Incidence Rate of Emergency Department Visits for Hypoglycemia by Diabetes Drug Regimen in a Four Million Member Commercially Insured Population

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Background

- Hypoglycemia (HG) is a common adverse event caused by diabetes mellitus (DM) drug therapy that may put patients at risk of injury and even death.[1]
- An American Diabetes Association workgroup[2] proposed defining HG events as:
  - Asymptomatic HG, when not accompanied by symptoms but with a measured plasma glucose 70 miligrams per deciliter or lower;
  - Symptomatic HG, when there are symptoms typical of HG with measured or presumed plasma glucose 70 miligrams per deciliter or lower;
  - Severe HG, when requiring assistance of another person to actively administer carbohydrates, glucagon or take other corrective actions.
- Emergency department (ED) insurance claims with diagnosis codes for both DM and HG provide a means of estimating the frequency of severe HG events in large populations.
- The United States Food and Drug Administration (FDA) recently approved four new long-acting insulin products: the first "follow-on" insulin glargine (Basaglar®) after Lantus® patent expiration, a new higher-concentration form of insulin glargine (Toujeo®), and the novel insulin degludec as a single agent (Tresiba®) or in combination with rapid-acting insulin (Ryxodeg®).
  - Health plans are assessing these new products for safety and cost-effectiveness compared with alternatives.
  - Toujeo® and insulin degludec are both "ultralong-acting" insulins whose longer half-lives are hypothesized to lower the risk of HG.

Objective

- To estimate, in a commercially insured population, the incidence rate (IR) of emergency department visits for HG among members on DM drug therapy by the type of therapy from their pharmacy claims (Rxs).

Methods

- Among 9.5 million commercially insured members, those who were continuously enrolled between Jan. 1, 2011 and June 30, 2015 were selected.
- All emergency department visits with DM as a secondary diagnosis code and HG as first-line diagnosis code were identified using an algorithm validated by medical record review[3]
  - This algorithm classifies emergency department visits as HG cases if they had any of following diagnosis codes: 251.0, 251.1, 251.2, or 962.3. Emergency department visits are also classified as HG cases if they had diagnosis code 250.8x without any of the following diagnosis codes: 259.8, 272.7, 681.xx, 682.xx, 686.9x, 707.1, 707.8, 707.9, 709.3, 730.0, 730.1, 730.2, and 731.8. In the validation study, using HG as the first-line diagnosis code had a positive predictive value of 93 percent for confirmed HG.
  - This algorithm has been used in adverse event surveillance tracking[4] and in multiple research reports.[5,6,7]
- All pharmacy claims for antihyperglycemic agents (DM pharmacy claims) incurred for these members were identified, including non-insulin diabetes agents (NIDAs: biguanides, sulfonylureas, thiazolidinediones, DPP-4 inhibitors, GLP-1 receptor agonists, SGLT2 inhibitors, meglitinides, alpha-glucosidase inhibitors, and amylin agonists) and insulin. Insulin pharmacy claims were categorized as:
  - **Basal:** Insulin glargine, insulin detemir, insulin neutral protamine hagedorn (NPH)
  - **Rapid-acting (RA):** Insulin aspart, insulin lispro, insulin glulisine, inhaled regular insulin
  - **Pre-mixed:** 70 percent neutral protamine aspart (NPA)/30 percent aspart, 75 percent neutral protamine lispro (NPL)/25 percent lispro, 70 percent NPH/30 percent regular, 50 percent NPL/50 percent lispro
  - **Regular:** Insulin regular (excluding inhaled)
- To estimate the study sample's exposure to DM drug therapy:
  - Each member was assigned to a DM drug therapy category based on their DM pharmacy claims in each of nine, six-month intervals, January through June 2011 to January through June 2015.
  - Members were also categorized as Type 1 (T1) or Type 2 (T2) using an algorithm[8] based on diagnosis codes and pharmacy claims and by their age on June 30, 2015.
  - Patient years (pt-yrs) of exposure to any DM drug therapy and to different DM regimens plus/minus DM drug therapy were calculated by summing six month interval DM drug therapy by categories.
- Emergency department visits for HG were assigned to DM drug therapy categories based on the members' DM pharmacy claims in the six month interval preceding the visit.
- Incidence rate (IR) of emergency department visits for HG was calculated by dividing the number of visits by patient years of exposure and expressed as incidence rate per 1,000 patient years.

Results

- There were 3,947,165 members in the sample, with a mean age of 39.4 years, who had a total of 4,128 HG emergency department visits.
  - **Figure 1** shows the number of HG emergency department visits per 100,000 study members by the nine, six month intervals. This increased from 382 of 3.9 million (9.7 per 100,000) in January through June 2011 to 613 of 3.9 million (15.5 per 100,000) in January through June 2015.
  - 3,231 of 4,128 (78.3 percent) HG emergency department visits were by members with a pharmacy claim for insulin in the preceding six months.
  - Between January through June 2011 and January through June 2015, the number of study members with an insulin pharmacy claim increased from 38,509 of 3.9 million (0.98 percent) to 56,880 of 3.9 million (1.44 percent).
- **Figure 2** shows percentage of members with any DM pharmacy claim and the percentage with any insulin pharmacy claim during the six month interval of January through June 2015 by five year age groups. The prevalence of any DM drug and insulin use increases with age.
- **Figure 3** shows the percentage of members with any insulin pharmacy claim by insulin use category during January through June 2015 by five year age groups. The youngest members are predominantly T1 using either rapid-acting insulin (RA) by multiple daily injections or continuous infusion or combination RA plus basal. The older members are predominantly T2 using either basal insulin plus/minus NIDAs or basal plus RA insulin plus/minus NIDAs.
- Summing distributions such as **Figures 2** and **3** across all nine, six month intervals gives a total of 783,492 patient years of DM drug therapy.
  - **Table 1** shows patient years of DM drug therapy stratified into any insulin vs. only NIDAs by age category, with the number and incidence rate of HG emergency department visits.
  - **Table 2** shows patient years of DM drug therapy stratified by T1 vs. T2 and any insulin vs. only NIDAs. Insulin use is further stratified by categories of insulin and NIDA use by any use of a secretagogue (sulfonylurea or meglitinide) or no use of a secretagogue.
  - HG emergency department vists per 1,000 patient years was 14.9 for members with any insulin and highest for those under 35 and lowest for those 55 to 74 years old. Those categorized as T1 had an incidence rate of 25.6 HG emergency department visits per 1,000 patient years vs. 10.5 for T2 using insulin. Those who only had pharmacy claims for basal insulin (insulin glargine, detemir or NPH) had a lower incidence rate of HG emergency department visits than T2 members using other insulin categories.
  - Among members using only NIDAs those with a pharmacy claim for a secretagogue had a higher incidence rate of HG emergency department visits than those using only non-secretagogues (2.9 vs. 0.9 per 1,000 patient years).
- The estimated incidence rate of HG emergency department visits among members treated with insulin closely matches the result of one published study,[7] is lower than results from another study,[4] and higher than a third study.[6] These differences may be explained by differences in the methodology and the populations.

Limitations

- These results describe a continuously enrolled sample of members from a commercially insured population and may not be generalized to other populations.
- An accurate categorization of all utilizing members as T1 vs. T2 is not possible from claims data due to the high frequency of inconsistent diagnosis coding. Therefore these results reflect an unknown degree of misclassification.
- DM drug therapy at the time of the emergency department visit may have been misclassified for members due to the use of a six month preceding interval.
- Emergency department visits for HG may not always have represented severe HG events.
- Emergency department visits probably underestimate the total number of severe HG events as some may have not required medical intervention (e.g., were treated at home by a family member) or resulted in hospital admission without a preceding emergency department claim.

Conclusions

- Hypoglycemia coded emergency department visits provide an indicator for severe hypoglycemic event occurrence. In this commercially insured population, such visits occurred at a rate of about 15 per 1,000 patient years among members treated with insulin.
- The hypoglycemia emergency department visit rate was highest for individuals with Type 1 diabetes. In addition, the rate was higher among individuals with Type 2 diabetes on basal plus rapid-acting or premixed insulin therapy than those on basal insulin only.
- If new basal insulin products are demonstrated to result in lower severe hypoglycemia risk than alternative therapies, the results may be useful in modeling the new drugs comparative cost-effectiveness.

Figure 1. Hypoglycemia Emergency Department Visits Per 100,000 Members by Six Month Intervals, January 2011 to June 2015
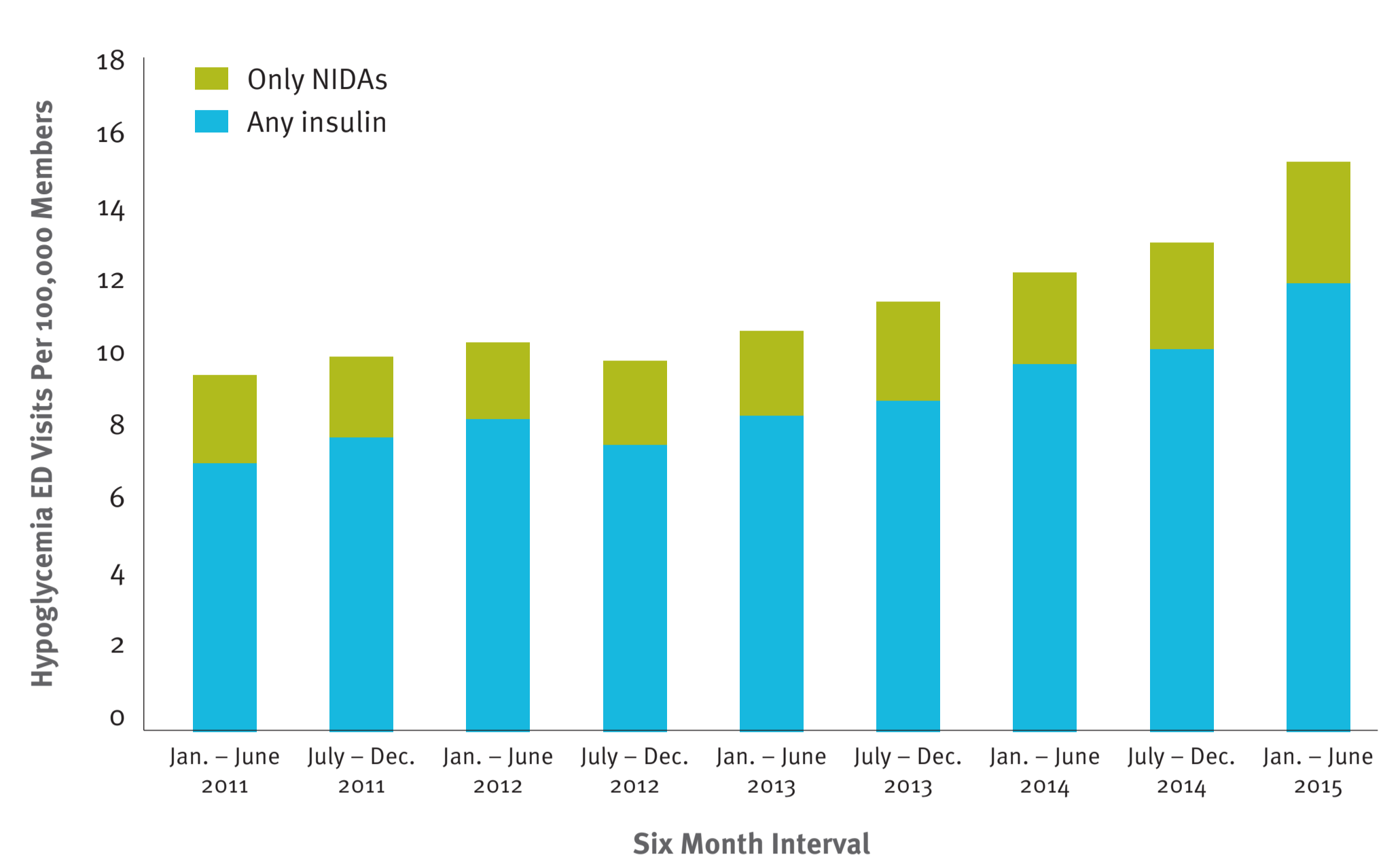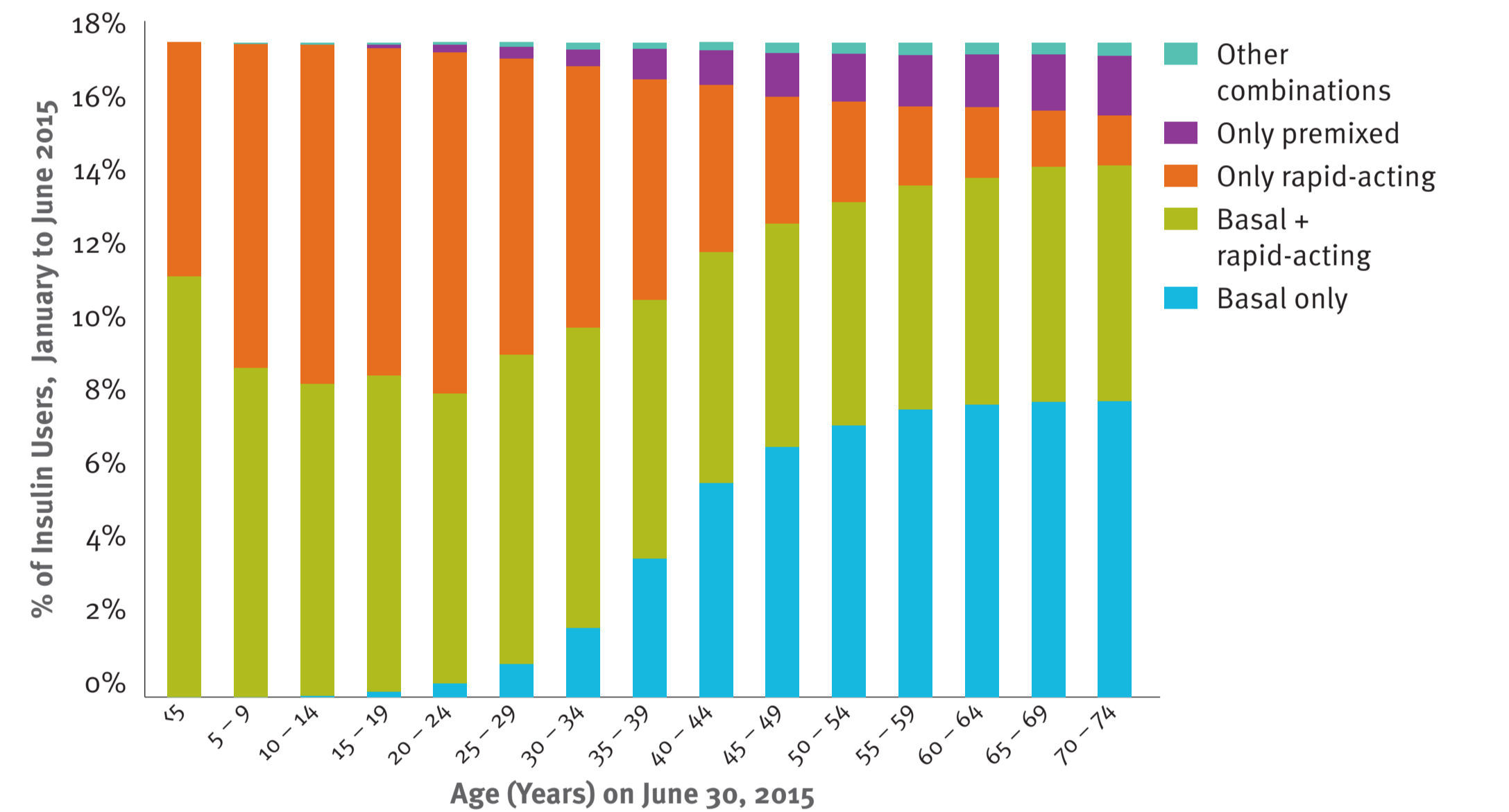

ED = emergency department, HG=hypoglycemia, Members = 3.9 million continuously enrolled commercially insured members, NIDAs = non-insulin diabetes agents.

Figure 2. Percentage of Study Members with Pharmacy Claims in the First Six Months of 2015 for Any Insulin or Only Non-Insulin Diabetes Agents by Five Year Age Groups
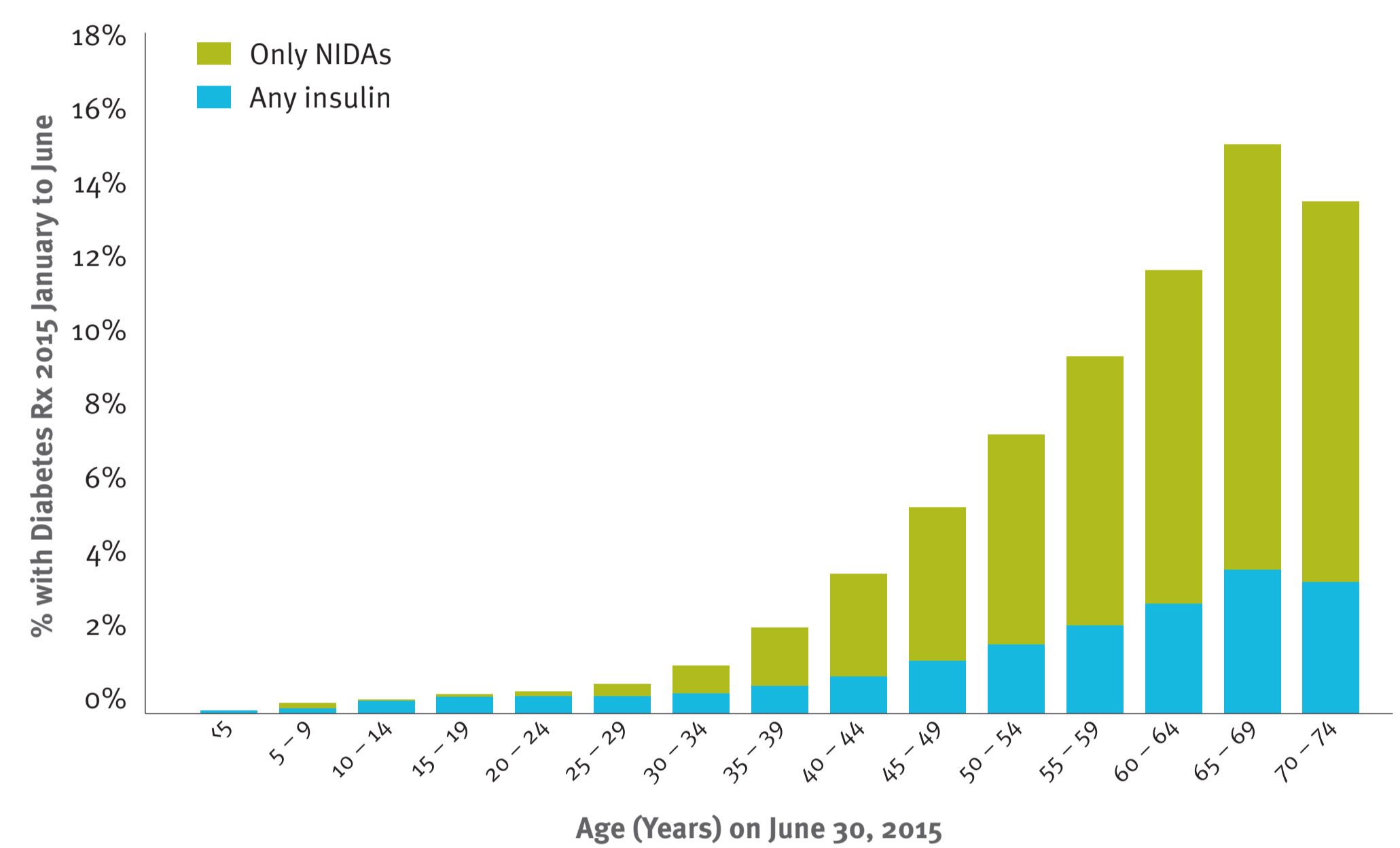
Rx = pharmacy claim, Members = 3.9 million continuously enrolled commercially insured members, NIDAs = non-insulin diabetes agents.

Figure 3. Percentage of Study Members with Insulin Pharmacy Claims in the First Six Months of 2015 by Insulin Use Categories and Five Year Age Groups

Basal = insulin glargine, detemir or NPH; RA = rapid-acting insulin aspart, lispro, glulisine or inhaled regular insulin; Premixed = 70% NPA/30% aspart, 75% NPL/25% lispro, 70% NPH/30% regular, 50% NPL/50% lispro; other combinations = pharmacy claims for more than two of preceding insulin categories or regular insulin, Members = 3.9 million continuously enrolled commercially insured members.

Table 1. Patient Years of Diabetes Mellitus Drug Therapy Stratified Into Any Insulin vs. Only Non-Insulin Diabetes Agents by Age Category, with the Hypoglycemia Emergency Department Visit Number and Incidence Rate

Diabetes therapy	Age (years)	Pt-yrs of diabetes drug therapy	ED visits for hypoglycemia	IR per 1,000 pt-yrs	IR 95% CI (per 1,000 pt-yrs)
Any insulin, with or without NIDA(s)	0–24	17,159	490	28.6	26.1 – 31.0
	25–34	7,575	193	25.5	21.9 – 29.0
	35–44	22,338	361	16.2	14.5 – 17.8
	45–54	54,721	857	15.7	14.6 – 16.7
	55–64	90,917	1,043	11.5	10.8 – 12.2
	65–74	23,820	287	12.0	10.7 – 13.4
Subtotal		**216,529**	**3,231**	**14.9**	**14.4 – 15.4**
Any NIDA(s) without insulin	0–24	2,418	8	3.3	1.0 – 5.6
	25–34	7,146	13	1.8	0.8 – 2.8
	35–44	49,635	104	2.1	1.7 – 2.5
	45–54	157,643	226	1.4	1.2 – 1.6
	55–64	278,026	401	1.4	1.3 – 1.6
	65–74	72,097	145	2.0	1.7 – 2.3
Subtotal		**566,963**	**897**	**1.6**	**1.5 – 1.7**
Total		**783,492**	**4,128**	**5.3**	**5.1 – 5.4**

NIDA = non-insulin diabetes agent; age = age as of June 30, 2015; Pt-yrs = patient years of exposure to diabetes drug therapy; ED = emergency department; visits for hypoglycemia = ED claims meeting diagnosis coding criteria for hypoglycemia; IR = incidence rate; CI = confidence interval; Members = 3.9 million continuously enrolled commercially insured members.

Table 2. Patient Years of Diabetes Mellitus Drug Therapy Stratified by T1 vs. T2 and Any Insulin vs. Only Non-Insulin Diabetes Agents, with the Hypoglycemia Emergency Department Visit Number and Incidence Rate

Diabetes category	Insulin use	NIDA use	Pt-yrs of diabetes drug therapy	ED visits for hypoglycemia	IR per 1,000 pt-yrs	IR 95% CI (per 1,000 pt-yrs)
T1	Basal + RA only	*	26,524	723	27.3	25.3 – 29.2
	RA only	*	29,897	646	21.6	20.0 – 23.3
	Premixed only	*	4,588	169	36.8	31.4 – 42.3
	Other combinations	*	2,978	97	32.6	26.2 – 38.9
Subtotal		*	**63,987**	**1,635**	**25.6**	**24.3 – 26.8**
T2	Basal only	Any or none	71,571	506	7.1	6.5 – 7.7
	Basal + RA only	Any or none	47,372	661	14.0	12.9 – 15.0
	RA only	Any or none	14,066	207	14.7	12.7 – 16.7
	Premixed only	Any or none	16,999	208	12.2	10.6 – 13.9
	Other combinations	Any or none	2,536	14	5.5	2.6 – 8.4
Subtotal		**Any or none**	**152,543**	**1,596**	**10.5**	**10.0 – 11.0**
T1 or T2 using insulin	Basal only	Any or none	71,571	506	7.1	6.5 – 7.7
	Basal + RA only	Any or none	76,964	1,447	18.8	17.8 – 19.8
	RA only	Any or none	40,896	769	18.8	17.5 – 20.1
	Premixed only	Any or none	21,587	398	18.4	16.6 – 20.2
	Other combinations	Any or none	5,514	111	20.1	16.4 – 23.8
Subtotal		**Any or none**	**216,530**	**3,231**	**14.9**	**14.4 – 15.4**
T2 using only NIDA	None	Any secretagogue	193,479	556	2.9	2.6 – 3.1
	None	No secretagogue	373,484	341	0.9	0.8 – 1.0
Subtotal		**Any NIDA**	**566,963**	**897**	**1.6**	**1.5 – 1.7**
Total T1 or T2			**783,492**	**4,128**	**5.3**	**5.1 – 5.4**

T1 = categorized as Type 1 diabetes by algorithm;[8] T2 = categorized as Type 2 diabetes; NIDA = non-insulin diabetes agent; Pt-yrs = patient years of exposure to diabetes drug therapy; ED = emergency department; visits for hypoglycemia = ED claims meeting diagnosis coding criteria for hypoglycemia; IR = incidence rate; CI = confidence interval; Basal = insulin glargine, detemir or NPH; RA = rapid-acting insulin aspart, lispro, glulisine or inhaled regular insulin; Premixed = 70% NPA/30% aspart, 75% NPL/25% lispro, 70% NPH/30% regular, 50% NPL/50% lispro; Secretagogue = sulfonylurea or meglitinide; Members = 3.9 million continuously enrolled commercially insured members.
*T1 criteria allow metformin or pramlintide use if member meets other T1 criteria (see reference 8) and study methods.

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