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Author/s:

Atlas, G;O'Connell, MA;White, M

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**Is there an optimal approach to elective stabilisation of glycaemic control in children
and adolescents with Type 1 Diabetes Mellitus?**

Running title: Interventions for sustained HbA1c reduction in adolescents

Dr Gabby Atlas^{a,b} (MBBS), Dr Michele A O'Connell^{a,b} (MRCPI, FRACP, MD), Dr Mary White^{a-c} (MRCPI, FRACP, MD)

Affiliations:

^aDepartment of Endocrinology and Diabetes, Royal Children's Hospital Melbourne, 50 Flemington Road, Parkville VIC 3052, Australia

^bMurdoch Children's Research Institute, 50 Flemington Road, Parkville VIC 3052, Australia

^cUniversity of Melbourne, Parkville VIC 3052, Australia

Corresponding author:

Gabby Atlas, Department of Endocrinology, Royal Children's Hospital Melbourne, 50 Flemington Road Parkville VIC 3052, Australia, gabby.atlas@rch.org.au, +61 3 93455951 (phone), +61 393455857 (fax)

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Keywords: Type 1 Diabetes Mellitus, adolescence, HbA1c

Author contributions: GA devised the project, designed the study and collected, interpreted and analysed the data. MW devised the project, designed the study, interpreted, and analysed the data. MOC devised the project, designed the study and interpreted the data. All authors discussed the results and contributed to the final manuscript. All authors have read and approved the final manuscript.

What is already known on this topic:

1. Adolescents with T1DM are identified to have a higher HbA1c as an age group
2. A reduction in HbA1c by 0.5% can be sufficient to decrease the risk of complications
3. Several intervention programs have been developed but none are universally successful

What this paper adds:

1. Demonstrates that strategies of intensified support and education can result in clinically meaningful improvements in glycaemic outcomes, sustained to 12 months
2. Highlights the importance of identifying more effective strategies to support and manage these individuals
3. If there has not been distinct improvement after 6 months of an intervention, an alternative approach should be considered in order to affect change

Abstract:

Aims: To investigate the effectiveness of inpatient and outpatient interventions in attaining improved glycaemic control in children/adolescents with Type 1 Diabetes Mellitus (T1DM) and persistently high/deteriorating HbA1c.

Methods: A retrospective study at a tertiary pediatric centre. Admitted individuals who had prior attempts at ambulatory stabilisation were matched with intervention naïve controls who underwent outpatient intervention. The mean age was 14.6 years in the admitted group and 14.7 years in the ambulatory group. Mean duration of diabetes was 6.1 years in the admitted group and 7.3 years in the ambulatory group. Change in HbA1c from baseline was assessed to 12 months.

Results: Mean baseline HbA1c was 11.3% [100mmol/mol], with 11.4% in the admitted group and 11.2% in the ambulatory group. Sustained reduction in HbA1c at 12 months was seen in both groups (n=35 in each): mean (SD) 10.1% (1.5) in admitted (mean reduction in HbA1c 1.4%) and 9.7% (1.4) in ambulatory (mean reduction in HbA1c 1.5%). Proportions achieving delta HbA1c $\geq 2\%$ [22 mmol/mol] at 12 months were 25% and 31% in admitted and ambulatory groups respectively. A sustained reduction in HbA1c of $\geq 2\%$ [22 mmol/mol] after 12 months was more likely in those who attained this reduction by 6 months (17/24 who achieved this at 6 months versus 3/41 who had not).

Conclusions: Both inpatient and outpatient stabilisation strategies achieved sustained improvements in HbA1c. We recommend an individualized approach to stabilisation, with review of the intervention's success at 6 months with further intensification as needed.

Introduction:

Whilst the importance of glycosylated haemoglobin (HbA1c) in the development of microvascular complications in type 1 diabetes mellitus (T1DM) is irrefutable (1-3), optimal glycaemic control continues to elude many, particularly during adolescence (4). Nonetheless, even a reduction in HbA1c by 0.5% (NGSP) is sufficient to decrease the risk of complications, hence small improvements have associated benefits(1, 2). Adolescents in particular are identified as having a higher HbA1c than other age groups, quantified as an average HbA1c 1% higher than adults despite intensive therapy (4). This may be related to reduced adherence and deterioration of glycaemic control in a period of physical, psychological and social changes with increasing independence from parental care (5, 6). The evidence base on which to inform management of children and adolescents with a persistently or markedly elevated HbA1c is limited. Several in-home, ambulatory and family-based intervention programs have been developed (7-9) but a universally successful model of care has not yet been defined. Even interventions involving intensive coaching and goal-setting have shown a minimal impact on improving glycaemic control (10).

Elective admission to hospital for “stabilisation” of diabetes is one potential intervention which is widely utilised in an effort to motivate a change in behaviors and glycaemic control. Milette et al published the first and only observational study to date which assessed the impact of this approach for suboptimal control of T1DM in 30 individuals over a 12 month period (11). No improvement in glycaemic control was seen 12 months after the initial elective admission and it was concluded that avoiding admission is likely more cost effective. There is a paucity of data in the literature pertaining to the outcomes of alternative strategies in comparable tertiary diabetes centres (12, 13). Elective admission for stabilisation is also implemented in other

chronic conditions such as cystic fibrosis and nephrotic syndrome, where suboptimal management has a clear impact on clinical outcomes. (14, 15).

The Diabetes clinic at the Royal Children's Hospital (RCH) in Melbourne is a large tertiary paediatric diabetes centre in Australia (16). As a first line for those seen in clinic with a persistently elevated or rising HbA1c, a range of step-wise strategies are employed, including outpatient/ambulatory interventions. Outpatient strategies include increased frequency of remote contact with the allied health team or face to face review sessions. An elective admission is suggested for a small proportion of individuals. A common trigger for consideration for elective admission is a persistently elevated HbA1c despite attempts at more intensive outpatient support.

Elective admissions typically involve an inpatient stay for up to 5 days with intensive input from the diabetes allied health team; regular contact with the team is established on discharge. The outcomes of these admissions has not yet been evaluated, nor have factors that may correlate with more successful outcomes. The primary aim of the study was to compare the effectiveness of inpatient and outpatient approaches in attaining improved glycaemic control 12 months after the intervention and to explore factors associated with a successful outcome. We hypothesised that there is a greater sustained clinical benefit of elective admissions for stabilisation of glycaemic control compared to ambulatory support.

Methods:

A retrospective cohort study was undertaken for all T1DM elective admissions to the Royal Children's Hospital Melbourne from January 2016 to December 2018 (inclusive) for children and adolescents with suboptimal and deteriorating glycaemic control. The data was retrieved

from a retrospective review of the electronic medical record (EMR) and correlated with the departmental record of admissions.

Goals of the admission are agreed to in advance with the young person and their family and typically include education, optimising the insulin regimen, identifying existing barriers to diabetes care and re-engaging the adolescent and their family in diabetes self-care.

Each individual who underwent elective admission was matched with another non-admitted (referred to as ambulatory) individual (1:1) with T1DM. The ambulatory patients were identified from the departmental database and did not have an elective admission in the 12 months prior to the baseline date, nor during the study period. Filtering for sex, they were matched first for HbA1c within 1% and then age within 12 months. The baseline HbA1c for admitted and ambulatory patients respectively was the HbA1c at the clinic visit where the admission was planned, versus that at the first clinic visit in the study period where a rising or static elevated HbA1c was noted. Given the finite number of individuals in the cohort with comparable characteristics to the admitted group, once all with an HbA1c within 1% and age within 12 months were exhausted, an HbA1c within 2% or age within 2 years was used (n=2).

Participants were excluded if data was not available at the 12-month time-point. For patients who had recurrent elective admissions over the study timeframe, only outcomes following the first admission were included in the analysis. None of these repeat admissions were within 12 months of the first admission and hence did not affect the data collected in that time.

Demographic and clinical data collected at baseline included participant age, duration of diabetes, baseline HbA1c (defined above), mean HbA1c in the 12 months prior to baseline insulin regimen and dose (U/kg/day), history of diabetic ketoacidosis (DKA) presentations

(excluding at diabetes diagnosis) and length of stay (for admitted individuals). Psychosocial complexity was assessed on review of the clinical notes, and the presence or absence of each of the following was noted: cultural and linguistic diversity (CALD), single or separated parent households, child protective services involvement, child or parental mental health issues, family trauma, school refusal, rural location and drug/alcohol use.

The primary outcome measure was the proportion of individuals with a reduction in HbA1c (delta HbA1c) by more than 2% [22mmol/mol] at 12 months from baseline. Secondary outcomes were the change in HbA1c by more than 1% [11mmol/mol] at 12 months from baseline, the delta HbA1c at 3, 6 and 12 months from baseline, as well as identification of any factors that may predict a reduction in HbA1c. Given that appointments were not always 3-monthly, a variation of +/- 1 month was included for all three time-points.

The 6-month time period post-baseline was analysed as a predictor of 12 months; specifically, whether the achievement (or lack) of a reduction in HbA1c by more than 2% [22mmol/mol] at 6 months would correlate with maintenance at 12 months.

HbA1c was collected through point-of-care testing (POCT) (analyser Bio-Rad D-10), with the exception of rural participants who had local pathology collection prior to the appointment. All individuals were consistent with their assay method throughout the study period.

Comparisons between admitted and ambulatory groups were tested using paired t-test and chi square analyses for continuous and categorical variables respectively for the primary and secondary outcomes. Logistic regression analysis was used to identify the independent relationship between baseline factors and a reduction in HbA1c $\geq 2\%$ at 12 months post-intervention. Statistical significance was defined as $p < 0.05$. Analysis was performed using Stata version 15.0 (StataCorp, College Station, TX, USA, 2017).

Institutional human research ethics approval was received prior to study commencement (HREC QA/54307/RCHM-2019).

Results:

There were 38 elective admissions for diabetes stabilisation in the study period. One participant was lost to follow-up in the months following the admission and two individuals had recurrent admissions (first admission included, as above in Methods), hence 35 patients were included for analysis who were matched with a corresponding ambulatory patient. The mean (SD) length of stay of these admissions was 3.1(1.0) days with a mean (SD) of 6.9 (2.4) allied health encounters during the admission. All of the admitted patient group had previously been offered intensive outpatient interventions including allied health clinic appointments and regular contact.

Within the ambulatory patient group (n=35), the intensity of allied health intervention varied; 13 had a dedicated allied health outpatient session with subsequent regular phone/email contact, 13 had weekly phone/email contact initiated by the allied health team and 9 were requested to maintain regular contact with the team with the responsibility placed on the family.

All individuals had a baseline HbA1c >9% [75mmol/mol] ranging from 9.2% to 14.3%. There were no differences between the diabetes-related baseline characteristics of the two groups (Table 1).

A similar proportion of individuals in both groups had a reduction in HbA1c by $\geq 1\%$ [11mmol/mol] or $\geq 2\%$ [22mmol/mol] at 3, 6 and 12 months. More than 1 in 4 adolescents in

both groups attained a sustained reduction of more than 2% at 12 months, regardless of the strategy adopted, whilst two thirds attained a reduction of at least 1%. A target HbA1c <7% [53mmol/mol] was not attained by any individual at 12 months. Proportions who attained an HbA1c of either <9% [75mmol/mol] or <8% [64mmol/mol] were similar between groups, at 7/35 and 11/35 ($p=0.3$) and 3/35 and 3/35 ($p=0.6$) for the admitted and ambulatory groups respectively. The glycaemic trajectory of the cohort is shown in Table 2. Both groups demonstrated a reduction in HbA1c that was sustained at 12 months. There was no significant difference in either the delta or absolute HbA1c at any time point, where the greatest reduction was demonstrated at 6 months.

Possible factors predicting a successful outcome (HbA1c reduction by $\geq 2\%$) at 12 months were investigated using logistic regression analysis (Table 3). A sustained reduction in HbA1c of $\geq 2\%$ [22mmol/mol] at 12 months post intervention was more likely in those who had already achieved this reduction by 6 months compared to those who had not (17/24 versus 3/41, $p<0.01$) regardless of the intensification strategy employed (admitted 9/12 versus ambulatory 8/12, $p=0.7$). In those who had not attained an improvement in HbA1c of $\geq 2\%$ [22mmol/mol] by 6 months, no individual in the admitted group and only 3/22 in the ambulatory group went on to demonstrate an HbA1c reduction $\geq 2\%$ by 12 months ($p=0.1$, Figure 1).

In the 12 month follow-up period, two from the admitted group and six from the outpatient group presented in DKA ($p=0.1$).

Discussion:

Suboptimal and deteriorating glycaemic control in adolescence is a well-established phenomenon in contemporary diabetes care (4), however these data clearly demonstrate that

strategies of intensified support and education can result in clinically meaningful improvements in glycaemic outcomes, sustained to 12 months. In this cohort, outpatient intervention was equally effective as inpatient stabilisation. Notably, two thirds of all individuals achieved a sustained reduction in HbA1c of more than 1% [11mmol/mol] while a HbA1c reduction of 2% [22mmol/mol] or greater was seen in approximately 30% of our cohort at 12 months after the intervention, whether through inpatient admission or intensification of ambulatory support. Disappointingly, no individual reached a target HbA1c of <7% [53mmol/mol] (17), and few approached the contemporaneous Australian mean HbA1c of 8.1% [65mmol/mol] (18). This group of individuals represents a very small proportion of the clinic cohort (~5%), yet utilises a disproportionate amount of clinical time and resources. Almost all individuals remained well above the HbA1c target and at high-risk for development of diabetes related complications, the likelihood of which increases exponentially from an HbA1c of 9% [75mmol/mol] (3). Nonetheless, given that each additional HbA1c increase of 1% [11mmol/mol] in childhood/adolescence confers an odds ratio of 2.9 for the development of severe retinopathy in adulthood (19), intensive interventions which reduce HbA1c by the margins demonstrated herein are worthwhile.

Management of impaired glycaemic control in T1DM is a common challenge worldwide, with varying strategies proposed that have limited evidence of demonstrated efficacy or sustained results (7-9, 13). A systematic review in 2015 concluded that psychological approaches appear to have more benefit in short term reduction of HbA1c compared to outpatient education or telehealth intervention, however this data comes from a limited number of studies (9) and has had limited translation into clinical practice to date. These programs can be expensive and time-consuming and do not typically achieve a significant reduction in HbA1c, especially after the cessation of the intervention (7-9). There is minimal literature regarding the effectiveness of elective admissions for improvement of glycaemic control, particularly in adolescents. This

study (n=70) has comparable numbers to the only previous report (n=60) (11) which also found reductions in both groups but concluded there was no clear additional benefit from inpatient admission over outpatient strategies to improve HbA1c outcomes.

Our results indicate that regardless of the nature of an intervention, if there has not been distinct improvement (characterised here by a reduction in HbA1c by 2% or more) after 6 months, an alternative approach should be considered in order to affect change. An inpatient bed at our hospital costs an estimate of \$AUD1900 per night and is highly time-intensive for the team members involved. In addition to the ethical implications of bed allocations (a precious resource for patients with acute care needs), hospital admissions likely have the additional burden for families regarding time required off work and studies. Therefore, it would seem sensible to offer additional/more intensive outpatient support in the first instance, with inpatient stabilisation reserved for those who do not attain a significant improvement in HbA1c on an outpatient/ambulatory basis.

Our study has several strengths. This is a reflection of “real-world” practice at a large tertiary paediatric centre with a clinic mean HbA1c of 8.2% [66mmol/mol] (median 8% [64mmol/mol]) (18). This is comparable to the Australian mean of 8.3% [67mmol/mol] (median 8.1% [65mmol/mol]) (18) and American mean in the 13-17 year old age-group of 9.2% [77mmol/mol] (4). We have assessed two approaches to improving glycaemic outcomes in those with suboptimal diabetes control that are used internationally. Data collection was standardised and all individuals were followed through to 12 months. The control group was closely matched to the admitted group for both HbA1c and age (and all were matched for sex), hence addressing potential confounders.

There are however limitations that need to be considered. As a retrospective study, it is problematic to understand the clinician's rationale for decisions made in patient management and to fully grasp the complexities of individual cases. Attempts had already been made to engage with the admitted group through outpatient measures prior to the admission, hence the ambulatory approach will not be universally successful for all. Importantly, our data show that lack of success with an outpatient strategy does not preclude improvements using an inpatient approach. Persistent evidence of an HbA1c above 9% [75mmol/mol] prompted a decision for intervention for these individuals, however, the cut-off of 9% is arbitrary and each patient should be approached on an individual level. One could argue that a persistent HbA1c above 8% [64mmol/mol] (the clinic mean) should trigger the same response, however this is limited by finite healthcare resources. The International Society of Paediatric and Adolescent Diabetes (ISPAD) recommends resource allocation per 100 patient numbers of 0.75 doctors, 1.0 diabetes nurse educators, 0.5 dieticians and 0.33 social workers/psychologists (16, 20). Unfortunately there continue to be limited healthcare resources and no Australasian centres are currently able to achieve these recommendations (16).

Any individuals with an admission over the study period were captured in the data, and then matched with an individual (non-admitted) who had a comparable HbA1c. Other non-admitted individuals with an elevated HbA1c who were not matched weren't included, as this was not the focus of the study, however there would be very few in the clinic cohort who were not reflected in the study.

In this cohort, outpatient intervention was equally effective as inpatient stabilisation. However, we note that since the inpatient group had already failed outpatient intervention, they cannot be compared directly with the intervention naïve outpatient group. Whilst we set out to compare approaches to stabilisation of glycaemia between individuals matched for HbA1c and demographics, the prior failure of the outpatient intervention of those in the inpatient group is

a notable difference between the two arms. Results in each category can therefore also be considered separately in the context of each patient group.

Use of continuous glucose monitoring (CGM), which is now a common feature of management in Type 1 Diabetes, was not very prevalent in this cohort during the study period. This is likely related to the fact that the Australian Government CGM initiative was only introduced mid-2017. As some of the data for the study predated this, there were very few individuals using CGM in the study period. For this reason, sensor use was not presented in the data.

Accurate assessment of psychosocial complexity of these individuals is challenging and difficult to quantify in a retrospective study and the absence of recorded issues cannot be interpreted unequivocally. We note that almost all individuals had at least one identified psychosocial adversity factor.

Whilst each diabetes team will have their own approach to both inpatient and outpatient interventions with their population base, as our teams' approach and interventions are based around implementation and attainment of ISPAD targets, our findings can be generalised and applied to similar settings.

Notwithstanding the overall improvements seen in glycaemic control, our data reaffirm the known difficulty in achieving target HbA1c levels in the adolescent population with T1DM (4) and highlight the importance of identifying more effective strategies to support and optimally manage this cohort. If an attempt at stabilisation on an outpatient basis is unsuccessful, inpatient stabilisation can offer significant benefit to those who have previously not seen significant reductions in HbA1c. As it is possible that an inpatient intervention may offer additional benefit for those who have deteriorating control, we still feel it is a worthwhile endeavour. Based on our data, we recommend that review of the impact of the chosen intervention should occur after 6 months with rationalization of approach if a meaningful

improvement in glycaemic control has not been achieved. Additional longitudinal data collection will provide more insight; however, prospective studies with a standardised model of care are required to assess the optimal intervention strategy for different patient groups.

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Table 1. Baseline characteristics of the two groups.

		Admitted (case) n=35	Ambulatory (control) n=35	p value
Male (n, %)		15 (43)	15 (43)	1.0
Baseline HbA1c, mean(SD)	%	11.4 ±1.3	11.2 ±1.1	0.5
	mmol/mol	101 ± 14.3	99 ±12.1	
Age (years)		14.6 ±2.0	14.7 ±2.0	0.9
Duration of diabetes, years		6.1 ±3.8	7.3 ±3.9	0.2
Insulin regimen n(%)	Pre-mix	19 (54%)	13 (37%)	0.1*
	BD			
	BD	7 (20%)	5 (14%)	
	MDI	6 (17%)	16 (46%)	
	CSII	3 (9%)	1 (3%)	
Insulin dose, units/kg/day		1.42 ±0.5	1.4 ±0.4	0.6
Mean (SD) HbA1c in the preceding year	%	10.3 ±1.5	9.7 ±1	0.06
	mmol/mol	89 ±16	83 ±11	
History of DKA, n(%)		6 (17%)	8 (23%)	
Number of identified psychosocial factors		1.9(1.3)	1.5 (1.1)	0.3

Between group comparisons were made using Student's t-test and chi square analysis for continuous and categorical variables respectively.

*Comparing all regimen proportions between the groups.

BD = twice daily injections (short and intermediate acting insulin), MDI = multiple daily injections/basal-bolus,

CSII = continuous subcutaneous insulin infusion/insulin pump, DKA = diabetic ketoacidosis

Psychosocial risk factors were determined based on 10 features as outlined in the text.

DKA history excludes original diabetes diagnosis.

Table 2. HbA1c trajectory.

HbA1c		Admitted (case) n=35	Ambulatory (control) n=35	p value
+3 months	Mean (SD)	9.9 ±1.4	9.9 ±1.4	1.0
	Delta HbA1c, mean (SD)	-1.2 ±1.3	-1.4 ±1.3	0.7
	Delta reduction ≥1%, n (%)	15 (42.9%)	17 (48.6%)	0.2
	Delta reduction ≥2%, n (%)	7 (20%)	6 (17.1%)	1.0
+6 months	Mean (SD)	9.8 ±1.8	9.5 ±1.1	0.4
	Delta HbA1c, mean (SD)	-1.5 ±1.6	-1.7 ±1.3	0.6
	Delta reduction ≥1%	22 (62.9%)	26 (74.3%)	0.6
	Delta reduction ≥2%	12 (34.3%)	12 (34.3%)	0.8
+12 months	Mean (SD)	10.1 ±1.5	9.7 ±1.4	0.3
	Delta HbA1c, mean (SD)	-1.4 ±1.2	-1.5 ±1.4	0.7
	Delta reduction ≥1%	24 (68.6%)	23 (65.7%)	0.8
	Delta reduction ≥2%	9 (25.7%)	11 (31.4%)	0.6

Between-group comparisons were made using Student's t-test and chi square analysis for continuous and categorical variables respectively.

Delta HbA1c at 3, 6 and 12 months from baseline.

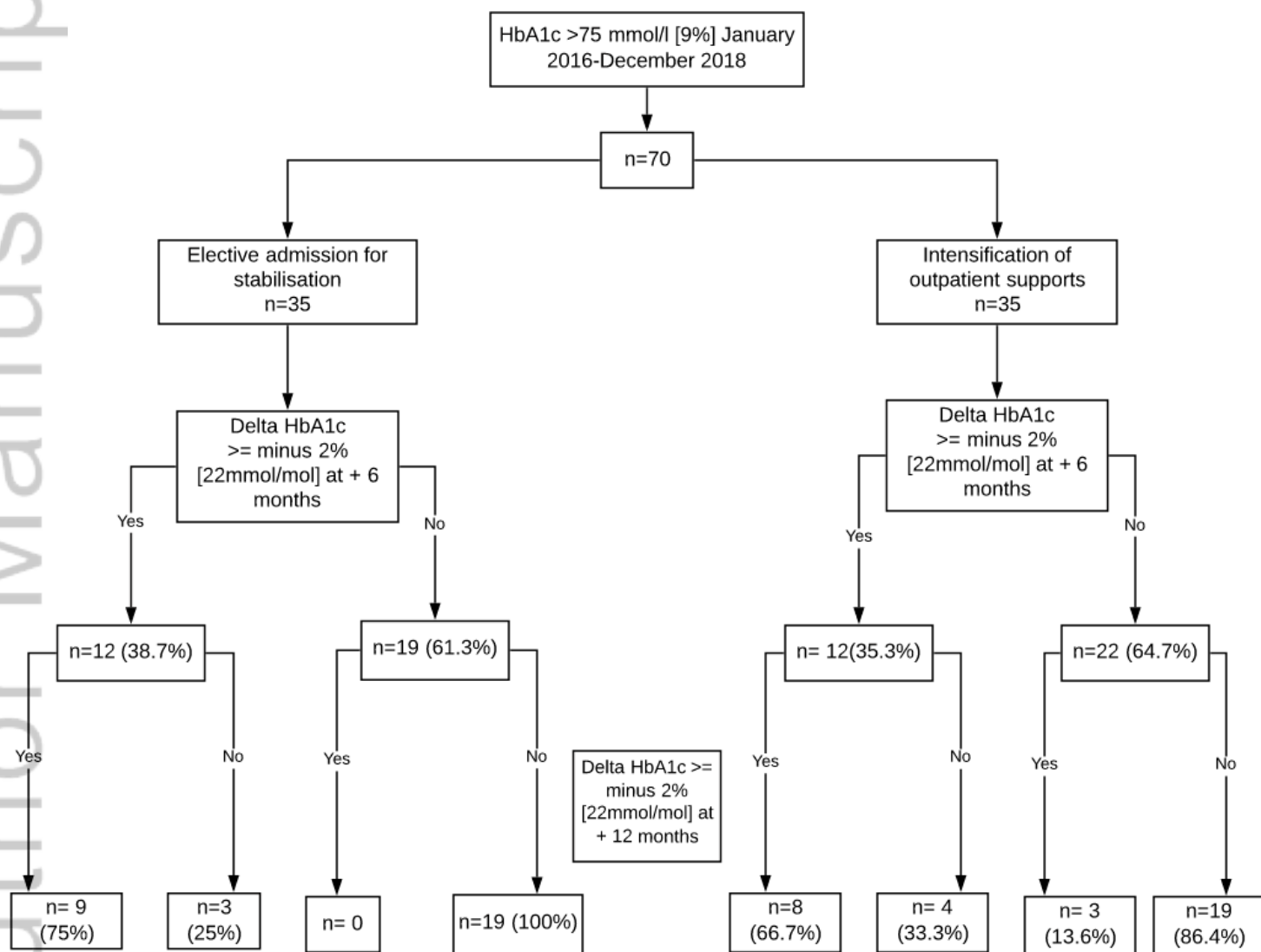
Table 3. Factors contributing to a reduction in HbA1c $\geq 2\%$ 12 months post intervention

	OR	95% confidence interval	p value
Admitted	0.6	0.1-2.8	0.5
Baseline HbA1c $\geq 12\%$	4	0.7-21.8	0.1
Age, years	0.8	0.5-1.3	0.3
Duration of diabetes, years	1.1	0.9-1.3	0.6
Psychosocial score	0.9	0.6-1.4	0.8
Intense regimen on admission	1.9	0.3-12	0.5
Male sex	0.4	0.1-1.9	0.2
Delta HbA1c $\geq 2\%$ at 6 months	40	6.7-234.7	<0.01

Logistic regression analysis; OR = odds ratio
 Intense regimen refers to multiple daily injections or pump therapy.

Figure 1. Comparison of delta HbA1c $\geq 2\%$ at 6 and 12 months in both cohorts.

Delta HbA1c refers to the change in HbA1c from baseline. Not all patients had an HbA1c at 6 months (n=31 for admitted, n=34 for ambulatory).



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Is there an optimal approach to elective stabilisation of glycaemic control in children and adolescents with Type 1 Diabetes Mellitus?

Running title: Interventions for sustained HbA1c reduction in adolescents

Dr Gabby Atlas^{a,b} (MBBS), Dr Michele A O'Connell^{a,b} (MRCPI, FRACP, MD), Dr Mary White^{a,c} (MRCPI, FRACP, MD)

Affiliations:

^aDepartment of Endocrinology and Diabetes, Royal Children's Hospital Melbourne, 50 Flemington Road, Parkville VIC 3052, Australia

^bMurdoch Children's Research Institute, 50 Flemington Road, Parkville VIC 3052, Australia

^cUniversity of Melbourne, Parkville VIC 3052, Australia

Corresponding author:

Gabby Atlas, Department of Endocrinology, Royal Children's Hospital Melbourne, 50 Flemington Road Parkville VIC 3052, Australia, gabby.atlas@rch.org.au, +61 3 93455951 (phone), +61 393455857 (fax)

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What is already known on this topic:

1. Adolescents with T1DM are identified to have a higher HbA1c as an age group
2. A reduction in HbA1c by 0.5% can be sufficient to decrease the risk of complications
3. Several intervention programs have been developed but none are universally successful

What this paper adds:

1. Demonstrates that strategies of intensified support and education can result in clinically meaningful improvements in glycaemic outcomes, sustained to 12 months

2. Highlights the importance of identifying more effective strategies to support and manage these individuals
3. If there has not been distinct improvement after 6 months of an intervention, an alternative approach should be considered in order to affect change