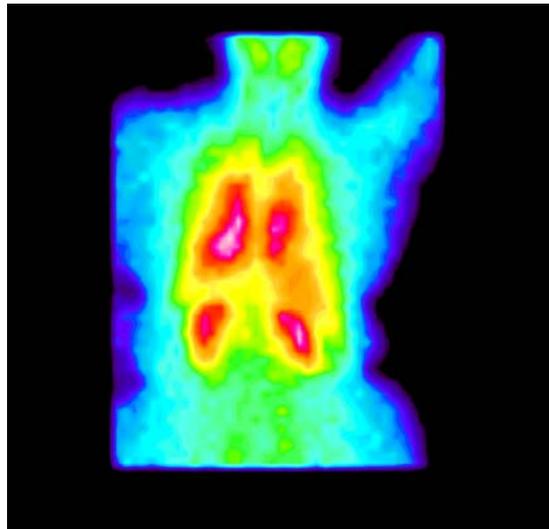
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71 year-old type 2 diabetic woman with BP controlled on Avalide with basal GFR 19.8 ml/min based on 2 to 3 minute image shown here, this value found reproducible within 3% on different days as the patient study was repeated in order to demonstrate response to 600 mg Tekturna after usual dose of 300 mg caused no significant change in GFR, as expected from Avapro (irbesartan) effect in doubling Tekturna metabolism. Note good visualization of the cardiac blood pool in this patient with a low GFR.



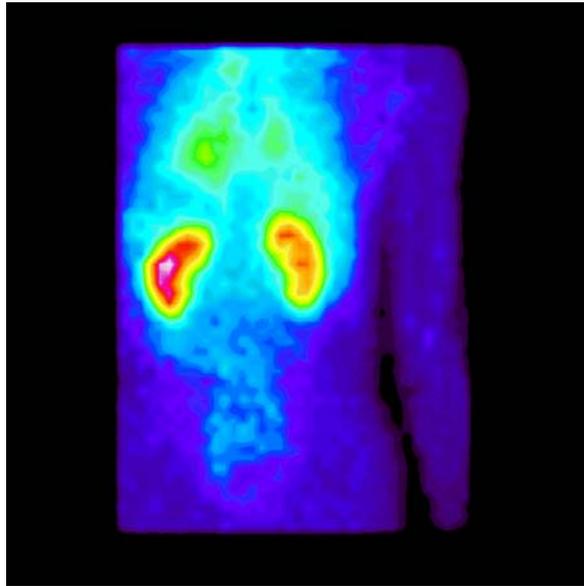
Same 71 year-old type 2 diabetic woman with 2 to 3 minute image obtained one hour post 600 mg Tekturna oral, showing symmetrical increase in GFR to 28.5 ml/min, a 44% increase over the basal GFR shown above.

Absence of functional renal artery stenosis despite the relatively low GFR indicates that this patient is a good candidate for continued RAAS inhibitor therapy, including combined therapy with Tekturna, the only RAAS inhibitor routinely associated with increased renal blood flow.

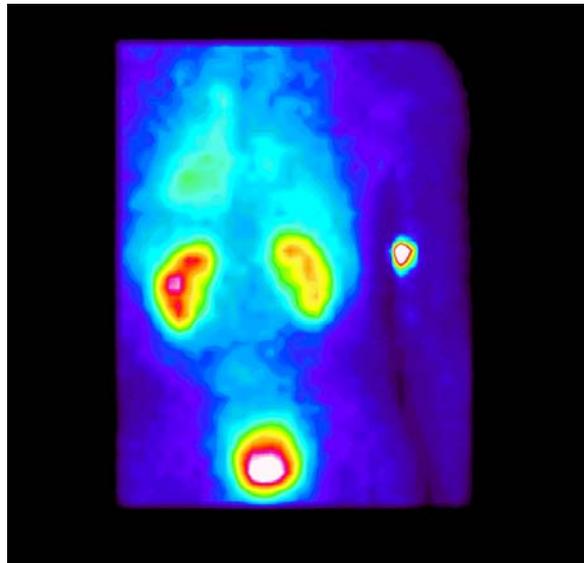


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A 42 year-old African American, type 1 diabetic has the basal 2 to 3 minute renal scan shown here, with GFR 78.1 ml/min and split function 46.1% right and 53.9% left and BP 130/82 on Tarka 4/240 mg(Mavac/Verapamil ACEi/Calcium blocker) and Losartan 50 mg (ARB). Shows minor asymmetry in split renal function with reasonable but perhaps suboptimal hypertension control raising question of whether triple therapy (ACEi, ARB, DRI) might be appropriate in a typically low renin population.

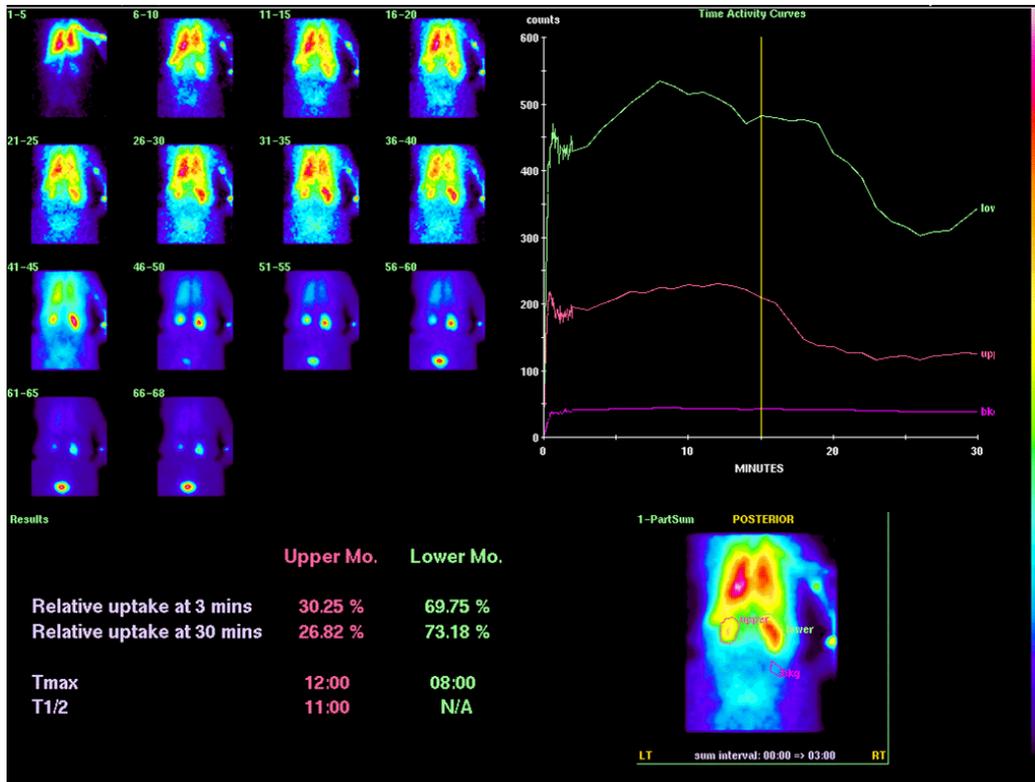


The post 300 mg Tekturna 2 to 3 minute renogram shown here required correction for the minor infiltrate shown in the right arm and renormalization to peak renal uptake since the bladder is in the field of view. Total GFR increased to 86.8 ml/min, an 11.1% increase, with split function 43.4% for the right and 56.6% for the left kidney, the split function not significantly changed from 46.1% right and 53.9% left above. Absence of functional renal artery stenosis was considered suitable for triple RAAS inhibitor therapy trial.

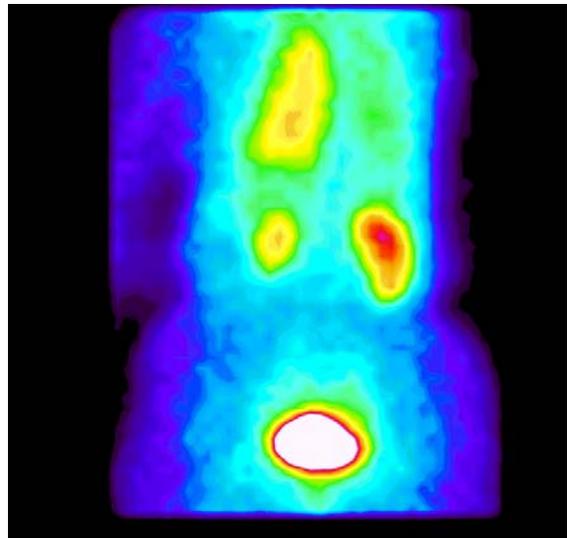
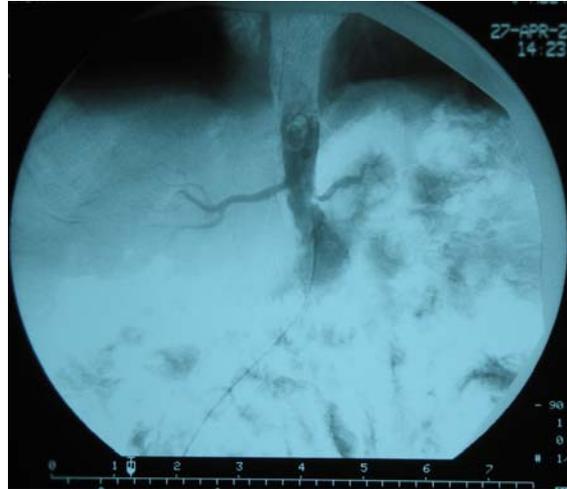


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82 year-old diabetic woman with resis-tant hypertension showing abnormal split renal function, significantly decreased on the left. Patient developed hypertension exacerbation, basal BP 160/90 rose to 210/110 post Tekturna 150 mg and expected increase in calculated GFR was not seen on the left. BP returned to 150/86 within 2 hours observation. Although MRA was false negative, arterial angiography showed left renal artery stenosis. BP control was improved post renal angioplasty.



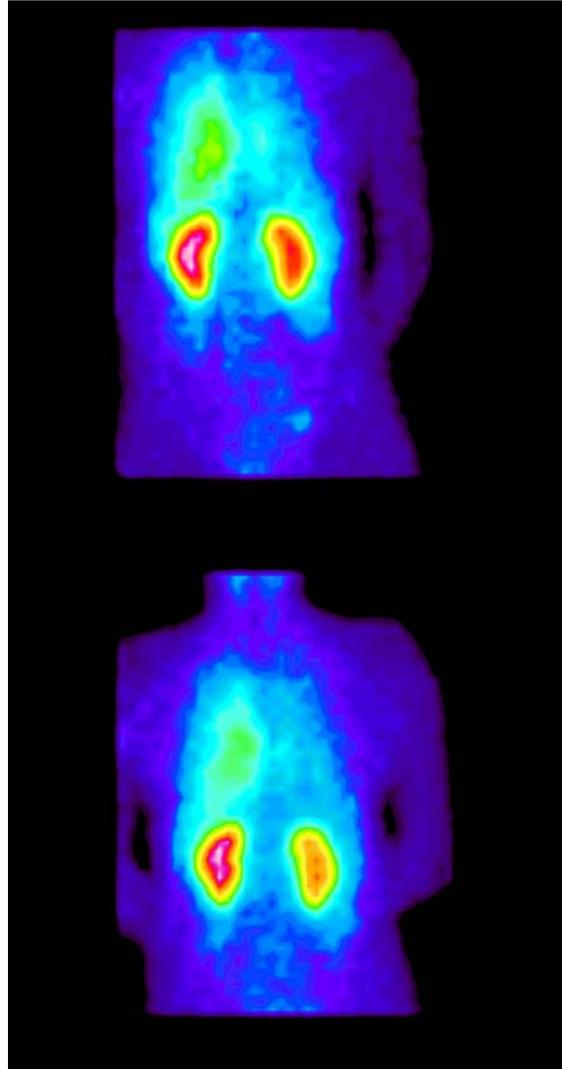
Renal angiography confirms left renal artery stenosis in the 82 year-old diabetic woman whose post Tekturna 2 to 3 minute image is shown just to the right of the angiogram. Minor positioning differences affect calculated split renal function; however, this is corrected by measuring renal depth with surface markers behind either kidney in lateral images and ratios of left to right lung activity. This patient's more intense left lung activity is greater than that due to cardiac activity (typically only about 7% at 2 to 3 min) and indicates minor rotation; however, this would tend to falsely increase left renal activity. Hence, the abnormal split renal function shown is clearly not due to positioning artifact. Tekturna renogram 2 to 3 min image shows abnormal split renal function corresponding to left renal artery stenosis.



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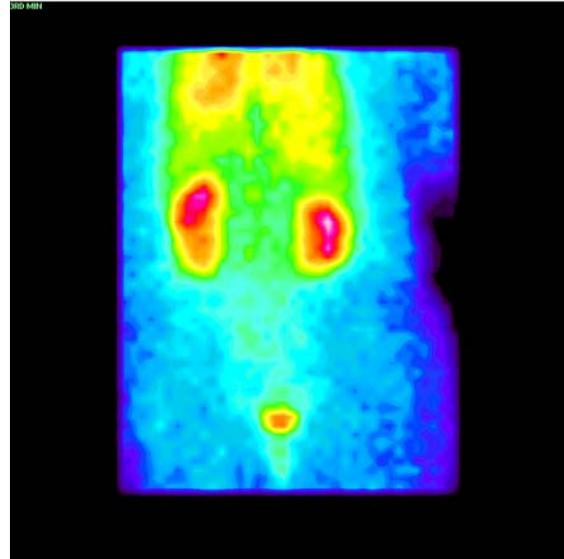
Example of equivocal Tekturna renography in a 38 year-old attorney with adrenal insufficiency who developed hypertension after several years of glucocorticoid and mineralocorticoid replacement. The probable low-renin state induced by mineralocorticoid replacement (florinef 0.1 mg po bid) may render equivocal such minor differences as shown here: basal 2 to 3 minute image has borderline GFR 59 ml/min and split renal function 43.9% for the right and 56.1% for the left kidney.

Same 38 year-old adrenal insufficient attorney as above, with post 300 mg Tekturna renogram 2 to 3 minute image here showing normal response, GFR increasing to 79.2 ml/min, a 19.5% increase. Split renal function 41.7% for the right and 58.3% for the left remains equivocal, although the increase is essentially symmetrical. The patient was considered appropriate for RAAS therapy with Tekturna as the post Tekturna renal function was significantly better. She also received beta blockers and improved migraine.

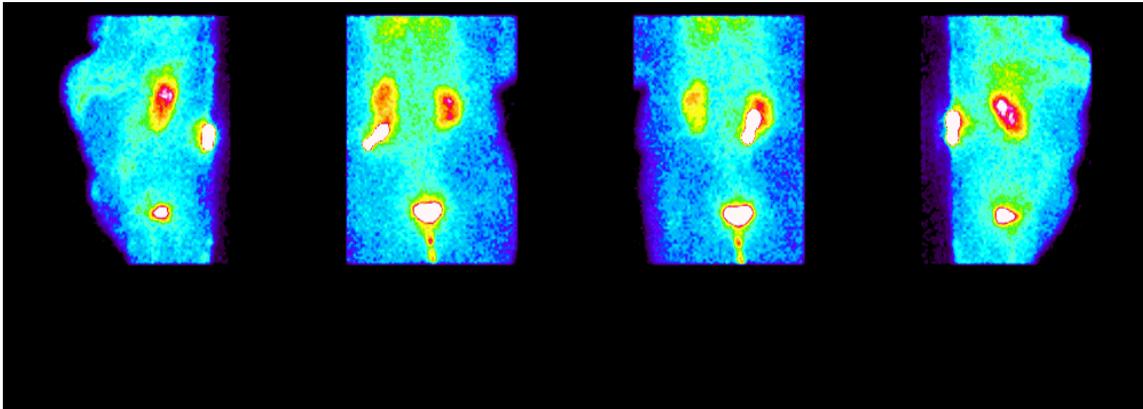


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A 61 year-old type 2 diabetic woman has the basal 2 to 3 minute renogram image shown with total GFR 65.0 ml/min and split function 51.3% on the right and 48.9% on the left. After 300 mg Tekturna GFR was 88.1 ml/min, a 35% increase, without significant change in split function: 53.4% right and 46.6% left. Although unproven as yet for this patient, the scan suggests stenosis of a second inferior renal artery on the left, which we have seen in others. Compare to lateral views below which show more tilt of the right than left kidney.



Lateral views of the 61 year-old type 2 diabetic woman whose basal 2 to 3 minute renogram is shown above. Note that the left lateral, shown on the left has only minor tilting, not likely sufficient to account for the decreased function noted inferiorly in the left kidney above. Moreover, post Tekturna there was exacerbation of the abnormality, the right kidney and total GFR increased while the left kidney and inferior left showed relative decreases. MRA is pending and if positive for a second inferior stenosed renal artery on the left, may warrant angiography.



Summary

The new method described, Tekturna renography, uses a nuclear camera and a direct renin inhibitor (DRI) to screen for renal artery stenosis (RAS) in hypertensive patients. The response to Tekturna renography, generally a bilateral increase in calculated GFR, predicts positive patient response to renin-angiotensin-aldosterone system (RAAS) inhibition. Patients with no response to Tekturna either have a very low renin state, eg. hyperaldosteronism, or functional bilateral RAS and not only may not have favorable therapeutic responses but may also have significant adverse side effects with RAAS inhibitor therapy. Patients with asymmetrical split renal response to Tekturna have unilateral functional RAS which also may be exacerbated by RAAS inhibition. In this series of patients in an endocrinology referral practice up to 26% (16 of 61) of patients had abnormal Tekturna renography and were felt inappropriate for added RAAS inhibitor therapy which would have otherwise been indicated in at least the 44% (6/16) of these patients who were diabetic.

Specific details of the Tekturna renography method contributing to accurate and reproducible results include proper bolus injections, calibrated gamma camera-based renal depth measurements, and attention to proper background corrections for same day studies in a physiologic state as similar as practicable. We have considered a dual acquisition study with eg. Tc-99m-glucoheptonate as baseline and I-131 iodohippuran as the stimulated study. However, using an identical tracer, Tc-99m-DTPA for basal and post Tekturna studies avoids assumptions about dissimilarities in renal response to different tracers and is cost effective and reproducible to within 2% even including day to day biological variation and interobserver technical measurement errors. Concurrent antihypertensives including other RAAS inhibitors (ACEi or ARB), calcium channel blockers, diuretics or alpha blockers do not generally interfere with Tekturna renography; however, aspirin, other nonsteroidal anti-inflammatory drugs, irbesartan (Avapro) or prior Tekturna therapy may reduce the response to Tekturna. Remarkably, cigarette smoking has little acute effect.

Conclusion: Tekturna, the first widely available DRI, used with a nuclear camera to measure split GFR in a same-day basal and stimulated study, shows promise in diagnostic screening for the increasing number of patients with RAS. Moreover, Tekturna renography categorizes patients for optimal hypertension therapy and Tekturna has renoprotective potential due to its GFR preservation.