TITLE: Paramedic assist-requiring hypoglycemia in adults in south west Ontario, Canada: a population-based retrospective cohort study.

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Competing Interests

S.L.L reports grants and personal fees from NovoNordisk and Sanofi and personal fees from Merck outside the submitted work. T.S. reports grants from NovoNordisk and personal fees from Eli Lilly, Insulet Canada and Sanofi Canada outside the submitted work. J.L.M., M.P and M.C. have no conflicts of interest to disclose.

ABSTRACT

Background: Hypoglycemia is a common treatment consequence in diabetes mellitus. Emergency department visits for hypoglycemia may represent a proportion of severe hypoglycemic events, as many individuals with assist-requiring hypoglycemia do not present to hospital, although in some cases paramedics are called. The study objective was to determine the incidence and characterize paramedic assist-requiring hypoglycemia in adults in south west Ontario, Canada.

Methods: This population-based retrospective cohort study used data extracted from ambulance call records of 8 paramedic services of the Southwest Ontario Regional Base Hospital Program from January 2008 to June 2014.

Results: There were 9185 paramedic calls for hypoglycemia (mean age 60.2 years, 56.8% male, 81.1% documented diabetes). The mean capillary blood glucose on paramedic arrival was 2.5 ± 1.0 mmol/L. There were 3883 (42.3%) and 1441 (15.7%) calls associated with insulin and oral antihyperglycemic agent use, respectively. Patients refused hospital transport in 24.5% of calls. The estimated annual incidence rate of paramedic assist-requiring hypoglycemia was 108 per 10,000 persons with diabetes per year.

Interpretation: Paramedic assist-requiring hypoglycemia in south west Ontario, Canada is common. Up to 25% of paramedic-treated hypoglycemia calls do not result in hospital transport and so physicians managing diabetes care are often unaware of their occurrence. This indicates a significant care gap in follow-up of those with paramedic assist-requiring hypoglycemia.

INTRODUCTION

Hypoglycemia is a common treatment consequence in diabetes mellitus. It has a negative impact on many health-related outcomes (1-10). Severe hypoglycemia (SHG) i.e. hypoglycemia requiring third-party assistance (11) is common—reported incidence ranges from 0.8 to 3.2 events per person/year (10,12-15) and annual prevalence from 10 to 53% (type 1 diabetes) (12) and 4.4 to 6% (type 2 diabetes) (7,13). Major negative outcomes are associated with SHG, including increased cardiovascular events (1,2), physical injury (3), and mortality (1,2,4,5). SHG impairs quality of life (6,7) and discourages patients from aiming for tighter glycemic control (8,9). The economic costs of SHG are also significant, accounting for the associated healthcare utilization (16). In Canadians presenting to Emergency Departments (EDs) with SHG between 2008-2010, 82% needed further diagnostic testing and 23% were hospitalized (3). In the United States (US), insulin and oral antihyperglycemic agents (OHA), respectively, were the 2nd and 4th medication classes most frequently associated with emergency hospitalization in adults age ≥ 65, with 40.6% and 51.8% of ED visits resulting in hospitalization (17).

However, despite these serious consequences, it is possible that only some patients with SHG present to hospital as many are treated at the scene i.e. by family members. If paramedics are called for a SHG event, patients may subsequently refuse hospital transport. Although reported rates of SHG ED visits are high—a US study estimated > 97,000 ED visits per year for insulin-related hypoglycemia (18)—the true burden of SHG is likely higher when accounting for events not leading to an ED visit. There have been limited studies examining the rate of paramedic assist-requiring hypoglycemia in the pre-hospital setting. This study describes the incidence and

characteristics of adult paramedic assist-requiring hypoglycemia calls over 6.5 years in south west Ontario, Canada.

METHODS

We conducted a population-based retrospective cohort study in south west Ontario, Canada. Ontario is the most populous Canadian province. There are ~1.6 million residents in south west Ontario (19), ~12% of the provincial population (20). We used data extracted from the electronic ambulance call records (ACR) of 8 paramedic services (Supplementary Figure 1) under the direction of the Southwest Ontario Regional Base Hospital Program (SWORBHP). In Ontario, all paramedics are mandated to complete ACR for all calls attended. In our region, each call is assigned a unique identifier and data collected are stored in an electronic database housed at the SWORBHP. Data from all ACRs between January 2008 to June 2014 for adults age ≥ 18 in which paramedics provided treatment for hypoglycemia were included. The following patient characteristics were extracted from the ACR database: age, sex, diabetes mellitus history, insulin and OHA use, capillary blood glucose (CBG) (mmol/L) and Glasgow Coma Scale (GCS) score on paramedic arrival. Call characteristics collected include the time of call, the Canadian Triage Acuity Scale (CTAS) score, the attending paramedic crew type [Primary Care Paramedic (PCP), PCP with training to administer intravenous medications (PCP-IV) or Advanced Care Paramedic (ACP)], the hypoglycemia treatment provided (oral glucose, intravenous (IV) dextrose, glucagon), final primary problem code (1 of 63 problem codes classified by organ system) and the return priority code including disposition (transported to hospital or not). In 688 calls, the

documented initial CBG value on paramedic arrival was either missing or ≥ 4 mmol/L and thus these ACRs were manually reviewed for CBG value validation.

Statistical analysis was performed using SAS for Windows version 9.3 (SAS, Cary, NC, USA). Patient and call characteristics were summarized using means and standard deviations or proportions where appropriate. The characteristics of calls with and without transport refusal were compared using independent t-test (continuous variables) or Chi-square or Fisher's exact test (categorical variables) as appropriate. Logistic regression was performed to determine factors associated with hospital transport. An estimate of the annual incidence rate of paramedic assist-requiring hypoglycemia calls was determined for 2009-2013 (partial years 2008 and 2014 not included), using diabetes prevalence data from provincial administrative databases (21). The study was approved by the Western University Health Sciences Research Ethics Board. We used the STROBE cohort checklist when writing our report (22).

RESULTS

There were 9185 paramedic calls in which treatment for hypoglycemia to adult patient was provided during the study period. The number of calls per complete year by paramedic service is shown in Figure 1. The estimated incidence rate of paramedic assist-requiring hypoglycemia calls from 2009-2013 was ~108 per 10,000 persons with diabetes per year, based on the estimated number of adults with diabetes (134,449) in the geographic area covered by the SWORBHP in 2011 (21).

The patient and call characteristics are summarized in Table 1. The final primary problem code was "diabetic emergency" in 67.5% of calls, with 1 of 40 other primary problem codes noted for the remaining calls (Supplementary Table 1). Disposition data were available for 9173 calls, summarized in Table 2. Of the 2428 (26.5%) calls with no transport, 92.4% were due to patient refusal and thus transport refusal occurred in 24.5% of the total calls during the study period. Patient death occurred in 27 (0.3%) calls.

The characteristics of the calls with and without transport refusal were compared, summarized in Table 1. Patients who refused transport were younger (58.6 years vs. 60.8 years, $p<0.0001$), a higher proportion were male (59.6% vs. 55.9%, $p=0.002$), and had a higher mean CBG on paramedic arrival (3.2 vs. 2.3 mmol/L, $p<0.0001$). However, a smaller proportion had documented diabetes (77.8% vs. 82.2%, $p<0.0001$), used OHA (14.1% vs. 16.2%, $p=0.018$), had GCS < 9 (17.6% vs. 26.3%, $p<0.0001$) and CTAS ≤ 3 (91.7% vs. 96.6%, $p<0.0001$) compared to calls when transport to hospital was not refused. . A higher proportion of overnight (18:00 to 06:00) calls were in those with transport refusal (50.1% vs. 46.4%, $p=0.002$). There was a significant difference in hypoglycemia treatment ($p<0.0001$), with higher oral glucose and lower IV dextrose and glucagon in those who refused transport.

Univariate analyses showed that older age, female sex, documented diabetes, OHA use, lower CBG, lower GCS, lower acuity CTAS, daytime (06:00 to 18:00) call, hypoglycemia treatment, and final primary problem code of "diabetic emergency" were each significantly associated with transport to hospital (each $p<0.05$) but insulin use ($p=0.80$) and crew type ($p=0.37$) were not. On multivariate analyses, older age, female sex, no documented diabetes, lower CBG, lower GCS,

lower acuity CTAS, daytime call, hypoglycemia treatment and final primary problem code as a "diabetic emergency" were independently associated with increased odds of transport to hospital.

INTERPRETATION

There are limited population-based data on SHG in the pre-hospital setting. In this study, we described > 9000 calls for paramedic assist-requiring hypoglycemia in adults in south west Ontario, Canada over 6.5 years. The estimated annual incidence rate of calls was high: 108 per 10,000 persons with diabetes per year. We found that more calls occurred in older men with known diabetes, of whom only half used insulin. Patients who refused hospital transport following paramedic intervention differed significantly from those who did not with respect to age, sex, diabetes, mean CBG on paramedic arrival, GCS, CTAS, time of calls and treatment.

To our knowledge, this study is the largest population-based study of paramedic assist-requiring hypoglycemia in Canada, and is 1 of few studies (23-25) of longer duration i.e. > 5 years worldwide. Our inclusion criteria were predetermined and data were obtained from a comprehensive database of all calls in a geographically defined region. To ensure data validity, we manually reviewed the CBG value on paramedic arrival in 7.5% of calls. Our results confirm that, in our region, paramedic assist-requiring SHG is common and that a significant proportion (25%) of cases are not transported to hospital. Data from these patients would not be captured in administrative databases that collect information from ED visits so our results more accurately characterize paramedic assist-requiring SHG.

There are challenges comparing the frequency of paramedic assist-requiring calls between studies. Prior studies are mostly of shorter duration in varied populations (16,23-31) with reported incidence ranging from 4.8 to 103 per 10,000 person-years (PY) in Victoria, Australia (25) to 1150 per 10,000 PY (type 1 diabetes) and 1180 per 10,000 PY (type 2 diabetes) in Tayside, Scotland (16) (though the Tayside study was > 20 years ago, prior to the advent of newer analog insulins with lower hypoglycemia risk and more advanced glucose monitoring technology). There have been 2 prior Canadian studies (32,33) but both were ≤ 1-year duration and did not estimate annual incidence. The age and sex of patients in our study were similar to prior reports (23-28,30,31,33-36). A high proportion (81.1%) had documented diabetes, though only 42.3% used insulin, lower than prior studies (23,24,27,30) in which insulin use ranged from 74.0% (30) to 75.9% (type 2 diabetes) and 99.5% (type 1 diabetes) (23). Also notable, we report higher glucagon use (either alone or in combination) (36.9%) than other studies where it ranged from 0.01% (35) to 17.8% (33). A US emergency medical services (EMS) registry study also showed glucagon underutilization and postulated that crew type may be contributory, as ~75% of US EMS providers are not paramedics and thus unable to administer glucagon (37). In Ontario, Canada, both ACP and PCP may administer glucagon, but only ACP and PCP with specialized training (PCP-IV) can administer IV dextrose. In our study, PCP (73.3% PCP, 1.7% PCP-IV) attended 75% of calls, in contrast to a study in Ottawa, Ontario by Sinclair et al. in which ACP attended 80.1% of calls (33). Despite this crew type difference, the proportion of patients in our study treated with IV dextrose was similar to Sinclair et al. (42.8% vs. 37.8%), but in our study a much higher proportion received glucagon (36.9% vs. 17.8%) (33). Thus, differences in paramedic scope of practice by jurisdiction may explain some, but not all, differences between

hypoglycemia treatment in our study and other reports. We did not have information on whether patients self-treated prior to paramedic arrival.

In our study, patients refused transport to hospital in ~one-quarter of the total calls. Patient refusal of transport has been commonly reported elsewhere (26,28,33,35,37) with similar transport refusal rates (17.7% to 29.7%). We showed that in calls with transport refusal, patients were younger, more often men, had a higher mean CBG on paramedic arrival, and a higher proportion were overnight. A lower proportion had diabetes, GCS < 9, CTAS ≤ 3, and used OHA, similar to other studies reporting transport refusal by younger men and those less likely to be on OHA (33,38). We speculate that in our study, those who refused transport may represent younger patients with less severe hypoglycemia potentially related to more remediable causes (i.e. missed meal, miscalculation of insulin dose) rather than more serious underlying illness. Thus, although they did require a paramedic call and subsequent SHG treatment, after recovery they were less willing to seek further care in the ED. Contrary to our results, other studies have shown higher prevalence of insulin use in patients who refused transport (33,38).

Given the significant proportion of SHG paramedic calls with transport refusal, many patients may not receive appropriate follow-up care. In the United Kingdom, strategies to facilitate timely access to care post-paramedic assist-requiring SHG have been assessed, including early referral for education (39) and phone calls/reminder cards to contact their diabetes care providers (40). Although patients perceived these programs positively (39,40), the interventions did not increase follow-up diabetes care attendance (40). Another study evaluated an “opt-out” referral pathway where patients declining participation had to telephone within 3 days, which led to follow-up

hypoglycemia education delivery in 72.1% of the first 2000 referrals (41). To our knowledge, no such programs exist in North America. In our region, follow-up for patients with diabetes presenting to the ED with SHG is individualized depending on the context (i.e. with family physician/endocrinologist or diabetes educator, with referrals made as necessary), but these arrangements are not possible if patients are not seen in the ED. Since our study showed that this represents a sizable proportion of paramedic-assisted SHG cases, we are completing a project assessing the impact of a direct paramedic referral pathway in which electronic referrals were sent at the time of paramedic assessment for patients with SHG to receive follow-up focused hypoglycemia education.

A study limitation is that we were not able to identify unique individuals, only unique calls; thus we did not have data on repeated calls by individuals. The repeat SHG call rate in the Middlesex-London Paramedic Service (the largest paramedic service in the SWORBHP) over 6 months in 2014 was 26% (personal communication), similar to other studies (32-34) with repeat call rates ranging from 13.5% to 25.9%. We were also not able to distinguish diabetes type, i.e. type 1 or 2, though variation in the incidence of paramedic assist-requiring hypoglycemia by diabetes type has been reported (16,26-29). However, since insulin use was reported in only 42.3% of calls, it may be inferred that a high proportion of our study patients had type 2 diabetes. Finally, although our study encompassed a large geographic area served by the SWORBHP, the results may not be generalizable to other populations.

This large population-based study demonstrates the high incidence of paramedic assist-requiring hypoglycemia in south west Ontario, Canada. It also highlights the high transport refusal rate in

paramedic-treated SHG, and thus diabetes care providers are often unaware and unable to provide recommendations to help decrease SHG frequency. This is an important care gap as it represents missed opportunities to intervene with strategies to prevent recurrent SHG events, which could ultimately decrease morbidity and mortality and improve quality of life. Future studies are required to identify approaches to facilitate more direct communication of SHG occurrence between patients, emergency medical services, and physicians involved in their diabetes care, and to elucidate patient-important barriers to presenting to the ED for SHG.

AUTHOR CONTRIBUTIONS

S.L.L. contributed to the design and conduct of the study and analysis plan, and interpretation of the data, wrote the first draft of the manuscript, reviewed and approved the manuscript, and is the guarantor of the work. J.L.M. conceived the study idea, contributed to the design and conduct of the study and interpretation of the data, and reviewed and approved the manuscript. M.P. and M.C. contributed to the design and conduct of the study and interpretation of the data, and reviewed and approved the manuscript. T.S. contributed to the design and conduct of the study and analysis plan and interpretation of the data, and reviewed and approved the manuscript.

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Table 1 – Patient and paramedic call characteristics (January 2008- June 2014) (N=9185 calls), stratified by refusal of transport.

	Total	Transport Refusal	No Refusal of Transport	p-value*
Calls	9185	24.4% (2243)	75.6% (6942)	
Patient Characteristics				
Age (years), mean ± SD (N=9162)	60.2 ± 19.0	58.6 ± 19.7	60.8 ± 18.7	<0.0001
Male (N=9146)	56.8% (5197)	59.6% (1333)	55.9% (3864)	0.002
Documented diabetes diagnosis	81.1% (7450)	77.8% (1746)	82.2% (5704)	<0.0001
Insulin use	42.3% (3883)	42.9% (963)	42.1% (2920)	0.483
Oral antihyperglycemic agent use	15.7% (1441)	14.1% (316)	16.2% (1125)	0.018
Mean capillary blood glucose on paramedic arrival (mmol/L), mean ± SD (N=9026)	2.5 ± 1.0	3.2 ± 1.1	2.3 ± 0.9	<0.0001
Capillary blood glucose on paramedic arrival <2.5 mmol/L (N=9026)	54.6% (4931)	23.5% (504)	64.4% (4427)	<0.0001
Initial Glasgow Coma Score <9 (N=9019)	24.2% (2181)	17.6% (385)	26.3% (1796)	<0.0001
Call Characteristics				
Canadian Triage Acuity Score ≤ 3 (N=7731)	95.5% (7383)	91.7% (1561)	96.6% (5822)	<0.0001
Time of Calls (N=9092)				
00:00 to 05:59	20.5% (1860)	22.6% (502)	19.8% (1358)	
06:00 to 11:59	22.9% (2084)	22.2% (493)	23.2% (1591)	0.0074
12:00 to 17:59	29.8% (2706)	27.7% (615)	30.4% (2091)	
18:00 to 23:59	26.9% (2442)	27.5% (612)	26.6% (1830)	
Type of crew (N=9168)				
Emergency Medical Assistant	0.02% (2)	0.04% (1)	0.01% (1)	
Primary Care Paramedic	73.3% (6717)	74.1% (1657)	73.0% (5060)	0.1711
Primary Care Paramedic-IV	1.7% (159)	1.3% (29)	1.9% (130)	
Advanced Care Paramedic	25.0% (2290)	24.6% (550)	25.1% (1740)	
Treatment				
Oral glucose alone	22.6% (2072)	38.8% (871)	17.3% (1201)	
IV dextrose alone	34.7% (3189)	29.3% (656)	36.5% (2533)	
Glucagon alone	18.3% (1679)	15.1% (339)	19.3% (1340)	<0.0001
Oral glucose and IV dextrose	5.8% (534)	3.7% (84)	6.5% (450)	
Oral glucose and glucagon	16.3% (1501)	11.8% (264)	17.8% (1237)	
IV dextrose and glucagon	2.0% (186)	1.1% (24)	2.3% (162)	

Oral glucose, IV dextrose and glucagon	0.3% (24)	0.2% (5)	0.3% (19)	
Treatment (Not mutually exclusive†)				
Oral glucose	45.0% (4131)	1224 (54.6%)	2907 (41.9%)	<0.0001
IV dextrose	42.8% (3933)	769 (34.3%)	3164 (45.6%)	<0.0001
Glucagon	36.9% (3390)	632 (28.2%)	2758 (39.7%)	<0.0001

Data are presented as % (N) unless otherwise indicated. SD, standard deviation; IV, intravenous.

*Comparison of those who refused transport vs. those who did not refuse transport using independent t-test (continuous variables) or Chi-square or Fisher's exact test as appropriate (categorical variables).

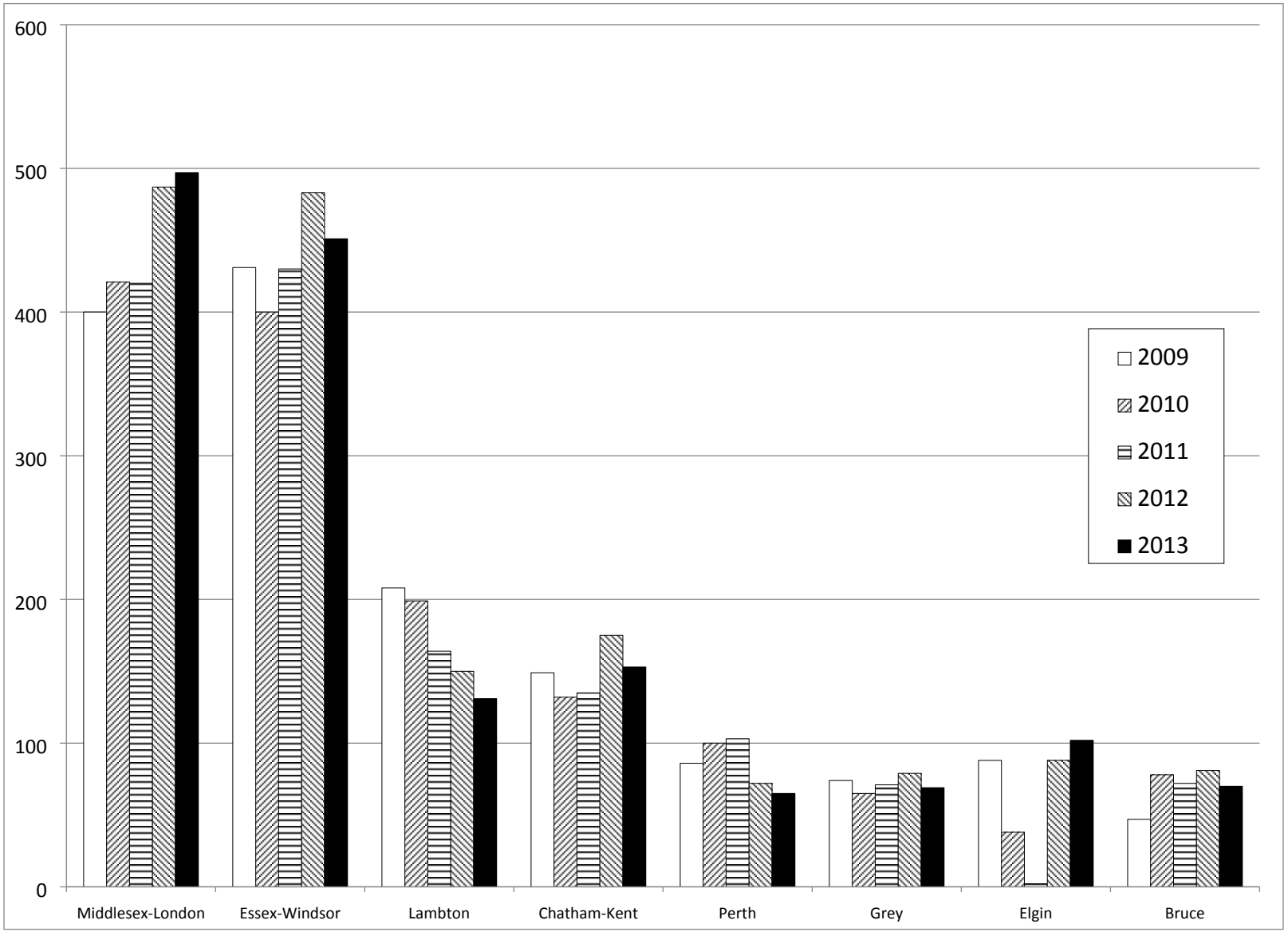
†More than one type of treatment may have been administered (so sum is greater than total number of calls).

Table 2 – Patient disposition as per return priority code (N=9173)

Patient Transported by Paramedics			
	N	% of those transported	% of total calls*
Transport of Deceased Patient	1	0.01%	0.01%
Scheduled	8	0.1%	0.09%
Deferable	66	1.0%	0.7%
Prompt	4462	66.2%	48.6%
Urgent	2208	32.7%	24.1%
Subtotal	6745		73.5%
Patient Not Transported by Paramedics			
	N	% of those not transported	% of total calls*
Patient in Police Custody	3	0.1%	0.03%
No Patient Found	9	0.4%	0.1%
Patient Deceased	26	1.1%	0.3%
Transported by Other Ambulance	147	6.1%	1.6%
Patient Refused	2243	92.4%	24.5%
Subtotal	2428		26.5%

*total calls with disposition data available (N=9173).
Note: percentages may not add up to 100% due to rounding.

Figure 1 – Paramedic assist-requiring calls for hypoglycemia per year 2009-2013, by paramedic service



Supplementary Figure 1 – Paramedic Services of the Southwest Region Base Hospital Program

Paramedic Services included in the study:

Middlesex-London Paramedic Service

Essex-Windsor EMS

The County of Lambton EMS

Medavie EMS Chatham-Kent

Perth County Paramedic Services

Grey County Paramedic Services

Medavie EMS Elgin Ontario

Bruce County Paramedic Services

Paramedic Services not included:

Huron County Paramedic Services

Oneida Nation Paramedic Services

Oxford County Paramedic Services

Supplementary Table 1 – Final Primary Problem Code of Calls (N=9185)

Diabetic Emergency	67.5% (6196)
Other Medical/Trauma	5.1% (469)
Invalid Code	5.0% (461)
Weakness/Dizziness/Unwell	4.1% (374)
Interfacility Transfer	3.5% (324)
Altered Level of Consciousness	2.6% (235)
Missing Code	1.9% (175)
Active Seizure	1.3% (119)
Confusion/Disorientation	0.9% (80)
Drug/Alcohol Overdose	0.8% (78)
Unconscious	0.7% (62)
Dyspnea	0.7% (61)
Musculoskeletal	0.7% (60)
Stroke/Transient Ischemic Attack	0.6% (56)
Vital Signs Absent - Cardiac/Medical	0.6% (53)
Hypotension	0.6% (51)
Ischemic	0.5% (49)
Behaviour/Psychiatric	0.5% (44)
Nausea/Vomiting/Diarrhea	0.4% (40)
Gynecologic Emergency	0.4% (36)
Non-Traumatic Abdominal/Pelvic/Perineal/Rectal Pain	0.4% (34)

Headache	0.2% (22)
Temporary Loss of Consciousness	0.2% (19)
Treatment/Diagnosis & Return	0.2% (14)
Poisoning/Toxic Exposure	0.1% (12)
Palpitations	0.1% (10)
Back Pain	0.1% (9)
Environmental Emergency	0.1% (9)
Allergic Reaction	<0.1% (5)
Suspected Sepsis	<0.1% (5)
Hemorrhage	<0.1% (5)
Pulmonary Edema	<0.1% (4)
Obstetric Emergency	<0.1% (4)
Vital Signs Absent - Traumatic	<0.1% (2)
Convalescent/Invalid/Return Home	<0.1% (2)
Post-Arrest	<0.1% (1)
Cardiogenic Shock	<0.1% (1)
Anaphylaxis	<0.1% (1)
Infectious Disease	<0.1% (1)
Organ Recipient	<0.1% (1)
Newborn/Neonatal	<0.1% (1)

Data are presented as % (N).