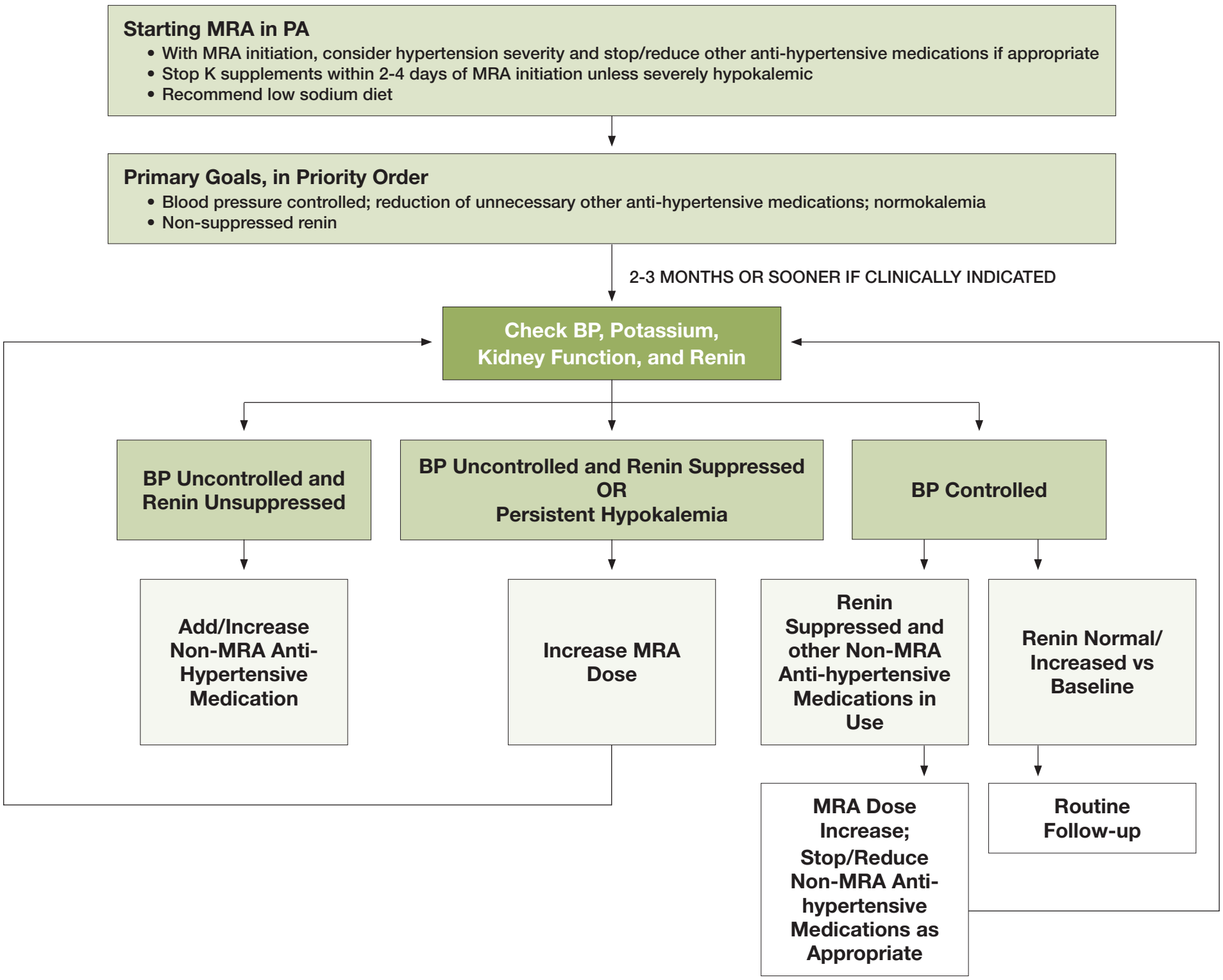
## Figure 3. Initiating and Following MRA Therapy.




This is a general guide and there is a wide range of inter-patient responsiveness to varying doses of MRA. The process of MRA initiation and titration is expected to be multi-step for many patients; each MRA adjustment is followed by an assessment of both blood pressure and biochemical response, then re-entering the treatment algorithm as appropriate. The primary goal of therapy is control of blood pressure. The secondary goal of therapy is achievement of normokalemia. Measurement of renin (as a marker of MR blockade) may assist in the process of MRA dose titration for achieving these goals, and possibly reducing other non-MRA anti-hypertensive drugs where possible.

1. Clinicians may start at a relatively low dose MRA (spironolactone 12.5-25 mg/d or eplerenone 25 mg daily or twice daily). The medically complex or frail patient, or those in whom MRA-drug interactions are possible may need careful monitoring (eg. ACE inhibitor or ARB together with and MRA). For patients with more severe PA, especially if profound hypokalemia is present, a higher initial dose could be considered (spironolactone 50 mg/d or eplerenone 50 mg twice daily).
2. All patients should get routine measurement of serum electrolytes, renal function and renin within 2-3 months of starting MRA therapy; more frequent serial measures may be needed in those with prior severe hypokalemia or renal impairment. Some panelists recommend enquiring about dietary sodium or measuring 24-hour urine sodium at baseline and periodically throughout follow up, as a means of tracking dietary salt restriction; a target of less than 100 mmol/d sodium is recommended representing 2.3 g sodium/d (McEvoy, McCarthy et al. 2024).
3. MRA dose changes to target BP control should occur at 8 to12-week intervals, or sooner if clinically indicated, and the full drug effect may take up to 3 months in more severe PA forms (Brown, Davies et al. 1972). Typical doses required to de-suppress renin are variable and likely higher than doses used as empiric add-on for resistant hypertension (Fourkiotis, Vonend et al. 2013; Saiki, Otsuki et al. 2022); most patients will achieve renin de-suppression with spironolactone doses (or spironolactone dose equivalents) between 50-100 mg/day. Spironolactone may be increased in 25-50 mg increments, and eplerenone in 25-100 mg increments. With each MRA dose change, repeat electrolytes, renal function and renin 2-3 months later is recommended. Where possible, off- titration of other anti-hypertensive medications may be possible.
4. Normalization of serum potassium usually occurs, even with lower dose MRA, in the first 3-5 days; it is reasonable to reduce or discontinue any potassium supplements at day 2-4 of MRA initiation in all but the most severe hypokalemic cases. Dietary salt restriction is a critical part of determining response to MRA therapy (Schneider, Sarkis et al. 2023); patients should be explicitly instructed and assisted with salt reduction strategies. Ongoing high salt diet is a very common reason for apparent non-response to MRA therapy.
5. GFR may decrease in PA patients upon introduction of PA-targeted therapy or with successive titration of MRA (Nakano, Murakami et al. 2023; Katsuragawa, Goto et al. 2023). The time course of change may be over days to weeks and in most cases, represents a marker of treatment efficacy as opposed to adverse effect. The natural history of an appropriate treatment-induced decrease in GFR is usually one of eventual long-term stability, anticipating a renal-sparing effect of effective MRA therapy (Nakano, Murakami et al. 2023; Katsuragawa, Goto et al. 2023). If there are progressive declines in renal function, consider referring to nephrology and consider discontinuing ACE inhibitors or ARBs.
6. Gynecomastia from spironolactone is dose-related and may appear as early as 1-2 months into therapy but more commonly after 6 or more months of treatment. In some cases (especially younger men) a dose reduction to 50 mg per day or less will allow for gynecomastia resolution. Some men may request a switch to a more selective MRA antagonist such as eplerenone or other new MRA classes. This almost always allows complete resolution of the gynecomastia if it has not already progressed to advanced size.