Appendix 15 (as supplied by the authors): Adverse events (excluding hypoglycemia) reported in RCTs of long-acting insulin analogues in type 2 diabetes.

Study*	Total number or % of subjects experiencing adverse events	Description of Adverse Events
Eliaschewitz *et al.*, 2006[92]	IGlar+Glim: 137 patients (59.3%) reported AEs 10 patients (4.3%) reported SAEs, 39 patients (16.9%) with treatment-related events NPH+Glim: 150 patients (60%) reported AEs; 10 patients (4.0%) reported SAEs; 31 patients (12.4%) with treatment-related events	Treatment-related adverse events were categorized as possibly related by the investigator. The most common possibly related AEs were injection site reactions, which were seen in: IGlar+Glim: 19 patients (8.2%) NPH+Glim: 17 patients (6.8%)
Fritsche *et al.*, 2003[128]	Bedtime IGlar: 414 (36 considered possibly treatment-related) Morning IGlar: 403 (45 considered possibly treatment-related) NPH: 423 (55 considered possibly treatment-related)	Only AEs specified were weight gain.
Haak *et al.*, 2005[129]	IDet+IAsp NPH+IAsp	Most common AEs were gastro-intestinal disorders in IDet patients; skin and appendage disorders in NPH patients. Weight gain was experienced by both groups.
Hermansen *et al.*, 2006[91]	IDet+OAD: 3 patients withdrew due to AEs; 1 case was considered related to trial product (mild allergy) NPH+OAD: 4 patients withdrew due to AEs; 1 case was considered related to trial product (mild injection site reaction)	Both insulins were well tolerated with no major safety issues arising. The adverse event profiles of the two insulins were similar, with most adverse events mild or moderate and considered unlikely related to trial products. The only between-treatment difference with a probable relation to trial medication concerned injection site reports, which were seen in: IDet+OAD: 14 events in 13 patients (9 patients suffered injection-site reactions, 2 reports of pain, and 2 reports of hematoma) NPH+OAD: 6 events in 6 patients (6 patients suffered injection-site reactions)
HOE 901/2004 Study Group, 2003[140]	IGlar 30: 3/64 patients (4.7%) experienced AEs possibly related to treatment IGlar 80: 3/72 patients (4.2%) experienced AEs possibly related to treatment NPH: 2/68 patients (2.9%) experienced AEs possibly related to treatment	IGlar 30: tachycardia, tongue edema, and injection site reaction. One serious adverse event (myocardial infarction) was not considered to be treatment-related. IGlar 80: paresthesia, dyspepsia, and increased appetite NPH: headache and nausea with asthenia One patient in each group experienced an injection site reaction. Mean body weight increased in all groups.
Massi *et al.*, 2003[131]	IGlar: 185 patients (65%) reported at least one AE; 5.5% possibly treatment-related NPH: 193 (69%) reported at least one AE; 7.5% possibly treatment-related	Most common AEs were infection, upper respiratory tract infection, bronchitis, back pain, and injection site reactions. Other AEs included increased insulin antibodies and development of E. coli antibodies.
Pan *et al.*, 2007[108]	IGlar+Glim: 120 patients (54.3%) experienced AEs; 22 patients (10%) experienced possibly treatment-related AEs; 10 patients reported 13 SAEs NPH+Glim: 130 patients (58.3%) experienced AEs; 23 patients (10.3%) experienced possibly treatment-related AEs; 12 patients reported 12 SAEs	The majority of the possibly treatment-related AEs were injection site reaction (45 events in 31 patients) IGlar+Glim: 10 patients reported 13 SAEs (3 myocardial infarction, 1 myasthenia, 1 neuropathy, 1 pneumonia, 1 cellulitis, 1 retinal disorder, 1 eye disorder, 1 angina pectoris, 1 arthritis, 1 bone fracture, and 1 cystitis) NPH+Glim: 12 patients reported 12 events (2 hypoglycemia†, 2 myocardial infarction, 2 accidental injury, 1 back pain, 1 breast neoplasm, 1 bone disorder, 1 bone fracture, 1 urinary tract disorder, and 1 enteritis)

Study*	Total number or % of subjects experiencing adverse events	Description of Adverse Events
Philis-Tsimikas *et al.*, 2006[99]	IDet (morning)+OAD: 123 AEs in 70 patients; 8 SAEs in 8 patients; 1 death in IDet group (could be in evening group) IDet (evening)+OAD: 150 AEs in 67 patients; 5 SAEs in 5 patients NPH+OAD: 144 AEs in 82 patients; 9 SAEs in 9 patients; 1 death	All 3 insulin regimens were well tolerated and no abnormalities were detected in routine biochemical or hematologic investigations or in vital signs. The overall profiles of AEs were statistically similar among 3 groups. Most AEs, including all of the serious events and 2 deaths were considered unrelated to the study insulins. No statistically significant between-group differences were detected in incidences of AEs, serious AEs, and potential allergic reactions possibly related to study medication. Injection site reactions were considered possibly or probably related to the study insulins. IDet (morning)+OAD: 2 injection site reactions in 2 patients; 2 potential allergic reactions in 2 patients IDet (evening)+ OAD: 7 injection site reactions in 6 patients; 5 potential allergic reactions in 5 patients NPH+OAD: 2 injection site reactions in 2 patients; 1 potential allergic reactions in 1 pt
Raskin *et al.*, 2006 [106]	IDet+IAsp: NR IGlar+IAsp: NR	IDet+IAsp: Patients gained 1.4 kg IGlar+IAsp: Patients gained 2.9 kg
Raslova *et al.*, 2004[94]	IDet+IAsp: 2 patients reported; 5 patients withdrew due to AEs NPH+HI: 3 patients reported; 2 patients withdrew due to AEs	The incidence and pattern of AEs was similar between treatments, with the majority of events being mild and considered unrelated to trial products. SAEs were judged as being possibly/probably related to trial products The incidence of sudden death was considered to be unrelated to the trial products. All people recovered completely. Biochemical standard safety variables were comparable between treatments and no clinically relevant changes were observed. IDet+IAsp: 2 patients with SAE, including one who was hospitalized because of an accidental overdose of insulin and the other due to deterioration in physical ability secondary to shortness of breath at minimal exertion; 5 patients withdrew due to AEs: 1 cutaneous allergic reaction at the insulin injection site, 1 weight gain and peripheral edema, 1 pruritus, 1 shortness of breath on exertion, and 1 sudden death with unknown cause. NPH+HI: 3 patients with SAEs including 1 episode of hypolycemic coma†, one episode of severe hypoglycemia†, and one case of palpitation; 2 withdrawals were due to 1 hyperglycemia† and 1 macropapular rash with breast abscess.
Riddle *et al.*, 2003[132]	IGlar+OAD NPH+OAD	Weight gain reported for both groups
Rosenstock *et al.*, 2006[104]	IDet+OAD: NR IGlar+OAD: NR	IDet+OAD: Body weight increased 2.7 kg IGlar+OAD: Body weight increased 3.5 kg
Rosenstock *et al.*, 2001[111]	IGlar: 27 patients (10.4%) experienced treatment-related AEs; 9 withdrew due to AEs NPH: 20 patients (7.7%) experienced treatment-related AEs; 7 withdrew due to AEs	Mild pain or cellulitis at the injection site was the only AEs specified.
Tajima *et al.*, 2006[110]	NR	No apparent differences in safety parameters.

Study*	Total number or % of subjects experiencing adverse events	Description of Adverse Events
Wang *et al.*, 2007[109]	IGlar+Glip: NR NPH+Glip: NR	IGlar+Glip: the body weight gain was 1.47±1.04 kg NPH+Glip: the body weight gain was 1.20±1.17 kg
Yki-Järvinen *et al.*, 2006[139]	IGlar: 33 patients (54%); one serious AE, not considered to be related to treatment NPH: 24 patients (49%); 4 serious AEs, not considered to be related to treatment	Most common AEs were infections and musculoskeletal and gastrointestinal disorders, with no differences between the groups IGlar: mean weight gain of 2.6±0.6 kg; serious AE was endometriosis; one withdrawal due to pancreatic cancer NPH: mean weight gain of 3.5±0.7 kg; serious AEs were anaphylactic reaction, atrial fibrillation and cardiac failure, gastroenteritis, and pulmonary emphysema
Yki-Järvinen *et al.*, 2000[138]	IGlar: NPH:	No difference in treatment-emergent AEs possibly related to study medication

AE=adverse events; DM=diabetes mellitus; Glim=glimepiride; Glip=glipizide; HI=conventional human insulin; IAsp=insulin aspart; IDet=insulin detemir; IGlar=insulin glargine; Metf=metformin; NPH=neutral protamine Hagedorn; NR=not reported; OAD=oral antidiabetic agent; RCTs=randomized controlled trials; SAEs=serious adverse events.

*Citations of the studies are listed in the main article, available at www.cmaj.ca/cgi/content/full/180/4/385.

†Hypoglycemia could not be separated from other AEs.