Validity of the Good Practice Guidelines: The example of type 2 diabetes

Benoit Tudrej, Delphine Favard, Hélène Vaillant-Roussel, Denis Pouchain, Nemat Jaafari, Rémy Boussageon

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Authors

Benoit V. TUDREJ MD, PhD [1,2] : dr.tudrej@gmail.com

Delphine FAVARD MD [1] : delphinefavard@gmail.com

Hélène VAILLANT-ROUSSEL MD, PhD [3,4] : vaillanthelene@yahoo.fr

Denis POUCHAIN MD [5] : denis.pouchain@free.fr

Nemat JAAFARI MD, PhD [6] : nemat.jaafari@ch-poitiers.fr

Rémy BOUSSAGEON MD, PhD [7,8] : remy.boussageon@univ-lyon1.fr

(1) Universite de Poitiers UFR Medecine et Pharmacie, General Practice Department, 6 rue de la miletrie, Poitiers, Nouvelle Aquitaine, FR 86073

(2) Société Française et Francophone d'Ethique Médicale, SFFEM, 45 Rue des Saints-Pères, Paris, FR 75006

(3) Department of General Practice, Faculty of Medicine, Clermont Auvergne University, 28 place Henri Dunant, 63001 Clermont-Ferrand, France.

(4) UPU, ACCePPT, Clermont Auvergne University, 28 place Henri Dunant, 63001 Clermont-Ferrand, France.Tours University, General Practice Department

(5) Département universitaire de médecine générale – Faculté de médecine de Tours, 10 Boulevard Tonnellé - BP 3223, 37032Tours

(6) Centre Hospitalier Henri Laborit, Unité de recherché clinique Pierre Deniker, INSERM CIC-P 1402

(7) Universite Claude Bernard Lyon 1, University College of General Medicine, 8 Avenue Rockefeller, 69008 Lyon

(8) Universite Claude Bernard Lyon 1, UMR 5558, LBBE CNRS, 8 Avenue Rockefeller, 69008 Lyon

Corresponding author :

Benoit Tudrej, dr.tudrej@gmail.com, +33(0)5 49 45 11 11,

Present adress : Cabinet Médical, 99 avenue Jean Mermoz, 69008 Lyon France

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Abstract

Aims: To assess the methodological quality of the systematic reviews of the literature for Good Practice Guidelines (GPGs) for treatment of type 2 diabetes (T2D).

Methods: The GPGs on treatment of T2D from May 2012 onwards were searched on PubMed, the Guidelines International Network, the National Guidelines Clearing House and the *Infobanque des guides de pratique clinique*. Quality of the GPGs was assessed by means of grading of levels of evidence, strength of recommendations, statements pertaining to systematic reviews, description of their methods, search for Randomized Controlled Trials meta-analyses, and citations from three meta-analyses which contested the strategy of intensive glycemic control and metformin as first-line treatment.

Results: Fiflty-two GPGs were included; half of them had and applied a system of grading and strength of recommendation and 58% stated they had carried out a systematic review. Only one GPG cited the three meta-analyses. Three quarters of the GPGs failed to detail their bibliographic research methods.

Conclusion: The GPGs for treatment of T2D were of poor quality and their methodological rigor was insufficient. Even though the meta-analyses had a higher level of evidence, they were seldom cited.

Keywords

Type 2 diabetes, Good Practice Guidelines, methods, systematic review, evidence based medicine, meta-analyses,

Abreviations

GPG : Good Practice Guidelines
IF : Impact Factor
IOM : Institute of Medicine
RCT : Randomized Controled Trials
T2D : Type 2 Diabetes
UKPDS : United Kingdom Prospective Diabetes Study

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Introduction

Since 1980, the number of diabetic subjects throughout the world has quadrupled, reaching 422 million in 2014 [1]. There currently exist twelve pharmacological classes of antidiabetic medicines including insulin, rendering possible a large number of therapeutic combinations [2]. That is one of the explanations for the complexity of treating diabetic patients. Good Practice Guidelines (GPG) based on data presenting a high level of evidence, are consequently needed to orient practitioners and patients in their decision-making about which medicines to use, and to improve the quality of care [3].

Ever since its publication in 1998, the UKPDS 33-34 (United Kingdom Prospective Diabetes Study) [4,5] has been considered as a major study in treatment of type 2 diabetes. It has served for all subsequent recommendations, in practically all of which it is cited. UKPDS 33 is the source of the intensive glycemic control strategy aimed at lowering HbA1C to under 7% [4]. As for UKPDS 34, it spearheaded a recommendation establishing metformin as a first-line treatment for type 2 diabetes [5].

However, several meta-analyses have called into question the results of UKPDS 33-34. For example, Boussageon et al. [6] and de Hemmingsen et al. [7] have shown that an intensive glucose-lowering strategy does not significantly reduce the risk of cardiovascular and overall mortality for type 2 diabetes. In addition, the meta-analysis by Boussageon et al. [8] showed that metformin does not significantly reduce cardiovascular mortality (RR = 1.05; CI 95% [0.67-1.64]), overall mortality (RR = 0.99 ; CI 95% [0.75-1.31]), or macro and microvascular complications.

Even though Randomized Controled Trials (RCT) meta-analyses are the studies in which the level of evidence demonstrating the effect of an intervention is the highest, GPGs continue to recommend an intensive glycemic control strategy and metformin as first-line treatment [2,9-13]. However, quality standards exist for doctors to base their practice on reliable guidelines. In March 2011, the Institute of Medicine (IOM) published the report “Clinical Practice

97 Guidelines We Can Trust", of which the aim was to develop reliable GPGs[3]. In this
98 document, it is recommended that GPGs be based on a systematic review of the literature and
99 that the method of bibliographic research, the level of evidence of each trial and the grading
100 system for recommendations be clearly described.
101
102 The objective of the present study was to assess the methodological quality of the GPGs on
103 T2D treatment published subsequent to the three meta-analyses of RCTs previously cited.
104

Methods

Search strategy

Between August 2015 and March 2020, GPGs on treatment of type 2 diabetes were searched in Medline, the main data bases indexing GPGs: the Guidelines International Network (www.g-i-n.net), the National Guideline Clearing House (www.guidelines.gov), and the *Infobanque des guides de pratique clinique* of the *Association Médicale Canadienne* (www.cma.ca). We also conducted a manual country-by-country search on Google on the basis of the 197 United Nations recognized countries.

The keywords used in this search were the following combined words: type 2 diabetes; treatment or management; guideline, consensus, recommendation or position statement. Research was limited to publications in French and English. (Figure 1).

In order to be included, the GPGs had to involve treatment or management of type 2 diabetes in adults or elderly subjects, to indicate the period of search of the literature, to have included the July 2011 – May 2012 period (period during which the three meta-analyses [6-8] were published), and to have been published in French or in English after May 2012, that is to say subsequent to publications of the last meta-analysis in Plos Medicine [8].

As a first step, the GPG titles and abstracts were examined. The following exclusion criteria were applied: GPGs published before May 2012 or in 2012 without indication of month of publication, those not dealing with oral antidiabetic medicines, those dealing only with prevention or screening for diabetes or with its complications, gestational diabetes, children, hospitalized patients, wilderness athletes, the Ramadan period and aborigines.Those written by a single author or not covered by an organization were also excluded because many of them just cite or adapt institutional GPGs and an exhaustive search couldn't be guaranteed.

As a second step, GPG methods were examined; GPGs in which the method indicated a research period completed before May 2012 and which did not indicate that updating had been carried out after May 2012 were excluded.

Those 2 steps were examined by two authors. No conflict had to be resolved .

GPG assessment criteria

To evaluate the methodological qualities of the GPGs, the following types of information were searched: existence of a research method with precise indications on the period of search

in the literature, the sources and the key words employed, existence of a system of grading level of evidence and strength of recommendations, statement of systematic review or search for meta-analyses of RCTs, citations from UKPDS 33 [4] and 34 [5], the meta-analyses by Boussageon et al. of 2011 [6] and 2012 [8], and the meta-analysis by Hemmingsen et al. if 2011 [7]. Choice of Boussageon et al. [8] is justified by the fact this meta-analysis was the first which showed that metformin does not significantly reduce cardiovascular mortality, overall mortality or macro and microvascular complications.

Choice of the meta-analyses by Boussageon et al. [6] and Hemmingsen et al. [7] is justified by the fact that these two meta-analyses are the only ones to date to have evaluated intensive glycemic control of the different macro and microvascular T2D complications. Those 3 meta-analysis respecting the PRISMA quality recommendations were published in journals with an impact factor exceeding 10, making them impossible to miss in a literature review.

Results

GPGs included

Fifty-four GPGs were published from May 2012 onwards (Figure 2). Two GPGs were excluded because their period of bibliographic research had been completed before the date of publication of the 2012 meta-analysis [8], and because they did not mention any updating since May 2012.

All in all, 52 GPGs were included (Table 1). Publication or updating took place between September 2012 and March 2020. The most GPGs were produced in the United States (n=15; 29%) [2,14-18,49-50,56,62, 65,66,69], followed by Canada (n=4; 8%) [19-21,54] and Australia (n=4; 8%) [9,22,52-53]. Twelve GPGs came from organizations in European countries (n=12; 23%): France [23], the United Kingdom [24,25,58], Scotland [10,60-61], Ireland [26], Belgium [27], Germany [64] and Switzerland [28,59]. Three GPGs came from countries in southeast Asia (n=4; 8%) [29-31,68]. Two GPGs came from countries in the Middle East (n=3; 6%) [32,33,71], and a GPG likewise originated in Morocco [34] and one from Colombia [70]. The American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) jointly produced a GPG [11,12,51], and an international organization, the International Diabetes Federation (IDF) produced three GPGs [35,36,57], while two European organizations, the European Society of Cardiology (ESC) was responsible for one GPG [37] and the European Society of Endocrinology [63].

Methodological quality of the GPGs

Among the selected GPGs, 10 (19%) described their sources, their research period and the key words used (Table 2).

Strength of recommendations was indicated by 25 (48%) of the GPGs, and 27 (51%) graded their level of evidence (Table 3).

Out of the 52 GPGs included, the 2012 meta-analysis by Boussageon et al. [8] on metformin was cited by 10% (n=5). The 2011 meta-analyses by Boussageon et al. [6] and by Hemmingsen et al. [7] were both cited in 6% of the GPGs (n=3) (Table 2). In comparison, UKPDS 33 [4] was cited in 65% of the GPGs (n=34) and UKPDS 34 [5] (metformin) in 48% (n=25).All of them recommended metformin as first-line treatment (Table 2).

Out of the 30 GPGs stating that they had carried out a systematic review and/or searched for meta-analyses of RCTs, there is just the Canadian Diabetes Association GPGs of 2018 [54] which cited the three meta-analyses, while 13% cited at least one of three meta-analyses (n=7). The 2011 meta-analysis by Boussageon et al. [6] was cited in three GPGs (6%), the 2012 meta-analysis by Boussageon et al. [8] in five (1%) and the meta-analysis by Hemmingsen et al. [7] by 3 (6%). The CDA [54] is the only GPG citing the 3 meta-analysis. (Table 2).

Out of the 42 GPGs that did not detail their methods (neither period, nor sources, nor key words), 12% cited at least one of the meta-analyses (n=5).

Out of the 9 GPGs that detailed their methods by indicating the period, the sources and the key words, and that stipulated having carried out a systematic review and/or searched for meta-analyses, two (22%) cited at least one of the meta-analyses.

Discussion

The present study confirms the results reported by Burgers et al.[38], who compared the references cited by the GPGs on treatment of type 2 diabetes in 13 countries. Their results showed that 52% of the GPGs mentioned having carried out a systematic review of the literature and also showed that between the different GPGs, there was very little overlap between the references associated with the recommendations.

All of the GPGs analyzed more frequently cited studies with a low level of evidence than the three meta-analyses [6-8]. Having or not having carried out a systematic review consequently did not substantially modify the citation of meta-analyses.

Hence, if systematic reviews of the literature indeed take place and the authors choose to exclude the meta-analyses, their choice must be rendered explicit and convincingly justified in the GPGs. When this fails to occur, the methodological quality of the systematic review is dubious.

Quite obviously, there exist other GPG meta-analyses liable to corroborate the recommendations of intensive glucose control [39,40]. However, what we are analyzing here is not justification of how well-founded the recommendations are, but rather the rigor and quality of their methods. We could have considered other meta-analysis in our paper. However, we thought those 3 were of sufficient relevance in terms of methodological quality to assess the quality of guidelines methodology. If we had added other ones, it wouldn't change the fact a guideline should consider all the meta-analysis in a literature review and explain why it excludes some and consider studies of lower evidence. With this objective in mind, a search for citations from UKPS33-34 and the 3 meta-analysis we selected will suffice, as an example, as an expression of that principle. Since those 3 meta-analysis, there has been no new RCT published that could change the results of the 3 meta-analyses.

The low rate of description of the bibliographic research methods shows that the criteria for rigorous elaboration of the IOM criteria [3] are far from having been fulfilled in existing GPGs for treatment of T2D patients. Only 52% mention having carried out a systematic review or having searched for meta-analyses, a result nonetheless largely superior to the one reported in the study by Holmer et al. [41], in which a mere 29% of the GPGs had carried out

a systematic review, even though application of a detailed and transparent research methodology is, according to the WHO, a key criterion for GPG quality.

A 2002 study [42] showed that the percentage of GPGs not having cited a randomized controlled trial decreased from 95% in 1979 to 53% in 1999 : "However, several guidelines in major journals still cite few or no RCTs".[42] "Among 4853 references of the guidelines, there were 393 RCTs (8.1% of total), 19 systematic reviews (0.4%), and 23 meta-analyses of RCTs (0.5%). Among 19 guidelines published in 1999 or 1994 with < 2 RCTs cited, in eight cases additional pertinent RCTs were identified that had not been cited by the guideline" [42].

Concerning the GPG of AACE/ACE and ADA/ESAD which have a significant influence on Amerian and European practice, we can observe that while the 2015 GPG of AACE/ACE [14] indeed indicated the level of evidence and the grade of its recommendations, the supplementary 2016 and 2020 documents [15] on the treatment algorithm did not do so. By the same token, the updated version of the ADA/ESAD GPGs [12,51] graded neither their level of evidence, nor the strength of their recommendations. While the NICE GPG [24-25,58] possesses a system for grading level of evidence, it has no ordinal scale designed to grade strength of recommendations. NICE nonetheless claims to reflect strength of recommendations by means of the formulation "The intervention must/should/could be used", but this vocabulary is not employed in the formulation of final recommendations. The 2016 and 2020 ADA GPG [2,50] present in a table a lettered gradation system entitled "ADA evidence-grading system" with level of evidence designated as A, B, C or E. However, the explanation of this table in the GPG is confusing, insofar as at times, the letters refer to levels of evidence ("recommendations supported by A- or B-level evidence"), while at other times they refer to strength of recommendations ("ADA recommendations are assigned ratings of A, B, or C, depending on the quality of evidence").

At this point, it bears mentioning that levels of evidence and strength of recommendations provide information indispensable for GPG users, information allowing them to form their own opinion. While the quality of evidence reflects the degree of confidence that a practitioner can maintain with regard to the estimated effects supporting the recommendations, the strength of a recommendation reflects the level of confidence that it can have that the benefits of an intervention shall outweigh any adverse effects [43,44].

Moreover, users should realize that when GPGs are presented as "evidence-based", it implies that they are based on the best available evidence, even if this evidence is not of high quality.

When proffering judgments regarding levels of evidence, most GPGs take into account only

the nature of a given study and its internal validity; unfortunately, in and of themselves these two criteria seem insufficient. For example, a study has shown that out of the 338 recommendations for treatment and management of cardiovascular risk in nine GPGs, two thirds were based on evidence originating in RCTs with satisfactory internal validity; however, only half of this evidence was considered as being of high quality [45]. The evidence was most often devalued due to doubts on the applicability of the RCTs to the population specified in the recommendations or on account of a problem of clinical relevance insofar as the RCTs used biological outcomes rather than the clinical criteria of importance from the standpoint of the patient [45].

To conclude, it would seem indispensable that GPGs incorporate a transparent system for grading the level of evidence underlying the recommendations by using scales taking into account not only the internal validity, but also the external validity of the studies; one example is the GRADE [46] system (Grading of Recommendations Assessment, Development and Evaluation), which was designed as a way of standardizing grading systems, thereby enabling practitioners to apply the recommendations in a manner suited to the individual particularities of their patients.

Studies have shown that even if they have doubts about their reliability, practitioners tend to comply with GPGs, especially when they are published by respected organizations or influential scholarly societies : “when promulgated by highly respected professional societies, they sometimes serve as de facto “standards of care” that may be used to devise institutional protocols, to develop measures of physician performance, and for insurance coverage decisions” [47].

However, the GPGs in accordance with IOM quality standards are hardly numerous: “Fewer than half of the guidelines surveyed met more than 50% of the IOM standards. Barely a third of the guidelines produced by subspecialty societies satisfied more than 50% of the IOM standards surveyed” [48].

It is of paramount importance to possess reliable GPGs insofar as they serve to constitute a frame of reference in ambulatory care, in hospitals, in universities and in other institutions; moreover, experts utilize them as baseline references in their assessment of practices [47].

Unfortunately, the present study has shown that the objective of evidence-based medicine is

far from having been reached in the treatment of type 2 diabetes, and it should impel GPG users to employ their critical spirit.

Conclusion:

The quality of the GPGs for treatment and management of T2D patients published between 2012 and 2016 is low, showing insufficient rigor of development. According to the IOM criteria, the reliability of these GPGs is questionable. Indeed, more often than not GPGs cite UKPDS 33-34 with a low level of evidence rather than three meta-analyses of RCTs, and they refrain from justifying their choice.

In order for a GPG to be credible, its internal validity must be unassailable, and with this in mind, it is indispensable that at the very least, the GPG indicate: the research period, the key words used, the sources consulted and a complete explanation for the reasons for inclusion or exclusion of studies with a high level of evidence (meta-analyses and RCTs). These undeniably objective elements could enhance description of GPG quality and enable them to be assigned a high degree of confidence.

Competing interests

The authors declare that they have no competing interest.

Funding

The authors received no funding from an external source.

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528

Table 1. Characteristics of the 25 GPGs included

Organization responsible for the GPG	Country	Title of the GPG	Year of publication
AACE/ACE	United States	- American Association of Clinical Endocrinologists and American College of Endocrinology –Clinical Practice Guidelines for Developing a Diabetes Mellitus Comprehensive Care Plan – 2015 [14] - Consensus Statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the Comprehensive type 2 Diabetes management Algorithm – 2016 Executive Summary [15] - Consensus statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the Comprehensive Type 2 Diabetes Management Algorithm – 2020 Executive Summary [49]	2015 2016 2020
ACD	Colombia	Clinical practice guideline for the prevention, early detection, diagnosis, management and follow up of type 2 diabetes mellitus in adults [70]	2016
ACP	United States	Oral Pharmacologic Treatment of Type 2 Diabetes Mellitus: A Clinical Practice Guideline Update From the American College of Physicians [69]	2017
ADA	United States	- Standards of Medical Care in Diabetes—2016 [2] - Standards of Medical Care in Diabetes—2020 [50]	2016 2020
ADA/EASD	United States/ Europe	- Management of hyperglycaemia in type 2 diabetes: a patient-centered approach. Position statement of the American Diabetes Association and the European Association for the Study of Diabetes [11] - Management of hyperglycaemia in type 2 diabetes, 2015: a patient-centered approach. Update to a Position Statement of the American Diabetes Association and the European Association for the Study of Diabetes [12] - Management of hyperglycaemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) [51]	2012 2015 2018
ADS	Australia	- A new blood glucose management algorithm for type 2 diabetes A position statement of the Australian Diabetes Society [14] - A new blood glucose management algorithm for type 2 diabetes A position statement of the Australian Diabetes Society. Update. [52] - Blood Glucose Treatment Algorithm for Type 2 Diabetes Evidence Table. Update [53]	2014 2016 2020
CDA	Canada	- Lignes directrices de pratique clinique 2013 de l'Association canadienne du diabète pour la prévention et le traitement du diabète au Canada [19] - Pharmacologic Management of Type 2 Diabetes: 2016 Interim Update[20] (update) - Pharmacologic Glycemic Management of Type 2 Diabetes in Adults [54]	2013 2016 2018

Organization responsible for the GPG	Country	Title of the GPG	Year of publication
ESC	Europe	- ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD [37] - ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD [55]	2013 2019
ESE	Europe	- Treatment of Diabetes in Older Adults: An Endocrine Society* Clinical Practice Guideline [63]	2019
GDA	Germany	- Practical Recommendations for Glucose Measurement, Glucose Monitoring and Glucose Control in Patients with Type 1 or Type 2 Diabetes in Germany [64]	2018
GPAC	British Columbia (Canada)	- Diabetes Care [21]	2015
Group Health	United States	- Type 2 Diabetes Screening and Treatment Guideline [16] - Type 2 Diabetes Screening and Treatment Guideline [56]	2015 2019
HAS	France	- Stratégie médicamenteuse du contrôle glycémique du diabète de type 2 [23]	2013
HKGSE	Hong Kong	Diabetes in older people: position statement of The Hong Kong Geriatrics Society and the Hong Kong Society of Endocrinology, Metabolism and Reproduction [68]	2017
ICGP	Ireland	- A Practical Guide to Integrated Type 2 Diabetes Care [26]	2016
ICSI	United States	- Health Care Guideline. Diagnosis and Management of Type 2 Diabetes Mellitus in Adults [17]	2014
IDF	International	- Global Guideline for Type 2 Diabetes. International Diabetes Federation Guideline Development Group [35]	2014
IDF	International	- Managing older people with type 2 diabetes. Global guideline [36] - New IDF clinical practice recommendations for managing type 2 diabetes in primary care [57]	2013 2017
INDC	Israel	- Treatment of Type 2 Diabetes: From “Guidelines” to “Position Statements” and Back. Recommendations of the Israel National Diabetes Council [32]	2016
JDC	United States	Clinical Guideline for Pharmacological Management of Adults With Type 2 Diabetes [65]	2018
KDA	South Korea	Antihyperglycemic agent therapy for adult patients with type 2 diabetes mellitus 2017: a position statement of the Korean Diabetes Association [67]	2017

Organization responsible for the GPG	Country	Title of the GPG	Year of publication
MOH KOAS	Saudi Arabia	- Guidelines for Diabetes [33]	2013
MOH Malaysia	Malaysia	- Clinical Practice Guidelines. Management of Type 2 DiabetesMellitus [29]	2015
MOH Singapore	Singapore	- Diabetes Mellitus. MOH Clinical Practice Guideline [30]	2014
MOPH Qatar	Qatar	The diagnosis and management of type 2 diabetes in adults and the elderly [71]	2016
NICE	United Kingdom	- Type 2 diabetes in adults: management Clinical Guideline Update (NG28) Methods, evidence and recommendations [24] - Type 2 diabetes in adults: management. Updated July 2016 [25] - Type 2 diabetes in adults: management. Updated August 2019 [58]	2015 2016 2019
PCD	Switzerland	- Recommandations de bonne pratique clinique [28] - Recommandations pour la pratique clinique [59]	2015 2017
RACGP	Australia	- General practice management of type 2 diabetes [22]	2014
SIGN	Scotland	- Management of diabetes A national clinical guideline [10] - SIGN 154: Pharmacological management of glycaemic control in people with type 2 diabetes [60] - SIGN 116: Management of diabetes A national clinical guideline [61]	2013 2017 2017
SMEDIAN	Morocco	- Recommandations de Bonnes Pratiques Médicales, Diabète de type 2 [34]	2013
SSMG	Belgium	- Diabète sucré de type 2. Recommandations de Bonne Pratique [27]	2015
UFDP	Philippines	- Philippine Practice Guidelines on the Diagnosis and Management of DiabetesMellitus [31]	2014
UMHS	United States	- Management of Type 2 DiabetesMellitus [18] - Management of Type 2 DiabetesMellitus [62]	2014 2019
US DVA	United States	- Clinical Practice Guideline: Management of Type 2 Diabetes Mellitus [66]	2017

AACE = American Association of Clinical Endocrinologists; ACE = American College of Endocrinology; ACD = Asociación Colombiana de Diabetes; ACP = American College of Physicians; ADA = American Diabetes Association; ADS = Australian Diabetes Society; CDA = Canadian Diabetes Association ; EASD = European Association for the study of Diabetes ; ESC = European Society of Cardiology; ESE = European Society of Endocrinology; GDA = German Diabetes Association; GPAC = Guidelines and Protocols Advisory Committee; HAS = Haute Autorité de Santé; HKGSE = The Hong Kong Geriatrics Society and the Hong Kong Society of Endocrinology, Metabolism and Reproduction; ICGP = Irish College of General Practitioners ; ICSI = Institute for clinical systems improvement; IDF = International Diabetes Federation ; INDC = Israel National Diabetes Council ;

JDC = Joslin Diabetes Center, Harvard Medical School; KDA = Korean Diabetes Association; MOH KOAS = Ministry of Health Kingdom of Saudi Arabia ; MOH Malaysia = Ministry of Health Malaysia ; MOH Singapore = Ministry of Health; MOPH Qatar = Ministry of Public Health Qatar; NICE = National Institute for Health and Care Excellence; PCD = Programme Cantonal Diabete ; RACGP = Royal Australian College of General Practitioners and Diabetes Australia; SIGN = Scottish Intercollegiate Guidelines Network; SMEDIAN = Société Marocaine d'Endocrinologie, de diabétologie et de Nutrition ; SSMG = Société Scientifique de Médecine Générale ; UFDP = Unite For Diabetes Philippines; UMHS = University of Michigan Health system; US DVA = U.S. Department of Veterans Affairs/U.S. Department of Defense

Table 2. Data extraction results

GPG : good practice guideline

GPG	Period	Sources	Key words	Declaration of meta-analysis search or systematic review	Citation meta-analysis Boussageon et al. 2011 [6]	Citation meta-analysis Boussageon et al. 2012 [8]	Citation meta-analysis Hemmingsen et al. 2011 [7]	Citation UKPDS 33 [4]	Citation UKPDS 34 [5]
AACE/ACE[14]				✓		✓		✓	✓
AACE/ACE[15]									
AACE/ACE[49]									
ACD[70]				✓				✓	
ACP[69]	✓			✓					
ADA[2]	✓	✓		✓				✓	✓
ADA[50]								✓	✓
ADA/EASD[11]								✓	✓
ADA/EASD[12]								✓	✓
ADA/EASD[51]	✓	✓	✓	✓				✓	✓
ADS[9]								✓	
ADS[52]								✓	
ADS[53]								✓	
CDA[19]	✓	✓		✓	✓	✓		✓	✓
CDA[20]									
CDA[54]	✓	✓		✓	✓	✓	✓	✓	✓
ESC[37]							✓	✓	✓
ESC[55]								✓	✓
ESE[63]				✓				✓	
GDA[64]									
GPAC[21]								✓	✓
Group Health[16]				✓					
Group				✓					

Health[56]									
HAS[23]	✓	✓	✓	✓	✓	✓		✓	✓
HKGSE[68]				✓				✓	
ICGP[26]									
ICSI[17]	✓	✓	✓	✓				✓	
IDF[35]								✓	✓
IDF[36]						✓		✓	
IDF[57]									
INDC[32]	✓	✓							
JDC[65]				✓					✓
KDA[67]	✓			✓				✓	✓
MOH KOAS[33]									
MOH Malaysia[29]		✓		✓				✓	✓
MOPH Qatar[71]				✓					
MOH Singapoure[30]								✓	
NICE[24]	✓	✓	✓	✓			✓	✓	
NICE[25]				✓					
NICE[58]				✓					
PCD[28]		✓	✓	✓					
PCD[59]				✓					
RACGP[22]		✓		✓				**	**
SIGN[10]	✓	✓	✓	✓				✓	✓
SIGN[60]	✓	✓	✓	✓				✓	✓
SIGN[61]	✓	✓	✓	✓				✓	✓
SMEDIAN[34]	✓	✓		✓				✓	✓
SSMG[27]	✓	✓	✓	✓				✓	✓
UFDP[31]		✓	✓					✓	✓
UMHS[18]	✓	✓	✓					✓	✓
UMHS[62]	✓	✓	✓	✓				✓	✓

US DVA[66]			✓	✓				✓	✓
Number (%)	17 (33)	19 (37)	13 (25)	30 (58)	3 (0.6)	5 (1)	3 (0.6)	34 (65)	25 (48)

Notes Table 2 :

*: The 2015 GPGs by AACE/ACE [14] recommended that treatment begin with metformin, an analog of GLP1 (glucagon-like peptide 1), an inhibitor DPP-4 (dipeptidyl peptidase 4), an inhibitor of SGLT2 (sodium glucose cotransporter 2), or an inhibitor of α-glucosidase for patients with starting Hb A1C <7.5%. However, the "consensus statement 2016 : executive summary" of AACE/ACE[15] recommends metformin as first-line treatment.

: « UKPDS » is cited 4 times within the GPG but without indicating whether this meant UKPDS 33[4] and/or 34[5]. UKPDS is not cited in the reference section at the end of the GPG.*: The link for more information about the methodology of ACD GDP is out of service.

Table 3. Grading of level of evidence and recommendation strength

GPG	Levels of evidence	Strength of recommendations
AACE/ACE[14,]	✓	✓
AACE/ACE[15]		
AACE/ACE[49]		
ACD[70]	✓	✓
ACP[69]	✓	✓
ADA[2]	*	✓ *
ADA[50]	*	✓ *
ADA/EASD[11]		
ADA/EASD[12]		
ADA/EASD[51]		
ADS[9]		
ADS[52]		
ADS[53]		
CDA[19]	✓	✓
CDA[20]		
CDA[54]	✓	✓
ESC[37]	✓	✓
ESC[55]	✓	✓
ESE[63]	✓	✓
GDA[64]		
GPAC[21]	✓	
Group Health[16]		
Group Health[56]		
HAS[23]	✓	✓
HKGSE[68]		
ICGP[26]		✓
ICSI[17]	✓	✓
IDF[35]		
IDF[36]		
IDF[57]		
INDC[32]		
JDC[65]		
KDA[67]	✓	✓
MOH KOAS[33]		
MOH Malaysia[29]	✓	✓
MOH Singapoure[30]	✓	✓
MOPH Qatar[71]	✓	✓
NICE[24]	✓	**
NICE[25]	✓	**
NICE[58]	✓	**
PCD[28]		
PCD[59]		
RACGP[22]	✓	
SIGN[10]	✓	✓
SIGN[60]	✓	✓
SIGN[61]	✓	✓
SMEDIAN[34]	✓	✓

SSMG[27]	✓	✓
UFDP[31]	✓	✓
UMHS[18]		
UMHS[62]	✓	✓
US DVA[66]	✓	✓

* : The GPG of ADA presents a table entitled “ADA evidence-grading system” with levels of evidence graded as A, B, C or E. However, the associated explanation is confusing, insofar as the letter system at times makes reference to levels of evidence (“recommendations supported by A- or B-level evidence”), and at other times makes reference to strength of recommendations (“ADA recommendations are assigned ratings of A, B, or C, depending on the quality of evidence”).

** : The GPG of NICE[24,25] did not use an ordinal scale to grade recommendation strength. NICE chose to reflect strength of recommendation according to the formulation “The intervention must/should/could be used”, but this vocabulary was not employed in the formulation of the final recommendations.

Legends of Figures :

The “country-by-country” search was done in those countries :

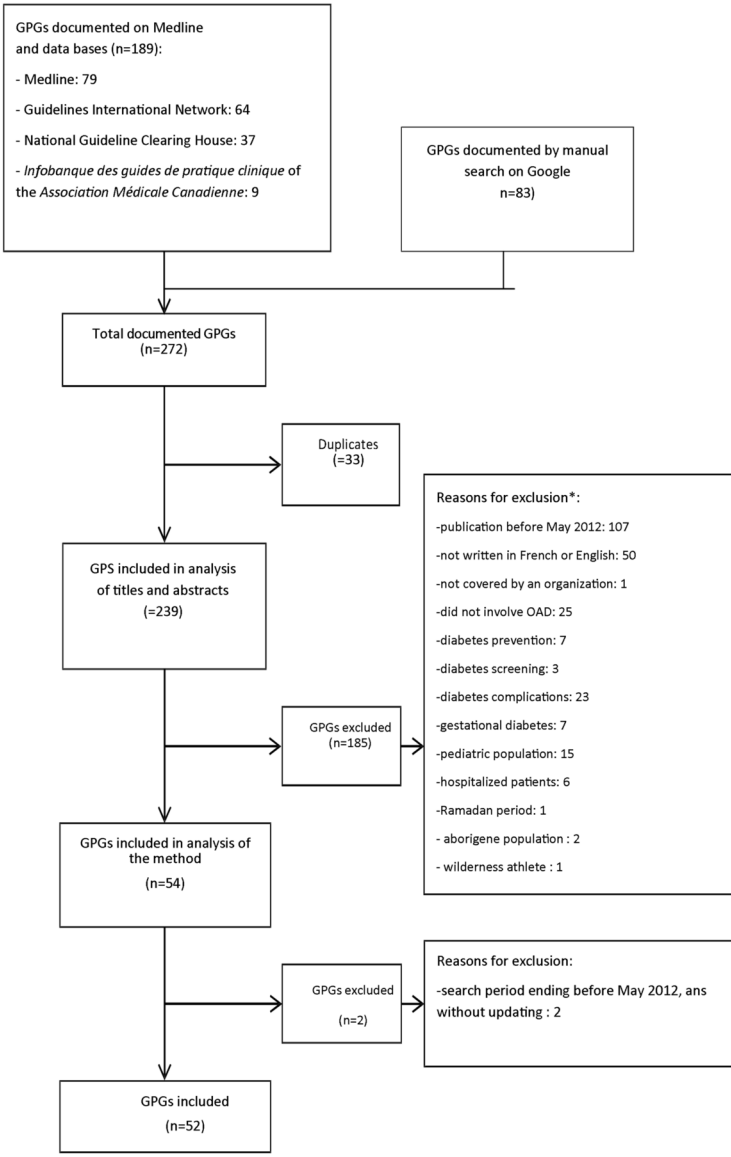
Europe : Germany, Austria, Belgium, Denmark, Scotland, Spain, Finland, France, Greece, Hungary, Italy, Ireland, Iceland, Lebanon, Luxembourg, Malta, Norway, The Netherlands, Wales, Poland, Portugal, Romania, United-Kingdom, Russia, Sweden, Switzerland.

America : West Indies, Brazil, Canada, Caribbean British Columbia, United States of America, Hawai, Mexico

Africa : Algeria, South Africa, Saudi Arabia, Ivory Cost, Egypt, United Arab Emirates, Maroco, Tunisia

Asia : China, South Korea, India, Indonesia, Iran, Israël, Japan, Malaysia, Pakistan, Philippines, Singapour, Taiwan, Thaïland, Vietnam

Oceania : Australia, New Zealand



* The total number exceeds the corresponding number of excluded GPSs because GPGs could be excluded for more than a single reason.

OAD: Oral Anti-Diabetics