STUDY PROTOCOL

Self-Management to Achieve Reduction in proTeinuria in IgA Nephropathy (SMART-IgAN)

Version 2

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Good clinical practices statement

This clinical study will be conducted in accordance with applicable Health Canada regulations, International Conference on Harmonization guidelines on current Good Clinical Practice, and the Declaration of Helsinki.

Confidentiality Statement

This clinical study protocol contains information which is of a confidential, trade-secret or proprietary nature. The protocol is for the use of Dr. Mark Canney and his designated representatives participating in the investigational trial. It is not to be disclosed to any other person or party without the prior written approval of Dr. Mark Canney.

Co-development process

Starting in April 2024, our research team has incorporated patients with lived experience of IgA nephropathy as co-investigators on this study. Through a series of monthly 1-hour meetings, each aspect of the protocol was discussed openly with our patient partners to obtain their feedback and address potential challenges particularly related to participant burden and safety. All patient-facing materials have been created and reviewed by the patient partners.

Abbreviations

BP	Blood pressure
CI	Confidence interval
CRF	Case report form
DSMB	Data Safety and Monitoring Board
eGFR	Estimated glomerular filtration rate
GN	Glomerulonephritis
IgAN	Immunoglobulin A nephropathy
OHRI	Ottawa Hospital Research Institute
RAAS	Renin angiotensin aldosterone system
RCT	Randomized controlled trial
REB	Research ethics board
SGLT2	Sodium glucose transport protein 2
STOP-IgAN	Intensive Supportive Care Plus Immunosuppression in IgA Nephropathy
TASMIN-SR	Effect of Self-monitoring and Medication Self-titration on Systolic Blood Pressure in Hypertensive Patients at High Risk of Cardiovascular Disease
TESTING	Effect of Oral Methylprednisolone on Decline in Kidney Function or Kidney Failure in Patients With IgA Nephropathy

Lay summary

Can self-management of blood pressure lead to better outcomes for patients with IgA nephropathy?

Background

IgA nephropathy is a kidney condition in which an imbalance in the patient's immune system causes injury to the tiny filters within their kidneys leading to leakage of protein and blood into the urine, and decreased kidney function. Because IgA nephropathy tends to occur when patients are young, they have a high risk of developing kidney failure over their lifetime. Controlling blood pressure (BP) can protect their kidney filters from further injury. When done well, this treatment can help reduce the amount of protein in the urine (the best marker of kidney damage) and preserve kidney function. Despite the importance of BP control, there is no accepted standard for how BP should be measured and treated in patients with IgA nephropathy. By checking BP only at clinic visits, there are missed opportunities to detect and treat high BP appropriately.

Purpose

This study aims to test whether patients with IgA nephropathy who self-manage their BP will have better BP control and less protein in their urine compared to patients whose BP is measured and treated only at kidney clinic visits.

Methods

Self-management means that patients measure their BP at home and adjust the dose of their medications to a target BP value. A previous clinical trial conducted in patients without kidney disease showed that patients and their family doctors were able to successfully develop a self-management protocol. Working with our patient partners, we have adapted that protocol for patients with IgA nephropathy. The next step is to conduct a pilot clinical trial involving approximately 25 patients with IgA nephropathy who attend kidney clinics in Ottawa and Vancouver. Trial participants will be randomly chosen to either manage their BP using the self-management protocol or to be in the control group. Participants in the self-management group will be taught how to accurately measure their BP at home over a 7-day period each month. If most of these BP values are above target, they will contact the clinic for a new medication prescription

based on a 3-step plan which was developed with their doctor. Participants in the control group will have their BP measured and treated at clinic visits only. All participants will be followed for 6 months. At the end of the study period, we will measure BP and urine protein levels in all participants and compare these between the self-management and control groups. We will also interview participants in the self-management group to ask them about their experiences.

Anticipated outcomes

The main outcome of the pilot trial is to find out if patients with IgA nephropathy will be willing to enter a trial of self-management of BP and to ensure that the protocol can be implemented safely and is not overly burdensome. The trial will also get preliminary information about whether self-management leads to better BP control and less protein in the urine.

Patient engagement

Patients have been involved in every stage of this study from its design, including creation of patient-facing documents. The team of patient partners will continue to be involved through to completion of the pilot trial and sharing of the results.

Relevance to patients and the kidney community

Patients living with IgA nephropathy have told us that their number one priority is preserving their kidney health and they would like to have more control over managing their condition. By developing an intervention with patients that can be implemented at home, this study seeks to meet both these needs. Protein in the urine is a strong risk factor for kidney failure and heart disease. If shown to be successful, a self-management approach could improve the long-term health of patients with IgA nephropathy and reduce healthcare costs.

Conclusion

Good control of BP is critical to reduce the risk of kidney failure in patients with IgA nephropathy. What is learned from this pilot trial will be used to design a larger trial to answer the question of whether self-management of BP should be first choice in how to manage BP in patients with IgA nephropathy.

Study synopsis

Study title	Self-Management to Achieve Reduction in proTeinuria in IgA Nephropathy (SMART-IgAN)
Study duration	Participants will be followed until 26 weeks after randomization
Study design	Multi-centre, open-label, randomized controlled trial Randomization (2:1) will be stratified by site and carried out with a web-based randomization system
Primary objective pilot trial	To determine if self-management of blood pressure is acceptable to patients and achievable in the clinic setting Measure: Recruitment, completeness of follow-up and adherence to the study protocol
Primary objective full-scale trial	To compare the achieved blood pressure between patients randomized to self-management and patients randomized to usual care Measure: Mean difference in systolic blood pressure at the end of the trial period
Secondary objective pilot trial	Patient experience outcomes Measure: Patient diary (monthly) and a 1:1 semi-structured interview at study completion
Main secondary objective full-scale trial	Compare the reduction in proteinuria between patients randomized to self-management and patients randomized to usual care Measure: Percentage reduction in proteinuria from baseline to the end of the study period
Other outcome measures	1. Efficacy • Difference in systolic BP from baseline to 6-month follow-up • Difference in diastolic BP from baseline to 6-month follow-up • Proportion of patients who achieve an absolute reduction in proteinuria to less than 0.5 g/day at the 6-month visit • Change from baseline in exercise, 24-hour urinary sodium excretion (surrogate for dietary salt intake) and waist circumference at the 6-month visit. 2. Safety • Orthostatic hypotension • Change in eGFR during the 6-month study period • Hyperkalemia (serum potassium >5.3 mmol/L) • Frequency of coordinator intervention required in the self-management arm due to protocol deviations/errors
Inclusion criteria	All of the following: • Adult patients aged ≥18 years who provide written informed consent • Biopsy-confirmed diagnosis of IgAN

	• Proteinuria > 0.5 g/day quantified from 24-hour urine collection or urine protein:creatinine ratio >50 mg/mmol or urine albumin:creatinine ratio >30 mg/mmol • Clinic systolic BP >130 mmHg or diastolic BP >85 mmHg (automated office BP measurement) • Willing to self-manage BP
Exclusion criteria	Any of the following: • Currently receiving immunosuppression or in need of urgent start immunosuppression (e.g., rapidly progressive glomerulonephritis or nephrotic syndrome) • Kidney failure defined by the need for dialysis, kidney transplantation or eGFR <15 mL/min • Recent (within 3 months) history of acute myocardial infarction or stroke • Heart failure with reduced ejection fraction • Concomitant diabetic nephropathy on kidney biopsy • Pregnancy (or actively planning a pregnancy) or breastfeeding • Life expectancy <12 months • Allergy or intolerance to both an angiotensin converting enzyme inhibitor and angiotensin II receptor blocker • Severe hypertension (>180/100 mmHg)
Treatments	**Intervention arm (study treatment)** Self-management of BP including self-monitoring of home BP values and self-titration of medications according to a pre-specified individualized treatment plan **Control arm** Usual management of BP and anti-hypertensive therapy by a physician at regularly scheduled clinic visits
Sample size pilot trial	Target recruitment: 25 patients over 2 years across three sites (The Ottawa Hospital Glomerulonephritis Clinic and the Glomerulonephritis Clinic in Vancouver General Hospital and St. Paul's Hospital, Vancouver) Justification: The target sample size is primarily based on the incidence of IgA nephropathy and the anticipated recruitment rate from the clinic. We will seek to recruit newly diagnosed patients but will also include prevalent patients at each site. The target sample size should be sufficient to address practical questions regarding the feasibility of conducting a larger clinical trial with respect to recruitment, ease of implementation of the intervention, and collection of efficacy and safety outcomes. The total sample size of 25 participants is further supported by a sample size calculation for the

	feasibility metric of retention of participants in the trial. The progression criterion for this outcome is 80%. Assuming 90% of participants complete the 6-month study duration, a total of 26 participants would be needed to provide a one-sided 95% confidence interval of 10% (i.e. a lower bound estimate of 80%).
Expected outcomes from pilot trial	The pilot trial will ensure the feasibility of the full-scale trial for recruitment of patients and adherence to the trial protocol. Participants in the self-management arm will have a positive experience and will perceive the intervention as sustainable in the longer term.
Sample size estimation for full-scale trial	For a definitive trial, a sample size of 186 patients would provide 80% power to detect a mean between-group difference in systolic BP of 7 mmHg (a more conservative effect size compared to previous studies) assuming a standard deviation of 17 mmHg.
Analysis for pilot trial	Feasibility will be defined as achieving target thresholds for both recruitment and retention. The protocol will be refined based on metrics of adherence to the intervention as detailed below: 1. The probability of successful recruitment will be calculated as the percentage of eligible participants who are randomized. A threshold of >50% will be required for progression to a full-scale trial. 2. The probability of retention will be calculated as the percentage of randomized patients who complete the study. A threshold of >80% will be sought for progression to a full-scale trial. 3. Adherence to the self-management protocol will be quantified for each participant using the median number of recorded home BP readings per measurement week and further explored in participant diaries and interviews. There is no threshold for progression to a full-scale trial; however, the protocol will be refined based on these factors.
Analysis for full-scale trial	The between-group difference in mean systolic BP will be the primary outcome in a future full-scale trial. This will be evaluated using mixed models adjusting for baseline BP, sex, and site (as a random effect). The proportional change in proteinuria across study visits will be analyzed using a ratio of geometric least squared means.
Study visits	Study visits will occur in-person at baseline (time of randomisation), then at week 12 and a final study visit at 26 weeks. Participants in the self-management group will have one additional visit at or close to the time of randomization for teaching and training.

1. Background and rationale

1.1 Reducing proteinuria is an important goal in IgA nephropathy

Immunoglobulin A nephropathy (IgAN) is a type of glomerulonephritis, a group of autoimmune diseases that cause inflammation of the filtration units of the kidney and lead to leakage of protein and blood into the urine (proteinuria and hematuria). Patients with IgAN are typically diagnosed at a relatively young age compared to those with other forms of chronic kidney disease, and as such they have a high lifetime risk of kidney failure.[1] Observational studies and meta-analyses of clinical trials have consistently demonstrated that reducing proteinuria is associated with lower risk of disease progression and kidney failure in patients with IgAN,[2-4] and a reduction in proteinuria is now accepted as a surrogate endpoint in clinical trials.[5] Our previous work with the International IgA Nephropathy Network showed that each 3 months in proteinuria remission was associated with an additional 9% reduction in the risk of kidney failure.[6] Achieving a sustained reduction in proteinuria is therefore an important outcome for patients because it can reduce the risk of needing dialysis or a kidney transplant in the future, translating to fewer complications for patients and lower costs to the health care system.

1.2 How can a reduction in proteinuria be achieved?

Although immunosuppression treatment is available for patients with IgAN, it comes with a risk of serious infections[7,8] and is therefore typically reserved for high-risk patients (defined as the presence of persistent high-grade proteinuria, usually ≥1 g/day). Consideration for immunosuppressive treatment is determined after an observational period of approximately 6 months following diagnosis via kidney biopsy, during which time patients receive non-immune or “supportive” therapy.[9] The cornerstone of supportive therapy in IgAN is blood pressure (BP) control through the use of renin angiotensin aldosterone system (RAAS) inhibitors which have been shown to reduce proteinuria and improve kidney outcomes in non-diabetic patients with proteinuria,[10] including patients with IgAN.[11,12] In prospective studies, with BP management alone, up to 50% of patients with IgAN can achieve partial or complete remission of their disease based on a reduction in proteinuria.[13] Since IgAN is a chronic disease, supportive care

needs to be maintained throughout the patient's illness trajectory, irrespective of the decision to pursue short courses of immunosuppression.

1.3 How should supportive care be delivered?

Despite the recognized benefits of supportive therapy, there is no uniform strategy that defines optimal supportive care. This can be readily seen from two recent randomized controlled trials (RCTs) of immunosuppression for IgAN, which entered participants who met inclusion criteria in a run-in phase with the intent of maximizing supportive care prior to randomization. The STOP-IgAN trial (N=309) followed patients monthly for 6 months and titrated the dose of RAAS inhibitor to target BP <125/75 mmHg at each visit, along with offering lipid-lowering therapy and counseling about a low-sodium diet and smoking cessation,[7] while the TESTING trial (N=523) had a run-in phase of 4 to 12 weeks (for a total of two to three study visits) to ensure that all participants were on a RAAS inhibitor for 3 months prior to randomization but had no BP target.[8] Despite the different approaches used, 34% (n=106) of patients who completed the run-in period in STOP-IgAN achieved a response (reduction in proteinuria to <0.75 g/day),[7] and 24.5% (n=128) of patients in TESTING experienced a reduction in proteinuria to the extent that they no longer met the inclusion criteria for randomization.[8] These two RCTs show that a substantial proportion of patients can achieve at least a short-term reduction in proteinuria with supportive therapy alone. However, there remain some important knowledge and care gaps. It is unclear whether the need for frequent in-person visits, beyond what is typical in routine care, would be feasible in most settings, as well as potentially placing additional burden on patients. Trial participants have not been randomized during the run-in phase of contemporary RCTs and no specific supportive care interventions have been formally tested, including the systolic BP target of 120 mmHg suggested by international guidelines.[14]

The current standard of care for BP treatment is according to automated office BP readings at in-person clinic visits. Among 91 patients with incident IgAN diagnosed on a kidney biopsy between January 2020 and December 2022 at The Ottawa Hospital, 58% of patients had a systolic BP >120 mmHg and 38% of patients were receiving sub-

maximal doses of a RAAS inhibitor at six months' follow-up (Dr. Akbari, personal communication). Studies of ambulatory BP monitoring in patients with glomerulonephritis have shown a high prevalence of masked hypertension, nocturnal hypertension, and non-dipping status,[15,16] highlighting the limitations of relying solely on clinic BP readings. In one cross-sectional study, systolic BP from ambulatory monitoring had a stronger correlation with both kidney function and albuminuria compared to systolic BP from clinic readings.[16] In a small prospective study, patients with glomerulonephritis who had normal clinic BP and preserved kidney function were found to have higher ambulatory BP values compared to matched controls, along with early evidence of left ventricular hypertrophy.[17] Targeting ambulatory BP has not been systematically evaluated in patients with IgAN and could provide opportunities for earlier intensification of RAAS inhibitor therapy, better overall BP control and improvements in proteinuria.

1.4 Could patients manage their own blood pressure?

Self-management is well established for chronic health conditions such as diabetes mellitus (glucose monitoring and insulin titration), heart failure (weight monitoring and diuretic adjustment), and asthma (peak flow monitoring for earlier detection of exacerbations).[18-21] Self-management can in turn promote self-efficacy, with downstream health benefits for patients living with a chronic disease.[22] A report from the Standardizing Outcomes in Nephrology-Glomerular Disease initiative found that patients with glomerular disease prioritized preservation of their kidney function above all else, and reported impaired agency or loss of control over their health.[23] Furthermore, an international focus group study of self-management in glomerular disease involving 135 patients and their care partners found that a key facilitator to self-management was "Empowered in Autonomy" whereas an important barrier was frustration arising from fragmented and inflexible care models.[24] Patients sought greater responsibility for treatment decision-making, home monitoring, and making positive lifestyle changes. A key recommendation from this work was to utilize existing self-management interventions that have been shown to be effective in other conditions to inform

strategies for use in glomerular disease, as well as co-designing and co-implementing these interventions with patients.

A series of RCTs in the primary care setting have evaluated the efficacy and safety of self-monitoring of home BP values and self-titration of anti-hypertensive therapy.[25,26] Of particular interest to us is the Effect of Self-monitoring and Medication Self-titration on Systolic Blood Pressure in Hypertensive Patients at High Risk of Cardiovascular Disease (TASMIN-SR) trial, which demonstrated that self-management of BP was superior to usual care after 12 months of follow-up with mean reduction in systolic BP of 9.2 mmHg (95% CI 5.7 to 12.7) in individuals with hypertension at high-risk for cardiovascular events.[27] The majority of participants in the self-management group measured their BP properly and recorded the values accurately.[28] No significant differences in adverse events were noted compared to usual care.

1.5 Why is a trial needed?

There are important differences between the population studied in TASMIN-SR and patients with IgAN. First, it is recommended that patients with IgAN receive maximally tolerated doses of a RAAS inhibitor as first-line therapy. Second, many of these patients have reduced kidney function at the time of diagnosis, and the efficacy and safety of self-management has not been studied in this context. Third, supportive care should be optimized within a shorter time-frame than that studied in TASMIN-SR (6 months versus 12 months) and the feasibility of self-management to achieve this has not been demonstrated. To improve the likelihood of achieving proteinuria reduction, there is a need to standardize the approach to supportive care in IgAN with a treatment strategy that is co-developed with patients to ensure appropriateness and acceptability, can be delivered outside of clinic visits, is readily implementable in clinical care, and can be up-scaled for use in the run-in phase of clinical trials.

1.6 Benefits and risks

Self-management could have many benefits for patients. First, it could facilitate earlier control of BP by helping patients achieve their target BP more efficiently. This, in turn,

could lead to earlier reduction in proteinuria, which has been identified as a surrogate outcome for future kidney health. Second, self-management provides a way for patients to take more ownership over their kidney health. The need for patient autonomy in aspects such as home monitoring and lifestyle measures was identified in focus groups as a key priority for patients and caregivers. Third, if patients feel that self-management strategies are sustainable this approach could have the potential to improve the long-term kidney and cardiovascular health of patients with IgAN through better monitoring of BP and earlier identification of suboptimal BP control.

Prior studies have demonstrated that self-management of BP and self-titration of medications can be achieved safely, including in individuals with complex medical problems such as a prior stroke. We recognize that participants may feel apprehensive or overwhelmed about having to self-manage their blood pressure. The potential for participant burden has been a major focus for our team in development of this protocol. Our patient partners have provided feedback about each step of the process to mitigate this risk. Other potential risks are described in section 9.1.

2. Study objectives and research questions

2.1 Primary objective of SMART-IgAN pilot

To determine the feasibility of a full-scale trial by showing that self-management of blood pressure is acceptable to patients and achievable in the clinic setting.

Hypothesis: At least 50% of eligible patients will be randomized; at least 80% of participants will complete the study.

2.2 Secondary objective of SMART-IgAN pilot

To evaluate patient experience of self-management through a monthly diary entry and a semi-structured interview at the end of the study.

Hypothesis: Participants who self-manage their BP will view the intervention as a positive experience and will perceive the intervention as sustainable in the longer term.

2.3 Primary objective of SMART-IgAN full-scale trial

Compare the achieved BP in patients randomized to self-management versus patients receiving usual care in the clinic.
Hypothesis: Patients who self-manage their BP will have lower BP at the end of the study period compared to patients whose BP is managed in the clinic.

2.4 Secondary objective of SMART-IgAN full-scale trial
Evaluate the effect of self-management on proteinuria reduction.
Hypothesis: Patients who self-manage their BP will experience a greater reduction in proteinuria compared to patients whose BP is managed in the clinic.

3. Outcomes

3.1 Primary outcome

The primary outcome of the pilot trial will be feasibility defined as achieving target threshold for both recruitment and study completion. The study protocol will be revised based on adherence metrics and participant feedback as detailed below:

1. The probability of successful recruitment will be calculated as the percentage of eligible participants who are randomized. A threshold of >50% will be required for progression to a full-scale trial.
2. The probability of retention will be calculated as the percentage of randomized patients who complete the study. A threshold of >80% will be sought for progression to a full-scale trial.
3. Adherence to the self-management protocol will be quantified for each patient in the intervention group using the median number of recorded home BP readings per measurement week. Adherence will be further explored from participant feedback in longitudinal diary entries and a semi-structured interview. Fidelity of the intervention will also be explored retrospectively by comparing the submitted BP readings to the BP readings downloaded from the machine at the end of the study period. There is no progression criterion for adherence but the study protocol for a future full-scale trial will be refined based on these factors.

3.2 Secondary outcomes

The main secondary outcome of the pilot trial will be patient experience of self-management. This will be captured longitudinally during the trial in a monthly diary entry and at the end of the trial via a 1:1 semi-structured interview.

Efficacy outcomes will be assessed on an exploratory basis only:

1. Mean difference in achieved BP between the groups at the end of the study period (primary efficacy outcome in a future full-scale trial)
2. Difference in systolic BP from baseline to 6-month follow-up (using an automated office BP measurement)
3. Difference in diastolic BP from baseline to 6-month follow-up (using an automated office BP measurement)
4. Difference in percentage proteinuria reduction between the groups from baseline to 6 months (key secondary outcome in a future full-scale trial)
5. Proportion of patients who achieve an absolute reduction in proteinuria to less than 0.5 g/day at the 6-month visit
6. Change from baseline in exercise, 24-hour urinary sodium excretion (surrogate for dietary salt intake) and waist circumference at the 6-month visit

Safety outcomes:

1. Orthostatic hypotension (measured at clinic visits)
2. Change in estimated glomerular filtration rate (eGFR) during the study period
3. Hyperkalemia episodes (serum potassium >5.3 mmol/L)
4. Frequency of coordinator intervention required in the self-management arm due to protocol deviations/errors

4. Trial design

4.1 Setting and Participants

SMART-IgAN is a pilot, unblinded, randomized controlled trial of self-management of blood pressure versus usual care in patients with IgA nephropathy attending Glomerulonephritis (GN) clinics at The Ottawa Hospital, Ottawa, Ontario, and in Vancouver, British Columbia (Vancouver General Hospital and St. Paul’s Hospital).

4.2 Study duration

Participants will be followed for 6 months and will have three dedicated study visits embedded within their regularly scheduled clinic visits at baseline (day of randomization), 3 months and at 6 months (study completion). Outcomes will be assessed at the 6-month mark.

4.3 Randomization and allocation process

Randomization will be 2:1 intervention-to-control, and will be carried out with a web-based randomization system. A 2:1 allocation was chosen because there is already extensive experience of the usual care arm of the trial, and the intent is to determine the acceptability and safety profile of the intervention. The randomization website will be managed by the Data Management Services of the Ottawa Methods Centre Ottawa Hospital Research Institute. Randomization will be stratified by site (Ottawa versus Vancouver).

4.4 Blinding and protection against bias

SMART-IgAN will be an open-label trial as there is no way to blind participants or investigators due to the nature of the intervention. The primary efficacy outcome is the achieved systolic BP which will be measured using an automated office BP measurement with the participant left unattended in the room. This is an objective measure that would not be influenced by knowledge of the intervention.

5. Study population

The target population for SMART-IgAN includes adult patients with a diagnosis of IgA nephropathy confirmed on a kidney biopsy and suboptimal BP control. Potential participants at The Ottawa Hospital will be identified using (i) an existing registry of patients who have biopsy-confirmed IgA nephropathy (the Ottawa GN database) and/or (ii) a clinic planner (a Word document that is completed by a physician prior to the clinic that lists the patients attending the clinic on a specific day and includes information about their underlying diagnosis and a summary of their care plan). The Ottawa GN database is housed within the Ottawa Hospital Research Institute (OHRI) and is

password protected. The clinic planners are housed in a folder on SharePoint and are only accessible to physicians, nurses and administrative staff who work in the GN clinic.

Clinic patients who are potentially eligible for recruitment will be contacted by phone outside of their regularly scheduled clinic visit by either a healthcare professional within their circle of care or by a research coordinator. Patients who indicate a willingness to participate in the study will be offered the opportunity to read the consent form prior to their in-person clinic visit, at which time full eligibility will be determined based on their BP value in the clinic. Patients who meet all inclusion criteria will be consented and randomized on the same day as their scheduled clinic visit. If this is not feasible (for example due to time constraints), they will be offered an alternative date to return to the clinic for completion of the consent form.

Individuals who decline to participate will be asked if the following information may be collected so that the investigators can compare individuals who complete the study to those that elect not to participate: (i) reason(s) for not wishing to participate; (ii) demographic characteristics (sex, decade of age); (iii) clinical characteristics (level of kidney function, degree of proteinuria, clinic blood pressure value).

5.1 Inclusion criteria

- Adult patients aged ≥18 years who provide written informed consent.
- Biopsy-confirmed diagnosis of IgAN.
- Proteinuria > 0.5 g/day quantified from 24-hour urine collection or urine protein:creatinine ratio >50 mg/mmol or urine albumin:creatinine ratio >30 mg/mmol.
- Clinic systolic BP >130 mmHg or diastolic BP >85 mmHg (automated office BP measurement)
- Willing to self-manage BP

5.2 Exclusion criteria

- Currently receiving immunosuppression or in need of urgent start immunosuppression (e.g., rapidly progressive glomerulonephritis or nephrotic syndrome).
- Kidney failure defined by the need for dialysis, kidney transplantation or eGFR <15 mL/min.
- Recent (within 3 months) history of acute myocardial infarction or stroke.
- Heart failure with reduced ejection fraction.
- Concomitant diabetic nephropathy on kidney biopsy.
- Pregnancy (or actively planning a pregnancy) or breastfeeding.
- Life expectancy <12 months.
- Allergy or intolerance to both an angiotensin converting enzyme inhibitor and angiotensin II receptor blocker.
- Severe hypertension requiring urgent treatment (>180/100 mmHg).

5.3. Use of SGLT2 inhibitors

The use of SGLT2 inhibitors has become more widespread in IgAN based on findings from recent large clinical trials, which included a sizeable number of participants with chronic kidney disease secondary to IgAN.[29,30] Although there is strong evidence to support their use in the long-term management of IgAN, their precise role in the short-term after biopsy diagnosis is not clear especially for patients who are candidates for immunosuppression. Additionally, access to these medications is not uniform across Canada for patients who do not have diabetes. Variable use of SGLT2 inhibitors would likely lead to unbalanced co-interventions with a greater likelihood that a SGLT2 inhibitor would be started in the control group due to persistent proteinuria from suboptimal BP control and/or slower titration of RAAS inhibition. To overcome this potential limitation, patients who have already been started on a SGLT2 inhibitor will be allowed to enter the trial as long as they have been on stable doses for at least 4 weeks and the dose is not titrated during the 6-month follow-up period. Patients who are not receiving a SGLT2 inhibitor at the time of randomization will not be prescribed the medication until they have completed the 6-month trial period. For a future full-scale trial, randomization will be stratified on SGTL2 inhibitor use at baseline to ensure that it

is balanced between intervention and control groups. This approach was taken in a recent trial of semaglutide in patients with chronic kidney disease.[31]

6. Participant withdrawal and study discontinuation

6.1 Withdrawal of participants

Study participants will be followed until either the final study visit at 26 weeks. A participant may withdraw consent from the study at any time and for any reason. If a participant withdraws consent, they will be withdrawn from the trial. Participants will be assured that their withdrawal from the trial will not in any way affect the on-going management of their kidney condition (as would have been done had the patient not entered the study). The decision of an investigator to withdraw a study subject will be based on any or all of the following:

i) Any clinical adverse event, safety concerns, laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant

ii) It is in the participant's best interest according to the Investigator's clinical judgment

iii) The participant meets an exclusion criterion (either newly developed or not previously recognised) that precludes further study participation

iv) The study is prematurely terminated

If a participant withdraws consent for further study follow-up procedures and assessments, every effort will be made to continue to follow the participant for their safety and vital status outcomes. Consent for collection of any adverse events as well as their clinical and biological data will be sought by the research team. The participant will be asked if they wish to:

i) Withdraw from study intervention/treatment only and agree to be followed at study visits as stipulated in the protocol/consent form; OR

ii) Withdraw from study intervention/treatment and permit follow-up by phone or review of clinic/hospital records for data collection and vital status; OR

iii) Withdraw from study intervention/treatment and decline further contact however permit data obtained to date to be included in the analysis; OR

iv) Withdraw from study intervention/treatment, decline further contact and access to personal health information and indicate data collected to date cannot be used in the final analysis.

Subjects who are withdrawn will not be replaced. Source documents will not be destroyed until completion of the long-term storage period.

The primary reason for premature withdrawal and the participant's decision to decline study follow-up will be recorded in the participant's source documents and related case report form (CRF). If a withdrawal is a result of a serious adverse event, the conditions will be clearly documented and reported to the research ethics board (REB). If withdrawal is a participant's decision due to concerns about the use of their personal health information, these will be reported to the REB and the privacy office. If withdrawal is a participant's decision due to concern about their rights, safety, or wellbeing, the participant will be instructed to contact the REB at the number listed in the informed consent form. Additionally, the REB will be contacted by the study team to discuss the participant's concern.

Major deviations from the trial treatments or cessation of medications by the patient do not require withdrawal of the participant; these patients shall remain in the study and followed up until the end of the study (except where the participant withdraws consent).

6.2 Management of losses to follow-up

If a participant is being lost to follow-up (for instance, not showing up to their study visits), the following procedures will be performed:

i) Participant will be contacted three times and efforts will be clearly documented. Contacts may be done either by telephone, electronically, or mail correspondence;

ii) Obituaries will be verified online;

iii) If unsuccessful after three attempts, a registered letter will be sent to the participant's address requesting the participant to sign for the letter to attempt to confirm survival status. If no response, efforts will be clearly documented, status as lost to follow-up.

Participants who voluntarily withdraw early from the study will be asked about permission to have their data used (as detailed in section 6.1).

6.3 Premature termination or suspension of trial

The study may be suspended or prematurely terminated if there is sufficient reasonable cause. If the study is prematurely terminated or suspended, it will be promptly reported to the REB and the reason(s) will be provided.

7. Study treatments

Participants will be randomized 2:1 to self-management (intervention) or usual care (comparator). The current standard of care for patients with IgA nephropathy attending the Glomerulonephritis Clinic is to measure their blood pressure at scheduled clinic visits and make treatment decisions based on those values. Clinical guidelines recommend RAAS inhibitors as first-line therapy. Patients not requiring immunosuppression treatment are typically followed in the clinic every 4 to 6 months. Participants in the intervention and control group will be assessed in the clinic at baseline, at 3 months and at 6 months. In both groups, the dose of RAAS inhibitor will be progressively increased to achieve a systolic BP <120 mmHg. The use of other anti-hypertensive medications will be permitted in both groups at the discretion of the treating physician after the dose of RAAS inhibitor has first been maximized. For patients receiving other (non-RAAS inhibitor) antihypertensive therapy at the time of recruitment, these medications will be replaced by a RAAS inhibitor at study entry. As such, they will be receiving care at a level at or above the current standard of care. Patients in the intervention group will additionally measure their blood pressure at home and follow the algorithm as described below.

7.1 Intervention

Participants randomized to self-management will receive training in home BP measurement and adjustment of anti-hypertensive medications according to a pre-specified plan.

7.1.1 Home BP measurement

Participants will be provided with a home BP monitor with an appropriately sized cuff, and will receive a 30-minute in-person teaching session from a research nurse (or research coordinator) about how to accurately measure their BP at home. Written instructions will also be provided (these are already available in the clinic in both English and French). Participants will have a practice week of BP measurement to ensure that the training was successful and to identify participants who would benefit from additional training. Participants will be asked to measure their BP twice daily (morning and evening) for 7 consecutive days at the beginning of each month (measurement week). They will be advised to measure their BP in a seated position with their arm supported such that the middle of the cuff is at the level of the heart. Each measurement will include 3 values taken 1 minute apart after 5 minutes of rest. The average of values 2 and 3 will be recorded as the BP for that measurement. A complete week of measurements will therefore encompass 14 BP values (7 morning and 7 evening values). An instruction sheet will be provided to each participant to explain what should be done based on their BP values. Very low readings (<100 mmHg systolic) or very high readings (>180 mmHg systolic) that persist after repeating another set of 3 measurements will prompt a phone call to the clinic staff for advice.

7.1.2 Adjusting anti-hypertensive therapy

Within the same encounter, a second 30-minute teaching session will be delivered to participants regarding the treatment algorithm for titration of anti-hypertensive medications. Each participant will have an individualized three-step treatment plan that is developed with their physician, and which is based on their recorded home BP values during the measurement week of each month. The choice of anti-hypertensive agent and dose is at the physician's discretion. Participants who record 50% or more values above target during their measurement week will move to the next step of their

treatment plan (either increasing their home dose of RAAS inhibitor or contacting their physician for a new medication prescription). In this way, there is no requirement for an additional clinic encounter. Once the three steps have been completed, the participants will return to the clinic to create a new three-step plan. In consultation with our patient partners, we established that a minimum of 8 BP values during a measurement week (equivalent to 4 out of 7 measurement days) would be required in order for any medication changes to be made. If a participant is unable to complete the requisite number of BP measurements, they will be given an opportunity to repeat the set of BP measurements the following week (as opposed to waiting until the following month).

7.2 Control

Participants randomized to usual care (control group) will be asked to attend their scheduled clinic visit with their nephrologist for monitoring and treatment of their blood pressure. The physician who assessed them in the clinic will be notified to ensure that any planned changes to anti-hypertensive medications from their clinic visit are actioned.

8. Study procedures

As described in Section 5, potentially eligible patients will be approached about the study either at a regularly scheduled clinic visit or a few days prior to the visit. Full eligibility will be established at the clinic visit based on their blood pressure measurement that day. Eligible patients who are willing to participate in the trial will be consented and then randomized to determine treatment allocation. No treatment will be started until all of these steps have been completed. Participants will have three dedicated study visits embedded within their regularly scheduled clinic visits at baseline (day of randomization), 3 months and at 6 months (study completion). Participants in the self-management (intervention) group will have one additional study visit in close proximity to their baseline clinic visit for training.

<u>Visit 1 (Week 0)</u>

All participants will attend a baseline research visit at which time a research nurse or coordinator will explain the study procedures and obtain written informed consent. All participants will be asked to complete a CRF regarding demographics (age, sex, gender identity), current medications (name, dose and frequency), and health conditions including diabetes, pre-existing cardiovascular disease (prior heart attack or stroke, coronary artery disease, peripheral arterial disease) and pre-existing hypertension. All participants will be asked to complete the Simple Lifestyle Indicator Questionnaire which includes questions about healthy eating, exercise, alcohol consumption and smoking. Height, weight and waist circumference will be measured. An automated clinic blood pressure measurement (BpTRU) will be taken with the participant left unaccompanied in the clinic room for 8 minutes during which time an average of 3 blood pressure measurements will be recorded after a 5-minute period of rest. This BP measurement approach is the current standard of care for all patients who attend the GN clinic and will serve as the baseline BP value. This research visit is anticipated to last one hour.

Participants who are randomized to self-management will be given the option of either: (i) completing the training on the same day as their clinic visit; or (ii) scheduling the training on a different day within 7 days of randomization. The training is anticipated to last between 30 and 60 minutes depending on how familiar patients are with measuring their own BP. As long as creatinine and electrolytes have been checked recently (within 4 weeks), there will be no need for additional blood tests at the baseline visit. All participants will be provided with a urine collection jar for 24-hour protein, creatinine and sodium excretion. Written instructions will be provided with the jar. The jar should be returned to the laboratory at The Ottawa Hospital or to the research team within 2 days. Expenses related to the research visit and return of the urine specimen (e.g., parking) will be reimbursed to each participant.

Visit 2 (Week 12)

Each participant will have a clinic visit with their treating physician during which laboratory tests (including creatinine and potassium) will be repeated along with a BpTRU measurement. Participants will be evaluated for orthostatic hypotension by

measuring their BP while sitting followed by a BP measurement with the participant standing for 1 and 3 minutes. Orthostatic hypotension will be defined as a drop in systolic BP of at least 20 mmHg or a drop in diastolic BP of at least 10 mmHg. All participants will be asked to complete the Simple Lifestyle Indicator Questionnaire. A medication reconciliation will be performed as per standard of care in the clinic.

Visit 3 (Week 24)

All participants will have a clinic visit with their nephrologist including medication update, a BpTRU measurement, weight and waist circumference, laboratory tests (creatinine and potassium), and a 24-hour urine collection for daily sodium and protein excretion. Participants will be evaluated for orthostatic hypotension as previously described. All participants will be asked to complete the Simple Lifestyle Indicator Questionnaire.

Patient experience outcomes

Participants in the self-management arm will be asked to complete a short journal entry once during each measurement week. The purpose of this is to obtain a longitudinal evaluation of their experience during the 6 months of the trial. Participants will be asked to rank their confidence on a Likert scale with respect to measurement of BP, interpretation of the values, and the actions taken based on the treatment algorithm. Participants will be encouraged to provide additional information about their experience in a free-text box. At the end of the trial period, all participants in the self-management arm will be invited to participate in a semi-structured interview by phone. Our team of patient partners felt that a one-on-one interview would be superior to a group interview and would provide richer feedback about their personal experiences of participating in the study. Information from the journal entries will be used to identify themes that can be explored further during the interview.

9. Safety assessments

9.1 Potential risks to participants

Participants in the intervention arm could be at a higher risk of adverse events from more rapid escalation of their anti-hypertensive therapy. Serum creatinine and

potassium will be checked within 7 to 10 days of initiating a RAAS inhibitor. Laboratory tests will be rechecked within 7 to 10 days of increasing the dose of a RAAS inhibitor in the following situations: (i) previous serum potassium value ≥4.8 mmol/L; (ii) eGFR <30 mL/min; or (iii) physician discretion. Participants will be encouraged to contact the clinic staff outside of scheduled encounters if they develop symptoms indicative of low blood pressure (light-headedness, weakness). Sitting and standing BP will be measured at each study visit to look for evidence of orthostatic hypotension. Each participant will be provided with "sick day guidance" with respect to stopping their RAAS inhibitor during acute illness. Participants may feel apprehensive or overwhelmed about having to self-manage their blood pressure. The potential for participant burden has been a major focus for our team in development of this protocol. Our patient partners have provided feedback about each step of the process to mitigate this risk.

9.2 Safety definitions

An adverse event (AE) is any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product, which does not need to have a causal relationship with that treatment. Examples of study-specific AEs are laboratory abnormalities (see 9.1 above), symptoms of low BP or orthostatic hypotension.

A serious adverse event (SAE) is any adverse event that:

- Results in death
- Requires attendance at an emergency room or hospitalization (defined as admission to a medical facility for at least 24 hours)
- Any medically important events that, in the opinion of the local investigator, may jeopardise the participant or may require intervention to prevent one of the other outcomes listed in the definition above

9.3 Adverse event recording and reporting

The adverse event recording period will begin with entry into the study (day of randomization) and end on the last study visit approximately 26 weeks after randomization. All AEs will be recorded in the electronic CRF. Adverse events will be

captured by the site investigator or designee by inquiring about safety events since the last visit. Safety assessments may also be collected from participant report prior to the study visit by the patient contacting the research personnel, or by review of the clinical chart by the research personnel. Investigators have the primary responsibility for adverse event identification, documentation, grading, attribution of causality and reporting. AEs that are related to study treatment will be reported to the individual site's ethics board.

Local investigators will record the causality of the SAE in relation to the study treatment. Causality will be assessed as follows:

- Unrelated: There is not a reasonable possibility that the adverse event may have been caused by the study intervention.
- Possibly related: The adverse event may have been caused by the study intervention, however there is insufficient information to determine the likelihood of this possibility.
- Related: There is a reasonable possibility that the adverse event may have been caused by the study intervention.

When deciding about causal relationship, the investigator will consider whether the event may be the result of diseases or concomitant medications which typically can occur in this patient population such as: the natural progression of an existing disease, the development of a new and unrelated disease, or a known side effect of other concomitant therapies that the participant may be taking.

9.4 Data Safety and Monitoring Board (DSMB)

This study will be monitored by an independent DSMB consisting of 2 content experts (1 nephrologist and 1 hypertension expert) and a clinical epidemiologist. The DSMB will be blinded to the treatment allocation. The DSMB will be immediately informed of any SAEs which may potentially be related to the study intervention. Other SAEs will be reviewed during DSMB meetings. Interim reports, prepared by the data management team of the coordinating centre, for review by the DSMB will include data on recruitment, adherence and AEs. An interim report will be sent for review after 50% of

participants have been enrolled in the pilot trial. Should safety issues arise that the DSMB feel compromises the trial and/or participant safety, then a meeting of all co-investigators will be convened to consider amending or stopping the trial.

10. Quality assurance

10.1 Monitoring

The trial will have a quality control monitoring process in place to verify that all data are accurate and complete. The investigator/institution will permit trial-related monitoring, audits, REB review and regulatory inspections(s), and will provide direct access to source data/documents as required.

10.2 Protocol Amendments

All protocol amendments will be reviewed and approved by the study sponsor REB.

10.3 Protocol Deviations

Study related procedures must be conducted in compliance with the protocol, amendments, regulations and guidelines, in order to ensure participant safety and data integrity. Any deviations from the protocol, or violations of the protocol, will be accurately documented, reported and reconciled.

Protocol deviations refer to incidents involving non-compliance with the protocol that are unlikely to have a significant impact on the participant's rights, safety or welfare, or on data integrity. Examples of deviations include: forgetting to complete a procedure at a specified visit (weight, missing lab value, etc.). If a protocol deviation occurs the following procedures will be followed:

i) The local investigator or delegate will document and explain any deviation from the approved protocol
ii) Deviations from the protocol must be reported in the CRF

Participants will not be withdrawn from the study for protocol deviations unless a criterion for discontinuation or withdrawal is met.

11. Trial management

11.1 Day-to-day management

The Ottawa Hospital Research Institute, University of Ottawa, Ottawa, Ontario, Canada is the coordinating centre for the SMART-IgAN pilot trial and is primarily responsible for the development of the trial protocol, organization of the trial, trial database, data analyses, and coordination of the trial centres.

The OHRI Project Office is responsible for the daily conduct of the trial including: data management (data validation and quality), producing and presenting reports on screening, follow-up, data quality, and outcome events, develop and communicate to trial investigators and research personnel periodic trial reports, identifying and contacting participating centres with recruitment issues, communication with investigators and research personnel regarding protocol and other procedural questions, be available to answer phone calls or emails from investigators or trial personnel to resolve any problems or questions that arise, maintenance of required documentation for regulatory agencies, preparation of presentations to the study committees, organization of Investigator meetings, and Project Office meetings with the Principal Investigator and Project Manager.

11.2 Site Principal Investigator and responsibilities

All participating centres will have a site PI. The site PI is responsible for ensuring compliance with respect to the intervention, visit schedule, and procedures required by the protocol. The site PI will ensure the provision of all information requested in CRF in an accurate and timely manner according to instructions provided. The site PI will maintain patient confidentiality with respect of all information accumulated in the course of the trial, other than that information to be disclosed by law.

The Site PI at each participating center is responsible for:

1. Obtaining ethics approval from the institutional review board or the ethics board and forwarding this to the Project Office.
2. Ensuring recruitment does not begin until study approval is obtained.

3. Ensuring the protocol is followed.
4. Ensuring that an Informed Consent Form is correctly completed for each patient included in the study.
5. Ensuring all relevant physicians and nurses involved in the care of patients potentially eligible for the trial are aware and informed about the trial. This may involve organizing and presenting educational in-services and/or rounds about the trial.
6. Ensuring that potentially eligible patients are screened for the trial.
7. Ensuring that all enrolled patients have relevant laboratory tests obtained in accordance with the protocol.
8. Ensuring that all enrolled patients are followed appropriately.
9. Ensuring that CRFs completed by their study staff are promptly and accurately completed and submitted to the Project Office, and that all inquiries from the Project Office regarding patient forms or other matters are addressed promptly.
10. Ensuring they maintain for at least 25 years after the publication of the main results, the list of patient identification numbers and patient names to enable identification of hospital records at a later date.

11.3 Steering committee

A Trial Steering Committee comprising of study co-investigators will be determined and will manage the overall conduct of the study. The committee will meet every 6 months via teleconference.

12. Analysis plan

12.1 Sample size justification

IgAN is the most common condition treated in the Glomerulonephritis Clinic at both sites. Approximately 30 individuals are diagnosed with IgAN on a kidney biopsy each year in Ottawa. Over the course of 2 years, we anticipate that half of these patients (30 out of 60) would be eligible for the trial, and we are seeking to recruit at least 50% of eligible patients (n=15). The Glomerulonephritis Clinic at Vancouver General Hospital has a larger patient population and we are seeking to recruit 10 patients from that site.

The total sample size of 25 participants is supported by a sample size calculation for the feasibility metric of retention of participants in the trial. The progression criterion for this outcome is 80%. Assuming 90% of participants complete the 6-month study duration, a total of 26 participants would be needed to provide a one-sided 95% confidence interval of 10% (i.e. a lower bound estimate of 80%).
For a definitive trial, a sample size of 186 patients would provide 80% power to detect a between-group mean difference in systolic BP of 7 mmHg (a more conservative effect size compared to TASMIN-SR) assuming a standard deviation of 17 mmHg.

12.2 Efficacy analysis

The between-group difference in mean systolic ambulatory BP will be the primary outcome in a future full-scale trial. In an exploratory analysis from this pilot trial, this outcome will be evaluated using mixed models adjusting for baseline BP, sex, and site (as a random effect). The proportional change in proteinuria across study visits will be analyzed using a ratio of geometric least squared means, as done previously.[32]

13. Data handling and record keeping

13.1 Source Documents and Case Report Forms

Data collection is the responsibility of the study team under the supervision of the investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. The Investigator will maintain adequate and accurate source documents upon which CRFs for each participant are based.
These records should include detailed notes on:

i) Oral and written communication with participant regarding the study treatment (risks/benefits)
ii) Participation in trial and signed and dated informed consent forms
iii) Enrollment number
iv) Inclusion and exclusion criteria details
v) Visit dates
vi) Study assessments
vii) Adverse events (if applicable)

viii) Reason for premature discontinuation (if applicable)

ix) Compliance/non-compliance and protocol deviation information

The study CRF is the primary data collection instrument for the study. All data requested on the CRF must be recorded and substantiated by a source document. All missing data must be explained. If a space on the CRF is left blank because the procedure was *not done* or the question was not asked, “N/D” will be entered. If the item is *not applicable* to the individual case, “N/A” will be entered. An electronic CRF must be completed for each participant. The electronic CRFs will be created and maintained by the sponsor using the OHRI Ottawa Methods Centre Data Management Services. Data entry should be completed within 5 business days of the study visit. The completed electronic CRFs are not to be made available in any form to third parties, except for authorized representatives of appropriate Regulatory Authorities.

13.2 Personal Health Information

Personal health information including CRFs, evaluation forms, reports, etc. will be kept strictly confidential. All records will be stored on-site in a secure, locked facility. Records will be destroyed after 15 years, in accordance with Health Canada Regulations.

13.3 Record Retention

To enable evaluations and/or audits, the site investigator will keep records, including the identity of all participating participants (sufficient information to link records, e.g., master list and hospital records), all original signed Informed Consent Forms, copies of all worksheets and detailed records of drug disposition. To comply with Health Canada regulations, the records are to be retained for at least 15 years.

14. Ethics

14.1 Ethical Conduct of the Trial

The trial will be performed in accordance with the Tri-Council Policy Statement and the ICH GCP Guidelines. This protocol, related informed consent form, recruitment materials, and all participant materials will be submitted to the REB for review and approval. Approval of both the protocol and the consent form will be obtained before any

participant is enrolled. Any amendment to the protocol (and consent, if applicable) will be reviewed and approved by the REB before the changes are implemented in the study.

14.2 Participant Information and Consent

The investigator, or their designee, will inform each participant (or the participant's acceptable representative) prior to inclusion in the trial, full and adequate verbal and written information regarding the objective and procedures of the trial and the possible risks involved. The participants must be informed about their right to withdraw from the trial at any time. Written participant information will be given to each participant before enrolment. Furthermore, it is the responsibility of the investigator or their designee to obtain signed informed consent (or witnessed verbal consent according to applicable regulations) from all participants prior to inclusion in the trial. Informed consent is an ongoing process and it is the responsibility of the investigator or their designee to continue to the informed consent process throughout the trial on a verbal or written basis if necessary.

15. Scientific reporting and publication

This study will be conducted in accordance with OHRI Publication Policy and will be registered with clinicaltrials.gov. The sponsor does not have any control on publication policy or authorship. Authorship will be determined by the Steering Committee and will be guided by the extent of participation in the development of the protocol, accrual of participants to the study, involvement in the study analysis and the drafting of the final manuscript. Results of the study will be disseminated through publications and presentations at international meetings. Any other publication or presentation related to the study and the results by any investigator or participant must receive prior approval from the Steering Committee. No other publication or presentation is permitted before the primary publication or presentation by the Steering Committee. The information developed during the conduct of this clinical study is considered confidential.

16. References

1. Pitcher D, Braddon F, Hendry B, et al. Long-Term Outcomes in IgA Nephropathy. *Clin J Am Soc Nephrol*. Jun 1 2023;18(6):727-738. doi:10.2215/CJN.0000000000000135

2. Reich HN, Troyanov S, Scholey JW, Cattran DC, Toronto Glomerulonephritis R. Remission of proteinuria improves prognosis in IgA nephropathy. *J Am Soc Nephrol*. Dec 2007;18(12):3177-83. doi:10.1681/ASN.2007050526

3. Donadio JV, Bergstralh EJ, Grande JP, Rademcher DM. Proteinuria patterns and their association with subsequent end-stage renal disease in IgA nephropathy. *Nephrol Dial Transplant*. Jul 2002;17(7):1197-203. doi:10.1093/ndt/17.7.1197

4. Inker LA, Mondal H, Greene T, et al. Early Change in Urine Protein as a Surrogate End Point in Studies of IgA Nephropathy: An Individual-Patient Meta-analysis. *Am J Kidney Dis*. Sep 2016;68(3):392-401. doi:10.1053/j.ajkd.2016.02.042

5. Thompson A, Carroll K, L AI, et al. Proteinuria Reduction as a Surrogate End Point in Trials of IgA Nephropathy. *Clin J Am Soc Nephrol*. Mar 7 2019;14(3):469-481. doi:10.2215/CJN.08600718

6. Canney M, Barbour SJ, Zheng Y, et al. Quantifying Duration of Proteinuria Remission and Association with Clinical Outcome in IgA Nephropathy. *J Am Soc Nephrol*. Feb 2021;32(2):436-447. doi:10.1681/ASN.2020030349

7. Rauen T, Eitner F, Fitzner C, et al. Intensive Supportive Care plus Immunosuppression in IgA Nephropathy. *N Engl J Med*. Dec 3 2015;373(23):2225-36. doi:10.1056/NEJMoa1415463

8. Lv J, Wong MG, Hladunewich MA, et al. Effect of Oral Methylprednisolone on Decline in Kidney Function or Kidney Failure in Patients With IgA Nephropathy: The TESTING Randomized Clinical Trial. *JAMA*. May 17 2022;327(19):1888-1898. doi:10.1001/jama.2022.5368

9. Kidney Disease: Improving Global Outcomes Glomerular Diseases Work G. KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases. *Kidney Int*. Oct 2021;100(4S):S1-S276. doi:10.1016/j.kint.2021.05.021

10. Randomised placebo-controlled trial of effect of ramipril on decline in glomerular filtration rate and risk of terminal renal failure in proteinuric, non-diabetic nephropathy.

The GISEN Group (Gruppo Italiano di Studi Epidemiologici in Nefrologia). *Lancet*. Jun 28 1997;349(9069):1857-63.
11. Coppo R, Peruzzi L, Amore A, et al. IgACE: a placebo-controlled, randomized trial of angiotensin-converting enzyme inhibitors in children and young people with IgA nephropathy and moderate proteinuria. *J Am Soc Nephrol*. Jun 2007;18(6):1880-8. doi:10.1681/ASN.2006040347
12. Li PK, Leung CB, Chow KM, et al. Hong Kong study using valsartan in IgA nephropathy (HKVIN): a double-blind, randomized, placebo-controlled study. *Am J Kidney Dis*. May 2006;47(5):751-60. doi:10.1053/j.ajkd.2006.01.017
13. Bagchi S, Mani K, Swamy A, et al. Supportive Management of IgA Nephropathy With Renin-Angiotensin Blockade, the AIIMS Primary IgA Nephropathy Cohort (APPROACH) Study. *Kidney Int Rep*. Jun 2021;6(6):1661-1668. doi:10.1016/j.ekir.2021.02.018
14. Rovin BH, Adler SG, Barratt J, et al. Executive summary of the KDIGO 2021 Guideline for the Management of Glomerular Diseases. *Kidney Int*. Oct 2021;100(4):753-779. doi:10.1016/j.kint.2021.05.015
15. Csiky B, Kovacs T, Wagner L, Vass T, Nagy J. Ambulatory blood pressure monitoring and progression in patients with IgA nephropathy. *Nephrol Dial Transplant*. Jan 1999;14(1):86-90. doi:10.1093/ndt/14.1.86
16. Wen RW, Chen XQ, Zhu Y, et al. Ambulatory blood pressure is better associated with target organ damage than clinic blood pressure in patients with primary glomerular disease. *BMC Nephrol*. Dec 11 2020;21(1):541. doi:10.1186/s12882-020-02200-1
17. Stefanski A, Schmidt KG, Waldherr R, Ritz E. Early increase in blood pressure and diastolic left ventricular malfunction in patients with glomerulonephritis. *Kidney Int*. Oct 1996;50(4):1321-6. doi:10.1038/ki.1996.444
18. Powers MA, Bardsley J, Cypress M, et al. Diabetes Self-management Education and Support in Type 2 Diabetes: A Joint Position Statement of the American Diabetes Association, the American Association of Diabetes Educators, and the Academy of Nutrition and Dietetics. *Diabetes Care*. Jul 2015;38(7):1372-82. doi:10.2337/dc15-0730
19. Jonkman NH, Westland H, Groenwold RH, et al. Do Self-Management Interventions Work in Patients With Heart Failure? An Individual Patient Data Meta-

Analysis. *Circulation*. Mar 22 2016;133(12):1189-98. doi:10.1161/CIRCULATIONAHA.115.018006

20. Gibson PG, Powell H, Coughlan J, et al. Self-management education and regular practitioner review for adults with asthma. *Cochrane Database Syst Rev*. 2003;(1):CD001117. doi:10.1002/14651858.CD001117

21. Bodenheimer T, Lorig K, Holman H, Grumbach K. Patient self-management of chronic disease in primary care. *JAMA*. Nov 20 2002;288(19):2469-75. doi:10.1001/jama.288.19.2469

22. Tang TS, Funnell MM, Oh M. Lasting effects of a 2-year diabetes self-management support intervention: outcomes at 1-year follow-up. *Prev Chronic Dis*. 2012;9:E109. doi:10.5888/pcd9.110313

23. Carter SA, Gutman T, Logeman C, et al. Identifying Outcomes Important to Patients with Glomerular Disease and Their Caregivers. *Clin J Am Soc Nephrol*. May 7 2020;15(5):673-684. doi:10.2215/CJN.13101019

24. Carter SA, Teng C, Gutman T, et al. A Focus Group Study of Self-Management in Patients With Glomerular Disease. *Kidney Int Rep*. Jan 2022;7(1):56-67. doi:10.1016/j.ekir.2021.10.011

25. McManus RJ, Mant J, Bray EP, et al. Telemonitoring and self-management in the control of hypertension (TASMINH2): a randomised controlled trial. *Lancet*. Jul 17 2010;376(9736):163-72. doi:10.1016/S0140-6736(10)60964-6

26. McManus RJ, Mant J, Franssen M, et al. Efficacy of self-monitored blood pressure, with or without telemonitoring, for titration of antihypertensive medication (TASMINH4): an unmasked randomised controlled trial. *Lancet*. Mar 10 2018;391(10124):949-959. doi:10.1016/S0140-6736(18)30309-X

27. McManus RJ, Mant J, Haque MS, et al. Effect of self-monitoring and medication self-titration on systolic blood pressure in hypertensive patients at high risk of cardiovascular disease: the TASMIN-SR randomized clinical trial. *JAMA*. Aug 27 2014;312(8):799-808. doi:10.1001/jama.2014.10057

28. Schwartz CL, Seyed-Safi A, Haque S, et al. Do patients actually do what we ask: patient fidelity and persistence to the Targets and Self-Management for the Control of Blood Pressure in Stroke and at Risk Groups blood pressure self-management

intervention. *J Hypertens*. Aug 2018;36(8):1753-1761. doi:10.1097/HJH.0000000000001738

29. The E-KCG, Herrington WG, Staplin N, et al. Empagliflozin in Patients with Chronic Kidney Disease. *N Engl J Med*. Jan 12 2023;388(2):117-127. doi:10.1056/NEJMoa2204233

30. Heerspink HJL, Stefansson BV, Correa-Rotter R, et al. Dapagliflozin in Patients with Chronic Kidney Disease. *N Engl J Med*. Oct 8 2020;383(15):1436-1446. doi:10.1056/NEJMoa2024816

31. Rossing P, Baeres FMM, Bakris G, et al. The rationale, design and baseline data of FLOW, a kidney outcomes trial with once-weekly semaglutide in people with type 2 diabetes and chronic kidney disease. *Nephrol Dial Transplant*. Aug 31 2023;38(9):2041-2051. doi:10.1093/ndt/gfad009

32. Lafayette R, Kristensen J, Stone A, et al. Efficacy and safety of a targeted-release formulation of budesonide in patients with primary IgA nephropathy (NefIgArd): 2-year results from a randomised phase 3 trial. *Lancet*. Sep 9 2023;402(10405):859-870. doi:10.1016/S0140-6736(23)01554-4