Published in final edited form as:

Diabetes Res Clin Pract. 2013 October ; 102(1): 25–34. doi:10.1016/j.diabres.2013.06.004.

Adherence and renal biopsy feasibility in the Renin Angiotensin-System Study (RASS) primary prevention diabetes trial^{☆,☆☆}

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Abstract

Aims—Enhancing adherence in research trials is fundamental to the proper testing of treatment hypotheses.

Methods—Regimen and follow-up adherence as well as factors associated with adherence in the Renin Angiotensin-System Study (RASS) diabetic nephropathy primary prevention trial were evaluated. Adherence to medication (i.e., pill count), follow-up visits, and follow-up renal biopsies was evaluated.

Results—89.8% of subjects completed the second renal biopsy. 96% of follow-up visits were attended within prescribed time windows. Mean medication adherence was 85.6%. Subgroup analyses revealed greater declines in the least adherent participants over time. Factors associated with greater adherence levels included older age, type 1 diabetes (T1DM) duration, lower HbA_{1c} and blood pressure, GFR, ethnicity, and participants', principal investigators' (PI), and trial coordinators' (TC) baseline predictions of adherence.

Conclusions—T1DM patients *without* nephropathy were willing to take experimental medications and undergo repeat renal biopsies. Although overall adherence was excellent, patterns of adherence varied among participants, suggesting the need to better track adherence and to

[☆]This work was supported by grants from the National Institutes of Health (NIH), the National Institute of Diabetes and Digestive and Kidney Diseases (DK51975), Merck (in the United States), Merck Frosst (in Canada), and the Canadian Institutes of Health Research (CIHR) (DCT 14281). RASS also was supported by a grant from the NIH National Center for Research Resources to the University of Minnesota General Clinical Research Center (GCRC) (M01-RR00400).

^{☆☆}Trial #: NCT00143949.

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Conflict of interest

There are no conflicts of interest.

develop customized and targeted approaches for promoting adherence to clinical research regimens. Staff subjective predictions of adherence were imprecise, supporting need for further development of adherence predictors.

Keywords

Adherence; Research; Clinical trial; Kidney biopsy; Diabetes; Psychology

1. Introduction

The Renin Angiotensin-System Study (RASS) was a 5-year multicenter, double blind, placebo-controlled, diabetic nephropathy primary prevention trial in normoalbuminuric and normotensive type 1 diabetes mellitus (T1DM) persons [1,2]. Diabetic nephropathy (DN), a serious complication of diabetes, develops in roughly 25% of T1DM patients over time [3,4]. The RASS was designed to determine whether a daily regimen of the angiotensin converting enzyme inhibitor (ACEI) enalapril (Vasotec, Merck & Co.) or angiotensin II receptor blocker (AIIIRB) losartan (Cozaar, Merck & Co.) could prevent or delay DN relative to placebo. The principal endpoint was the rate of progression of mesangial expansion as determined from measurements in baseline and 5-year renal biopsies [1]. Secondary endpoints included other DN biopsy changes, renal function changes and progression of retinopathy grade determined by fundus photography [4,5].

The RASS had the innovative design of having the primary outcome based on sequential research renal biopsies in a primary prevention clinical trial of individuals without clinical evidence of renal disease. This article describes adherence to the RASS regimen and methods used to monitor and promote adherence. It also explores the association between adherence and biological, behavioral, and psychological factors. Although the RASS was not primarily designed to study adherence, investigation of the effects of adherence, and factors affecting it was an important component of the trial. Pill-taking (i.e., pill count) and other protocol behaviors were tracked to elucidate adherence patterns across the protocol's behavioral elements.

Non-adherence to clinical regimens is a pervasive problem considered to undermine health care across diverse health conditions resulting in significant adverse outcomes [6]. Difficulty adhering to diabetes regimens (e.g., insulin administration, blood glucose monitoring, diet, exercise, weight management) results in heterogeneous adherence rates among these various elements of the treatment program [7-9] in both type 1 and type 2 diabetes [9]. One study reported that 19% of adult Finnish people with type 1 diabetes described negligent self-care patterns, and this group exhibited significantly poorer ($p = 0.003$) glycemic control than more adherent groups [10]. A review of 23 studies of people living with diabetes estimated mean adherence of 67.5% [11] while another estimated that only 28% of people with type 2 diabetes achieve good glycemic control [12]. Only 2% of adults with diabetes appear to perform all American Diabetes Association (ADA)-recommended cares [13].

Beyond the clinical context, two forms of adherence are critical to clinical investigations, regimen adherence and follow-up adherence [14,15]. *Regimen adherence* comprises fulfilling experimental tasks consistently (e.g., complying with medication schedule and

doses; avoiding potentially confounding factors). *Follow-up adherence* comprises following the protocol of assessment measures (e.g., follow-up clinic visits, laboratory tests) within scheduled windows [16,17].

Problems with both adherence types in clinical trials can undermine research objectives, add to research expenses by requiring larger trials, muddle treatment outcome assessments, and ultimately undermine healthcare advances. Lasagna and Hutt [18] estimated that 25–50% of research subjects are non-adherent. An extreme form is premature withdrawal. A review of industry-sponsored studies' IRB records revealed 74% of subjects completed their trials [19]. Achieving adherence in primary prevention studies, such as the RASS, may be more challenging than in trials treating overt disease [20,21].

2. Methods

2.1. Participants

The RASS enrolled 285 participants with T1DM between August 1997 and March 2001 through University of Minnesota, McGill University, and University of Toronto research centers, following informed consent procedures approved by institution's internal review boards (IRB). T1DM duration ranged from 2 to 20 years. Subjects 18 years old were recruited from endocrinology clinics and local advertising. Minnesota and Montreal centers also included some 16–17 year old subjects from the Natural History of Diabetic Nephropathy Study (NHS) [22,23]. Enrollment included 68 (24%) subjects from the NHS [22] who had undergone two renal biopsies and whose exit NHS biopsy served as RASS baseline biopsy.

Of 1065 potential participants, 707 (66%) refused participation; 73 (7%) were excluded for not meeting RASS eligibility criteria [1]. Eligible patients had no clinical or laboratory evidence of diabetic kidney disease. Thus, eligibility criteria included normal blood pressure (BP; 135/85 mm/Hg) and urinary albumin excretion rates (AER) ($<20 \mu\text{g}/\text{min}$), normal or elevated glomerular filtration rate ($\text{GFR} > 90 \text{ ml}/\text{min}/1.73 \text{ m}^2$), T1DM of 2–20 year duration, and adequate baseline renal biopsy [1]. Exclusion criteria included antihypertensive medication use, pregnancy, plans to become pregnant within two years, and planned location change. Table 1 presents baseline data. Pre-randomization screening included completion of a 2-week placebo run-in; subjects taking 85% of prescribed placebo pills (0.9%) were excluded.

RASS design was detailed earlier [1]. Participants were randomized in computer-generated blocks of six with stratification by center and sex into three groups: (a) enalapril 10 mg plus losartan placebo once daily; (b) losartan 50 mg plus enalapril placebo once daily; or (c) enalapril and losartan placebos once daily. Subjects took study drugs for 4.5–5 years. Approximately a third of the way through the trial, dosages were doubled for enalapril to 20 mg and losartan to 100 mg based on data suggesting greater proteinuria reduction with higher ARB doses [1,24]. Adverse events related to interventions were minimal (14 events in 14 patients) [2].

2.2. Clinical research protocol

The protocol specified quarterly clinic visits to monitor BP, HbA_{1c}, weight, AER, pregnancy tests (for women of child-bearing age), concomitant medications, adverse events (e.g., severe hypoglycemia), self-reported medication adherence, and pill counts. Annual visits included 5 h GFR testing, 24-h ambulatory BP monitoring, drawing fasting serum and plasma samples, documentation of socioeconomic changes, and completion of brief psychological measures. Fundus photography was performed at baseline, mid-point, and exit. Subjects received reminder calls for quarterly visits. Instructions for fasting and preparations for GFR measurements were mailed before annual visits. Quarterly and annual visits respectively took approximately 45 min and 5 h. The protocol included exit kidney biopsy and GFR the last day of participants' study medication followed by a 2-month drug washout. Clinic BP measurements were obtained after 2-weeks, BP and AER were obtained after 4-weeks, and BP (clinic and 24 h ambulatory monitoring), AER and GFR were measured after 8 weeks. Subjects were compensated for travel and time away from work and given parking and incentives to promote study commitment, but were not paid for participating. Visits were arranged to accommodate participants' schedules. At randomization PIs and TCs estimated participants' anticipated adherence and participants completed forms of personal characteristics and study commitment.

2.3. Baseline characteristics by site and treatment arm

There were modest differences at baseline across research sites in age, age at diagnosis, duration of diabetes, ethnicity, BMI, systolic and diastolic BP and GFR (Table 1). Centers did not differ for baseline AER or HbA_{1c}. The Montreal cohort was youngest and had highest GFR and lowest serum creatinine and BP. Minnesota participants had higher BMIs. Treatment arms were comparable in baseline characteristics and in terms of whether subjects later had exit renal biopsies or fundus photos.

2.4. Adherence-enhancing and monitoring approaches

Multimodal adherence-enhancing strategies described elsewhere for diabetes and other conditions [14,15,25,26] were integrated as study procedures to promote adherence with the medication regimen and were implemented across centers. These included: periodic newsletters, social and informational events, quarterly clinic visits, personalized cards (e.g., celebrating birthday, life events, and study milestones), symbolic incentives (e.g., RASS T-shirt, coffee mug, sweatshirts of research sites' universities), pill minders, and mid-visit telephone calls. Adherence challenges were discussed during trial coordinators' monthly conference calls with a health psychologist (WNR) to tailor strategies promoting problematic subjects' adherence (e.g., intensified frequency of communications; adherence-related problem-solving; scheduling week-end visits to obtain study-prescribed samples within protocol windows).

As reflected in the University of Minnesota data for the final series (Fig. 3), a concerted effort was made to target individuals whose adherence was between 70% and 85% to reinforce their adherence so as to prevent erosion of adherence and meet study adherence goals. Between 2003 and 2005 a pilot program of 14 participants at the Minnesota center was initiated to augment adherence in subjects with suboptimal medication compliance (70–

85%, i.e., those appearing somewhat committed, but not achieving study goals). It used monthly pill minders with 31 compartments (i.e., one for each day of the month) pre-filled by study staff. Minders were used for one to six sessions (3 month periods; *mean* = 3.2) based on when they reached their exit visit. For this subgroup, pill-minders yielded an increase in adherence from 79.5% to 91.5% ($t_{\text{(paired)}} = 3.97$; $p < 0.002$) suggesting it may be a useful medication adherence-enhancing strategy for some patients.

To meet the “80% rule” biomedical convention for regimen adherence [27], the RASS endeavored to promote 85% medication-taking for all subjects. Subjects brought their unused medication to quarterly and annual appointments where they were given the next 3-months’ medication. Medication adherence was monitored by covert pill counts conducted by trial coordinators. To preclude confounding adherence data (e.g., dumping unused pills before clinic visits) participants were not informed of pill counts. The number of pills dispensed was not constant. Subjects taking <85% of medications received greater staff efforts to promote adherence (i.e., intensified telephone contacts, discussion of the need for medication consistency, problem-solving to surmount barriers, optional pill minders pre-loaded by RASS staff).

2.5. Statistical analysis

Adherence was calculated by the Data Center (McGill University) comparing unused medication with the number of pills that should have been used during the interim 3-month period (i.e., number of days between visits minus number of pills taken). Professional Data Analysts, Inc. conducted additional data analyses. Statistical analyses included analysis of variance (ANOVA) chi-squares, *t*-tests, Fisher exact tests, and tests of equality of means.

Study drugs were withheld if pregnancy was suspected or until pregnancy and breastfeeding were completed and if important drug-related side effects were suspected. Medication adherence was calculated as the percentage of study pills presumed to have been taken relative to the number of pills prescribed. Medication “exposure” was estimated as the percentage of days the study medication was taken. If participants were required to stop study medications during pregnancy this would lower exposure but not adherence. Medications were discontinued in 14 (5%) subjects for medical reasons, i.e., pregnancy (4), elevated liver enzymes ALT (2), lethargy and depression (1), severe hypoglycemia and low BP (1), insomnia (1), hypotension and hyperkalemia (1); rash/hives (3), headaches (1), nausea and persistent cough (1), poor memory and inability to concentrate (1).

2.6. Adherence metrics

Two medication adherence indices were tracked based on pill counts. “Adherence” was defined as the percentage of prescribed pills taken (excluding time off drug prescribed by RASS personnel). “Adherence 85” was defined as the percentage of subjects’ research visits in which the minimal target of 85% medication adherence was achieved. Other metrics included continuation in the study, follow up adherence to clinic visit time windows (± 3 weeks for quarterly visits; ± 4 for annual visits), whether they completed all renal biopsies.

3. Results

3.1. Continuation in study and renal biopsy adherence

Two hundred fifty-six (89.8%) randomized subjects completed the study as defined by providing both baseline and 5-year biopsy (Table 2). Twenty-nine (10.2%) did not receive a second biopsy including 23 (8.1%) who declined or were lost to follow-up. Two had medical safety contraindications and one's second biopsy yielded inadequate tissue. There were no center differences in the repeat biopsy rates. Adverse events related to biopsies were minimal (2 perinephric hematomas; one bladder clot) with no permanent sequelae. Three subjects (0.1%) died of causes unrelated to the study.

3.2. Follow-up adherence

Nearly all (96%) of the 5606 scheduled visits were attended within prescribed time windows. Most participants (220; 77%) attended all 23 study visits within prescribed time windows. Of the 65 participants missing any visits, 30 missed just one; 9 missed 2; 4 missed three; 16 missed 4–9; and 6 missed 12. There were no differences among treatment arms for clinic visit adherence (ANOVA $p = 0.92$). Adherent attendance at scheduled clinic visits was virtually always associated with adherence to the required procedures within each visit (e.g., GFR, ABP, UAE, HbA_{1c}), reflecting overlapping compliance measures.

3.3. Medication regimen adherence

Overall, mean medication adherence was 85.6%. Treatment arms had similar medication adherence (ANOVA $p = 0.87$). Most participants (207; 73%) maintained >85% of adherence throughout the study. Thirty-five (12%) achieved 70–85% adherence; 43 (15%) were <70%. Within the > 85% adherence subset, only one participant maintained perfect adherence (i.e., 100%); 118 (41%) achieved 95% adherence, and 176 (62%) sustained 90% adherence during the 5 years.

Medication adherence varied across sites ($p < 0.037$). Test of hypothesis of equality of means revealed differences between Montreal and Toronto centers ($p = 0.014$; Table 3). Across centers, medication adherence gradually eroded from a mean of 93% during the first quarter to 84% for the final quarter (Fig. 1). Centers maintained their relative adherence rankings throughout the study (Fig. 1). A slight increase in the Minnesota center's adherence² emerged toward the end of data collection, corresponding with use of the pre-filled pill minder described earlier.

Fig. 2 summarizes adherence data for participants who remained in the study for the entire data collection period. The group that met the RASS target of >85% adherence maintained remarkable consistency over the 5 years of the study (Fig. 2). Participants completing the study whose mean adherence was 70–85% demonstrated considerably greater variability in pill taking and steeper erosion of adherence over time (Fig. 3). The increase in medication

²Although these numbers and the limited time period render this trend anecdotal, the method may be replicated in future studies to see its impact on enhancing compliance. The other two centers were less successful in implementing the pill-minder strategy (e.g., reflecting greater participant resistance and more erratic staff and participant use of the pill-minders) and were not included in the analysis of this pilot study.

compliance in the Minnesota group toward the end of the study was temporarily related to increased compliance efforts by the staff, including the provision of one-month pill reminders. On the other hand, the rapid decrease in compliance in the Toronto center at this late stage of the study (Fig. 3) was temporarily related to changes in study coordinator personnel.

3.4. Methodological factors in estimating medication adherence

Two estimates of medication adherence were derived to monitor adherence and to permit comparisons (quarterly self-reports; pill counts). Two analyses were conducted comparing the two approaches. Across all 283 participants, 86% adherence was evident by pill count, which was lower ($p < 0.001$) than the 94% adherence estimated in quarterly self-reports revealing participants' overestimation of adherence. A second analysis, based on the subgroup of 149 participants demonstrating flawless follow-up adherence (i.e., attended each scheduled clinic visit), revealed higher levels of adherence, and somewhat closer alignment between pill count (92%) and self-reported adherence (96%), though the difference between pill counts and self-reports differed ($p < 0.001$).

3.5. Factors associated with medication adherence

Several baseline characteristics were different between the $\geq 85\%$ and the $<85\%$ adherence groups (Table 4). The $<85\%$ adherence group was younger (adjusted odds ratio = 1.08; $p < 0.0001$), younger at diabetes onset, and had shorter diabetes duration (adjusted odds-ratio = 1.07; $p < 0.009$). They also had worse glycemic control (HbA_{1c}). When combining age and diabetes duration, only age at baseline remained in the model.

3.6. Research experience and pre-randomization screening

A trend was seen for increased likelihood for research-experienced participants (i.e., NHS subjects) to maintain $\geq 85\%$ medication adherence than for research-naïve participants ($\chi^2 = 2.46$; $p = 0.08$). At entry, PIs and TCs estimated adherence levels for individual participants. Overall, PIs' and TCs' estimates of participants' adherence ranging from excellent (55%) to moderate (31%) to minimal ($<1\%$) were nearly identical. Their ratings were significantly correlated with medication adherence and adherence to clinic visits, but only accounted for 4.6–11.8% of the variance (Table 5). At study entry, participants also rated their anticipated consistency in doing things asked of them and in following their recommended treatment. Most indicated that they were moderately consistent (16.5%) or very consistent (71.7%) in doing what they were asked. Most also indicated that they usually (46.3%) or always (38.6%) followed recommended treatment. Their self-assessments had limited predictive value of their adherence, accounting for ≈ 2 –6% (Table 5).

4. Discussion

Adherence within clinical studies is essential in evaluating treatment related research hypotheses. Lengthy prevention and treatment trials require that participants fulfill complex, consistent behavioral sequences including adherence with the clinical regimen (e.g., medication) associated with treatment arms and with objective measurements to determine treatment impact. Therefore, ensuring adherence as part of trial implementation warrants

careful consideration from the beginning of a study's design to the end of data collection, incorporating adequate processes to promote and confirm protocol fidelity.

This a priori designed compliance ancillary study to the RASS provided an opportunity, in a primary prevention trial, to examine adherence patterns over time, including quantification of medication compliance, adherence to interval protocol tasks, as well as submission to the performance of a repeat renal biopsy. Whereas studies of participants with clinical renal disease have included repeated renal biopsies [28-31], to our knowledge this is the first native kidney sequential biopsy primary prevention trial with *renal-asymptomatic* diabetic participants. This approach was undertaken to study whether the investigational treatments could attenuate morphological changes associated with very early pathological disease progression. Hard clinical disease expression end-points in a primary prevention study would have necessitated a wholly impractical trial length. Renal biopsies proved to be a surmountable barrier to study accrual and implementation, but sequential biopsies may have dissuaded some candidates who otherwise might have volunteered since only 29% of eligible participants volunteered. The number who specifically declined for this reason is unknown. Given the demanding and lengthy study design, it is possible the study attracted a subset of the participants who were more likely to be compliant than the general T1DM population. If so, this may have enhanced the RASS's ability to discern treatment effects.

4.1. Follow-up adherence

Participants were motivated to fulfill commitments to attend research visits. During the 5 years, nearly all arrived for most visits. Among those who did not meet all time windows, relatively few visits were actually missed, reflecting participants' and study staff's strong commitment to the study.

RASS demonstrates the feasibility of incorporating biopsy-derived morphological analyses in primary prevention studies: 91% underwent the second renal biopsy and only 23 declined, withdrew consent, or were lost to follow-up. This reflects subjects' understanding of the need for repeat biopsies to reach study objectives and their acceptance and tolerance of baseline biopsy. Subjects' willingness to endure minor discomfort and small risk [32] associated with biopsy points to their recognition of the goal shared with investigators to find treatments to minimize diabetic nephropathic effects. This precedent may assuage future candidates' concerns about entering preventative trials involving renal biopsy.

4.2. Regimen adherence

Pill counts, albeit imperfect adherence indices [33,34], nevertheless provide objective evidence of problematic medication-taking that is more sensitive than self-report. Dispensing random numbers of pills in excess of those required presumably increased the validity of this index. Most participants took study medications at levels consistent with research convention. The 85.6% overall medication adherence satisfactorily met the threshold behavioral study objectives, but was not as high as hoped, possibly reflecting barriers encountered [35]. Although individual participants were generally consistent, heterogeneity in medication taking persisted despite efforts to promote adherence, underscoring the challenge of maintaining optimal levels in lengthy trials. Anecdotally,

study staff noted that participants demonstrating problematic adherence required the most staff time and attention and were disproportionately perceived as being challenging to motivate. Further efforts are needed to develop protocols for intensively working with participants to improve consistency in taking study medications.

Variability in adherence was also noted among centers. This is not uncommon in multicenter trials (e.g., it was observed in the Diabetes Control and Complications Trial [DCCT]) [36,37]. It can reflect differences among sites' sample populations (e.g., age variation), as well as variability in how adherence efforts are organized and implemented, and how committed individual study personnel may be (e.g., staff turnover, fidelity to protocols, consistency in addressing adherence issues). There were no center differences in adherence to the second biopsy (a successful first biopsy was an entry criterion). Some subjects in the Montreal and Minnesota centers had previously participated in kidney biopsy studies while none had in the Toronto cohort. There was better medication compliance in the Toronto vs. the Montreal group, but not between the Minnesota and either of the other two groups. Thus, prior participation in similar studies did not appear to have any systematic effect on the present study.

Participants' heterogeneous behavior patterns do not justify assuming that study volunteers will fulfill stated adherence intentions. Vigilance throughout studies for indications of suboptimal adherence and resources to address it (e.g., staff time, behavioral consultation, design and implementation of monitoring systems) are warranted.

4.3. Predictive factors for study adherence

Data from the two week placebo run-in revealed mean 98.5% adherence, with all but one individual demonstrating adherence 85%. Thus, such screening is an imperfect predictor of adherence to longer study regimens [38,39]. Since only individuals who were consistent enough to meet run-in eligibility were randomized, the truncated range of run-in behavior precluded predicting compliance over the 5 years.

To the extent that glycemic control is associated with medication adherence, it was hypothesized that better glycemic control would augur more consistent regimen adherence. As expected, poorer glycemic control during RASS was associated with worse medication compliance. However, selecting patients with meticulous glycemic control could have reduced the progression of diabetic complications thus limiting the study's ability to detect RASS treatment effects. The delicate balance among cofactors warrants consideration in designing investigations.

Although the subjective adherence predictions for participants as rated by PIs and TCs accounted for limited variance of participants' actual adherence in RASS, it was statistically significant across all three dimensions of medication and follow-up adherence. Staff ratings appear to be of some, albeit limited, value in predicting adherence. Similarly, specific questions of participants, such as their consistency and their historical adherence to treatment regimens, were modestly predictive of their adherence patterns in the trial. However, if participants do acknowledge adherence challenges, it is reasonable to provide extra assistance. At least, in part, the low predictive values of patients and staff may reflect

participants' overall strong adherence. Even if queries during recruitment have limited predictive value, they may be useful in beginning vital conversations about the importance of adherence. The association between predictive variables and trial adherence offers fertile ground for further study.

4.4. Study fatigue

Participants' adherence to medication regimens decreased over time, most prominently in the least adherent group. Overall, RASS retention and follow-up adherence patterns were similar to earlier studies. For example, 99% of participants in the DCCT completed the study and >95% of scheduled examinations were completed. However, many long-term studies are confounded by "study fatigue" [40]. We do not know if RASS's persistent efforts at improving compliance resulted in lesser erosion, but RASS and DCCT both had clear and persistent adherence strategies and unusually good long-term adherence, suggesting that this may be the case. Most RASS subjects had excellent (>85%) adherence throughout the study. In the group with 70–85% adherence, adherence gradually eroded throughout the study. Anecdotally, redoubled effort in one of the centers was associated with some improvement in medication adherence toward the end of the study while study personnel changes in another center were temporarily related to more rapid adherence deterioration. These observations suggest that study fatigue may be a factor still amenable to investigator variables and efforts. Nonetheless, in design of long studies, consideration should be given to the potential impact of study fatigue on compliance and the resultant potential negative effects on the study's statistical power.

4.5. Limitations of study

The chief limitations for extrapolating from RASS are that it was based on urban North American, almost entirely Caucasian, participants with T1DM, most obtaining care at urban University settings, some veterans of previous studies and all with normal clinical laboratory values for the primary study endpoint. The generalizability to more diverse populations and treatment studies for other conditions (e.g., manifest nephropathy) is not known. This study reports on patients living with T1DM. It is not known how generalizable the results are to type 2 DM. However, it is noted that some investigations report fairly comparable nonadherence levels in these two patient groups [41]. On the other hand, one study of structural behavioral intervention toward improved glycemic control found better compliance among patients with type 2 diabetes [42]. However, this finding was no longer statistically significant ($p = 0.09$) after adjustment for baseline age, diabetes duration and pedometer steps. On the other hand, in a comparison of youth with diabetes, adherence with exercise recommendations was greater among those with type 1 vs. type 2 diabetes [43]. Given this background, it is reasonable to consider that factors such as age, diabetes duration and study design, and the nature of the research question and intervention may be as or more important than diabetes type as determinants of study adherence.

Electronic monitoring (e.g., Medication Event Management System[®], MEMS[™]AARDEX Group, Sion, Switzerland) could have provided more precise and timely analysis of medication adherence. Unfortunately, there was no readily measurable biological parameter of compliance with the study medications (i.e., as HbA_{1c} in the DCCT).

4.6. Future directions

Clinical investigations are dependent on the efforts of cohorts of motivated and adherent participants. Studies that fail to achieve acceptable levels of adherence squander resources and needlessly expose other participants and patients to avoidable health risks while reducing studies' power to demonstrate benefit or harm. More effective strategies for maximizing research adherence are essential, especially for the long-term studies needed for investigating slowly progressive diseases. New methodologies could leverage technological advances (e.g., MEMS, GlowCaps), expand communication options (Wi-Fi, social media, smart phones) to enhance communication between participants and study personnel, promote real-time indicators of adherence and troubleshoot potential factors that might undermine it. In addition, educating clinical research personnel on how fundamental adherence is to successful research and on techniques for promoting adherence (e.g., motivational interviewing [44]) may enhance future studies. Developing clear plans for addressing predictable adherence challenges, for dealing with unforeseen circumstances that may undermine adherence, and for tracking behavioral and physiological adherence metrics are critical. Such tracking may provide earlier identification of problems, allowing for targeted interventions for at-risk participants to promote adherence. Since adherence is likely to decline over the course of trials, planning and budgeting for ongoing surveillance of adherence and interventions to maximize adherence should be incorporated in study designs. Such approaches have potential to yield more cost-effective, productive, and accurate clinical research [15].

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Fig. 1.

Mean medication adherence of subjects enrolled through visit 20. Notes. Visit 20 was the final visit in which pill counts were obtained and when the second renal biopsy was obtained. M = Montreal; T = Toronto; U = Minnesota Center. Center refers to all centers. $N = 273$.

Fig. 2.

Mean medication adherence of subjects who maintained adherence >85%. Notes. Based on subjects enrolled through visit 20 (the final visit in which pill counts were obtained and when the second renal biopsy was obtained). M = Montreal (58); T = Toronto (74); U = Minnesota (69); Center = All centers combined. $n = 201$.

Fig. 3.

Mean medication adherence of subjects who maintained adherence 70–85%. Notes. Based on subjects enrolled through visit 20. M = Montreal (11); T = Toronto (9); U = Minnesota (13); Center = All centers combined. $n = 33$.

Table 1

Baseline characteristics of RASS subjects.

Characteristic	Overall M	S.D.	Range	Toronto (94)	Minnesota (96)	Montreal (95)	<i>p</i> ^a
<i>Demographic attributes</i>							
Age (years)	29.7	9.7	15.0–58.0	33.6	29.9	25.5	<0.0001
Age at DM diagnosis (years)	18.5	10.0	0.6–41.0	23.0	17.8	14.5	<0.0001
Duration of T1DM (years)	11.2	4.7	2.0–20.0	10.6	12.1	11.0	<0.08
Ethnicity (% Caucasian)	97.9			94.7	100.0	99.0	<0.01
Gender (% female)	53.7			50.0	44.8	44.2	ns
<i>Clinical attributes</i>							
Serum creatinine (mg/dl)	0.80	0.14	0.45–1.12	0.85	0.81	0.76	<0.0001
GFR ^c (ml/min/1.73 m ²)	128.7	20.1	88.0–221.0	121.7	129.3	134.9	<0.0001
Diastolic BP (mmHg)	70.2	8.4	42.0–96.5	73.3	68.8	68.5	<0.0001
Systolic BP (mmHg)	119.7	11.5	90.5–151.5	122.1	120.6	116.3	<0.002
Body mass index (kg/m ²)	25.7	3.7	19.8–43.8	25.6	26.5	24.9	<0.01
Urinary AER ^b (µg/min)	6.4	5.9	0.5–57.8	7.0	6.4	5.9	ns
HbA _{1c} (%; mmol/mol)	8.6	1.6	5.5–15.3	8.4	8.5	8.8	ns

^a Tests for equality among centers were ANOVA for continuous variables and Fisher exact test for proportions. Montreal subjects were younger (25.5 years), were diagnosed earlier (14.5 years), and had lower systolic (116.3), diastolic (68.5) BP, and higher GFR, presumably reflecting their age.

^b AER, albumin excretion rate; AER is median; all other values are mean.

^c GFR, glomerular filtration rate; GFR is corrected up to 1.73 m².

Table 2

Status of enrolled subjects at end of medication trial (visit 20).

	<i>n</i>	% of randomized subjects ^a
Completed final renal biopsy	256	89.8%
Missed final renal biopsy	29	10.2%
Declined or lost to follow up	23	8.1%
Deceased	3	1.1%
Medical contraindication to having final biopsy	2	0.7%
Inadequate tissue in final biopsy	1	0.4%
Total <i>n</i>	285	

^aDenominator = 285 (i.e., all randomized subjects).

Table 3

Medication regimen adherence by center.

Participant status	Total	Montréal	Toronto	Minnesota
Participants with at least one pill count	285	95	94	96
Participants with Adherence >85%	206	61	73	72
<i>n</i> (%)	(72.3)	(64.2)	(77.7)	(75.0)
Participants with adherence 70–85%	36	12	11	13
<i>n</i> (%)	(12.6)	(13)	(11.7)	(13.5)
Participants with adherence <70%	43	22	10	11
<i>n</i> (%)	(15.1)	(23.2)	(10.6)	(11.5)
Mean adherence ^a (%)	(85.6)	(81.5)	(88.5)	(86.8)

^a Adherence was calculated as the ratio between the number of days participants took pills and the number of days they were asked to take the medication. If the participant took one pill while instructed to take two, compliance for that day is 50%. Days on single and double dose contributed equally to the mean. This convention was derived due to the change in doses that was introduced during the study.

Table 4

Baseline characteristics between medication adherent and non-adherent subjects.

Attribute	Adherent ^a		Low adherent		p-value ^b
	Mean	S.D.	Mean	S.D.	
Demographic attributes					
Age (years)	31.4	9.7	24.3	7.7	<0.0001
Age at diagnosis (years)	20.0	10.0	14.4	8.8	<0.0001
Duration of T1DM (years)	11.7	4.6	9.9	4.9	<0.005
Ethnicity (% Caucasian)	97.6		98.7		ns
Gender (% female)	51.5		59.5		ns
Clinical attributes					
HbA _{1c} (%; mmol/mol)	8.3	1.4	9.1	1.8	<0.0001
Diastolic BP (mmHg) ^c	71.4	7.6	66.9	9.4	<0.0001
Systolic BP (mmHg) ^c	120.8	11.2	116.8	11.9	<0.01
GFR ^{c,d} ml/min/1.73 m ^b	127.0	19.4	133.1	21.4	<0.03
Body mass index (kg/m ²) ^c	25.8	3.7	25.3	3.7	ns
UAE baseline (µgm/min)	6.2	5.7	7.0	7.0	ns
Serum creatinine (mg/dl)	0.81	0.13	0.80	0.15	ns
Health behaviors					
Smoking	25.2		25.2		ns
Alcohol use	73.8		64.6		ns

^a Adherent subjects defined as maintaining mean adherence >85%.

^b Probability values for continuous variables (mean ± s.d.) and dichotomous variables (%) were respectively based on *t*-tests and either chi-square or Fisher exact tests.

^c Noted to be associated with age effect.

^d GFR is standardized for BMI only if body surface area >1.73 m².

Table 5

Correlation between staff predictions of participants' adherence at entry to study and actual adherence.

	<u>Medication adherence</u>		<u>Medication adherence 85</u>		<u>Visits kept within time window</u>		<i>n</i>
	<i>r</i>	<i>p</i>	<i>r</i>	<i>p</i>	<i>r</i>	<i>p</i>	
<i>Staff</i>							
Principal investigator	0.237	0.001	0.270	0.001	0.215	0.001	240
Trial coordinator	0.243	0.001	0.343	0.001	0.227	0.001	247
<i>Participant</i>							
How consistently are you able to do the things asked of you?	0.172	0.006	0.191	0.002	0.139	0.027	255
How often do you follow your recommended treatment	0.182	0.003	0.251	0.000	0.134	0.032	257