

**Review of the Tuberous Sclerosis renal guidelines from the 2012 Consensus conference, current data and future study**

**Ahead of the Curve: Time to Update Renal Guidelines for Tuberous Sclerosis**

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## Abstract

Renal-related disease is the most common cause of tuberous sclerosis complex (TSC)-related death in adults, and renal angiomyolipomas can lead to complications that include chronic kidney disease (CKD) and hemorrhage. International TSC guidelines recommend mammalian target of rapamycin (mTOR) inhibitors as first-line therapy for management of asymptomatic, growing angiomyolipomas >3 cm in diameter. This review discusses data regarding patient outcomes that were used to develop current guidelines for embolization of renal angiomyolipomas and presents recent data on 2 available mTOR inhibitors—sirolimus and everolimus—in the treatment of angiomyolipoma. TSC-associated renal angiomyolipomas can recur after embolization. Both sirolimus and everolimus have shown effectiveness in reduction of angiomyolipoma volume, with an acceptable safety profile that includes preservation of renal function with long-term therapy. The authors propose a hypothesis for mTORC1 haploinsufficiency as an additional mechanism for CKD and propose that preventive therapy with mTOR inhibitors might have a role in reducing the number of angiomyolipoma-related deaths. Because mTOR inhibitors target the underlying pathophysiology of TSC, patients might benefit from treatment of multiple manifestations with 1 systemic therapy. Based on recent evidence, new guidelines should be considered which support earlier initiation of mTOR inhibitor therapy for the management of renal angiomyolipomas to prevent future serious complications, rather than try to rescue them after the complications have occurred.

## Overview of Renal Disease in Tuberous Sclerosis Complex

Guidelines relevant for TSC-related angiomyolipoma, including updated diagnostic criteria and surveillance and management recommendations, were developed from the second International TSC Consensus Conference in Washington, DC [1,2], in which 79 experts from 14 countries participated. Table 1 summarizes the surveillance and management recommendations relevant to the kidney. The nephrology subcommittee recommended the use of mammalian target of rapamycin (mTOR) inhibitors for first-line therapy for management of asymptomatic, growing angiomyolipomas >3 cm in diameter [1,2]. These guidelines were based on a search of PubMed and Scopus databases performed on March 12, 2012, for the consensus guidelines [2] and of the OVID database from 2000 to 2014. This review is based on those and subsequent relevant published papers.

The renal presentation of tuberous sclerosis complex (TSC) most often encompasses renal cysts, angiomyolipoma, impaired kidney function and, more rarely, renal cell carcinoma (RCC) [3,4]. Cysts occur in approximately 30-45% of patients with TSC and may be associated with kidney failure and hypertension [4]. The *TSC2* and *PKD1* contiguous gene deletion syndrome affects approximately 1 in 20 patients with TSC. People with this syndrome have deletions involving both the *TSC2* and the *PKD1* genes [5]; in these patients, cystic disease is severe and commonly associated with early renal failure. Angiomyolipomas are benign tumors composed of blood vessels, smooth muscle cells, and adipose tissue [1]. They are rarely reported extra-renally but occur in the kidneys in up to 80% of patients with TSC and contribute to renal disease as the most common cause of TSC-related death ([Kingswood JC et al. The natural history of renal angiomyolipomata in tuberous sclerosis complex. Presented at the 49th ERA-EDTA Congress; 24–27 May 2012; Paris, France; unpublished data](#)) [5]. A strong association between age, angiomyolipoma size, and chronic kidney disease (CKD) has been reported; patients with higher CKD stage tend to be older and have more advanced angiomyolipoma [6]. CKD may develop as a

result of loss of renal parenchyma because of growth of angiomyolipoma or cysts, or as a complication from surgery or embolization [3,6]. Fat-poor angiomyolipomas (i.e. the epithelioid variant) are commonly observed in patients with TSC, whereas, in the general population, they account for <0.1% of angiomyolipomas [1,4]. RCCs (occurring in 2–3% of patients with TSC) [4] may be confused diagnostically with fat-poor angiomyolipomas [7,8]. Contrast enhanced magnetic resonance imaging (MRI) or computed tomography (CT) may help in making this differentiation but it remains challenging even in high volume centers. Biopsy might nevertheless be needed. A slower growth rate has been postulated as another way to distinguish fat-poor angiomyolipoma from RCC [8].

A retrospective analysis assessed the risk of long-term renal outcomes, including CKD, by evaluating records from patients diagnosed with TSC who were included in the UK Clinical Practice Research Datalink (CPRD) linked to the Hospital Episode Statistics database ([Kingswood JC et al. Real-world assessment of renal involvement in tuberous sclerosis complex \(TSC\) patients in the United Kingdom \(UK\); Presented at the European Association of Urology; 11–15 April 2014; Stockholm, Sweden; unpublished data](#)). [9] Overall, 105 of 341 total TSC patients (31%) had renal involvement (defined as presence of renal cysts, polycystic kidney disease, CKD, kidney stones, or kidney neoplasms such as angiomyolipomas). Among adult patients, 38% (91 of 237 patients) had recognized renal involvement or renal-related comorbidity (CKD, 35%; single cyst, 16%; hematuria, 21%; anemia, 21%). The prevalence of CKD (stage 3–5) in the TSC population up to age 64 years was greater in every age group compared with the UK general population. The crude prevalence estimates showed that TSC patients developed stage 3+ CKD 30 years earlier than the general UK population, and rates of stage 3+ CKD were more than 5 times higher than in the general UK population (relative risk = 5.4, 95% CI: 3.7–8.0;  $p < 0.001$ ) ([Kingswood JC et al. Real-world assessment of renal involvement in tuberous sclerosis complex \(TSC\)](#)

[patients in the United Kingdom \(UK\); Presented at the European Association of Urology; 11–15 April 2014; Stockholm, Sweden; unpublished data](#)]{9}.

Patients with TSC-associated angiomyolipoma have an increased risk for hemorrhage, with risk factors considered to be angiomyolipoma size (>3 cm or >4 cm), aneurysm size >0.5 cm, and serial growth [3] ([Kingswood JC et al. The natural history of renal angiomyolipomata in tuberous sclerosis complex. Presented at the 49th ERA-EDTA Congress; 24–27 May 2012; Paris, France; unpublished data](#)){4,5}.

Although small angiomyolipomas are usually asymptomatic, angiomyolipomas  $\geq 4$  cm become symptomatic in 68–80% of patients, with 50–60% presenting as hemorrhage [9].

Renal complications associated with TSC were also assessed in retrospective analyses of natural history data collected from 2 large databases ([reported by Kingswood JC et al. The natural history of renal angiomyolipomata in tuberous sclerosis complex. Presented at the 49th ERA-EDTA Congress; 24–27 May 2012; Paris, France; unpublished data](#)){5}. The first analysis evaluated retrospective data collected by questionnaires from 296 patients with TSC in the UK Renal Registry. Twenty-seven of 52 patients (52%) with serial measurements of angiomyolipoma lesions captured over 5 years showed growth. Serial growth was found to be a risk factor for bleeding (21% of patients with growing angiomyolipomas experienced renal bleeding, compared with only 4% of patients with stable angiomyolipomas;  $X^2 = 7.42$ ;  $p < 0.01$ ). The second analysis evaluated data from 278 patients with TSC who were followed up at the St. George's Hospital Clinic (London, UK), of whom 130 had renal angiomyolipoma. Data were analyzed from 53 adults with TSC and renal angiomyolipoma for whom serial imaging data were available. Sixty-seven percent of the angiomyolipomas exhibited serial growth in these adults, with a mean rate of growth of 5.5 mm/year. The growth rate of the angiomyolipomas was not correlated with size of lesion

or age of patient, although growth rate tended to be greater in younger patients ([Kingswood JC et al. The natural history of renal angiomyolipomata in tuberous sclerosis complex. Presented at the 49th ERA-EDTA Congress; 24–27 May 2012; Paris, France; unpublished data](#)) [5].

### **Outcome of Intervention**

~~Based on a search of PubMed and Scopus databases performed on March 12, 2012, for the consensus guidelines [11] and of the OVID database from 2000 to 201~~From our review<sup>4</sup>, we identified 16 case series that reported embolization of renal angiomyolipoma with sufficient data to characterize patient details and outcomes (supplemental table 1). Thereby, we found that after embolization, approximately 25% of TSC-associated renal angiomyolipoma recur.

The incidence of CKD was assessed in a retrospective chart review of a TSC cohort treated in a single center in the Netherlands [10]. The mean duration of follow-up was 15.8 years, and the median age at the end of follow-up was 40 years. Of 351 patients with TSC, 244 (69.5%) had confirmed renal angiomyolipoma. Patients were assigned a renal angiomyolipoma stage (from none detected to 6) based on the number of angiomyolipomas in both kidneys, size of angiomyolipoma, and kidney anatomy (Table 2). Fifty-nine percent of patients (144 of 244) with a confirmed renal angiomyolipoma reached a highest angiomyolipoma stage  $\geq 3$ , which indicated that the patient was at a high risk for hemorrhage and was a candidate for elective embolization. Hypertension, anemia, impaired kidney function, and need for blood transfusions increased with angiomyolipoma stage. Patients in higher stages were more likely to require more embolization. Yearly embolization rates ranged from 0.08 to 0.14 depending on angiomyolipoma stage, suggesting that patients with large, growing asymptomatic angiomyolipomas will

require an embolization every 7–11 years. Additionally, impaired kidney function was more common in patients who had undergone embolization (29%) than in those who had not (10%) [10].

#### Effectiveness/Risk of mTOR Inhibitors

mTOR inhibitors represent the first systemic approach to treating the underlying pathophysiology of TSC disease by blocking the activation of mTOR complex 1 and downstream signaling (fig. 1) [4][2]. Two oral mTOR inhibitors—sirolimus and everolimus—have been evaluated for management of angiomyolipoma (supplemental table 2). Four small, open-label studies showed the effectiveness of sirolimus in management of renal angiomyolipoma [11-14].

The data for effects of everolimus on angiomyolipoma are more robust; results from 2 large randomized, double-blind, placebo-controlled, phase 3 trials are available [15,16]. In a subgroup analysis of patients in the EXIST-1 trial, after a median follow-up duration of 9.7 months, angiomyolipoma response rate (an exploratory end point) was 53.3% for everolimus compared with 0% for placebo. Angiomyolipoma volume reductions with everolimus were sustained over 48 weeks of treatment (fig. 21) [17][19]. In EXIST-2, the primary end point of angiomyolipoma response was achieved in 42% of patients (33 of 79) compared with 0% for placebo (0 of 39,  $p < 0.0001$ ) after a median everolimus exposure of 8.7 months, and the median time to reach an angiomyolipoma response was 2.9 months [15]. Data from an open-label extension of the EXIST-2 study showed sustained reduction in angiomyolipoma volume to at least 192 weeks of treatment (fig. 32), with an angiomyolipoma response rate of 56.3% (63 of 112 patients) over a median 39.8 months of everolimus exposure. Among the 63 patients achieving angiomyolipoma response at any time, only 2 progressions were observed. Long-term

data show continued shrinkage of angiomyolipoma with everolimus therapy. Notably, at this cutoff, no bleeding was observed with everolimus in a population with high risk for bleeding events before initiation of mTOR inhibitor therapy ([Bissler JJ et al. Everolimus for renal angiomyolipoma associated with tuberous sclerosis complex \(TSC\) from EXIST-2: continued efficacy and diminishing adverse events after ~3.5 years of treatment. Presented at the 30th Annual European Association of Urology Congress; 20–24 March 2015; Madrid, Spain; unpublished data](#)).<sup>[20]</sup>

### Safety of mTOR Inhibitors

Class effects of mTOR inhibitors include stomatitis/mucositis/mouth ulceration (~50%), hypercholesterolemia (20–40%), hypertriglyceridemia (12–50%), infections (40–70%), hypophosphatemia (11%), amenorrhea (13–38%), hematologic abnormalities (leukopenia, neutropenia, 10–40%), and proteinuria (4–30%) [11-16]. The EXIST-2 extension data show a decrease in the number of newly emergent adverse effects over time [18]<sup>[20,21]</sup>. In addition, data from the 3.5-year analysis of EXIST-2 reported that severe renal impairment (glomerular filtration rate [GFR] <30 ml/min/1.73 m<sup>2</sup>) was observed in only 7.1% of patients, all of whom had compromised renal function prior to everolimus initiation. Furthermore, overall, GFR remained stable over time; median GFR at baseline was 85 mL/min/1.73 m<sup>2</sup>, and median GFR at Week 120 was 84 mL/min/1.73 m<sup>2</sup> ([Bissler JJ et al. Everolimus for renal angiomyolipoma associated with tuberous sclerosis complex \(TSC\) from EXIST-2: continued efficacy and diminishing adverse events after ~3.5 years of treatment. Presented at the 30th Annual European Association of Urology Congress; 20–24 March 2015; Madrid, Spain; unpublished data](#)).<sup>[20]</sup><sup>[20]</sup>. This might suggest preservation of renal function with everolimus treatment in patients who did not have pre-existing kidney impairment.

### Potential Mechanisms for Renal Complications

CKD may not be entirely attributable to angiomyolipoma hemorrhage and subsequent treatment (i.e. surgery/embolization). A mechanism independent of bleeding may occur where large, benign angiomyolipomas encroach on normal renal tissue and lead to CKD [4]. We propose 2 additional hypotheses for the development of CKD. The first postulates that normal replacement renal tissue becomes TSC tissue because of somatic second-hit mutations [19] occurring during rapid cell division (when the kidney still has growth and repair potential at age <35–40 years); this ~~w~~eould cause an accelerated loss of normal renal tissue leading to CKD. A second hypothesis is that *TSC1* or *TSC2* haploinsufficiency may lead to modest mTORC1 overactivity and, therefore, glomerular hypertrophy and hyperfiltration. It has been postulated that mTORC1 overactivity is a mechanism of CKD progression, especially in diabetic nephropathy [20] and may be 1 mechanism by which patients with TSC develop CKD in middle age. Data show that mTOR is activated in patients with diabetic nephropathy and that inhibition of mTOR signaling prevented glomerulosclerosis and ameliorated progression of glomerular disease in a mouse model [21]. In addition, either haploinsufficiency or second somatic mutation in the tubule cells could predispose to premature apoptosis or maldifferentiation, or might be associated with loss of function due to an undiscovered novel mechanism (e.g. microcystic renal disease) that may not be identified by imaging. ~~If this hypothesis is correct. Therefore, mTOR inhibition might help ameliorate loss of GFR independent of its effect on renal angiomyolipomas. TSC1/2 haploinsufficiency also may predispose patients with TSC to renal damage and premature CKD even in those without a severe angiomyolipoma burden.~~ However, it has also been postulated that mTOR inhibition may potentially worsen progression of CKD [20,21], and additional research in this area is necessary.

### Defining an Investigating a Possible New Treatment Paradigm

We propose ~~a clinical trial in which that~~ mTOR inhibitors ~~are~~ used as preventative therapy, not just as therapy. The use of mTOR inhibitors is nephron sparing, compared with embolization or surgery, and usually prevents further growth of angiomyolipoma [3]. Patients with TSC have a high *a priori* risk for severe renal disease, with approximately 40% progressing to CKD by age 45–54 years ([Kingswood JC et al. Real-world assessment of renal involvement in tuberous sclerosis complex \(TSC\) patients in the United Kingdom \(UK\); Presented at the European Association of Urology; 11–15 April 2014; Stockholm, Sweden; unpublished data](#)) [10][9]. Data from EXIST-1 and ~~EXIST-2~~ support the success of early treatment in preventing progression of renal disease. If haploinsufficiency of *TSC1/2* does cause hyperfiltration, ~~as proposed herein, then the risks of mTOR inhibitors may be counterbalanced by the increased benefit of downregulating mTOR overactivity in affected cells. However, there is no published evidence in humans yet to support any benefit beyond controlling angiomyolipomas. Furthermore, the current published evidence suggests that angiomyolipomas regrow if mTOR inhibitor therapy is discontinued [11,13], so that therapy may need to be lifelong. patients with TSC will be at risk for CKD even if they have no overt angiomyolipomas. This concern must be evaluated in trials and additional epidemiologic studies. The ongoing Tuberous Sclerosis Registry to Increase Disease Awareness (TOSCA) might enable studies to address this issue.~~

Preliminary evidence has shown that early treatment of renal angiomyolipomas in children prevents progression and preserves renal function [17]. To date, follow-up data have shown that risk for serious adverse events in this population is low and suggest that growth and physical development in treated children are normal, although long term issues such as potential effects on fertility necessitate further study [22].

Patients with TSC are at lifelong risk for appearance and progression of many of TSC-associated complications. With the availability of oral mTOR inhibitors, the underlying pathogenic dysregulation of mTORC1 signaling can be controlled, which might allow multiple clinical manifestations to be treated with a single targeted therapy. The potential benefits of preventative therapy in reducing ~~angiomyolipoma-related morbidities may~~ ~~the number of angiomyolipoma-related deaths may well~~ outweigh the risks of long-term therapy. Furthermore, because other complications of TSC also respond to mTOR inhibitor therapy, including subependymal giant cell astrocytomas (SEGAs) [16], ~~facial~~ ~~angiofibromas~~ ~~skin rash~~ [15,16], lymphangioleiomyomatosis (LAM) [23,24], and epilepsy [25], a holistic approach to preventive therapy might be appropriate to avoid many serious manifestations of the condition.

## Conclusions

Based on recent evidence, ~~the 2012 international~~ ~~new~~ guidelines for the management of angiomyolipomas should be ~~updated to include the use~~ ~~considered for earlier initiation~~ of mTOR inhibitor therapy ~~as first choice for pre-emptive treatment of growing angiomyolipomas >3 cm in diameter. In addition, we propose a new study to determine the efficacy and risks of initiating preventative treatment in younger patients with a high angiomyolipoma burden (e.g. >5) before they grow larger than 3 cm. to prevent future serious complications. Whether this guidance should be based on the diagnosis of TSC (given the high a priori risk) or when renal angiomyolipoma burden first becomes more severe (e.g. >5 angiomyolipomas of any size) has yet to be determined.~~

## Disclosures [TBA]

~~Klemens Budde, J. Chris Kingswood, Julian Sampson, Bernard A. Zonnenberg, Matthias Sauter, and John J. Bissler have received honoraria and/or research grants or served as consultants for Novartis. Klemens~~

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Budde has also served as consultant for Bristol-Myers Squibb, Effimune, Hexal, Pfizer, and Veloxis, and has received research grants for clinical studies, speaker fees, honoraria, travel expenses and payment for development of educational presentations from Astellas, Aicuris, BmT GmbH, Bristol-Myers Squibb, Chiesi, Fresenius, Hexal, Otsuka, Pfizer, Roche, Siemens and Veloxis. John Hulbert serves on the speakers' bureau for Novartis Corporation, for which he may receive remuneration, and is a member of the National Scientific Advisory Board of the Tuberous Sclerosis Alliance, for which he receives no compensation. Julian Sampson serves on the Tuberous Sclerosis Alliance International Scientific Advisory Board (non-remunerated). Lisa Guay-Woodford has served as a consultant for Otsuka and is a member of the Board of Trustees for the Polycystic Kidney Disease Foundation, for which she receives no compensation. Uday Patel has received travel expenses from Novartis to speak at a conference on a Tuberose Sclerosis. Jane Cox has received honoraria (paid to a renal charity) for serving on an advisory board for Novartis, and is a former employee of the Tuberous Sclerosis Association.

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**Table 1.** Kidney-related surveillance and management recommendations of the International Tuberous Sclerosis Complex Consensus Group [2]

Surveillance of kidneys	
Newly diagnosed or suspected TSC	Diagnosed with definite or possible TSC
<ul style="list-style-type: none"> <li>Obtain MRI of the abdomen to assess for the presence of angiomyolipoma and renal cysts</li> <li>Screen for hypertension by obtaining accurate BP</li> <li>Evaluate renal function by determining GFR</li> </ul>	<ul style="list-style-type: none"> <li>Obtain abdominal MRI of the abdomen to assess angiomyolipoma progression and renal cystic disease (every 1–3 years for life)</li> <li>Assess renal function (GFR and BP) at least annually</li> </ul>

Management recommendations for renal angiomyolipoma	
Clinical presentation	Recommendation
<ul style="list-style-type: none"> <li>• Angiomyolipoma with acute hemorrhage</li> </ul>	<ul style="list-style-type: none"> <li>• Embolization (followed by corticosteroids for 7 days to mitigate post-embolization syndrome) [26]. Embolization should be as selective as technically feasible to preserve renal parenchyma</li> <li>• Avoid nephrectomy</li> </ul>
<ul style="list-style-type: none"> <li>• Asymptomatic, growing angiomyolipoma &gt;3 cm in diameter</li> </ul>	<ul style="list-style-type: none"> <li>• First-line: mTOR inhibitor</li> <li>• Second-line: selective embolization or kidney-sparing resection</li> </ul>

BP = blood pressure; GFR = glomerular filtration rate.

**Table 2.** Renal angiomyolipoma staging criteria proposed in a retrospective study.

Stage	Angiomyolipoma number	Angiomyolipoma size	Description of kidney anatomy
None detected <sup>a</sup>	None $\geq 1$ cm in longest diameter	-	Normal
1	$\leq 5$	$< 3.5$ cm	Normal
2	$> 5$	$< 3.5$ cm	Normal
3	$\leq 5$	At least 1 $\geq 3.5$ cm	Kidney intact
4	$> 5$	1 to 4 $\geq 3.5$ cm	Kidney intact
5	$> 5$	5 or more $\geq 3.5$ cm	Kidney recognizable
6	$> 5$	At least 1 $\geq 5.0$ cm	Kidney not recognizable

<sup>a</sup>Angiomyolipoma not detectable or lesions  $< 1$  cm unidentifiable as angiomyolipoma.

Reprinted with permission from Eijkemans et al. [12].

Figure Captions

**Fig. 1.** The mTOR pathway.

**Fig. 12.** Percentage change from baseline of sum of volumes (cm<sup>3</sup>) of target angiomyolipoma lesions by time window. Percentages were calculated relative to the number of patients evaluated at baseline and at the corresponding visit. Reproduced with permission from Kingswood et al. [17].

**Fig. 23.** Long-term efficacy of everolimus from EXIST-2: proportion of patients with ≥30% or ≥50% reduction in angiomyolipoma volume over time (Bissler JJ et al. Everolimus for renal angiomyolipoma associated with tuberous sclerosis complex (TSC) from EXIST-2: continued efficacy and diminishing adverse events after ~3.5 years of treatment. Presented at the 30th Annual European Association of Urology Congress; 20–24 March 2015; Madrid, Spain; unpublished data).