Treatment guideline for adult patients with type 1 diabetes ?

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ICDM 2014

Treatment guideline for T1D

- No guideline for T1D in Korea (KDA 2011, 2013)

- ADA guideline
  - Standards of Medical Care in Diabetes 2014 (Position statement)
    - Insulin therapy for type 1 diabetes
  - Type 1 Diabetes Through the Life Span: A Position Statement of the American Diabetes Association (Diabetes Care 2014;37:2034–2054)

Contents

- Diagnosis and Classification
- Initial evaluation and follow-up
- Insulin regimen
- Glucose monitoring (SMBG & CGMS)
- Education
- Summary

Halle Berry, T1D or T2D ?

She had collapsed on the of TV show “Living Dolls” and went into a diabetic coma in 1989, and shortly afterwards she was diagnosed with **type 1 diabetes**.

In 2007, she says, **'I've managed to wean myself off insulin**, so now I like to put myself in the **type 2 category**.'

Atypical Diabetes (Flatbush diabetes)
= **Ketosis prone type 2 diabetes**
- African American

Newly diagnosed DM with DKA

SMC, AMC, Severance

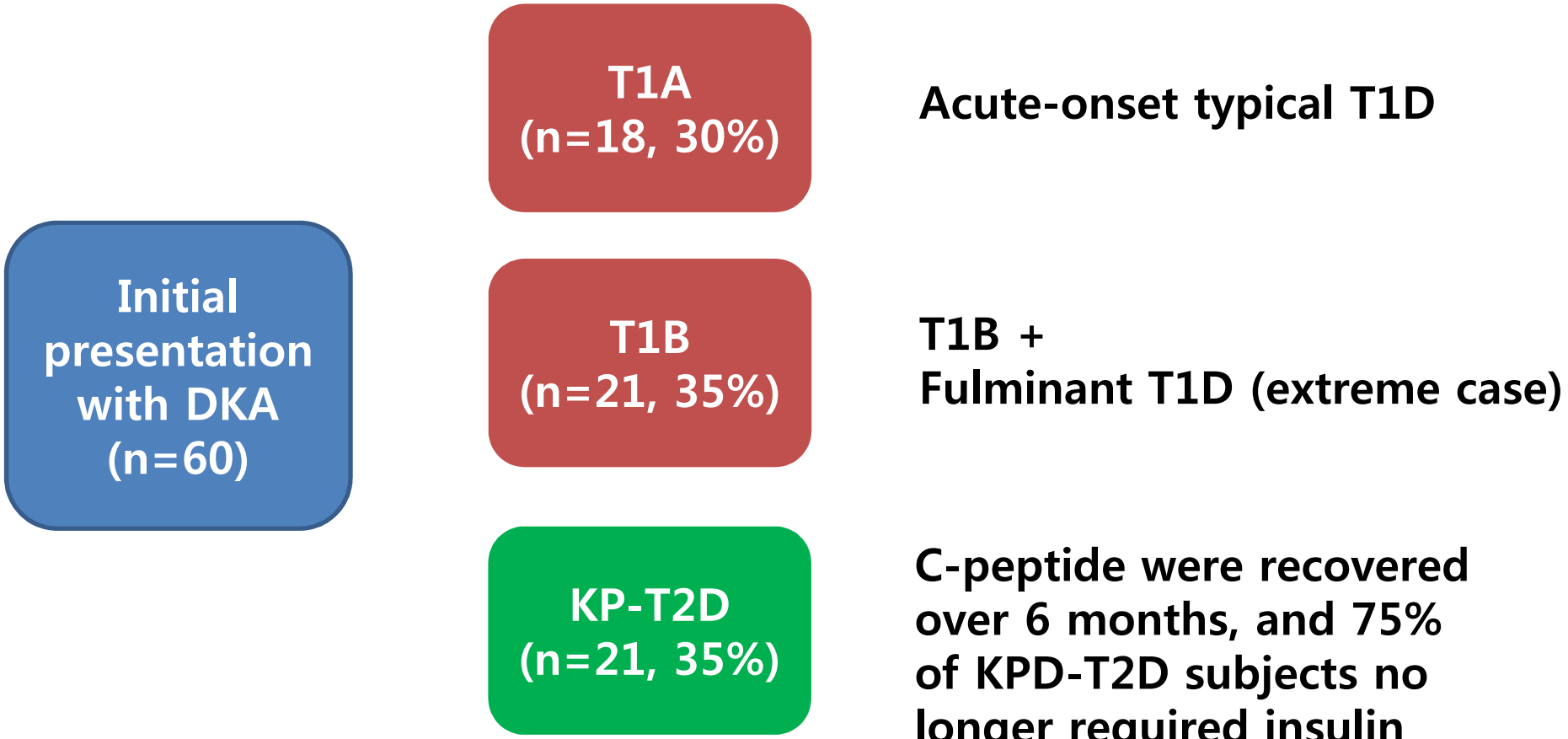
1) T1A: GAD (+)
2) T1B: GAD (-), fasting c-pep <1.0ng/dl
   – fulminant T1D
      : A1C < 8.5% & fasting c-pep <0.3ng/dl
3) KP-T2D: GAD (-), fasting c-pep ≥1.0ng/dl

KP-T2D: ketosis prone T2D

Seok H, DMRR 2013

Clinical characteristics and insulin independence of Koreans with new-onset type 2 diabetes presenting with diabetic ketoacidosis

Seok H, DMRR 2013



Classification of diabetes is not easy

Tremendous variability in the initial presentation of T1DM

Autoimmune (+): Acute-onset typical T1D (T1A) vs. Early stage-LADA (T2D feature)

1) All five autoAbs are not available. 2) Ab titers diminish over time. 3) In Asians, autoAbs are often negative.

Long standing T2D (insulin dependent) vs. Slowly progressive T1D (late stage-LADA)

	Beta cell function : β (+)	Beta cell function : β (-)
Autoimmune - A (+)	Early stage-latent autoimmune diabetes in adult (LADA) – T2D feature	Acute-onset typical T1D (T1A) Slowly progressive T1D (=late stage-LADA)
Autoimmune - A (-)	Ketosis prone-T2D (Atypical diabetes)	Fulminant T1D, Acute-onset T1B, long standing T2D ? (insulin dependent)

Initial Evaluation and F-U

Clinical evaluation	Initial	3m	Annual
Height, Weight, BMI	O		O
Blood pressure	O	O	O
Thyroid exam	O		O
Injection/infusion sites	O	O	O
Foot exam	O	△	O
Retinal exam (5 yrs after diagnosis; earlier if Sx)	O		O or 2yrs
Depression screen	O		O
Hypoglycemia assessment	O	O	O
Diabetes self-management skills	O	O	O
Assess clinically relevant issues (Alcohol, tobacco, drug, contraception, driving)	O	△	△
Nutritional knowledge	O	△	O
Immunizations	O	△	O

△: As needed

Initial Evaluation and F-U

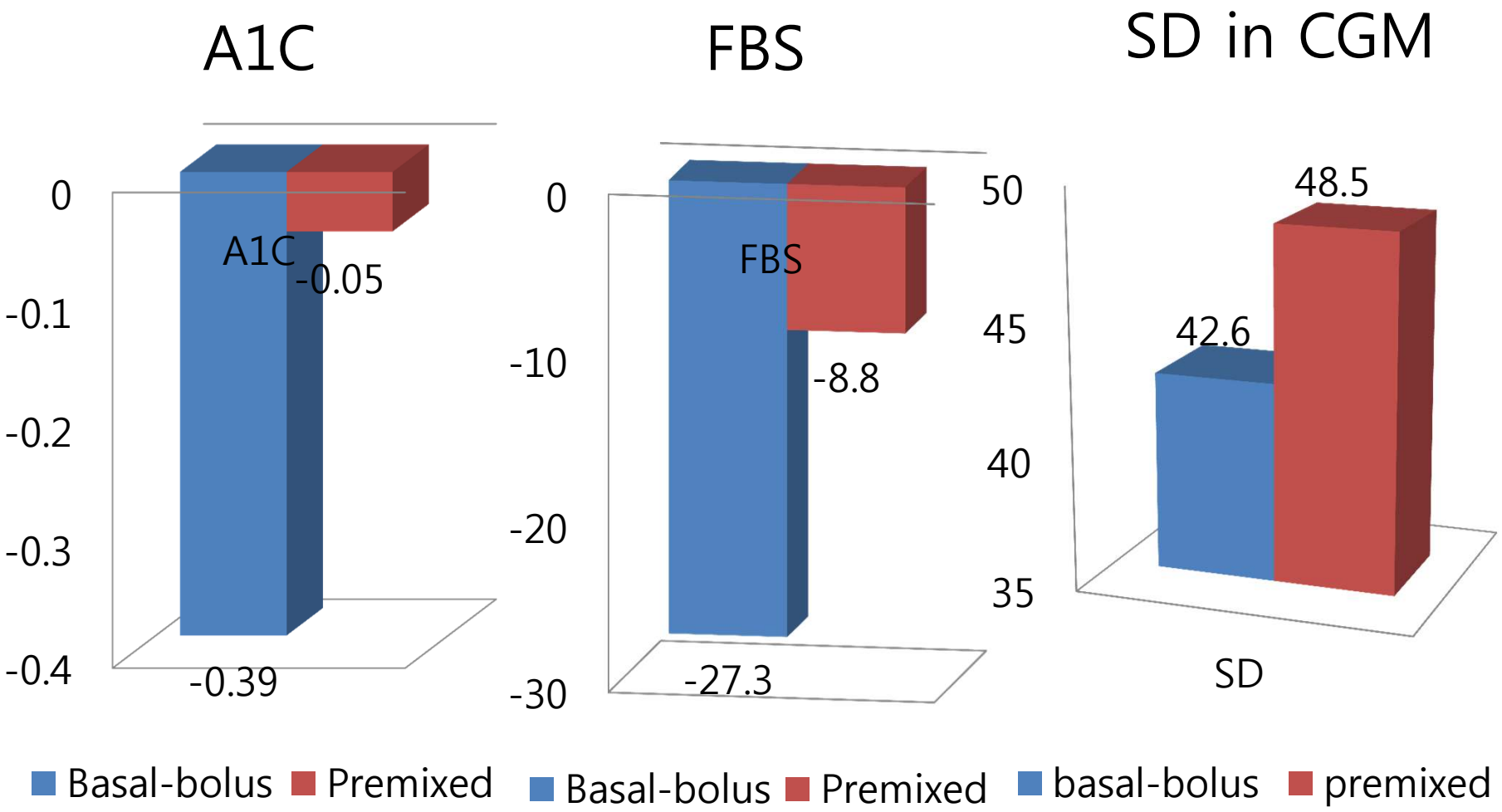
Laboratory assessment	Initial	3m	Annual
A1C	O	O	O
eGFR	O		O
Fasting lipid (**direct LDL if fasting unavailable**)	O	△	O
TSH	O	△	O
Antithyroid antibodies	O		
Urine albumin-to-creatinine ratio (UACR)	O		O
GAD	O		
C-peptide*	O		

△: As needed based on treatment

***: always measure a simultaneous blood glucose level (>80mg/dL)**

Basal bolus vs. premixed in T1D

Testa et al. JCEM 2012



Treatment satisfaction & quality of life (QoL) measurement

		Basal-bolus	Premixed	P-value
Net Benefit	**T1D**	**56.2 ± 2.6**	**28.5 ± 2.6**	<0.0001
	T2D	61.3 ± 1.3	49.7 ± 1.3	<0.0001
Advocacy, perceived efficacy		↑	↓	
Preference, general satisfaction		↑	↓	
Regimen acceptance	**T1D**	**84%**	**16%**	
	T2D	**69%**	**31%**	
Burden, convenience, pain		↓	↑	
Flexibility, overall satisfaction		↑	↓	
Quality of life		↑	↓	

Testa et al. JCEM 2012

Insulin regimens for T1DM (ADA 2014)

- Most individuals with T1D should be treated with **multiple daily insulin injections (three or more injections per day of prandial insulin and one to two injections of basal insulin) or CSII**. (A)
- Most individuals with T1D **should use insulin analogs** to reduce hypoglycemia risk. (A)
- Most individuals with T1D **should be educated in how to match prandial insulin dose to carbohydrate intake, premeal blood glucose, and anticipated activity.** (E)

Hospital based Korean T1D registry

- **Five tertiary referral hospitals** (SMC, KBSMC, Severance, CMC, AMC)
- Subjects – **Patients with T1D who participated in strip refund program** (n=869)
- Inclusion Criteria: 1) and one of 2)
  1. Requiring insulin
  2. One or more of the following criteria
     - **Fasting C-peptide ≤ 0.6ng/ml**
     - **Stimulated C-peptide ≤1.8ng/mL**
     - **History of DKA at initial diagnosis**
     - **Positive for GAD Ab, insulin Ab, or ICA**

Clinical characteristics of Korean T1D patients

Index	Results
Insulin type	*(n, %)*
NPH/RI	104 (12)
Mixpen	117 (13)
MDI	**574 (66)**
CSII	**40 (5)**
Etc.	34 (4)
A1c according to age	*Mean ± SD*
≤18 yrs [n=66]	8.2 ± 1.5
19-25 yrs [n=87]	8.4 ± 2.1
26-35 yrs [n=200]	8.3 ± 2.0
36-50 yrs [n=246]	8.1 ± 1.7
≥51 yrs [n=206]	8.0 ± 1.4

Index	Results
SMBG (n=465)	*(n, %)*
0/day	53 (11)
1-2/day	208 (45)
3-4/day	92 (20)
5-6/day	58 (12)
≥7/day	54 (12)
HbA1c	*(n, %)*
≤ 6.5%	100 (12)
6.5-7.0%	129 (15)
7.0-7.5%	122 (14)
7.5-8.0%	119 (14)
8.0-8.5%	88 (10)
8.5-9.0%	69 (8)
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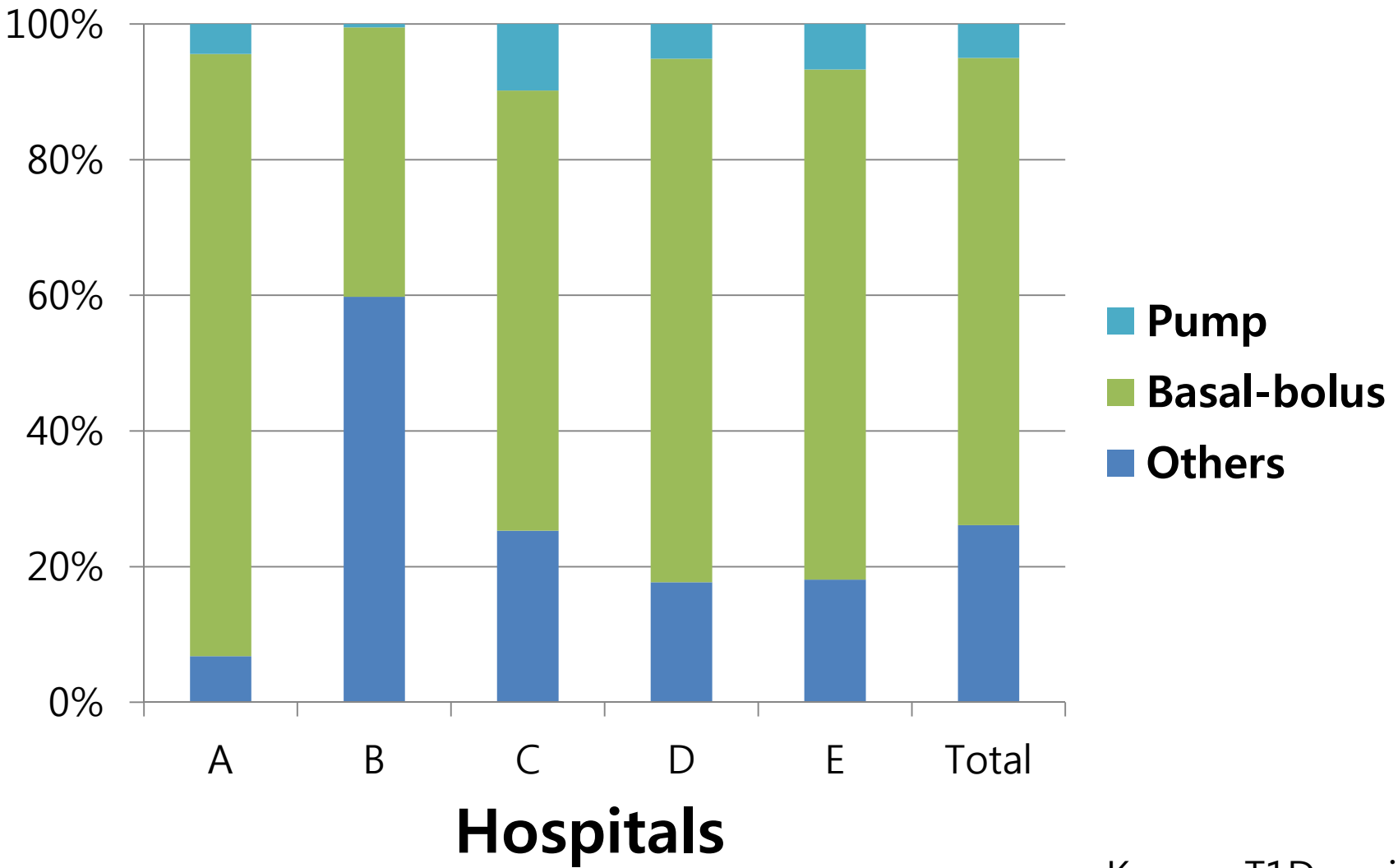
≥10%	92 (10)

Korean T1D registry

Insulin regimens according to hospitals



Korean T1D registry

Intensive regimen vs. others

	MDI/CSII (n=614)	Others (n=221)	P-value
Age (yrs)	35 (26-47)	48 (35-57)	<0.001
Sex (M:F)	295:319	120:101	NS
BMI (kg/m2)	22.1 ± 3.0	22.7 ± 2.9	0.01
Onset Age (yrs)	25.5 (16-35)	34 (26-46)	< 0.001
Duration (yrs)	9 (4-16)	12 (5-18.3)	0.01
Insulin dose (IU/kg)	0.66 (0.52-0.85)	0.54 (0.42-0.74)	< 0.001
A1C (%)	**7.7 (7.0-8.8)**	**7.9 (7.1-9.2)**	**0.05**
C-peptide (ng/ml)	**0.10 (0.02-0.55)**	**0.20 (0.10-0.48)**	**0.005**
eGFR (ml/min/1.73m²)	97.3 (82.3-117.1)	92.2 (80.7-108.7)	0.038
Nephropathy (%)	37 (9%)	12 (12%)	NS
Retinopathy (%)	**165 (29.5%)**	**89 (42.6%)**	**0.001**

Median (25% - 75%)

김1
김2

Glycemic target in adults with T1D (ADA 2014)

- **Nonpregnant adults with T1D < 7%**
- **More stringent (A1C < 6.5%)**
  - Without significant hypoglycemia
  - Short duration, long life expectancy, hypoglycemic awareness, no significant CVD
- **Less stringent (A1C < 8.5%)**
  - History of severe hypoglycemia, hypoglycemic unawareness, limited life expectancy, advanced micro/macrovascular complications, extensive comorbid conditions

Youth (<18 yrs): A1C < 7.5%

슬라이드 17

김1 김재현, 2014-10-16
김2 김재현, 2014-10-16

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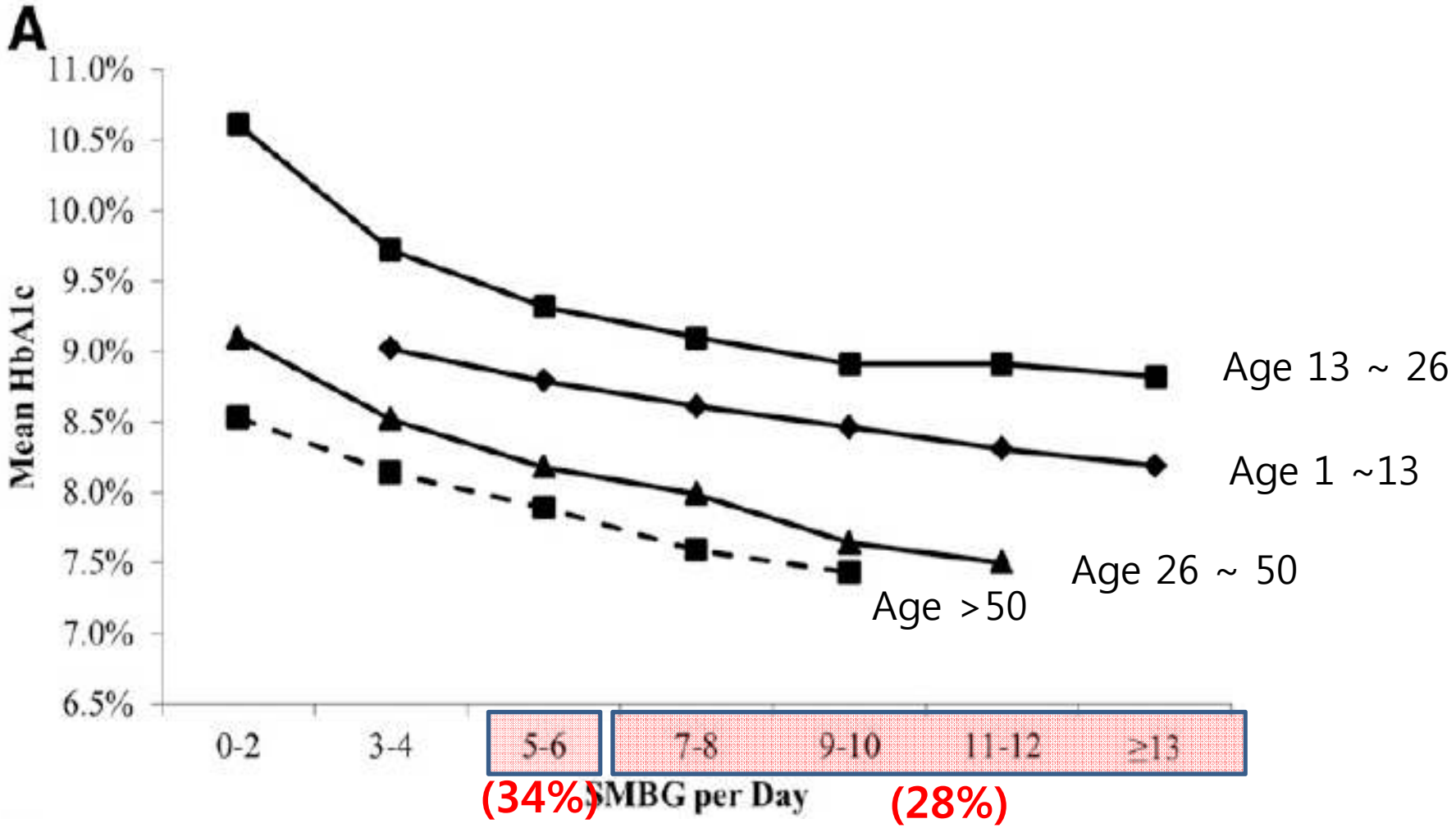
Korean T1D registry

SMBGs for T1D
(ADA 2014)

- Glycemic controls should be assessed based on frequent SMBG levels (& CGM data, if available) in addition to A1C (A)
- Individuals with T1D need to have **unimpeded access to glucose test strips** for glucose testing (may require **≥ 10 strips daily** to monitor for hypoglycemia….) (B)
- **Increased SMBG frequency was associated with lower A1C**

SMBG frequency and A1C (USA)



T1D Exchange Clinic Registry (USA)

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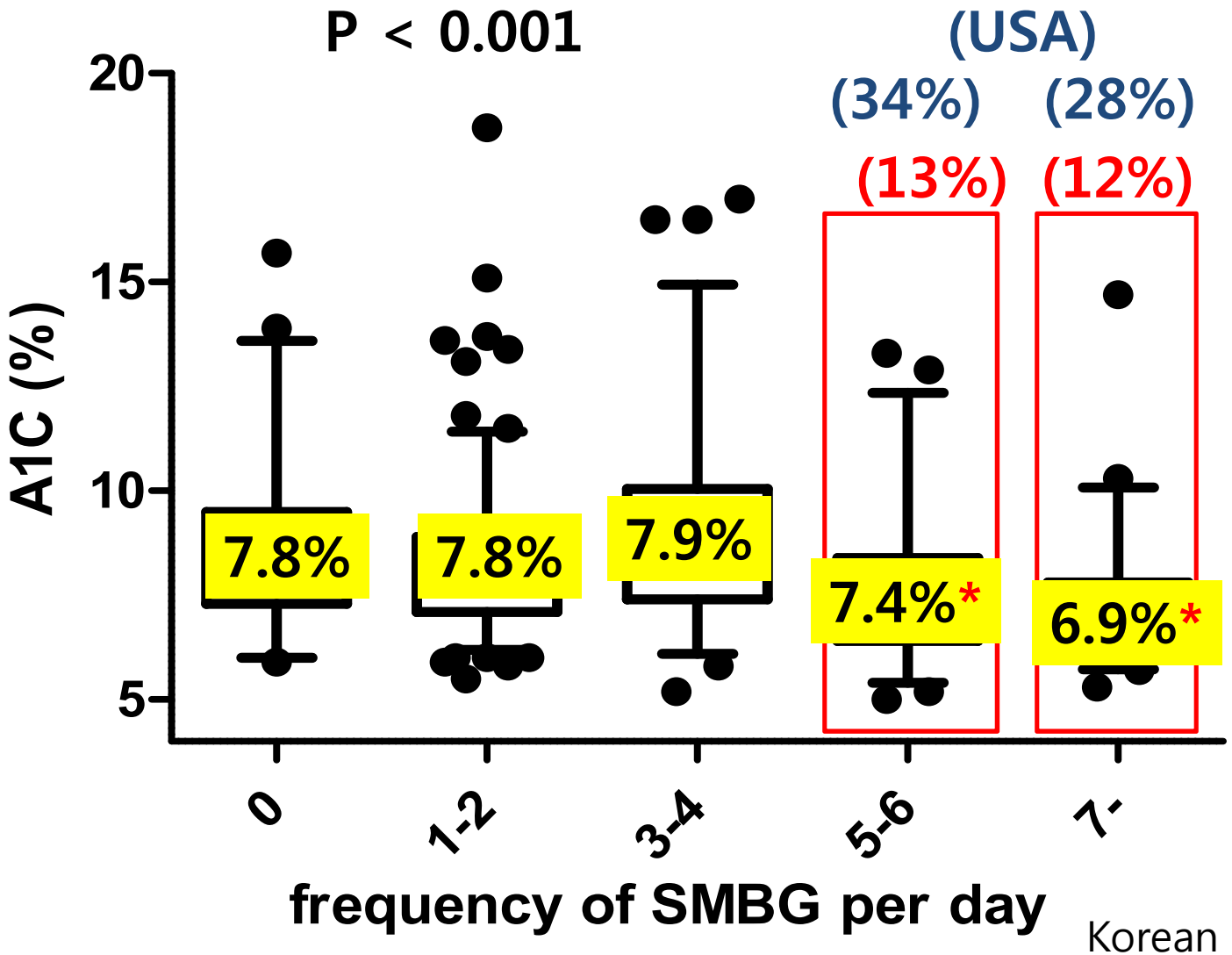
Korean T1D registry

SMBG frequency and A1C (%) (Korea)

A1C (%)	SMBG none		SMBG 1-2/d		SMBG 3-4/d		SMBG 5-6/d		SMBG ≥7/d		*P*
Age	N	median	N	median	N	median	N	median	N	median	
Age ≦25	4	**8.9**	16	**8.2**	12	**8.0**	13	**7.6**	5	**6.7**	0.072
Age 26-35	14	**7.2**	36	**7.8**	18	**8.3**	17	**7.3**	26	**7.0**	**0.001**
Age 36-50	17	**8.6**	65	**7.8**	27	**7.4**	12	**7.5**	10	**6.6**	**0.013**
Age > 50	11	**7.8**	73	**7.6**	29	**7.9**	11	**7.3**	6	**7.8**	0.678
Gender											
Male	28	**8.5**	93	**8.0**	51	**7.9**	22	**7.5**	14	**7.0**	**0.012**
Female	18	**7.5**	98	**7.6**	36	**7.5**	31	**7.3**	35	**6.9**	**0.046**
All ages	46	**7.8**	190	**7.8**	86	**7.9**	53	**7.4**	47	**6.9**	**<0.001**

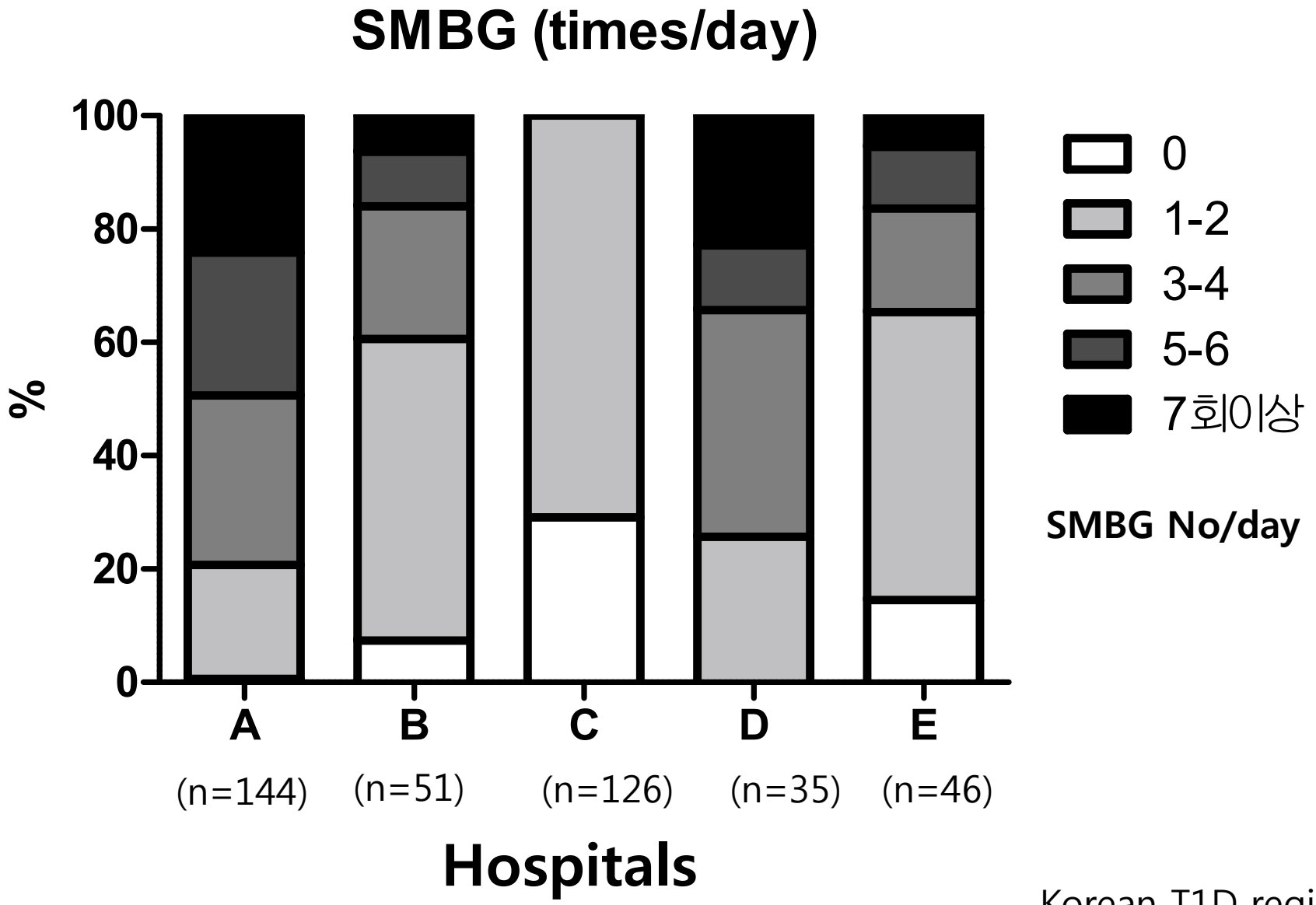
* p-value by Kruskal-Wallis test

SMBG frequency and A1C (%) (Korea)



Korean T1D registry

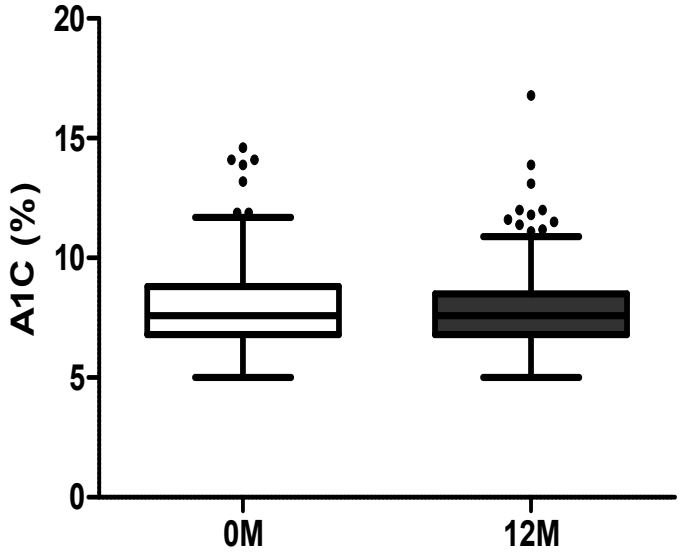
SMBG frequency according to hospitals (Korea)

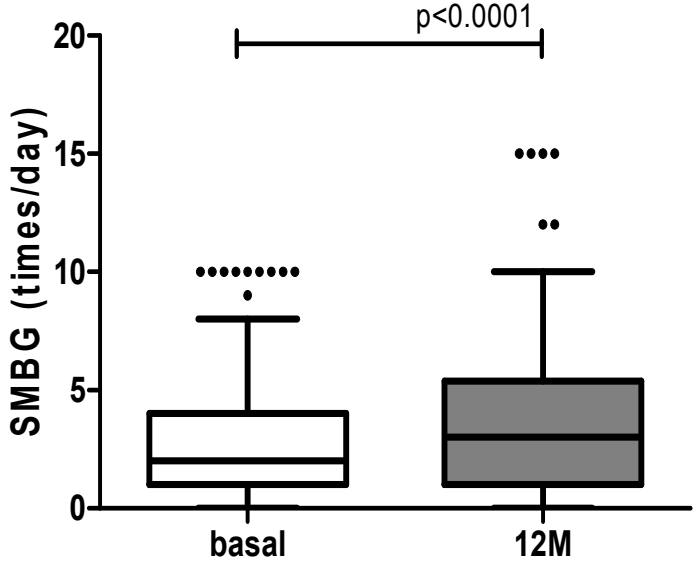


Korean T1D registry

Change of SMBG frequency & A1C 12m after starting insurance program

	Basal	12M	p-value
A1C (%)	7.6 (6.8-8.8)	7.6 (6.8-8.5)	0.57
SMBG (times/day)	2.8 (1-4)	3.7 (1-5.4)	<0.001





Subgroup with increased SMBG frequency reduced severe hypoglycemia and hypoglycemic unawareness (follow up for 1yr)

	A1C ↓	A1C ↑	P-value	OR (95% CI)
No. SMBG ↑	69 (53.5%)	60 (46.5%)	**0.058**	1.54(0.99-2.42)
No. SMBG ↓	82 (42.7%)	110 (57.3%)		

	Severe Hypo ↓	Severe Hypo ↑	P-value	OR (95% CI)
No. SMBG ↑	**23 (76.7%)**	**7 (23.3%)**	**<0.0001**	12.5(4.6-34.4)
No. SMBG ↓	**16 (20.8%)**	**61 (79.2%)**		

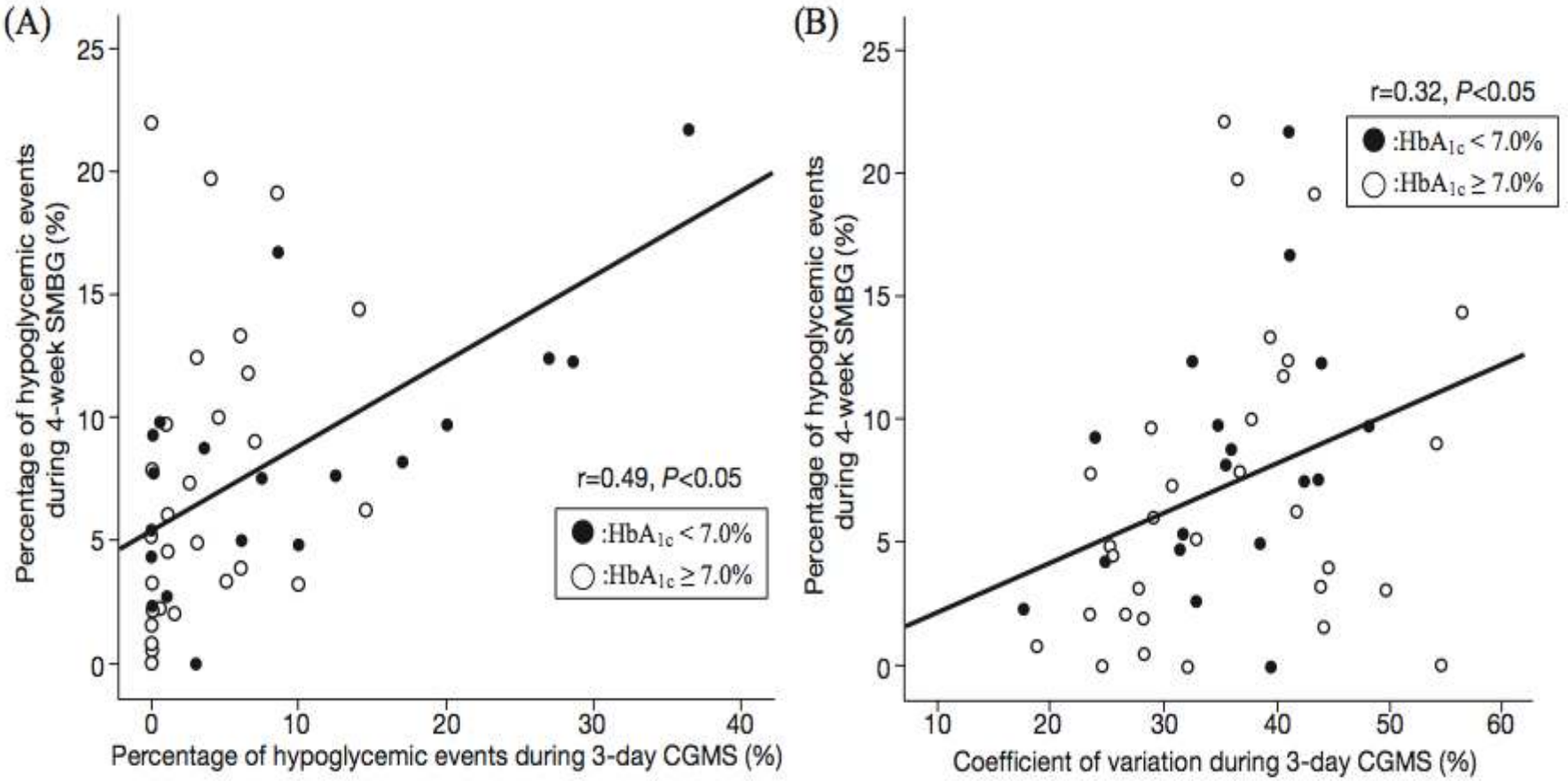
	Unawareness ↓	Unawareness↑	P-value	OR (95% CI)
No. SMBG ↑	**20 (64.5%)**	**11 (35.5%)**	**<0.0001**	35.5(10.2-123.2)
No. SMBG ↓	**4 (4.9%)**	**78 (95.1%)**		

Korean T1D registry

CGM (ADA 2014)

- **CGM is a useful tool to reduce A1C levels in adults** without increasing hypoglycemia (A)
- **CGM can reduce glycemic excursions in children** (A)
- Glycemic improvements are correlated with frequency of CGM use across all ages (A)

Percentage of hypoglycemic events and CV during 3-day CGMS correlated with hypoglycemic events during 4-week SMBG in patients with T1D



Kim SK et al. Endocrine J 2011

Clinical factors associated with glycemic variability in T1D (n=81)

Univariate analysis

	Type 1 diabetes (n = 81)	
	SD	log (CV)
Age (years)	0.139	0.042
BMI (kg/m²)	-0.061	**-0.320****
DM duration (years)	0.087	0.144
HbA1c (%)	0.190	-0.208
C-peptide (ng/mL)	**-0.285****	**-0.230***
HDL (mg/dL)	0.203	**0.345****
LDL (mg/dL)	-0.013	-0.120
Triglyceride (mg/dL)	-0.142	-0.179

* $p < 0.05$; ** $p < 0.01$

Jin SM et al. DRCP 2014

Multivariate analysis

	Type 1 diabetes (n = 81)	
	SD	log (CV)
Age (years)	0.158	-0.001
Male sex	-5.329	-0.053
BMI (kg/m²)	-5.330	**-0.032***
DM duration (years)	-1.281	**0.0162****
HbA1c (%)	2.172	-0.005
C-peptide (ng/mL)	**-16.438***	-0.136
HDL (mg/dL)	0.321	**0.006***
LDL (mg/dL)	-0.002	-0.001
Triglyceride (mg/dL)	0.007	0.000
Use of statins	-9.810	-0.080
Use of pre-mixed insulin (vs. MDI)	13.231	**0.189***

Participant characteristics by age groups (USA 2011)

		Age (yr)							
	Total	<6	6 to <13	13 to <18	18 to <26	26 to <31	31 to <50	50 to <65	≥65
n	25,833	1,278	6,973	6,341	3,890	1,050	3,440	2,153	708
Gender, female[a]	50	44	49	48	49	58	55	52	51
Race/ethnicity									
White non-Hispanic	82	79	77	78	81	86	89	94	97
Black non-Hispanic	5	5	6	6	5	4	4	3	2
Hispanic or Latino				10				1	<1
Native Hawaiian/other Pacific Islander				<1					
Asian				1				<1	<1
American Indian/Alaskan Native				<1				<1	<1
More than one race				3				<1	<1
First-degree family member with T1D	16	14	13	14	13	17	22	26	27
Criteria met for definite T1D[e]	87	100	99	94	87	77	72	60	55
Pump use	50	31	46	49	51	58	60	59	53
CGM use	6	2	3	2	3	12	14	15	8
Self-monitoring of blood glucose (mean ± SD)[f]	5.6 ± 2.5	6.8 ± 2.6	6.5 ± 2.2	5.2 ± 2.1	4.4 ± 2.4	5.1 ± 2.8	5.2 ± 2.6	5.5 ± 2.5	5.6 ± 2.2
Severe hypoglycemia[g,h]	7	5	4	5	7	9	11	13	16
Diabetic ketoacidosis[h]	8	8	6	10	10	5	5	4	4

USA (2011)
Pump 57%
CGM 12%
SMBG 5.6/day

Korea (2013)
Pump 5%
CGM 0%
SMBG 2.8/day

Educations (DSME & DSMS)

- No matter how sound the medical regimen, **it can only be as successful as the ability of the individuals and/or family to implement it**
- Adult learning theory can be used to tailor DSME and DSMS to the age, life stage, culture, literacy/numeracy, knowledge, experience, and cognitive ability of the patient (C)

Effective education and A1C level

	Education effect (n=101)	Education effect (-) (n=364)	*p*-value
Age (yrs)	39 (28-51)	40 (31-53)	NS
Sex (M:F)	51:50	177:187	NS
Onset age (yrs)	29 (18-41)	30 (20-40)	NS
Duration (yrs)	8.5 (2.0-17)	11 (5-18)	**0.011**
BMI (kg/m2)	21.9 (19.9-23.7)	22.1(20.4-24.1)	NS
HbA1c	**7.3 (6.6-8.6)**	**7.7 (7.0-8.8)**	**0.029**
C-peptide (nd/dl)	0.19 (0.02-0.59)	0.11 (0.02-0.48)	NS
No of SMBG/day	**4 (2-6)**	**2 (1-3)**	**<0.001**
eGFR **(**ml/min/1.73m²**)**	97 (85-113)	94 (80-115)	NS
Nephropathy (%)	6 (9.4%)	26 (9.3%)	NS
Retinopathy (%)	**22 (23.7%)**	**123 (35.9%)**	**0.034**

* p-value by Mann-Whitney test

Education effect (+): The patients answered the survey that they could modify their life style and adjust insulin dose after education

Nutrition therapy

- **Individualized MNT** is recommended for all people with T1D as an effective component of the overall treatment plan (A)
- **Monitoring carbohydrate intake**, whether by **carbohydrate counting, or experience-based estimation**, remains a key strategy in achieving glycemic control (B)
  - Carbohydrate counting and meal composition
  - Education on the impact of protein and fat on glycemic excursions should be incorporated in diabetes management

Education program for T1D

- DAFNE (Dose Adjustment For Normal Eating)
  - UK, Germany, Australia, New Zealand, Singapore

Promoting the '**expert patient**'

- 2030 CAMP in KDA
  - Diabetic patients with age 20-39
  - Biannually from 2004
  - n=546 (80% with age 20-39)

Not specific for T1D

Summary

- **Increased SMBG frequency (≥ 5-7/day) was associated with lower A1C**, and but mean frequency of SMBG in Korea is lower compared to USA.
- After coverage of insurance for glucose strip **increase SMBG frequency** and **individuals with increased SMBG frequency reduced severe hypoglycemia & hypoglycemic unawareness**
- Proportion of patients with intensive insulin regimen is still low in Korea **[insulin pump (5%) and basal-bolus (65%)]**

Summary

- **CGM** is effective to **reduce A1C** without increase in hypoglycemic risk in T1D.

- There are **still unmet needs for glycemic control, specific education program, insurance coverage of unlimited number of SMBG, CGM and insulin pump including SAP** in Korean adult patients with T1D

Scent of a Woman's Ferrari Joy Ride