Clinical Practice Guidelines for Type 2 Diabetes in a Diabetes Economy: What is the Type of Evidence to Support Drug Therapy Recommendations?

Merisa Mok, B.Sc.(Pharm); Cait O'Sullivan, B.A., B.Sc.(Pharm), PharmD; Stacey Tkachuk, B.Sc.(Pharm), ACPR; Aaron M Tejani, PharmD

Background

- In the 2011 report published by the U.S. Institute of Medicine on guideline methodology, clinical practice guidelines (CPG) provide "recommendations intended to optimize care". Guidelines should be based on a systematic review of existing evidence.
- Systematic reviews are available for Type 2 Diabetes Mellitus (T2DM) drug therapy.
- Given the many glucose-lowering medications available for managing T2DM, we were interested in exploring guideline utilization of systematic reviews to inform drug decision making.

Objectives

For each CPG identified in the search, the aim was to determine the following outcomes:

1. **Primary:** the type of evidence used to justify T2DM therapy recommendations in that appear anywhere within statements, algorithms, figures, or tables

   Recommendations were for drug initiation, selection, intensification (i.e. targets, increasing dose), deintensification (i.e. when to stop, decrease dose), safety

2. **Secondary:** the proportion of guideline recommendations in using systematic reviews

Methods

Design	• Descriptive analysis
Databases	• Canadian Medical Association Infobase, National Guideline Clearinghouse, Guidelines International Network, PubMed, EMBASE
Inclusion criteria	• Most current T2DM CPG issue including interim updates (until end of Dec 2016) • Developed in the English Language by national organizations in Canada, USA, Europe
Exclusion criteria	• Primary focus in specific populations (e.g. pediatrics, pregnancy, elderly, renal disease) • Primary focus in the use of non glucose-lowering medications for managing T2DM-related complications (e.g. nephropathy, neuropathy) • Unpublished, withdrawn, duplicate versions
Data collection	• Two reviewers independently extracted relevant information from each CPG • Discussion to achieve consensus when discrepancies where identified

Results

Figure 1: Categorization of Drug Therapy Recommendations (N=179)

Drug Safety 11%
Drug Deintensification 1%
Drug Initiation 6%
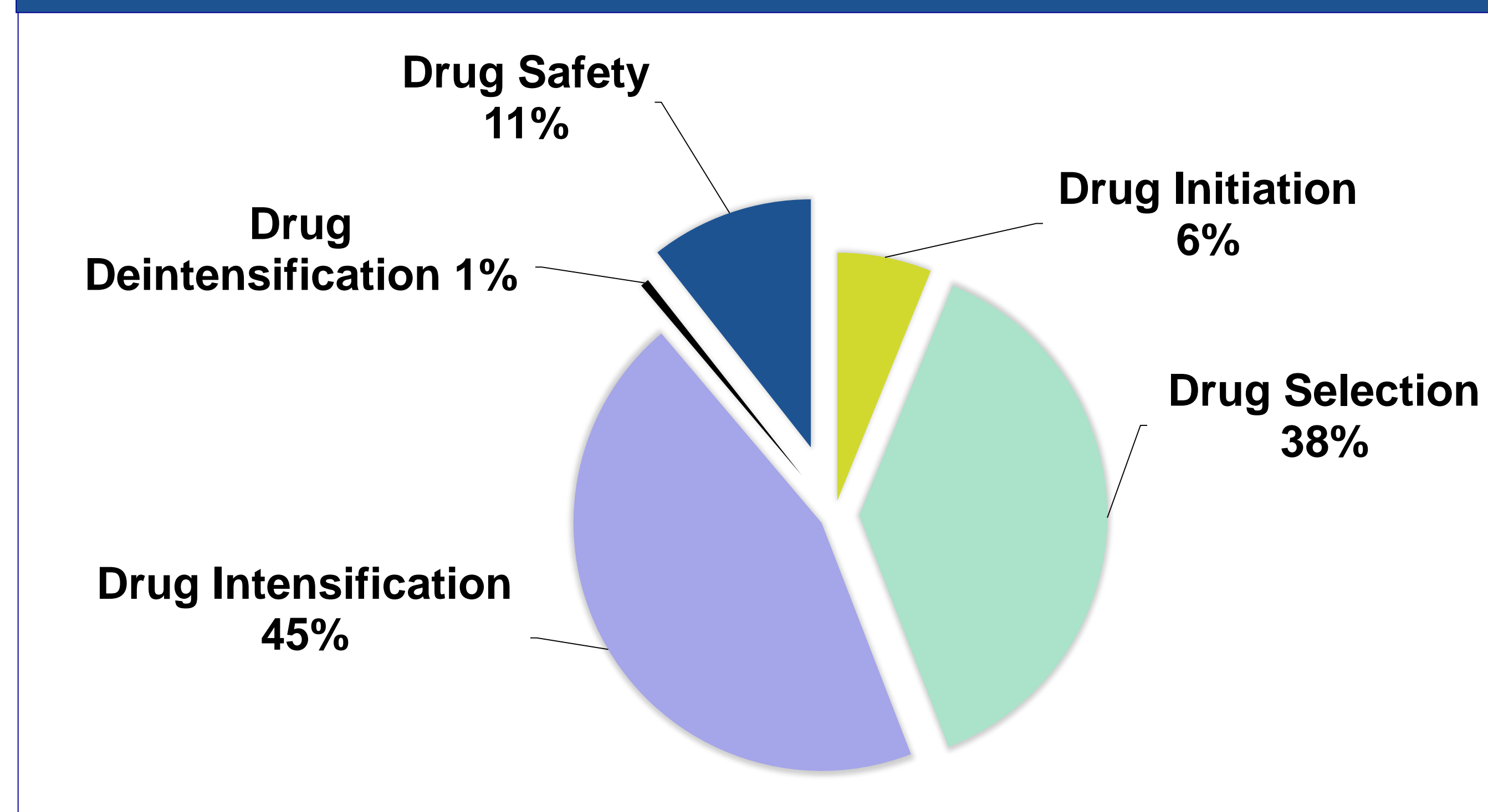Drug Selection 38%
Drug Intensification 45%

Table 1: Proportion of CPG Recommendations with References

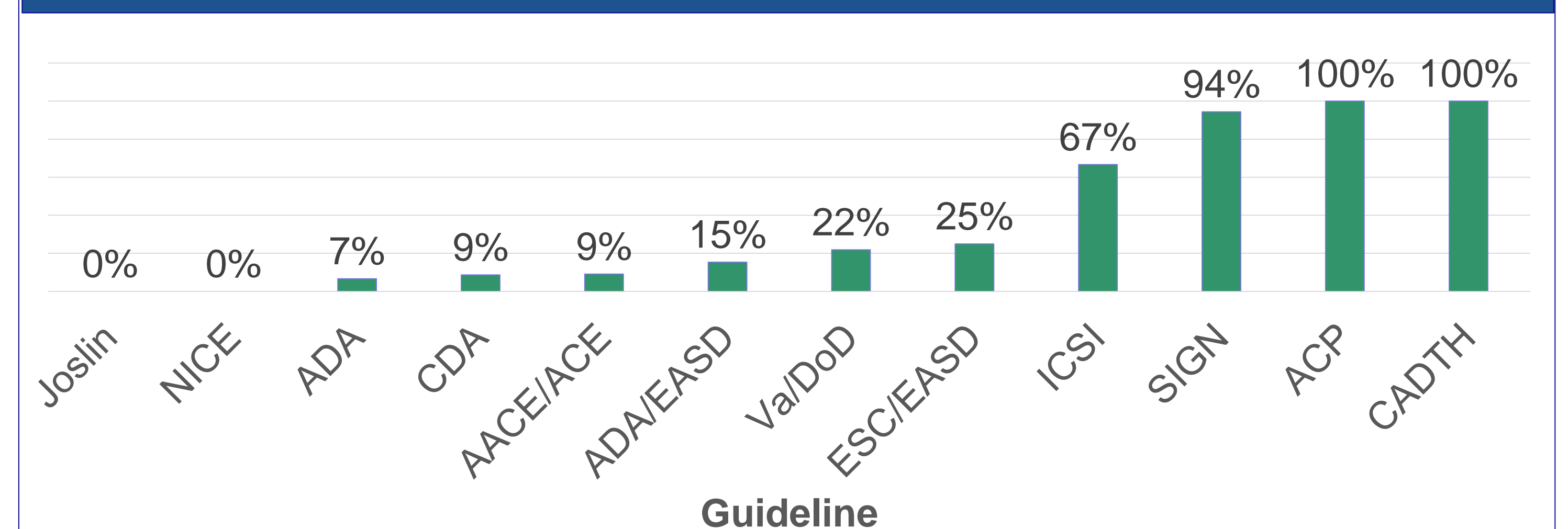| Guideline	From	Has recommendations In total	With no explicit or inferred references	With inferred references	With multiple references
AACE/ACE	USA	22	8 (36%)	14 (64%)	8 (36%)
ACP	USA	3	0	3 (100%)	3 (100%)
ADA	USA	15	7 (47%)	8 (53%)	7 (47%)
ADA/EASD	USA/EUR	13	7 (54%)	6 (46%)	5 (38%)
CADTH	CAN	3	0	3 (100%)	1 (33%)
CDA	CAN	23	0	2 (9%)	10 (43%)
ESC/EASD	EUR	4	0	2 (50%)	4 (100%)
ICSI	USA	3	1 (33%)	0	2 (67%)
Joslin	USA	15	7 (47%)	8 (53%)	8 (53%)
NICE	UK	28	27 (96%)	0	0
SIGN	UK	18	2 (11%)	16 (89%)	13 (72%)
Va/DoD	USA	32	8 (25%)	8 (25%)	7 (22%)

CAN = Canada, EUR = Europe, UK = United Kingdom, USA = United States of America. Recommendations lacking explicit or inferred references were found in 8 of 12 guidelines, and accounted for 37% of all recommendation statements. For recommendations with identifiable references, 63% of recommendations had references inferred from narrative.

Table 2: Distribution of Types of Evidence Across Recommendations (N=179) and References (N=407)

Type of Evidence	Recommendations using Evidence Type**	References Classified by Evidence Type
Systematic review (SR) of RCTs, +/- MA*	35 (19.6%)	63 (15.5%)
Meta-analysis (MA) of RCTs	19 (10.6%)	29 (7.1%)
Randomized controlled trial (RCTs)	49 (27.4%)	146 (35.9%)
RCT secondary publication	24 (13.4%)	42 (10.3%)
SR of different types of evidence or observational studies, +/- MA	5 (2.8%)	5 (1.2%)
MA of different types of evidence, or observational studies	3 (1.7%)	3 (0.7%)
Observational study	21 (11.7%)	34 (8.3%)
Clinical practice guideline	20 (11.2%)	33 (8.1%)
Review article	9 (5.0%)	16 (3.9%)
Consensus, expert opinion	27 (15.1%)	28 (6.9%)
Other	8 (4.5%)	8 (2.0%)

*SR +/- MA means "systematic review including or not including meta-analysis"
**All but one guideline had recommendations citing multiple types of references

Figure 2: Proportion of CPG Recommendations Citing SRs as Justification

Joslin 0%, NICE 0%, ADA 7%, CDA 9%, AACE/ACE 9%, ADA/EASD 15%, Va/DoD 22%, ESC/EASD 25%, ICSI 67%, SIGN 94%, ACP 100%, CADTH 100%

Guideline

Discussion and Conclusions

- In a cohort of 12 guidelines offering 179 relevant recommendations, 37% of recommendations lacked explicit or inferred references.
- Systematic reviews of RCTs were referenced in 19.6% of recommendations and accounted for 15.5% of all references (Table 2). There is inconsistency across guidelines for referencing systematic reviews (Figure 2). RCTs were referenced in 27.4% of recommendations (Table 2).
- While systematic reviews for T2DM drug therapy exist, we cannot be certain that current recommendations for T2DM glucose-lowering medications consistently take into account all relevant existing evidence.
- The implications of these findings are most relevant to recommendations that inform glucose lowering therapy selection and intensification (Figure 1).
- We did not directly assess whether or not the references utilized by guideline authors supported their recommendations.