HAUTE AUTORITÉ DE SANTÉ

ASSESSING
HEALTH TECHNOLOGIES

ASSESSMENT REPORT

Metabolic surgery: surgical treatment of type 2 diabetes

Validated by the HAS Board on 6 October 2022

Description of the publication

Title	Metabolic surgery: surgical treatment of type 2 diabetes
Working method	Selection of literature with the highest level of evidence and randomised controlled trials on the basis of criteria defined in advance during scoping of the project in PICOTS grids. Analysis of the methodological quality of the trials selected with a view to conducting a meta-analysis on the primary outcome measure: type 2 diabetes remission. Consultation of an expert group (healthcare professionals and patients) and stakeholder organisations.
Objective(s)	– To assess the benefit-risk balance of metabolic surgery, since it is a question of offering surgical management to a population currently only eligible for a pharmacological approach (oral and/or by injection). – To determine, as accurately as possible, the target population liable to benefit from metabolic surgery.
Targets concerned	– Patients with overweight or with class 1 obesity, and with type 2 diabetes. – Healthcare professionals from a variety of specialisations, including general medicine, diabetology, nutrition, bariatric surgery, gastroenterology, as well as other professionals involved in the care of these patients. – The institutional players involved in the organisation and funding of care: DGOS (Directorate General for Health, Ministry of Health), CNAM (National health insurance fund for salaried workers), ARS (Regional health agency), etc. – The healthcare facilities where the procedures (bariatric and metabolic surgery, interventional medicine) are performed using evaluated techniques (the techniques are listed in Table 1)
Applicant	This self-referral by the HAS falls within the scope of action 14 in the ministerial obesity roadmap: “Updating the guidelines and indicating those concerning specific situations, in particular surgery in the elderly and metabolic surgery, as well as adaptation of follow-up to the different surgical techniques”.
Sponsor(s)	French National Authority for Health (HAS)
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Declaration of interests	The members of the working group communicated their public declarations of interest to the HAS. These can be consulted on the website https://dpi.sante.gouv.fr. They were analysed according to the analysis grid of the HAS guidelines for the declaration of interests and management of conflicts of interest. The interests declared by the working group members were considered to be compatible with their participation in this work.
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Contents

Summary 5

1. Context and scope of the assessment 7

1.1. General aspects 7

1.2. Assessment questions and PICOTS diagrams 8

2. Working method 10

2.1. Literature search and literature selection process 10

2.2. Procedure for performance of meta-analyses by the HAS 12

2.2.1. Selection criteria for performance of the different meta-analyses 12

2.2.1.1. BMI level 12

2.2.1.2. Conditions to perform a meta-analysis (number of studies and lost-to-follow-up rate) 12

2.2.2. Methodological validity of the studies included 13

2.2.3. Primary analyses of MAs 13

2.2.4. Exploratory analyses of HAS meta-analyses 13

2.2.4.1. Published data 13

2.2.4.2. Unpublished data 14

2.2.5. Conservative approach 16

2.2.6. Statistical methods 16

2.3. Consultation of an expert group 16

2.4. Stakeholder consultation 16

3. Results of the literature analysis 18

3.1. Already published systematic reviews with MA 18

3.2. Details of the studies selected for the HAS analysis 18

3.2.1. Obesity and overweight classes 18

3.2.2. Surgical techniques performed 19

3.2.3. Methodological validity of the studies 19

3.3. Results of the HAS meta-analyses 21

3.3.1. Question 1: What is the benefit-risk balance of metabolic surgery in the treatment of T2DM in patients with class 1 obesity compared to conventional management? 21

3.3.1.1. Efficacy data on T2DM remission 21

3.3.1.2. Other primary outcome measures 26

3.3.1.3. Secondary outcome measures 27

3.3.1.4. Safety data 27

3.3.2. Question 2: What is the benefit-risk balance of metabolic surgery in the treatment of T2DM in patients with overweight compared to conventional pharmacological management? 28
3.3.3. Question 3: Based on the results of Q1 and Q2, is MS aimed at all patients with class 1 obesity or overweight or only at a proportion of these patients and, if so, which ones? 29
3.3.4. Question 4: Which of these surgical techniques can be preferentially offered to patients eligible for metabolic surgery? 29
3.3.5. Synopsis of results 31

4. Summary of experts' individual positions 33

5. Summary of stakeholders' perspectives 35

6. Summary, conclusions and outlook 36

Table of appendices 39

Bibliographic references 76

Participants 78

Abbreviations and acronyms 79

Summary

The development of bariatric surgery in the management of patients with class 2 or 3 obesity (severe or very severe) has resulted in the observation of favourable effects in terms of regulation of glucose metabolism with, in particular, type 2 diabetes (T2DM) remissions in certain patients. This has led to the emergence of the concept of surgical treatment of T2DM. The term “metabolic surgery” (MS) is used to differentiate this concept from “bariatric surgery”, primarily aimed at weight loss.

In this work, the HAS carried out an assessment of MS - until now only accessible to type 2 diabetes patients with class 2 or 3 obesity via bariatric surgery indications - for T2DM patients with class 1 obesity (BMI of 30 to 35 kg/m^2) or overweight (BMI of 25 to 30 kg/m^2).

The HAS reaches the following conclusions:

> **“Metabolic surgery may be offered to type 2 diabetes patients with class 1 obesity (BMI of 30 to 35 kg/m^2) when their individualised glycaemic targets have not been reached despite well-managed medical care, in particular diabetes treatment and nutritional measures, along with adapted physical activity, in accordance with current good practice guidelines, for at least twelve months.**
>
> **The decision is taken with the patient following discussion at a multidisciplinary team meeting including a diabetes specialist.**
>
> **Surgical techniques**: laparoscopic adjustable gastric banding (**LAGB**), sleeve gastrectomy (**SG**), Roux-en-Y gastric bypass (**RYGB**) **may be proposed.**
>
> **At this stage there is no evidence making it possible to favour one of these three techniques over the others.**
>
> **The contraindications for bariatric surgery and metabolic surgery are the same.”**

The HAS bases these conclusions, firstly, on the published data having enabled it to carry out meta-analyses (MA) that all point to the superiority of MS compared to the conventional medical management of type 2 diabetes (T2DM), via medication without surgery, whether at 24, 36 or 60 months of follow-up, for type 2 diabetes patients with class 1 obesity. According to these meta-analyses, a patient with class 1 obesity and type 2 diabetes treated by MS is at least two to three times more likely to achieve remission of T2DM at 24 and 36 months, respectively, than a patient treated by conventional medical management.

As regards serious or non-serious adverse events reported in the trials selected and analysed, concerning patients with class 1 obesity having undergone MS, no particular safety signals were identified that would differentiate MS from bariatric surgery (BS) in its current indications (class 2 and 3 obesity), in terms of perioperative and postoperative safety, in terms of either nature, severity or frequency. However, the published safety data is still very limited.

The experts consulted consider that these efficacy and safety results are clearly in favour of MS for T2DM patients with class 1 obesity.

> In the absence of direct comparative data, it is not possible to propose a preferred surgical technique among the three indicated with a sufficient level of certainty.

> There is too little data concerning patients in the overweight category (25 < BMI < 30kg/m^2) to be able to offer them MS as part of routine care.

> On the basis of currently available data, the OAGB, BPD-DS, SADI-Sleeve, SG-TB and Endosleeve techniques in the metabolic surgery indication for type 2 diabetes patients with class 1 obesity or overweight may only be performed in the context of clinical trials, after informing the patient. These techniques will be assessed by the HAS once additional results have been obtained, as in the bariatric surgery indication.

Alongside the development of MS, new antidiabetic drugs have also arrived on the market for routine care. The respective roles of these treatment options in the management of T2DM patients with class 1 obesity will be determined in the type 2 diabetes management guidelines that the HAS is in the process of drawing up.

The information to be provided to patients must include the following points, in particular:

- T2DM remissions are observed at three years in 30 to 40% of cases;
- **the T2DM remission may not be definitive, and patients may require antidiabetic drugs again after several months or years;**
- monitoring to identify micro- and macro-angiopathic complications must be continued;
- there are benefits other than T2DM remission**,** such as therapeutic de-escalation, weight loss, resolution of other comorbidities, etc.;
- they will have to undergo and adhere to lifelong follow-up after metabolic surgery.

In addition to the specific points listed above, patients should receive the same information as that provided for BS.

This work is part of a long-term strategy implemented by the HAS to improve the care of people with obesity. As part of this strategy, it has regularly published and updated guidelines on the management of obesity and T2DM, in addition to care pathways. The HAS is also one of the players involved in the ministerial obesity roadmap overseen by the French Directorate General for Healthcare Provision (DGOS), the Directorate General for Health (DGS) and the CNAM (2019-2022).[1]

[1] https://solidarites-sante.gouv.fr/IMG/pdf/feuille_de_route_obesite_2019-2022.pdf

1. Context and scope of the assessment

1.1. General aspects

The context and scope of this assessment were presented and defined in the scoping document validated by the HAS Board on 1 December 2021 (1).

In summary:

- metabolic surgery (MS) refers to the concept of treating type 2 diabetes mellitus (T2DM) using techniques "borrowed" from bariatric surgery (BS), consisting of making modifications to the gastrointestinal system and for which the main objective is weight loss in patients with obesity;
- this work aims to assess the **benefit-risk balance of MS** in the management of adult patients, with no upper age limit, with **pharmacologically treated (oral or by injection) T2DM** and **"moderate" class 1 obesity** (BMI of 30 to < 35 kg/m^2) or **overweight** (BMI of 25 to < 30 kg/m^2);
- **the surgical techniques assessed for the performance of MS are:**
  - **those already recommended by the HAS for class 3 obesity and class 2 obesity complicated by comorbidities such as T2DM; and which are included in the list of reimbursed treatments**: laparoscopic adjustable gastric banding (**LAGB**), sleeve gastrectomy (**SG**), Roux-en-Y gastric bypass (**RYGB**), biliopancreatic diversion with or without duodenal switch (**BP-DS**);
  - **those in the process of being disseminated in France and for which studies are underway in the management of obesity**: one-anastomosis gastric bypass or omega-loop bypass (**OAGB**), single-anastomosis duodeno-ileal bypass with sleeve gastrectomy (**SADI-Sleeve**), sleeve gastrectomy with transit bipartition (**SG-TB**), endoscopic sleeve gastroplasty (**Endosleeve**). These techniques were the subject of a report published by the HAS in 2020 in the BS indication (2), which concluded that they were all the subject of ongoing clinical studies and that they would be assessed by the HAS following the completion of these studies;
- **the comparator is conventional (pharmacological) management of T2DM**;
- this is a **self-referral by the HAS** within the scope of action 14 of the **ministerial obesity roadmap** (3):[2] "Updating the guidelines and indicating those concerning specific situations, in particular surgery in the elderly and metabolic surgery, as well as adaptation of follow-up to the different surgical techniques".

This publication is hinged around four assessment questions, indicated below, which were defined in the scoping document (1). Questions 1 and 2 have been transposed into a tabulated summary in PICOTS[3] format in order to guide the selection and analysis of published studies (see Table 1 and Table 2 below).

[2] Action 14 is overseen by the Directorate General for Healthcare Provision (DGOS) in liaison with the Directorate General for Health (DGS) and professionals (national councils of professionals (CNPs), learned societies, etc.).

[3] Population, intervention, comparator, outcomes, time, study design.

1.2. Assessment questions and PICOTS diagrams

> Question 1: What is the benefit-risk balance of metabolic surgery in the treatment of T2DM in patients with **class 1 obesity** compared to conventional management?

Table 1. PICOTS for assessment question 1 (Q1).

Target population	Adults with no upper age limit, with pharmacologically treated T2DM (oral or by injection), with **class 1** or "moderate" **obesity** (BMI of 30 to < 35 kg/m^2).
Intervention to be assessed	Metabolic surgery: – **surgical techniques already recommended and included in the list of reimbursable treatments**: laparoscopic adjustable gastric banding (**LAGB**), sleeve gastrectomy (**SG**), Roux-en-Y gastric bypass (**RYGB**), biliopancreatic diversion with or without duodenal switch (**BP-DS**); – **techniques in the process of being disseminated in France and for which studies are underway in the surgical or interventional management of obesity**, *i.e.*: one-anastomosis gastric bypass or omega-loop bypass (**OAGB**), single-anastomosis duodeno-ileal bypass with sleeve gastrectomy (**SADI-Sleeve**), sleeve gastrectomy with transit bipartition (**SG-TB**), endoscopic sleeve gastroplasty[4] (**Endosleeve**).
Comparators	The best T2DM management available at the time of inclusion in the study, optimised by a diabetes specialist: lifestyle changes (diet, adapted physical activity) and by medicinal treatment (non-surgical).
Outcome measures	These are derived from the BARIACT[5] (4). **Primary outcomes:** – benefit: mortality, morbidity (including cardiovascular events), T2DM remission as defined by Buse[6] *et al.* (5) or by Riddle[7] *et al*. (6); improvement in quality of life by validated scores, including: "Bariatric Analysis and Reporting Outcome System – BAROS", "Impact of Weight on Quality of Life – IWQOL", "Problem Areas In Diabetes – PAID"; – safety: complications specific to each surgical technique (leak, abscess, staple rupture, etc.), dysphagia/regurgitation, reflux, lower GI complications: diarrhoea/constipation, micronutrient status, postoperative pain. **Secondary outcome measures:** – weight change, repeat surgery (treatment of a technical complication, or conversion to another technique), reduction in HbA_{1c} and/or de-escalation of pharmacological treatment (dosage or number of drugs).
Observation time	At least two years of follow-up (standard follow-up time in the main studies concerning bariatric surgery and metabolic surgery, also used in previous HAS reports (7)).
Study design	Comparative, randomised prospective study, then if the B/R balance is favourable, cohort follow-up studies assessing the safety of MS.

[4] It should be noted that endoscopic gastroplasty is an interventional technique. However, to simplify reading, the term metabolic surgery will be used in this work to refer to all techniques.

[5] This is a list of nine primary outcome measures to assess the efficacy and safety of bariatric and metabolic surgery. These were selected at a professional consensus meeting with the participation of patients.

[6] ADA professional consensus defining "partial", "complete" and "prolonged" T2DM remission on the basis of glucose levels, absence of concomitant pharmacotherapy and duration of this status: "Complete remission defined as normal glucose levels without pharmacotherapy for at least one year".

[7] ADA professional consensus defining remission for surgery: "HbA1c < 6.5% (48 mmol/mol) measured three months after surgery and at least three months after cessation of antidiabetic treatments".

> Question 2: What is the benefit-risk balance of metabolic surgery in the treatment of T2DM in patients with **overweight** compared to conventional pharmacological management?

Table 2. PICOTS for assessment question 2 (Q2).

Target population	Adults with no upper age limit, with pharmacologically treated T2DM (oral or by injection), with **overweight** (BMI of 25 to < 30 kg/m^2).
Intervention to be assessed	Metabolic surgery: identical to **Q1**
Comparators	Identical to **Q1**
Outcome measures	**Primary and secondary outcomes**: identical to **Q1**
Observation time	Identical to **Q1**
Study design	Identical to **Q1**

> Question 3, **Target population**: Based on the results of Q1 and Q2, is MS aimed at all patients with class 1 obesity or overweight or only at a proportion of these patients and, if so, which ones?

This question does not require a PICOTS. Descriptions of the target populations of the studies selected to answer Q1 and Q2 will be collated to try to define these subgroups, and hence prognostic factors. The different characteristics of the patients in the studies will be listed:

- age, BMI, biological marker (i.e. % HbA_{1c}, fasting glucose, etc.);
- pharmacological treatment for T2DM, T2DM severity, T2DM duration;
- previous bariatric surgery procedure not resulting in therapeutic success, and any factor predictive of MS success or failure identified in the studies analysed.

> Question 4, **Preferential technique(s)**: Which of these surgical techniques can be preferentially offered to patients eligible for metabolic surgery?

Following **Q3,** the techniques used in these patients in the studies selected to answer Q1 and Q2 will be listed. Among these techniques, those with a preferential indication for metabolic surgery will be identified.

2. Working method

As decided in the scoping document (1), this work was conducted in accordance with the standard method for assessment of a professional procedure[8] consisting of:

- a critical analysis of the literature identified following a systematic literature search and then selected on the basis of explicit criteria, defined in the PICOTS grids presented above, with a view to performing a systematic review per assessment question, with meta-analysis (MA) depending on the data available;
- professionals and patients will also be consulted using two different methods:
  - face-to-face consultation of external experts (healthcare professionals and patients/users), assembled in an expert group, in order to collect their individual positions, backed up and supported by their knowledge, experience and practices, with regard to the data in the literature,
  - consultation of the professional bodies and patient and user associations concerned by the subject, contacted as stakeholders, in order to gather their collective views on a provisional version of the report containing the elements collected previously (data analysis and expert positions) and any conclusions that may be drawn from them;
- compilation of these different elements in a technological assessment report version that will be submitted to the Guidelines, relevance, pathways and indicators committee (CRPPI) for examination then to the HAS Board for validation.

2.1. Literature search and literature selection process

The literature search was conducted in accordance with the strategy defined in the scoping document (1). The search period ran from January 2008 to January 2022. Documentary monitoring was then conducted until June 2022. This search led to the identification of 182 references. It should be noted that as the performance of a meta-analysis was also scheduled, the literature search also concerned systematic reviews with a meta-analysis which might be able to answer the assessment questions without the performance of further meta-analyses.

The article selection process was the same for all four assessment questions and adhered to the selection criteria derived from the PICOTS grids. An initial selection based on titles and abstracts led to the exclusion of 126 references, primarily including publications that were not relevant or were duplicates. Full-text reading was then used to select articles with results that could answer the assessment questions. Hence, out of the 56 publications read in full, 42 were excluded and 14 were selected. The 56 publications read in full included 20 systematic reviews with meta-analysis; only the two most recent ones were selected (since the other 18 did not include the most recent studies). In addition, the expert group mentioned three publications that were not included since they did not meet the PICOTS criteria (see page 52).

Ultimately, following this search and selection process, presented in detail in Figure 1, the analysis therefore related to 14 publications, including two meta-analyses, seven clinical studies having been the subject of 11 publications and a “grouping” of randomised controlled trials. The seven clinical studies analysed are presented in Figure 2.

[8] *Haute Autorité de Santé* (French National Authority for Health). General description of the professional procedure assessment procedure. Saint-Denis La Plaine: HAS; 2018. https://www.has-sante.fr/jcms/c_2832949/fr/description-generale-de-la-procedure-d-evaluation-d-actes-professionnels

Figure 1. Literature selection flow chart.

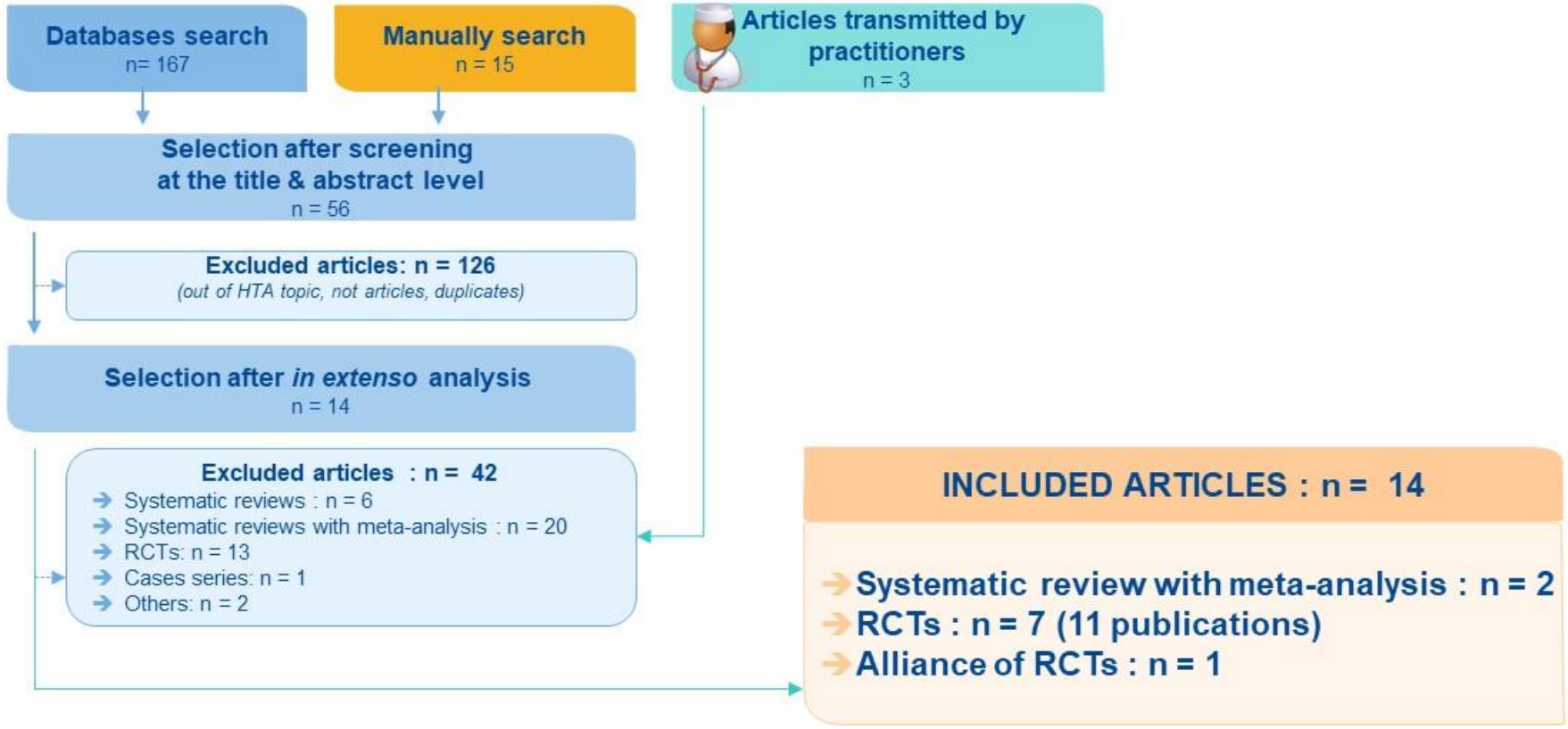


Figure 2. Presentation of the seven randomised controlled trials selected.

2.2. Procedure for performance of meta-analyses by the HAS

2.2.1. Selection criteria for performance of the different meta-analyses

2.2.1.1. BMI level

It was scheduled that only patients with class 1 obesity or overweight would be included in the analysis (see PICOTS grids reproduced in Table 1 and Table 2 above). No studies reporting only data from patients with class 1 obesity was identified. Therefore, studies for which only a proportion of the population was composed of patients of this type were nonetheless selected. Studies reporting the results for patients with class 2 or 3 obesity only were not retained.

The proportion of patients with class 1 obesity in the population for each study is reported as a percentage, along with the different characteristics of the studies and overall risk of bias level in chapter 3.2. Table 3 below indicates the selection criteria.

2.2.1.2. Conditions to perform a meta-analysis (number of studies and lost-to-follow-up rate)

The performance of meta-analyses was dependent on the identification of at least three studies that could be included in the MA, each with a lost-to-follow-up rate of less than 20%.

Table 3. Literature selection criteria.

Target population	Studies including adults with no upper age limit, with pharmacologically treated (oral or by injection) T2DM, **in which all or a proportion of the population** has **class 1 obesity** (BMI of 30 to < 35 kg/m^2) or is **overweight** (BMI of 25 to < 30 kg/m^2).
Intervention	Studies **including at least one of the following surgical or interventional techniques**: – **surgical techniques already recommended for the management of very severe or severe obesity with comorbidity and in the list of reimbursed treatments**: LAGB; SG; RYGB; BP-DS; – **techniques in the process of being disseminated in France and for which clinical studies are underway in the surgical or interventional management of obesity**: OAGB; SADI-Sleeve; SG-TB; Endosleeve.
Comparator	Studies in which the comparator is the **best available T2DM management**: lifestyle changes (diet, adapted physical activity) and by pharmacological treatment (non-surgical).
Minimum outcome measure	Studies with a primary outcome measure of, at least, **T2DM remission**: "HbA_{1c} <6.5% measured three months after surgery and at least three months after cessation of antidiabetic treatments". If other outcome measures were identified, such as mortality and improvement in quality of life, the studies were also selected.
Follow-up time	The studies had to present results following **at least two years of follow-up**.
Study design	**Comparative, randomised prospective study**; then if the B/R balance is favourable, consecutive cohort follow-up studies assessing the safety of MS with results after at least 24 months.

2.2.2. Methodological validity of the studies included

The methodological validity of the studies was assessed in accordance with the Cochrane collaboration ROB2 risk-of-bias analysis grid.[9] The results are presented in chapter 3.2.3.

2.2.3. Primary analyses of MAs

It was scheduled that an MA would be performed with the results after at least 24 months of follow-up and further analyses for longer follow-up depending on the data available for the techniques to be assessed.

To meet this objective, two primary analyses were performed, grouping together the results for T2DM remission, 24 months and 36 months after the surgery, for all three techniques for which data was identified (LAGB, SG, RYGB). These correspond to analyses No. 1 and No. 2 in the MA implementation plan presented in Figure 2. The results are presented in chapter 3.3.1.1 and in Appendix 5.

2.2.4. Exploratory analyses of HAS meta-analyses

2.2.4.1. Published data

Depending on the data available, it was scheduled that exploratory analyses would be performed to supplement the answers to the assessment questions provided by the primary analyses.

Hence, two exploratory analyses were performed:

- a first analysis on T2DM remission after 60 months of follow-up, on the three techniques for which data was identified (LAGB, SG, RYGB); this corresponds to analysis No. 3 in the meta-

[9] Sterne JA, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, *et al*. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ 2019;366:l4898. http://dx.doi.org/10.1136/bmj.l4898

analysis implementation plan (Figure 2); its results are presented in chapter 3.3.1.1 and shown in Appendix 6;

- another subgroup analysis after 36 months of follow-up concerning the RYGB technique only.[10] This analysis corresponds to No. 4 in the MA implementation plan (Figure 2); its results are presented in chapter 3.3.4 and shown in Appendix 6.

2.2.4.2. Unpublished data

As already mentioned (see chapter 2.2.1 above), the absence of data specifically relating to T2DM remission for patients with class 1 obesity led to the inclusion in the MA of studies with a proportion of patients with class 2 or 3 obesity. This absence also prompted the HAS to contact the authors of the different studies selected to specifically obtain data for patients with class 1 obesity. Only one, Courcoulas *et al*. (TRIABETES study) (12), supplied these results. They concern only a very small number of patients (n=21), and could not therefore be the subject of a meta-analysis.

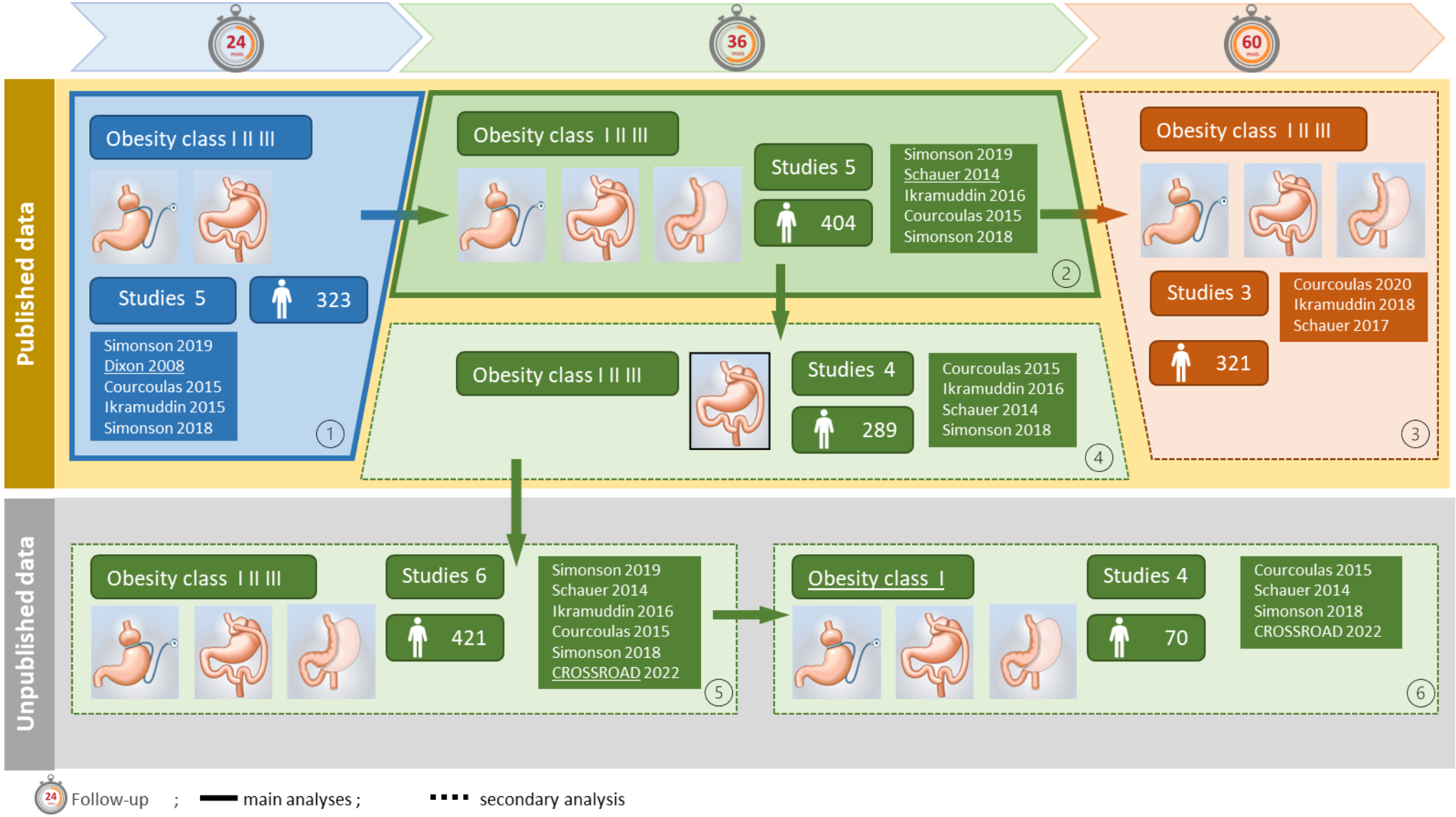
During this assessment, Kirwan *et al*. (19) published a collation of T2DM remission results after 36 months, entitled ARMMS-T2D. This research groups together four studies (chapter 3.3.1.1): STAMPEDE, TRIABETES, SLIMM-T2D and CROSSROAD, the first three of which are included in HAS MA No. 2 at 36 months (Figure 4). The CROSSROAD results at 24 months and 36 months were not found in the literature; only the results at 12 months were published by Cummings *et al*. (20).

Kirwan *et al*. were contacted by the HAS to obtain the number of T2DM remissions in the population with a BMI of under 35 kg/m^2. **In response, they communicated the T2DM remission data at 36 months for BMIs < 35kg/m^2, in aggregated form and individually for each of the four studies.** Since it is not possible to perform a complete analysis of the risk of bias for this data (since the CROSSROAD data at 36 months has not been published), and given the small sample size of patients with class 1 obesity I (< 100), it was decided to perform an additional two exploratory analyses:

- one - the third in this report - using the primary analysis at 36 months mentioned in chapter 2.2.3 (analysis No. 2) and implemented for the data from the CROSSROAD study, all obesity classes combined; this analysis corresponds to analysis No. 5 in the meta-analysis implementation plan (Figure 2); its results are presented in Appendix 6, in Figure 9;
- another, the fourth in this report, conducted as a subgroup analysis including only the unpublished data obtained for patients with a BMI < 35kg/m^2 for the four studies collated in the ARMMS-T2D study; this analysis corresponds to analysis No. 6 in the meta-analysis implementation plan (Figure 2); its results are presented in Appendix 6, Figure 10.

[10] For LAGB and SG, there were not enough studies to conduct an MA.

Figure 2. Implementation plan for the six HAS meta-analyses.



2.2.5. Conservative approach

All the meta-analyses were performed using a conservative approach, in accordance with the "moderate bias hypothesis". They all took into account lost-to-follow-up and intention-to-treat patients to quantify the number of events and interventions. Hence, the denominator for calculation of the absolute risk included patients lost to follow-up; the events observed were allocated to the initial randomisation arm. **Therefore, the value of the lower limit of the risk ratio is a satisfactory estimation of the expected minimum effect size for MS**.

2.2.6. Statistical methods

All the statistical analyses and figures presented in this report were performed using the Cochrane Collaboration's RevMan v5.4 (2020) tool.[11] A random effects model was used (Mantel-Haenszel, heterogeneity assessed with Tau^2 and I^2 estimation). The results are presented in terms of risk ratio. The central estimations were provided with their 95% confidence interval (95% CI). The statistical significance threshold was set at 0.05 with a two-tailed test. For the T2DM remission data after 36 months for patients with class 1 obesity whose data was provided by Kirwan *et al*. (19), a Chi-square test (χ^2) was performed at the probability of 1%.

2.3. Consultation of an expert group

A multidisciplinary expert meeting was organised on 10 May 2022. The experts were selected from the lists of experts proposed by the organisations consulted, listed in Table 7 in Appendix 7. As regards patient representatives, these responded to a call for candidates published on the HAS website, which had been relayed by the patient associations contacted.

The list of individuals having participated in the multidisciplinary meeting is presented in Appendix 8. In summary, the group consisted of two patients, three intestinal and digestive surgeons, three endocrinologists-diabetes specialists-nutritionists, two general practitioners (including one specialised in nutrition), two hepato-gastroenterologists and one dietitian.

The meeting minutes validated by all the experts in the group are presented in Appendix 8. A summary of these minutes produced by the HAS is presented in chapter 4.

2.4. Stakeholder consultation

This consultation was conducted from 27 July to 8 September in accordance with the stakeholder consultation procedure put in place by the HAS.[12] The list of professional bodies and patient and user associations contacted is presented in Table 8 in Appendix 9.

The different professional bodies and patient associations were consulted as stakeholders in accordance with the terms of decree 2013-413 of 21 May 2013.[13] In practice, the legally responsible person at each of the organisations concerned was directly consulted to express the collective view of

[11] Review Manager (RevMan) [Computer program]. Version 5.4. The Cochrane Collaboration; 2020. https://training.cochrane.org/online-learning/core-software-cochrane-reviews/revman/revman-non-cochrane-reviews

[12] HAS stakeholder consultation procedure, June 2014. http://www.has-sante.fr/portail/upload/docs/application/pdf/2014-09/c_2014_0115_adoption_procedure_parties_prenantes.pdf.

[13] Decree No. 2013-413 of 21 May 2013. The fourth paragraph of this decree states that: "If the purpose of the expert assessment so warrants, the decision may be based on consideration of the points of view of 'stakeholders' (or 'interested parties'), i.e. the persons or groups concerned or liable to be concerned, directly or indirectly, by the consequences of this decision, in particular associations and economic or professional players, or who represent the general interest of groups concerned by these consequences". http://legifrance.gouv.fr/affichTexte.do?cidTexte=JORFTEXT000027434015&categorieLien=id

the organisation they represented. A questionnaire drafted by the HAS was sent for this purpose, along with a copy of the provisional assessment report produced at this stage by the HAS, containing the background, the results of the literature review, the validated minutes of the expert group and the provisional conclusions drawn from them. The scoping document was also enclosed.

The stakeholders were consulted to:

- obtain their assessment of the report sent, in particular of its provisional conclusions;
- report the existence of French practices not mentioned in the report and that they wish to bring to the attention of the HAS;
- express other comments (of whatever type).

The responses of the professional bodies and patient and user associations are reproduced in full in Appendix 10. A summary of these responses, produced by the HAS is presented in chapter 5.

The following stakeholders responded:

- *Association française des diététiciens nutritionnistes* (AFDN) [French Association of dieticians and nutritionists];
- *Association française d'étude et de recherche sur l'obésité* (AFERO) [French Association for obesity studies and research];
- *Collectif national des associations d'obèses* (CNAO) [French national group of obesity associations]:
- *Collège de la médecine générale* (CMG) [French college of general medicine];
- *Conseil national professionnel d'endocrinologie, diabétologie, nutrition* (CNP-EDN) [French national council for endocrinology, diabetes and nutrition professionals];
- *Conseil national professionnel d'hépato-gastroentérologie* (CNP-HGE) [French national council for hepato-gastroenterology professionals];
- *Ligue contre l'obésité* (LCO) [French obesity league];
- *Société française et francophone de chirurgie de l'obésité et des maladies métaboliques* (SOFFCO.MM) [French and French-speaking Society for obesity and metabolic disease surgery];
- *Société francophone du diabète* (SFD) [French-speaking Diabetes Society].

The stakeholders who did not respond, despite a reminder and additional time, are as follows:

- *Conseil national professionnel de psychiatrie* (CNPP) [French national council for psychiatry professionals];
- *Fédération française des diabétiques* (FFD) [French Diabetics Federation];
- *Fédération française des psychologues et de psychologie* (FFPP) [French Federation of psychologists and psychology].

3. Results of the literature analysis

3.1. Already published systematic reviews with MA

The two meta-analyses selected are presented in Table 4 (see chapter 2.1 on the literature selection process).

Table 4. Most recent identified meta-analyses.

Authors, year, reference	Search period	Number of trials	Number of trials in the MA only including patients with class 2 and 3 obesity	Number of patients	Techniques
Cui *et al*., 2021 (21)	Until February 2021	5	2	n=477	RYGB
Khorgami *et al*., 2019 (22)	January 1990 to April 2018	7	1	n=463	LAGB, RYGB, SG

Like the MA by Cummings and Cohen in 2016 (23), identified in the scoping document (1), neither of these two MAs present results specific to the target population of the assessment: patients with type 2 diabetes and class 1 obesity or overweight. They all collate within the same statistical analysis the results of studies including patients from the target population of the assessment with studies including only patients with class 2 or 3 obesity (severe or very severe).

Therefore, these two meta-analyses cannot be used to answer the assessment questions with a satisfactory level of certainty. The HAS therefore conducted meta-analyses exclusively with studies for which the population included patients with class 1 obesity, incorporating the most recent available data.

3.2. Details of the studies selected for the HAS analysis

Seven studies were selected; they gave rise to 11 publications (8-18). Details of the characteristics of the trials and the publications are presented in Appendix 1.

3.2.1. Obesity and overweight classes

The distribution of the obesity and overweight classes of patients in these different studies is summarised in Table 5.

One of these seven studies, the study by Wentworth *et al*. (8), only included patients with overweight. Its results are presented in the response to question 2 of the assessment.

For the other six studies, the proportion of patients with class 1 obesity varies from 22 to 60%. The results are presented in the response to question 1 of the assessment. None of these studies specifically reported T2DM remission results for the population with class 1 obesity.

The transposability of the results of these six studies to the specific population of patients with class 1 obesity appears to be limited for five of them, since less than 45% of the patients included corresponded to the target population. It is more satisfactory for only one study, with more than 60% of patients presenting class 1 obesity.

There is no data available specifically concerning patients with class 1 obesity. These patients with a BMI of less than 35 kg/m^2 represent from 22 to 60% of the population in the studies selected. **The applicability of the results of the HAS meta-analysis to the target population of the assessment therefore needs to be considered with this reservation.**

3.2.2. Surgical techniques performed

The techniques performed in the seven studies selected are only three of those already recommended in the management of obesity; they are: laparoscopic adjustable gastric banding (LAGB), sleeve gastrectomy (SG), and Roux-en-Y gastric bypass (RYGB). This point is detailed in question 4 of the assessment in chapter 3.3.4. SG was only conducted in one of the seven studies, while the other two techniques were performed in four studies. In two of the seven studies, two techniques were performed in the same proportions (1:1 randomisation). Details of the techniques used for each study are presented in Table 5.

3.2.3. Methodological validity of the studies

Assessment of the methodological validity using the ROB2 grid is presented in detail in Appendix 2 and summarised in Table 5 for the overall risk of bias per study.

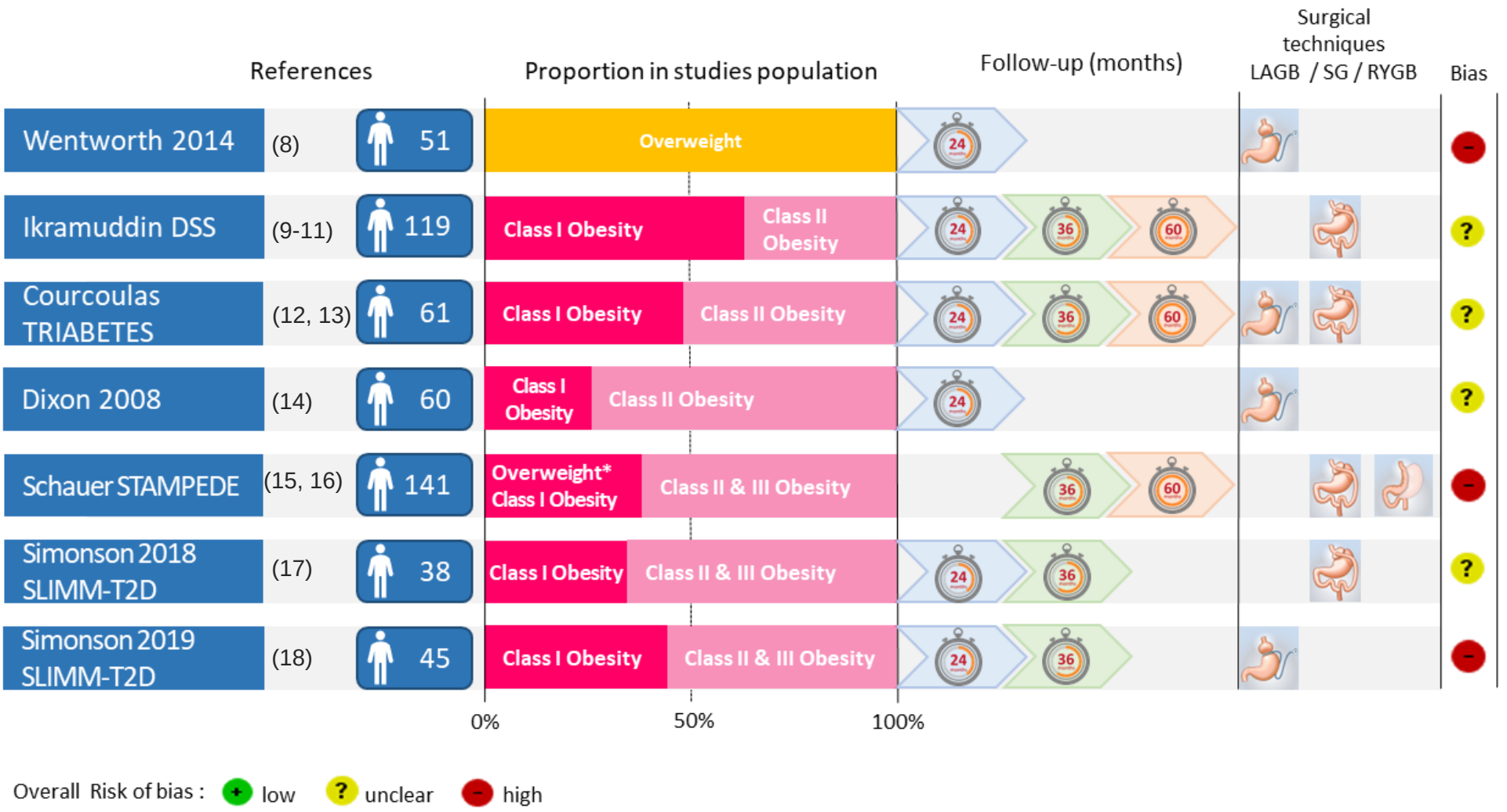
As concerns patients lost to follow-up at 24 months in particular, the rate varies from 4 to 15% for five studies, which is acceptable in view of the remission rate after MS, observed in at least 31 to 54% of patients (lower bound values of the 95% confidence interval); the risk of bias related to the lost-to-follow-up rate is therefore estimated to be low for these five studies. However, for the other two studies, the risk of bias related to the lost-to-follow-up rate is uncertain (data not supplied) or high (lost-to-follow-up rate of 17% and remission rate of 10%).

As regards blinding, since this is not possible, all the trials are “open-label” trials. Hence, recourse to adjustment of pharmacological treatment may be influenced by knowledge of the patient group and may impact the composite primary outcome measure, i.e.: type 2 diabetes remission demonstrated by HbA_{1c} level and recourse or otherwise to pharmacological treatment. The result reported is therefore uncertain.

The results for the other areas assessed by the ROB2 grid are presented in Appendix 2.

In total, taking into account the different parameters of the ROB2 grid, the seven studies included in the context of the HAS meta-analyses present an overall risk of bias that is uncertain for four of them, or high for three of them. **Hence, from a methodological point of view, the results of the meta-analyses should be interpreted with caution.**

Table 5. Summary of the seven studies selected: populations, proportion of patients with overweight or obesity, obesity classes, surgical techniques and overall risk of bias.



3.3. Results of the HAS meta-analyses

3.3.1. Question 1: What is the benefit-risk balance of metabolic surgery in the treatment of T2DM in patients with class 1 obesity compared to conventional management?

3.3.1.1. Efficacy data on T2DM remission

> As a reminder, T2DM remission is defined as: "HbA_{1c} < 6.5% (48 mmol/mol) measured three months after surgery and at least three months after cessation of antidiabetic treatments" (see chapter 1.2 and (6)).

Remission at 24 months

This endpoint is assessed thanks to the findings of MA No. 1 (see Figure 3), which included five studies presenting results for 323 obese patients, some of whom (between 22 and 60%) presented class 1 obesity (9, 12, 14, 17, 18). Two studies - those having included the lowest number of patients, present a confidence interval that straddles the limit of significance.[14] In these five studies, the remission rate (absolute risk) in the surgery arm varies from 13 to 73% versus 0 to 13% in the control arm (see Appendix 3). **The results of these five studies are all consistent.**

The result of this MA is significant and in favour of MS, with an expected mean risk ratio of at least 3 and up to 20 (see Figure 5 in Appendix 5).[15] The heterogeneity in this MA is moderate (I^2 = 15% and Tau^2 = 0.19; see Appendix 5) reinforcing the value of this work. The result of this MA is presented in diagram form in Figure 3.

> **Hence, according to this MA (No. 1) with a moderate heterogeneity, a patient undergoing metabolic surgery would be at least three times more likely to present T2DM remission at 24 months than a patient receiving conventional medical therapy.** As a reminder, the applicability of these results to the target population (class 1 obesity) nonetheless still needs to be considered with caution given the proportion of patients with class 1 obesity in the five studies, which ranged from 22 to 60%.

[14] Value one in the figure, presented as Risk Ratio.

[15] Lower and upper bound of the 95% confidence interval of the calculated RR 7.85 [3.09;19.94].

Figure 3. Diagram of results of MA No. 1: relative risk of presenting type 2 diabetes remission following metabolic surgery at 24 months.

Remission at 36 months

This endpoint can be assessed by four of the six meta-analyses performed for this assessment.

Firstly, it is the second primary analysis (MA No. 2) that was conducted with the five studies presenting results for 404 patients (9, 12, 15, 17, 18). Two of these present a confidence interval that straddles the limit of significance.

In these five studies, the remission rate (absolute risk) in the surgery arm varies from 8 to 44% versus 0 to 4% in the control arm (see Appendix 3). **The results of these five studies are all consistent.**

The result of MA No. 2 is significant and in favour of MS, with an expected mean risk ratio of at least 2 and up to 20 (see Figure 6 in Appendix 5).[16] The heterogeneity in this MA is moderate (I^2 = 27 % and Tau^2 = 0.44; see Appendix 5) reinforcing the value of this work. The result of this meta-analysis is presented in diagram form in Figure 4.

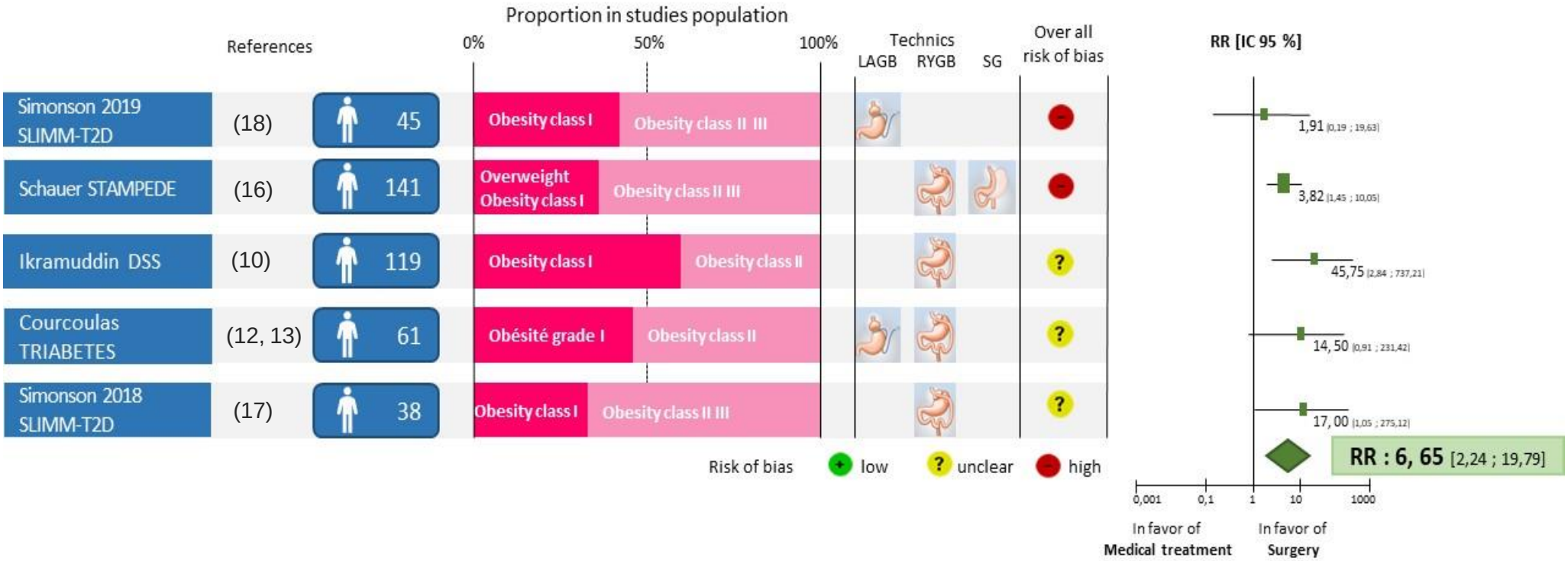
The exploratory analysis, MA No. 5 (see Appendix 6, Figure 9), also provides information on T2DM remission at 36 months. In addition to the five studies from the above MA (No. 2), it included unpublished data from the CROSSROAD study and concerned 421 patients. Three of these six studies present a confidence interval that straddles the limit of significance. The heterogeneity is low (I^2 = 9% and Tau^2 = 0.10; see Appendix 6) reinforcing the value of this work. The results of the six studies are all consistent.

The result of this exploratory MA is significant and in favour of MS and is consistent with primary analysis No. 2 (Figure 4). This exploratory MA No. 5 enables it to be concluded that the expected mean risk ratio would be at least 3 and up to 13.[17] The remission rate (absolute risk) in the surgery arm varies from 8 to 44% versus 0 to 4% in the control arm.

> **Hence, according to the results of these two MAs (No. 2 and No. 5) with a low to moderate heterogeneity, a patient undergoing metabolic surgery would be at least two to three times more likely to present T2DM remission at 36 months than a patient receiving conventional medical therapy.** However, the applicability of these results to the target population still needs to be considered with caution given the proportion of patients with class 1 obesity in the studies included in these two meta-analyses, which ranged from 36 to 60%.

[16] Lower and upper bound of the 95% confidence interval of the calculated RR 6.65 [2.24;19.79].
[17] Lower and upper bound of the 95% confidence interval of the calculated RR 5.74 [2.57;12.83].

Figure 4. Diagram of results of MA No. 2: relative risk of presenting type 2 diabetes remission following metabolic surgery at 36 months.



The work entitled ARMMS-T2D by Kirwan *et al*. (19), which presents an aggregation of the T2DM remission results at 36 months of four trials (STAMPEDE, TRIABETES, SLIMM-T2D and CROSSROAD (chapter 2.2.4.2)), reports that out of 195 surgical procedures, 60 patients presented remission, compared to 2 out of 121 in the standard medical therapy group. **The difference in favour of MS was also significant.** It should be noted, firstly, that these results are on an intention-to-treat basis, and hence the five cross-overs from medical therapy having ultimately received surgical management are counted in the medical therapy group and, secondly, that the lost-to-follow-up rate is 29% (36/121) for medical therapy and 12% (24/195) for surgical management. **The difference in favour of MS was also significant in this aggregation; the ARMMS-T2D results are consistent with the HAS meta-analysis** (Figure 4). However, it should be noted that the HAS meta-analysis concerns a larger number of patients (n=377) and studies (n=5). It also presents less missing data (15%).

In addition, at the request of the HAS, Kirwan *et al*. communicated unpublished data relating to the number of remissions in the population with a BMI of less than 35 kg/m^2: **15 remissions out of a total of 50 patients having undergone metabolic surgery**, i.e. a 30% remission rate, **compared to none among the 30 patients having received standard medical therapy at 36 months** (the difference is significant: χ^2 test of 1%). This data was used to perform an exploratory analysis, MA No. 6 (Appendix 6, Figure 10, the third analysis assessing T2DM remission at 36 months, see Figure 2). It only included patients with a BMI of less than 35 kg/m^2, i.e. 80 patients (four studies).

These four studies present a confidence interval that straddles the limit of significance and their results are all consistent. The heterogeneity is low (I^2 and Tau^2 = 0) reinforcing the value of this work.

The findings of this exploratory meta-analysis conducted by the HAS are significant and in favour of metabolic surgery. **The MA conducted by the HAS enables it to be concluded that the expected mean risk ratio would be 5.27 [1.31; 21.23]**. The remission rate (absolute risk) in the surgery arm ranges from 24 to 37% versus zero in the control arm.

> **On the basis of this last MA (No. 6) with a low heterogeneity, it is therefore possible to conclude, with a limited level of certainty (unpublished data, low sample size), that the efficacy of metabolic surgery on T2DM remission at 36 months for patients with class 1 obesity may be similar to that observed for all obesity classes combined** (results of meta-analyses Nos. 2 and 5, see above). However, more data would have been required to have a better level of certainty concerning the data for patients with class 1 obesity only.

Remission at 60 months

An exploratory analysis was conducted for this follow-up duration: MA No. 3 (see Figure 2). It is presented in Figure 7 in Appendix 6. It concerns three studies (11, 13, 16) and 321 patients, including some with class 1 obesity (between 35 and 60%). The results need to be interpreted with caution in view of the lost-to-follow-up rate of up to 18% (whereas it is a maximum of 15% for the other analyses) and the cross-over rate, which was either not indicted or was approximately 9%. The remission rate (absolute risk) in the surgery arm ranges from 16 to 37% versus zero in the control arm. The heterogeneity is low (I^2 and Tau^2 = 0) reinforcing the value of this work.

This MA **enables it to be concluded that the expected mean risk ratio would be at least 3 and may be as high as 83** (see Figure 7).[18]

> **According to this MA (No. 3) with a low heterogeneity, a patient undergoing metabolic surgery would be at least three times more likely to present T2DM remission at 60 months than a patient receiving conventional medical therapy.** As a reminder, the applicability of these results to the target population (class 1 obesity) nonetheless still needs to be considered with caution given the proportion of patients with class 1 moderate obesity in the three studies, which ranged from 35 to 60%.

The maintenance at 60 months of T2DM remission observed at 36 months or 24 months needs to be assessed with caution. In fact, the individual evolution of patients over time is not indicated; in addition, these are not strictly the same patients or the same proportions between surgical techniques for the analyses at 24, 36 and 60 months.

> **All the meta-analyses performed suggest a superiority of MS compared to conventional medical management of T2DM (medicinal, non-surgical), at either 24, 36 or 60 months.**
>
> According to the main meta-analyses (Nos. 1 and 2), a patient undergoing MS would be at least **2 to 3 more likely to present T2DM remission**, at 24 and 36 months respectively, than a patient receiving standard medical therapy.
>
> **The applicability of these results to the target population (type 2 diabetes patients with class 1 obesity) nonetheless needs to be considered with caution**. First of all, the risk of bias is uncertain to high for the studies selected and included in the meta-analyses. In addition, the proportion of patients with class 1 obesity in the six studies of these two meta-analyses was at least 60%. Finally, their sample sizes (fewer than 404 patients) remain limited in view of the size of the target population (more than one million people in France).
>
> However, the exploratory analysis, MA No. 6, on unpublished data relating to patients with class 1 obesity only, is consistent with the primary analyses (Nos. 1 and 2) and with similar effect size values (RR and remission rate), **suggesting that the effect size of metabolic surgery on T2DM remission does not differ in patients with class 1 obesity from that measured for all obesity classes combined**.

3.3.1.2. Other primary outcome measures

The aim of the seven studies selected was to demonstrate T2DM remission, not a reduction in mortality or cardiovascular morbidity. Only one of them - the SLIMM-T2D study (18) - reports cardiovascular risk scores and did not demonstrate any difference between the two groups.

[18] Lower and upper bound of the 95% confidence interval of the calculated RR 16.66 [3.32;83.62].

There is insufficient data available for these two outcome measures.

Four of these seven studies had assessed patients' quality of life. Three of them - the study by Wentworth *et al*., STAMPEDE and SLIMM-T2D - report a significant improvement in quality of life for patients having undergone surgery compared to those receiving standard medical therapy (8, 15-17). The fourth study, conducted by Simonson *et al*. in 2019, reports that no difference was demonstrated between the two arms (18). However, it should be noted that in these four studies, quality of life was only a secondary outcome measure. The details for these quality of life endpoints are presented in Appendix 4.

Despite the trend of these results, the data collected does not enable us to conclude with a sufficient level of evidence that there is an improvement in the quality of life for patients who have undergone metabolic surgery (secondary outcome measure).

3.3.1.3. Secondary outcome measures

As concerns the reduction in HbA_{1c}, the difference compared to T0 between the surgery group and the control group is significant in all the studies, except the one by Simonson *et al*. (18). The reductions are detailed in Appendix 4. It is not relevant to comment on the effect size between the studies (the magnitude of the difference between T0 and T24 months or T36 months); in fact, the initial HbA_{1c} levels differ depending on the studies, hence the "possible HbA_{1c} reduction margin" differs too.

Metabolic surgery often makes it possible to discontinue insulin therapy (43 to 100% of cases), and even all diabetes medications in almost half of patients. In fact, at 36 months, the total discontinuation of all diabetes medications was observed in 47 to 58% of patients having undergone surgery, compared to 0 to 5% of patients on conventional medical therapy. **This advantage of MS is significant and observed for all the studies.** The details of discontinuations are shown in Appendix 3.

As the reduction in the number of antidiabetic agents does not follow a codified process and is reported in a very heterogeneous manner between the different studies and at the different measurement times, it has not been reported in this assessment. This result also seemed to be secondary given the results obtained with the primary outcome measure (T2DM remission).

Where reported, the reduction in BMI was always greater in the surgery group. The difference between the groups is always significant and in favour of surgery. The values for each study are presented in Appendix 4.

3.3.1.4. Safety data

Three of the seven studies selected report repeat surgeries, including conversion surgeries, i.e. the performance of a different surgical technique. The majority of repeat surgeries are performed after the following complications: poor filling of the adjustable band, ulceration, fistulas, leaks, intestinal blockage, under-nutrition. Conversions from LAGB or SG to RYGB are reported, without the cause being documented.

The event rate is not reported in a homogeneous manner and the severity of events is not always reported.

As with the efficacy data, it is not possible to differentiate events occurring in patients with class 1 obesity.

The details of events subsequent to MS in these three studies are presented in Appendix 4.

It should be noted that none of the authors of these three studies report any particular events not usually observed in bariatric surgery.

The publications relative to the other four studies do not cover the issue of MS-related adverse events.

In addition, no consecutive cohort specifically dedicated to the recording of adverse events (AEs) or serious adverse events (SAEs) following metabolic surgery was identified in the target population.

As regards serious or non-serious adverse events reported in these trials, concerning patients with class 1 obesity having undergone MS, **no particular safety signals were identified that would differentiate metabolic surgery from bariatric surgery in terms of perioperative and postoperative safety** (in terms of either nature, severity or frequency). However, the published safety data is still very limited.

Hence, in view of the data collated to answer question 1, the benefit-risk balance of MS for T2DM patients with class 1 obesity appears to be positive.

3.3.2. Question 2: What is the benefit-risk balance of metabolic surgery in the treatment of T2DM in patients with overweight compared to conventional pharmacological management?

Only two studies included patients with overweight (see Figure 2 and Table 5).

The results of one of these, STAMPEDE (15, 16), which do not differentiate between the results for patients with overweight and those with class 1 obesity, with only the proportion of patients with a BMI < 35 kg/m^2 being given, cannot therefore be used to answer question 2.

The other study, by Wentworth *et al*. (8), only concerns patients with overweight (n=51), of whom 25 underwent MS (only LAGB was performed in this study). It presents a high risk of bias. At 24 months, it reported a 52% [30-73] T2DM remission rate in the LAGB group, compared to 8% [0.98-26]. The difference between the groups was significant (p<0.01). Patients lost to follow-up represented 6% of the study population. The details are presented in Appendix 1 and in Appendix 3.

The safety data reported in this study is presented in Appendix 4. In summary, this concerns non-serious adverse events related to band filling (n=10 events for 25 patients having undergone surgery).

The collated data is in favour of MS. However, they concern a **very limited number of patients with overweight, all come from a single study (with a high risk of bias), concerning a single technique (LAGB) and with only 24 months of follow-up**; on this basis, it is not possible to answer question 2 of the assessment.

3.3.3. Question 3: Based on the results of Q1 and Q2, is MS aimed at all patients with class 1 obesity or overweight or only at a proportion of these patients and, if so, which ones?

As a reminder, the lower and upper limits of the patient inclusion criteria in the seven studies included in the HAS analyses were as follows: age 18 to 65 years, with an HbA_{1c} level of 6.5 to 14%. All the patients had pharmacological treatment, including the antidiabetic drugs listed in the North American good practice guidelines (24), along with possible recourse to insulin. The duration of the type 2 diabetes was very heterogeneous, having been present for more than one year without any upper limit. Patients had had no previous bariatric surgery. The details for these outcome measures are presented in Appendix 1.

None of these studies presented a subgroup analysis based on a potentially predictive factor. In addition, **no data enabling factors predictive of the success or failure of the surgical procedure in terms of T2DM remission at 24 months or more were identified in these studies**.

> There is no particular age limit in the inclusion criteria of the studies used in the HAS meta-analyses. The age limits are identical to those for bariatric surgery, i.e. from 18 to 65 years old (25). The lower limits for T2DM duration and HbA_{1c} level are more than one year and over 6.5% respectively with antidiabetic treatment including insulin therapy or otherwise. The upper limit for HbA_{1c} is 14%.

> **It was not possible to identify any factors predictive of the success or failure of MS in the target population of the assessment, i.e. patients with class 1 obesity, with the data available.**

3.3.4. Question 4: Which of these surgical techniques can be preferentially offered to patients eligible for metabolic surgery?

Only three techniques had been performed in the seven studies selected (Figure 2, Appendix 1):

- **laparoscopic adjustable gastric banding** (LAGB);
- **sleeve gastrectomy** (SG);
- **Roux-in-Y gastric bypass** (RYGB).

These are three of the four surgical techniques already recommended by the HAS for the management of obesity (class 2 with comorbidity, and class 3) and included in the list of reimbursed treatments in France for more than 15 years (26). It should be noted that the greatest amount of data available at 36 months concerns RYGB (n=148 patients), compared to SG (n=49) and LAGB (n=43).

No data was identified for the following techniques: BP-DS, OAGB, SADI-Sleeve, SG-TB and Endosleeve.

Concerning LAGB, the available data comes from three studies: one, by Wentworth *et al*., for patients with overweight (8) and two for patients with class 1 obesity: the studies by Courcoulas *et al*. (12) and Simonson *et al*. (18). On this basis, it was not possible to perform an MA specific to LAGB. The data from the Wentworth *et al*. study was presented above (assessment question 2). For the two studies on class 1 obesity, a total of 8 remissions for 43 LAGBs versus 1 for 36 patients receiving standard medical therapy were reported at 36 months of follow-up.

Concerning SG, only one study, by Schauer *et al*. (15, 16), reports results for this technique. At 36 months, the following were observed: 14 remissions for 49 SGs versus none for 41 patients on standard medical therapy.

Concerning RYGB, an exploratory analysis could be conducted because three of the seven studies selected used this technique, they all present data for follow-up at 36 months and they had included 289 patients, including some with class 1 obesity (between 35 and 60%) (10, 12, 15, 17). This MA, No. 4 (see Figure 2), is presented in Figure 8 in Appendix 6. The heterogeneity is low (I^2 and $Tau^2 = 0$) reinforcing the value of this work. It should be noted that the lost-to-follow-up rate for RYGB specifically was not available, however, it was a maximum of 18% all techniques combined.

The findings of this exploratory MA conducted by the HAS are significant and in favour of MS with RYGB. **The MA conducted by the HAS enables it to be concluded that the expected mean risk ratio would be at least 6** (see Figure 8) .[19]. The remission rate (absolute risk) in the RYGB arm ranges from 37 to 44% versus 0% in the control arm.

> **The findings of MA No. 4 are in favour of MS with RYGB. However, there is not enough data to reach individual conclusions for the other techniques (LAGB and SG).**

The studies selected for this work did not compare the techniques with one another and therefore could not be used to answer this assessment question.

In addition, a network meta-analysis, in which the HAS participated in the context of EUnetHTA.[20], compared the various surgical techniques (without comparing them with conventional medical therapy) (27). It collated data for patients, including some with class 1 obesity and type 2 diabetes. The authors had not identified any significant difference between the techniques for T2DM remission that would make it possible to preferentially propose any one technique compared to another for the management of T2DM.

> **The greatest amount of data is available for RYGB, making it possible to conduct an MA on T2DM remission at 36 months. According to this MA, a patient undergoing metabolic surgery with RYGB would be at least six times more likely to present T2DM remission at 36 months than a patient receiving standard medical therapy.**
>
> The studies selected for this work did not compare the various techniques with one another.
>
> A network MA (EUnetHTA), comparing the various surgical techniques, did not identify any significant difference between the techniques for T2DM remission.

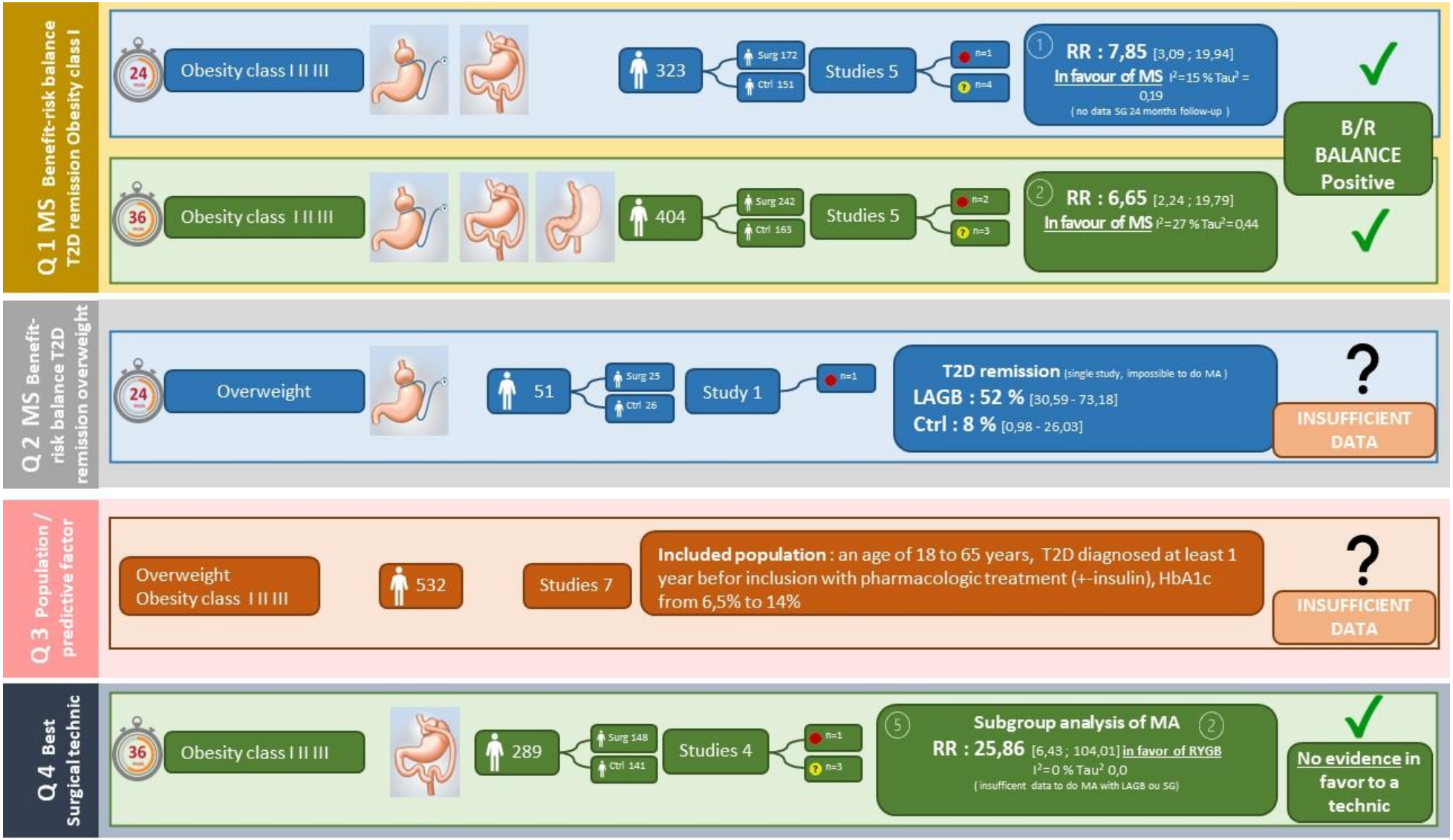
> **Based on the available data, it is not possible, therefore, to propose a preferred surgical technique among the three indicated with a sufficient level of certainty.**

[19] Lower and upper bound of the 95% confidence interval of the calculated RR 26.86 [6.43; 104.11].
[20] https://www.eunethta.eu/

3.3.5. Synopsis of results

The studies and results, in particular concerning T2DM remission at 24 and 36 months are presented in Table 6.

Table 6. Synoptic presentation of studies and answers to the assessment questions.



4. Summary of experts' individual positions

The complete minutes of the expert group meeting are presented in Appendix 8. A summary is presented below.

The experts indicate that they have no remarks concerning the meta-analyses conducted by the HAS, which reflect the observations they have made, and that the results are consistent with those reported in the available literature on the subject.

They consider that the results of the HAS meta-analyses (efficacy of metabolic surgery) are clearly in favour of MS for T2DM patients with class 1 obesity.

The experts do not report any elements suggesting that the improvements in T2DM observed, all obesity classes combined, including T2DM remission, would be different in class 1 obesity. However, they note that the number of studies and patients in the target population (class 1 obesity and T2DM) is small.

The experts consider that the risks of MS performed in type 2 diabetes patients with class 1 obesity are known and similar to those of BS (i.e. performed in type 2 diabetes patients with class 2 or 3 obesity). They indicate that this risk is acceptable in view of the T2DM improvements and other benefits (i.e. weight loss, reduction of comorbidities, reduction of cancer risk, etc.).

They specify that the same precautions as those taken for BS - concerning, in particular, poor T2DM control, macro- and micro-angiopathic complications and neuropathies - should be taken into account for patients, regardless of their obesity class, to prevent the development of these SAEs. No experts reported any safety signals specific to MS which would differentiate it from BS.

All the experts consider that the B/R balance of MS for type 2 diabetes patients with class 1 obesity is favourable.

All the experts consider that there are not enough data to reach a conclusion with respect to the B/R balance for MS for patients with overweight.

All the experts consider that there are no factors predictive of the success or failure of MS within the population of T2DM patients with class 1 obesity (question 3).

As regards question 4, the experts consider that there are no elements enabling a preferred surgical technique to be chosen from among LAGB, SG or RYGB, for performance of MS in patients with T2DM diabetes and class 1 obesity. In their opinion, all three may be proposed for MS. However, several experts point out that there is only one study reporting results following SG and that the efficacy of LAGB in terms of effect size (number of remissions) and T2DM remission duration appears to be more limited than that of RYGB.

The experts are not aware of any studies meeting the PICOTS criteria concerning the OAGB, BPD-DS, SADI-Sleeve, SG-TB and Endosleeve techniques. The group considers that these procedures can therefore only be performed in the context of clinical trials in the MS indication.

> The expert group retains the following indication for metabolic surgery:
>
> "In view of the data analysed, metabolic surgery may be offered to type 2 diabetes patients with class 1 obesity (BMI of 30 to 35 kg/m^2) when their individualised glycaemic targets have not been achieved despite well-managed medical care, in particular diabetes treatment and nutritional measures, in accordance with current good practice guidelines, for at least six months.
>
> The decision is taken with the patient following discussion at a multidisciplinary team meeting including a diabetes specialist.
>
> LAGB, SG and RYGB procedures may be proposed. At this stage there is no evidence making it possible to favour one of these three techniques over the others.
>
> The contraindications for bariatric surgery and metabolic surgery are the same."

The expert group indicates that the preparation, performance and follow-up of MS for T2DM patients with class 1 obesity are the same as for BS for T2DM patients with class 2 or 3 obesity.

The group indicates that patients should be provided information on:

- **the expected benefits** of MS in terms of improvement of T2DM and other comorbidities;
- **its risks**, differentiating these for each of the three techniques (LAGB, SG, RYGB);
- **and its constraints**, particularly in terms of postoperative follow-up, and lifelong follow-up, with nutritional supplements in the case of RYGB.

The group indicates that patients should be more specifically informed that:

- T2DM remissions are observed after three years in 30 to 40% of cases;
- the T2DM remission may not be definitive and patients may require antidiabetic drugs again after several months or years;
- monitoring to identify micro- and macro-angiopathic complications must be continued;
- there are benefits following MS other than T2DM remission, such as therapeutic de-escalation, weight loss, resolution of other comorbidities, etc.;
- they will have to undergo and adhere to lifelong follow-up after surgery.

Overall, the group specifies that, in addition to the specific points listed above, patients should receive the same information as that provided for BS.

5. Summary of stakeholders' perspectives

The list of stakeholders having responded is presented on page 16; their responses are reproduced in full in Appendix 10. The summary below was drafted by the HAS.

Not all of the stakeholders have any comments concerning the report, and five of them particularly highlight its clarity and quality. One adds that the limitations of the studies used were clearly highlighted.

They all agree with the indication proposed following the critical analysis of the literature and the position of the working group experts for MS. Five of them emphasise the importance of involving the patient's primary care physician in the pathway from the outset, and including all those involved, including the paramedical professions, ideally within a network experienced in the follow-up of these patients. One stakeholder more specifically highlights the limitations of the data available for MS, and nonetheless indicates that "only RYGB has enough data" and that the "current data is insufficient to conclude with respect to the Sleeve and LAGB". Two others specify and recall that LAGB presents numerous limitations in terms of its efficacy and that it is debatable whether it should be proposed to patients. One stakeholder indicates that the term "well-managed" is too vague without an alternative term being proposed. However, these comments do not lead these stakeholders to question the conclusions proposed, which include the three techniques.

The stakeholders agree with the information to be given to patients, listed in the conclusion.

Estimation of the target population appears to be difficult for all the stakeholders. Two highlight that the number of patients undergoing surgery will depend on the perception that patients with class 1 obesity have of the benefit-risk balance when this therapeutic option is offered to them. One specifies that the size of this population is made even more difficult to determine following the arrival of new antidiabetic agents. One indicates that the effects of lockdowns could increase the number of people eligible.

Four stakeholders indicate the arrival on the market of new antidiabetic agents that were not part of the routine care options at the time the studies included in this MS assessment were carried out. These antidiabetic agents appear to be able to achieve and maintain diabetes patients' glycaemic targets. Therefore, these therapies should be considered in the overall management of T2DM.

All the stakeholders highlight and reiterate the difficulties of local lifelong follow-up beyond two years after surgery and stress that it is essential. Most express reservations concerning the capacity of the healthcare system as it is currently organised in France to guarantee effective lifelong follow-up of all patients who might undergo MS in the future.

6. Summary, conclusions and outlook

On the basis of the assessment conducted in this report having consisted of i) a critical analysis of the literature identified by a systematic search then selected based on explicit criteria, having led to the performance of meta-analyses (MA), ii) the collection of the position of individual experts who are healthcare professionals involved in the management of type 2 diabetes (T2DM) and obesity[21] , and patients with diabetes or obesity, iii) collection of the viewpoints of their professional organisations and patient associations, the HAS reaches the following conclusions:

All the meta-analyses performed in the context of this assessment point to the superiority of metabolic surgery (MS) compared to conventional medical management of type 2 diabetes (T2DM), via medication without surgery, whether at 24, 36 or 60 months of follow-up, for type 2 diabetes patients with class 1 obesity (BMI of 30 to 35 kg/m^2).

Indeed, according to the main two meta-analyses (Nos. 1 and 2), a patient undergoing MS would be at least **two to three times more likely to present T2DM remission**, at 24 and 36 months respectively, than a patient receiving standard medical therapy.

The applicability of these results to the target population (type 2 diabetes patients with class 1 obesity) nonetheless needs to be considered with caution. First of all, the risk of bias is uncertain to high for the studies selected and included in the meta-analyses. In addition, the proportion of patients with class 1 obesity in the six studies of these two meta-analyses was at least 60%. Finally, their sample sizes (fewer than 404 patients) remain limited in view of the size of the target population (more than one million people in France).

However, the exploratory MA (No. 6), relating to patients with class 1 obesity only (with unpublished data), is consistent with the main two meta-analyses (Nos. 1 and 2) and with similar effect size values (RR and remission rate); **suggesting that the effect size of metabolic surgery on T2DM remission does not differ in patients with class 1 obesity from that measured for all obesity classes combined**.

The experts consulted to give their individual positions consider that these efficacy results are clearly in favour of MS for T2DM patients with class 1 obesity.

As regards the safety of MS, following analysis of serious or non-serious adverse events reported in the trials selected and analysed concerning patients with class 1 obesity, **no particular safety signals were identified that would differentiate MS from bariatric surgery (BS) in its current indications (class 2 and 3 obesity), in terms of perioperative and postoperative safety,** in terms of either nature, severity or frequency. However, the published safety data is still very limited. Nonetheless, the experts did not report any adverse events that appear to be specific to MS in the target population; they consider that the risks of MS performed in type 2 diabetes patients with class 1 obesity are known and similar to

[21] General practitioner, endocrine, diabetes and nutritional specialist, gastrointestinal surgeon, hepato-gastroenterology specialist, dietician

those of BS, and that this risk is acceptable in view of the T2DM improvements and other benefits.

Hence, in view of the efficacy and safety data collated to answer question 1, the benefit-risk balance of MS for T2DM patients with class 1 obesity appears to be positive (HAS analyses on published and unpublished data, as well as experts' positions).

Based on the available data, it was not possible to identify any validated factors predictive of the success or failure of MS (insufficient data in the literature and export group position).

The available data relates to three surgical techniques: laparoscopic adjustable gastric banding (**LAGB**), sleeve gastrectomy (**SG**) and Roux-en-Y gastric bypass (**RYGB**). In particular, in the absence of comparative data, it is not possible to propose a preferred surgical technique among the three indicated or, conversely, to exclude any, with a sufficient level of certainty (analysis of the literature and expert group position).

As regards type 2 diabetes patients with overweight (BMI of 25 to 30 kg/m^2), there is too little data to be able to offer them MS as part of routine care (insufficient published data and expert group position).

On the basis of currently available data, the OAGB, BPD-DS, SADI-Sleeve, SG-TB and Endosleeve techniques in the metabolic surgery indication for type 2 diabetes patients with class 1 obesity or overweight may therefore only be performed in the context of clinical trials, after informing the patient, in accordance with article L.1122-1 of the French Public Health Code, enabling the freely-given, informed consent of patients (HAS analysis and expert group position).

Overall, following this report, the MS indication therefore appears to be as follows:

"Metabolic surgery may be offered to type 2 diabetes patients with class 1 obesity (BMI of 30 to 35 kg/m2) when their individualised glycaemic targets have not been achieved despite well-managed medical care, in particular diabetes treatment and nutritional measures, along with adapted physical activity, in accordance with current good practice guidelines, for at least twelve months.

The decision is taken with the patient following discussion at a multidisciplinary team meeting including a diabetes specialist.

Surgical techniques: laparoscopic adjustable gastric banding (**LAGB**), sleeve gastrectomy (**SG**), Roux-en-Y gastric bypass (**RYGB**) **may be proposed. At this stage there is no evidence making it possible to favour one of these three techniques over the others.**

The contraindications for bariatric surgery and metabolic surgery are the same."

> The preparation, performance and follow-up of MS for T2DM patients with class 1 obesity are the same as for BS for T2DM patients with class 2 or 3 obesity. **In this patient pathway, the primary care physician plays a crucial role and must be included from the outset when metabolic surgery is suggested.**

The information to be provided to patients must include the following:

- the **expected benefits** of MS in terms of improvement of T2DM and other comorbidities;
- its **risks,** differentiating these for each of the three techniques (LAGB, SG, RYGB);
- and **its constraints**, in particular the irreversible nature of SG and RYGB procedures, the postoperative follow-up, then lifelong follow-up with, in particular essential routine vitamin, mineral and trace element supplementation tailored on the basis of the surgical technique used.

Patients should be more specifically informed that:

- T2DM remissions are observed after three years in 30 to 40% of cases;
- **the T2DM remission may not be definitive and patients may require antidiabetic drugs again after several months or years;**
- monitoring to identify micro- and macro-angiopathic complications must be continued;
- there are benefits other than T2DM remission, such as therapeutic de-escalation, weight loss, resolution of other comorbidities, etc.;
- they will have to undergo and adhere to lifelong follow-up after metabolic surgery.

In addition to the specific points listed above, patients should receive the same information as that provided for BS.

Outlook

> **Metabolic surgery for type 2 diabetes patients with class 1 obesity will be included in the "Overweight and obesity in adults" care pathway currently being developed at the HAS.**
>
> **Along with access to metabolic surgery in these patients, the HAS encourages the prospective and exhaustive collection of real-world data concerning the benefit (mortality, cardiovascular events, T2DM remission at over 60 months, impact on healthcare consumption and quality of life, etc.) and risks (failures, adverse events, revision, repeat surgery, etc.). It would then like to reassess this surgical procedure based on this new data.**
>
> **Along with the development of metabolic surgery, new antidiabetic drugs have also arrived on the market for routine care (in particular SGLT2 inhibitors). It will be necessary to specify the respective roles of these two therapeutic options in the guidelines for the management of T2DM patients.**
>
> **Following this report, the use of new procedures, including OAGB, BPD-DS, SADI-Sleeve, SG-TB, and Endosleeve, in the metabolic surgery indication remains within the scope of clinical research. These techniques will be assessed once additional results have been obtained, as in the bariatric surgery indication.**

Table of appendices

Appendix 1. Characteristics of the clinical trials included in the HAS analysis. 42

Appendix 2. Analysis of risks of bias of studies used in the meta-analysis in accordance with ROB2. 43

Appendix 3. Efficacy results of the clinical trials included in the HAS meta-analysis. 45

Appendix 4. Quality of life and safety results of the clinical trials included in the HAS meta-analysis. 47

Appendix 5. Main meta-analyses . 49

Appendix 6. Exploratory meta-analyses. 50

Appendix 7. Professional bodies and patient associations consulted to obtain expert names. 51

Appendix 8. Minutes of the expert group meeting. 52

Appendix 9. Lists of bodies consulted as stakeholders. 60

Appendix 10. Stakeholders' responses 61

Table of figures

Figure 1. Literature selection flow chart. 11

Figure 2. Implementation plan for the six HAS meta-analyses. 15

Figure 3. Diagram of results of MA No. 1: relative risk of presenting type 2 diabetes remission following metabolic surgery at 24 months. 22

Figure 4. Diagram of results of MA No. 2: relative risk of presenting type 2 diabetes remission following metabolic surgery at 36 months. 24

Figure 5. Relative risk at 24 months of presenting type 2 diabetes remission after surgery, MA No. 1. 49

Figure 6. Relative risk at 36 months of presenting type 2 diabetes remission after surgery, MA No. 2. 49

Figure 7. Relative risk at 60 months of presenting type 2 diabetes remission after surgery, MA No. 3. 50

Figure 8. Relative risk at 36 months of presenting type 2 diabetes remission after RYGB, MA No. 4. 50

Figure 9. Relative risk at 36 months of presenting type 2 diabetes remission after surgery (with CROSSROAD unpublished data), MA No. 5. 50

Figure 10. Relative risk at 36 months of presenting type 2 diabetes remission after surgery (with BMI < 35 kg/m^2 unpublished data), MA No 6. 50

Table of tables

Table 1. PICOTS for assessment question 1 (Q1). 8

Table 2. PICOTS for assessment question 2 (Q2). 9

Table 3. Literature selection criteria. 13

Table 4. Most recent identified meta-analyses. 18

Table 5. Summary of the seven studies selected: populations, proportion of patients with overweight or obesity, obesity classes, surgical techniques and overall risk of bias. 20

Table 6. Synoptic presentation of studies and answers to the assessment questions. 32

Table 7. Professional bodies and patient associations that were consulted to obtain expert names. 51

Table 8. Professional bodies and patient associations that were consulted. 60

Appendix 1. Characteristics of the clinical trials included in the HAS analysis.

Study, year, study registration number, name	Method, population (N), % patients BMI<35 kg/m², inclusion age range, BMI value, T2DM duration, HbA_{1c} value %, inclusion range	Technique(s), sample size (N)	Definition of T2DM remission in compliance with international consensus (5, 6)	Follow-up duration
Wentworth *et al.*, 2014 (8) ACTRN12609000286246	– Single-centre, prospective, RCT – (n=51), 100%, 18 to 65 years – 25 < BMI < 30 kg/m² – < 5 years; nr	– LAGB (n=25)	– No, glucose level < 7 mmol/L and <11.1 mmol/L after glucose tolerance test following discontinuation of antidiabetic treatment	– 24 months
Ikramuddin *et al*., 2015, 2016 and 2018 (9-11) NCT00641251 DSS-study	– Single-centre, prospective, RCT – (n=119), 60%: control n=35 (58%), RYGB n=36 (60%) – 30 to 67 years; 30 < BMI < 39.9 kg/m² – Mean 9 years; HbA_{1c} of 8 to 14%	– RYGB (n=59)	– Yes – Partial remission as defined in the study corresponds to the consensus definition	– 24, 36, 60 months
Courcoulas *et al.*, 2015 and 2020 (12, 13) NCT01047735 TRIABETES	– Single-centre, prospective, RCT – (n=61), 43%, 25 to 55 years – 30 < BMI < 40 kg/m² – Mean 6.5 years (+- 4.8); nr	– LAGB (n=21) – RYGB (n=20)	– Yes	– 24, 36, 60 months
Dixon *et al.*, 2008 (14) ACTRN012605000159651	– Single-centre, prospective, RCT – (n=60), 22%: Med n=7, LAGB n=6, 20 to 60 years – 30 < BMI < 40 kg/m² – < 2 years; nr	– LAGB (n=30)	– Yes	– 24 months
Schauer *et al*., 2014 and 2017 (15, 16) NCT00432809 STAMPEDE	– Single-centre, prospective, RCT – (n=141), 35%; 20 to 60 years – 27 < BMI < 43 kg/m² – 8.3 years (+- 5.1); HbA_{1c} > 7%	– SG (n=49) – RYGB (n=50)	– Yes – Partial remission as defined in the study corresponds to the consensus definition	– 36, 60 months
Simonson *et al*., 2018 (17) NCT01073020 SLIMM-T2D	– Single-centre, prospective, RCT – (n=38), 29% Med n=7, RYGB n=6; 21 to 65 years – 30 < BMI < 45 kg/m² – 10.6 years (+- 6.6); HbA_{1c} 6.5 to 12%	– RYGB (n=19)	– Yes	– 24, 36 months
Simonson *et al*., 2019 (18) NCT01073020 SLIMM-T2D	– Single-centre, prospective, RCT – (n=45), 40% Med n=8, LAGB n=7; 21 to 65 years – 30 < BMI < 45 kg/m² – >1 year; HbA_{1c} 6.5 to 12%	– LAGB (n=23)	– Yes	– 24, 36 months

Appendix 1. Analysis of risks of bias of studies used in the meta-analysis in accordance with ROB2.

Study, year	D1 Randomisation procedure	D2 Deviation of allocated procedure	D3 Missing data[22]	D4 Measurement of the assessment criterion	D5 Selection of the reported result[23]	Overall risk
Wentworth *et al.*, 2014 (8)	− Use of envelopes	? Cross-over not recorded	+ 6% lost-to-follow-up rate acceptable in view of the effect observed in 52% of patients	+	? Open-label study potentially influencing escalation or de-escalation of antidiabetic drugs	−
Ikramuddin *et al.*, 2015, 2016 and 2018 (9-11)	+	+ 4 to 9% cross-over in both directions	+ 7 to 15% lost-to-follow-up rate acceptable in view of the effect observed in 42% of patients	+	? ditto	?
Courcoulas *et al.*, 2015 and 2020 (12, 13)	+	? Cross-over not recorded	+ 15 to 18% lost-to-follow-up rate acceptable in view of the effect observed in 19 to 45% of patients	+	? ditto	?
Dixon *et al.*, 2008 (14)	? Few details	? Cross-over not recorded	+ 8% lost-to-follow-up rate acceptable in view of the effect observed in 73% of patients	+	? ditto	?
Schauer *et al.*, 2014 and 2017 (15, 16)	− Use of envelopes	+ 1% cross-over	+ 4% lost-to-follow-up rate acceptable in view of the effect observed in 43 to 23% of patients	+	? ditto	−
Simonson *et al.*, 2018 (17)	+	? Cross-over not recorded	? Not recorded	+	? ditto	?

[22] As regards missing data, the risk of bias is low for the five studies, which report a missing data rate of 4 to 15%. These rates are acceptable in view of the remission rate at 24 months after metabolic surgery observed in at least 31 to 54% of patients (lower bound values of the 95% confidence interval of the remission rates reported). For two trials, the risk of bias is uncertain or high.

[23] Since blinding is not possible, all the trials are “open-label”; hence, recourse to adjustment of pharmacological treatment may be influenced by knowledge of the patient group and may impact the composite primary outcome measure, i.e.: type 2 diabetes remission demonstrated by HbA_{1c} level and recourse or otherwise to pharmacological treatment. Selection of the result reported is therefore uncertain.

Study, year	D1 Randomisation procedure	D2 Deviation of allocated procedure	D3 Missing data[22]	D4 Measurement of the assessment criterion	D5 Selection of the reported result[23]	Overall risk
Simonson *et al.*, 2019 (18)	+	? Cross-over not recorded	− 17% lost-to-follow-up rate, high rate in view of the effect observed in 10% of patients	+	? ditto	−

Appendix 3. Efficacy results of the clinical trials included in the HAS meta-analysis.

LAGB: laparoscopic adjustable gastric banding; RYGB: Roux-en-Y gastric bypass; SG: Sleeve gastrectomy; Med: Non-surgical, standard pharmacological treatment; na: not available; stop ins: insulin stopped; stop med: antidiabetic drugs stopped, difference between the surgery group and the med group not significant.

Study, year	Follow-up duration (months)	T2DM remission, (N) and remission rate % [confidence interval]	Therapeutic de-escalation	Evolution of HbA_{1c} % (compared to T0)	Evolution off BMI kg/m^2 (compared to T0)
Wentworth *et al.*, 2014 (8)	24	– LAGB: 12 (52% [30, 59-73,18]) – Med: 2 (8% [0.98-26.03])	– LAGB: stop ins n=4/4 stop med n=5/20 – Med: none	– LAGB: -0.8 (-1.1 to -0.5) – Med: 0.0 (-0.5 to 0.5)	– LAGB: -4.18 (-5.1 to -0.5) – Med: -0.5 (-1.3 to 0.3)
Ikramuddin *et al.*, 2015, 2016 and 2018 (9-11)	24	– RYGB: 25 (42% [29.61-55.93]) – Med: none	– RYGB: stop ins n=25/57 stop med 25/57 – Med: none and stop med 3/56	– na	– na
	36	– RYGB: 22 (37% [25.04-50.85]) – Med: none	– RYGB: Stop ins n=27/57 Stop med 27/57 – Med: 4/56 none and stop med 13/56	– na	– na
	60	– RYGB: 9 (15% [7.22- 26.99]) – Med: none	– RYGB: Stop ins n=25/57 Stop med 25/57 – Med: 8/56 none and stop med 12/56	– na	– na
Courcoulas *et al.*, 2015 and 2020 (12, 13)	24	– RYGB: 12 (60% [36.05-80.88]) – LAGB: 6 (29% [11.28-52.18]) – Med: none	– RYGB: stop ins na stop med 14/18 – LAGB: stop ins 1/5 stop med 9/20 – Med: stop ins 1/3 stop med none	– RYGB: -1.17+ -0.31 – LAGB: -1.25+ -0.33 – Med: -0.52+ -0.36	– RYGB: -9.19+ -0.72 – LAGB: -5.49+ -0.72 – Med: -1.66+ -0.81
	36	– RYGB: 8 (40% [21.53-69.24]) – LAGB: 6 (29% [11.28-52.18]) – Med: none	– RYGB: stop ins na stop med 13/18 – LAGB: stop ins 1/5 stop med 9/20 – Med: stop ins 1/3 stop med none	– RYGB: -1.42+ -0.34 – LAGB: -0.80+ -0.32 – Med: 0.21+ -0.4	– RYGB: -8.69+ -0.73 – LAGB: -4.97+ -0.69 – Med: -1.60+ -0.81
	60	– RYGB: 6 (30% [19.12-63.95]) – LAGB: 4 (19% [5.45-41.91]) – Med: none	– RYGB: stop ins na stop med 9/16 – LAGB: stop ins 1/5 stop med 9/20	– RYGB: -1.41+ -0.35 – LAGB: -0.77+ -0.33 – Med: 0.45+ -0.39	– RYGB: -8.75+ -0.76 – LAGB: -4.38+ -0.71 – Med: -1.20+ -0.85

Study, year	Follow-up duration (months)	T2DM remission, (N) and remission rate % [confidence interval]	Therapeutic de-escalation	Evolution of HbA_{1c} % (compared to T0)	Evolution off BMI kg/m^2 (compared to T0)
			– Med: stop ins none (+1) stop med none		
Dixon *et al*., 2008 (14)	24	– LAGB: 22 (73% [54.11-87.72]) – Med: 4 (13% [3.76-30.72])	– LAGB: stop ins 1/1 stop med 24/28 – Med: stop ins na; stop med 4/26	– LAGB: -1.81+ -1.24 – Med: -0.36+ -1.26	na
Schauer *et al*., 2014 and 2017 (15, 16)	36	– RYGB: 22 (44% [29.99-58.75]) – SG: 14 (29% [16.58-43.26]) – Med: none	– RYGB: stop ins 19/22 stop med 32/47 – SG: stop ins 18/22 stop med 20/48 – Med: stop ins +1; stop med none	– RYGB: -2.5+ -1.9 – SG: -2.5+ -2.1 – Med: -0.6+ -2.5	na (expressed in kg)
	60	– RYGB: 15 (30% [17.86-44.61]) – SG: 11 (22% [11.77-36.62]) – Med: none	– RYGB: stop ins 17/23 stop med 22/49 – SG: stop ins 16/21 stop med 11/47 – Med: stop ins 5/20; stop med none	– RYGB: -2.1+ -1.8 – SG: -2.1+ -2.3 – Med: -0.3+ -2.0	na
Simonson *et al*., 2018 (17)	24	– RYGB: 7 (37% [16.29-61.64]) – Med: none	– na	RYGB: -1.91 (-2.49 -1.33) Med: -0.32 (-0.99 -0.35)	RYGB: -9.2 (-10.3 -8.0) Med: -1.6 (-2.9 -0.2)
	36	– RYGB: 8 (42% [20.25-66.50]) – Med: none	– na	RYGB: -1.79 (-2.28 -1.20) Med: -0.39 (-1.06 0.28)	RYGB: -8.7 (-10.3 -7.1) Med: -1.8 (-3.5 0.0)
Simonson *et al*., 2019 (18)	24	– LAGB: 3 (13% [2.78-33.59]) – Med: 1 (4% [0.12-22.84])	– na	LAGB: -1.0 (-1.69 -0.31) Med: 0.47 (-1.15 -0.22) ns	LAGB: -4.0 (-5.1 -3.0) Med: -1.6 (-2.6 -6)
	36	– LAGB: 2 (8% [1.07-28.04]) – Med: 1 (4% [0.11-21.95])	– na	LAGB: -0.89 (-1.62 -0.01) Med: 0.23 (-0.57 1.03) ns	LAGB: -3.9 (-5.2 -2.6) Med: -1.7 (-3.0 -4)

Appendix 4. Quality of life and safety results of the clinical trials included in the HAS meta-analysis.

LAGB: laparoscopic adjustable gastric banding; RYGB: Roux-en-Y gastric bypass; SG: Sleeve gastrectomy; Med: Non-surgical, standard pharmacological treatment; na: not available; SAEs: serious adverse events.

Study, year	Follow-up duration (months)	Quality of life score	Quality of life	Safety / AE and SAE
Wentworth *et al.*, 2014 (8)	24	– Short Form-36 questionnaire, physical and mental	– Physical improvement for the surgery group	– 1 stomach enlargement above the band – 4 episodes of food intolerance requiring a reduction in band fluid – 5 unscheduled procedures – No SAEs
Ikramuddin *et al*., 2015, 2016 and 2018 (9-11)	24, 36, 60	– na	– na	– More AEs in the surgery group (10 versus 5) but no SAEs, including under-nutrition, bone fractures, gastrointestinal events in the surgery group
Courcoulas *et al*., 2015 and 2020 (12, 13)	24, 36, 60	– na	– na	– SAEs: RYGB n=1; LAGB n=3, Med n=0. Anastomotic ulcer, over-filling of band, vertigo and hypertension
Dixon *et al*., 2008 (14)	24	– na	– na	– Revision surgery for recalibration of band (5%) and infection on filling port (2%)
Schauer *et al*., 2014 and 2017 (15, 16)	36	– RAND 36-ItemHealth Survey	– Physical improvement for the surgery group: 5/8 item physical and mental for RYGB and 2/8 for SG	– Revision surgery n=4 (RYGB+SG) – SG to RYGB conversion n=1 related to a recurrent fistula
	60	– ditto	– Significant improvement in overall health score of 17 points +- 20/100 for RYGB 16 points ±22/100 for SG versus 0.3±16, for Med	
Simonson *et al*., 2018 (17)	24, 36	– 36-Item Short-Form [SF-36] – Impact of Weight on Quality of Life [IWQOL]	– Significant improvement in quality of life for RYGB with IQWOL score	– SAEs: RYGB n=20 in 11 patients, Med n=7 in 5 patients. Including 6 unscheduled gastrointestinal procedures (cholecystectomy, adhesions, ulceration)

Study, year	Follow-up duration (months)	Quality of life score	Quality of life	Safety / AE and SAE
Simonson *et al*., 2019 (18)	24, 36	– Impact of Weight on Quality of Life (IWQOL) – Problem Areas in Diabetes (PAID),	– No difference	SAEs: LAGB n=15 in 9 patients and Med n=14 in 6 patients LAGB: – 1 band placement error – 2 prolonged hospitalisations (management of glucose levels, reduction in food intake) – 1 conversion to RYGB at 22 months for inadequate weight loss Med: cardiovascular events including one death

Appendix 5. Main meta-analyses .

Figure 5. Relative risk at 24 months of presenting type 2 diabetes remission after surgery, MA No. 1.

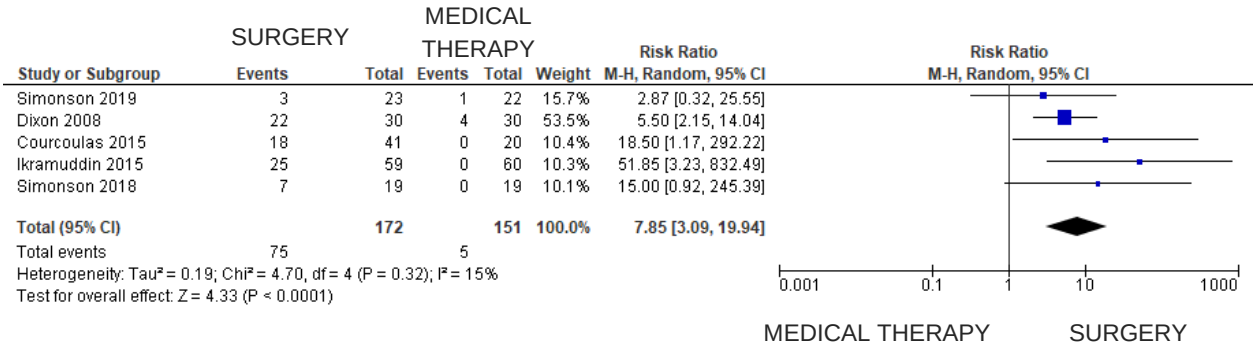
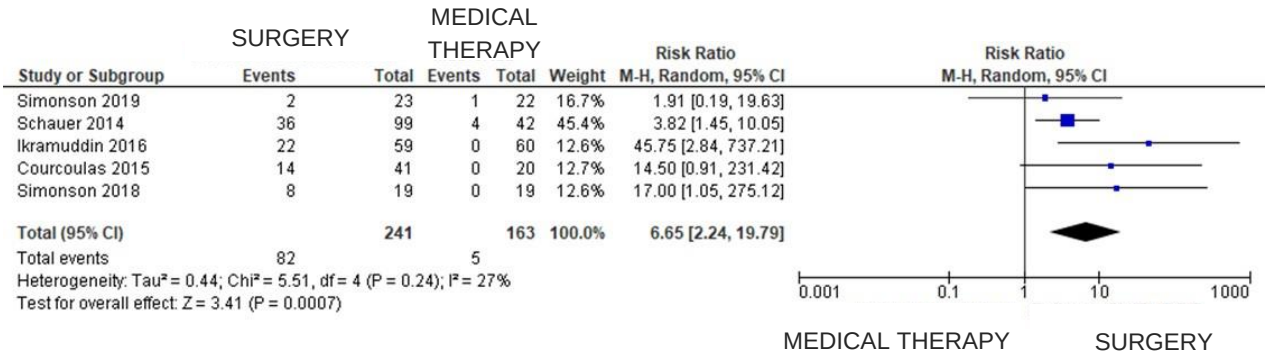


Figure 6. Relative risk at 36 months of presenting type 2 diabetes remission after surgery, MA No. 2.



Appendix 6. Exploratory meta-analyses.

Figure 7. Relative risk at 60 months of presenting type 2 diabetes remission after surgery, MA No. 3.

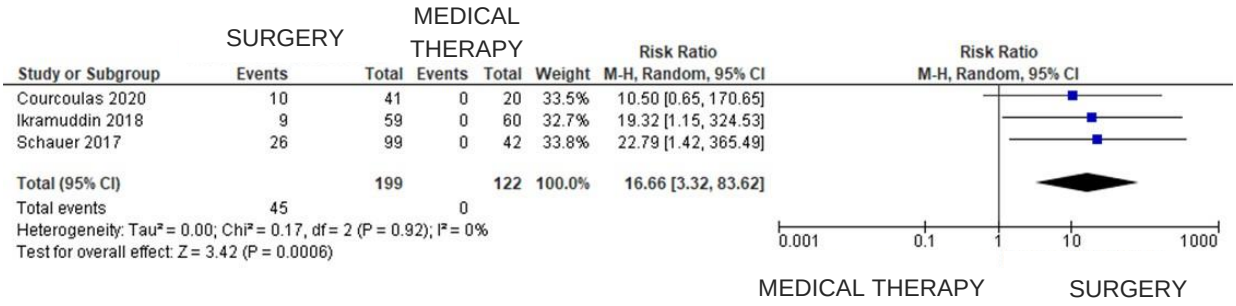


Figure 8. Relative risk at 36 months of presenting type 2 diabetes remission after RYGB, MA No. 4.

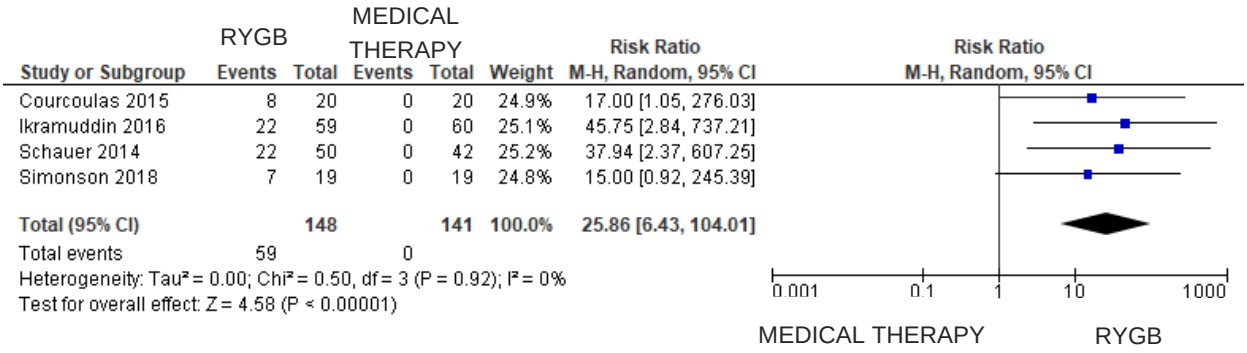


Figure 9. Relative risk at 36 months of presenting type 2 diabetes remission after surgery (with CROSSROAD unpublished data), MA No. 5.

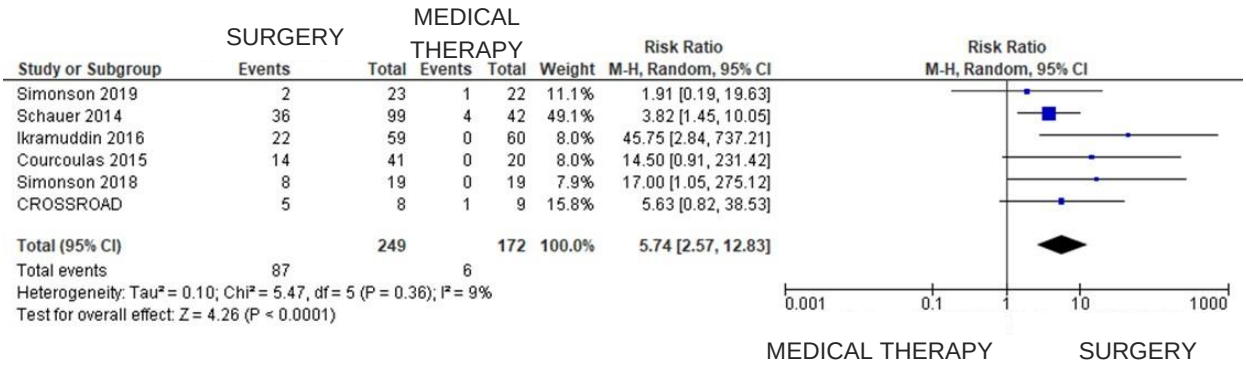
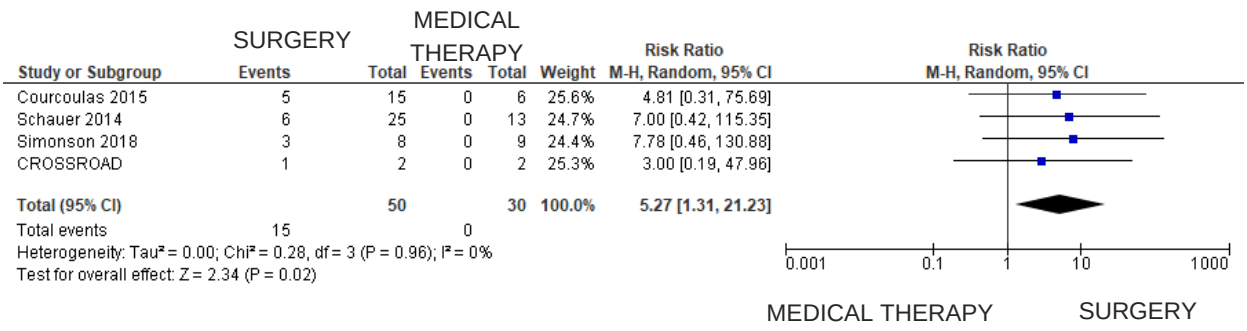


Figure 10. Relative risk at 36 months of presenting type 2 diabetes remission after surgery (with BMI < 35 kg/m² unpublished data), MA No 6.



Appendix 7. Professional bodies and patient associations consulted to obtain expert names.

Table 7. Professional bodies and patient associations that were consulted to obtain expert names.

Specialisations	Body name
General medicine	*Collège de la médecine générale*
Endocrinology, diabetology and nutrition	*Société francophone du diabète* (SFD) and *Association française d'étude et de recherche sur l'obésité* (AFERO), with copy to the *Conseil national professionnel d'endocrinologie, diabétologie, nutrition* (CNP-EDN)
Gastrointestinal surgery	*Société française et francophone de chirurgie de l'obésité et des maladies métaboliques* (SOFFCOMM), with copy to the *Conseil national professionnel de chirurgie viscérale et digestive* (CNP-CVD)
Hepato-gastroenterology	*Conseil national professionnel d'hépato-gastroentérologie* (CNP-HGE)
Psychiatry / psychology	*Conseil national professionnel de psychiatrie* (CNPP) *Fédération française des psychologues et de psychologie* (FFPP)
Nutrition	*Association française des diététiciens nutritionnistes* (AFDN)
Patient and user associations	*Ligue contre l'obésité*, *Fédération française des diabétiques*, *Collectif national des associations d'obèses*

It should be noted that only the CNPP and the FFPP did not provide a list of experts.

Appendix 8. Minutes of the expert group meeting.

MINUTES

Meeting type: Expert group

Title: Metabolic surgery: surgical treatment of type 2 diabetes

Date: 10 May 2022, HAS on-site and remote meeting.

Participants:

- Professor Fabrizio ANDREELLI, Endocrinology, diabetology and nutrition, Paris
- Professor Judith ARON-WISNEWSKY, Endocrinology, diabetology and nutrition, Paris
- Ms Claudine CANALE, patient
- Doctor Jean DU BREUILLAC, General medicine, Thenezay
- Doctor Florence GALTIER, Endocrinology and diabetology, Montpellier
- Doctor Sandrine KAMOUN-ZANA, Digestive surgery, Le Port-Marly
- Professor François PATTOU, Digestive surgery, Lille
- Professor Didier QUILLIOT, Gastroenterology and hepatology, Vandœuvre-les-Nancy
- Professor Maud ROBERT, Digestive surgery, Lyon
- Doctor Brigitte ROCHEREAU, General medicine and Nutrition, Antony
- Mr Alain ROMAN, patient
- Ms Amandine SALEMBIER, Diet-nutrition, Nice
- Professor Geoffroy VANBIERVLIET, Gastroenterology and hepatology and Digestive endoscopy, Nice

Participants for the HAS:

- Doctor Denis-Jean DAVID
- Doctor Jean-Charles LAFARGE

Objective

The objective of the meeting was to collect the personal positions of the experts. This meeting was an opportunity to discuss the data from the literature and the implementation conditions in view of the French context, expressing evidence-based positions concerning efficacy/safety, and the potential indications of metabolic surgery (MS).

Introduction by the HAS

After a brief presentation of the assessment process applied to metabolic surgery, the experts were reminded about the objective of the HAS assessment:

- to assess the benefit-risk balance of MS in the management of type 2 diabetes (T2DM) in patients with a BMI < 35 kg/m^2;
- if applicable, to define the target population as accurately as possible and the relevant techniques;

– to return an opinion on the validity of inclusion of MS on the joint classification of medical procedures (CCAM) list.

Meeting conduct

The main results of the assessment obtained at this stage were presented, i.e. the results of the literature analysis having led to performance of meta-analyses. The questions reported hereafter were sent to the group before the meeting and were used as the basis for debate and discussion during the meeting. The present minutes report the discussions having taken place during this meeting.

Answers to questions

Results of the literature search

L1 **Do you know of any relevant publications that meet the selection criteria but were not included in this work?**

Do you have any remarks concerning the document searches and selections employed?

Do you have any comments concerning the structure, content and legibility of the working document?

One expert mentioned the publication by Horwitz *et al.,* in 2016 (28) reporting T2DM remissions at two years in the target population of the assessment. This is a randomised study registered under NCT No. 01423877, which gave rise to two other publications: Parikh *et al*., in 2014 (29) and Horwitz *et al.,* in 2020 (30). It was identified by the systematic search and excluded from the selection after full reading because the definition of T2DM remission (glucose < 1.26 g/L and < 2 g/L after glucose tolerance test) did not correspond to those retained in the PICOT. However, it should be noted that the results of this study are consistent with those of the other studies included in the HAS MA and are in favour of MS.

The other experts did not know of any RCTs meeting the PICOTS selection criteria not included in the analysis.

One expert reported the existence of two meta-analyses published in 2015: Panunzi *et al.* (31) and Muller-Stich *et al.* (32) These two meta-analyses had been identified by the systematic search and excluded from the selection because they did not incorporate the most recent trials included in the HAS meta-analyses. As a reminder, the meta-analyses cited in the report are from 2019 for Khorgami *et al*. (22) and from 2021 for Cui *et al*. (21).

Different publications concerning national or French health insurance system cohorts were mentioned by the experts. As above, they do not meet the PICOTS literature selection criteria (no data on T2DM remission and not only on the target population) and are therefore not included in the report. All report efficacy results in favour of MS, in particular concerning the reduction of antidiabetic drugs (for example, the publication by Théreaux *et al*.) (33) or the reduction in cancer incidence (for example the publication by Sjöholm *et al*. (34)).

Several experts proposed using the terms “class 1, 2 and 3” to describe the severity of obesity, rather than the terms “moderate, severe and very severe”. The HAS assessment report was modified accordingly.

One expert indicated that the term “Metabolic surgery” does not fully reflect the range of techniques that might be used in the future. He pointed out that ongoing studies are being conducted on the Endosleeve, or duodenal mucosal resurfacing. It is recalled that “Metabolic surgery” is a frequently used generic term that covers surgical techniques and interventional medical procedures (endoscopic). This report is not limited to surgical techniques in the strict sense of the term. The HAS will re-examine this issue following studies (PHRC [Hospital Programme of Clinical Research] or *forfait innovation* [innovation funding]) or following a request for assessment of a professional procedure submitted by a CNP (council of professionals).

Finally, several experts highlighted the clarity and precision of the provisional report.

Content of the assessment

E1

Answer to question 1 of the assessment concerning the clinical benefit of MS in patients with class 1 obesity and type 2 diabetes.

Do you have any comments to make about the HAS meta-analyses (clinical significance of the results, convergence/divergence with your expertise, etc.)?

Do you have any comments to make about the transposability of the results of the HAS meta-analyses to patients with class 1 obesity?

Do you know of any data in favour of a different efficacy of MS in patients with class 1 obesity compared to its efficacy in other obesity classes?

The experts indicated that they had no comments concerning the meta-analyses conducted by the HAS, which reflect the observations they have made, and that the results are consistent with those reported in the available literature on the subject, in particular the literature concerning studies not included in these meta-analyses (see above). They indicated that, for them, these results are clearly in favour of MS.

The experts indicated that remission, as defined to perform the meta-analyses, is a “strong” clinical efficacy outcome measure. However, it must not mask the other benefits of MS, such as therapeutic de-escalation of antidiabetic drugs or improved glycaemic control and, in the longer term, the evolution of micro- and macro-angiopathic complications (prevention of their occurrence/improvement/stabilisation) or weight loss or reduction in other comorbidities. They indicated that a composite outcome measure, incorporating all of these improvements, would have been more relevant. However, there is no consensus in the literature identifying an outcome measure of this type. In addition, the group noted the difficulty in collating data for the other improvements in T2DM (i.e. other than remission), in particular therapeutic de-escalation or improved glycaemic control, since these are reported in a very heterogeneous manner in the different studies.

Several experts pointed out that T2DM is a progressive chronic disease and that any remission or improvements observed may only be temporary. All the experts indicated that T2DM remission following MS is not definitive and is not observed in all patients. Several experts indicated that MS may “gain time” in terms of the natural course of T2DM. They specified that it is imperative that this information be communicated to patients being offered MS. They also indicated that a patient with T2DM and class 1 obesity will not necessarily progress to class 2 or 3 obesity.

The experts did not report any elements suggesting that the improvements in T2DM observed, all obesity classes combined, including T2DM remission, would be different in class 1 obesity. However, they noted that the number of studies and patients in the target population (class 1 obesity and T2DM) is small. One expert indicated that the transposability of the results of studies conducted in the English-speaking world to the French population is only partial due to differences in cardiovascular risk between France and the population in English-speaking countries.

One expert pointed out to the group that the improvement in quality of life in terms of the number of drugs taken each day needs to be put into perspective. In fact, this improvement related to discontinuation of oral antidiabetic drugs needs to be put into perspective in the case of RYGB due to the lifelong requirement to take multivitamins and minerals following this procedure (and the need to take multivitamins and minerals for the first year following surgery in the case of a Sleeve procedure).

E2 **Answer to question 1 of the assessment concerning the safety of MS in patients with class 1 obesity and type 2 diabetes.**

Do you know of any particular safety signals specific to the performance of: LAGB, SG, RYGB in the metabolic surgery indication?

Do you know of any AEs other than those mentioned in the report: "poor filling of the adjustable band", ulceration, fistulas, leaks, intestinal blockage, under-nutrition, fractures, etc.?

Is the excess risk compared to control not likely to counter-balance the uncertain benefit for the target population of MS?

Do you know of a consecutive cohort concerning the safety of metabolic surgery for the target population with follow-up for two years or more?

The experts concerned indicated that the complications observed with MS are the same as for bariatric surgery (BS). They specified that the same precautions concerning poor T2DM control, macro- and micro-angiopathic complications and neuropathies should be taken into account for patients, regardless of their obesity class, to prevent the development of SAEs. Some experts pointed out the importance of preparation and follow-up, in particular to prevent bone fractures in the long term and the worsening of retinopathy in the immediate postoperative period due to the rapid improvement in glucose balance.

No experts reported any safety signals specific to MS which would differentiate it from BS.

The experts consider that the risk of MS is known and similar to that of BS. They indicated that it is acceptable in view of the T2DM improvements and other benefits (i.e. weight loss, reduction of comorbidities, reduction of cancer risk, etc.).

To the experts' knowledge, there is no consecutive cohort concerning the safety of metabolic surgery for the target population with follow-up for two years or more. The available cohorts concern the efficacy of BS and/or MS. They primarily include patients presenting class 2 and 3 obesity, Théreaux *et al*. (33), Sjöholm *et al*. (34) and Carlsson *et al.* (35).

In sum, all the experts consider that the B/R balance of MS for patients with class 1 obesity is favourable.

E3 **Answer to question 2 of the assessment concerning the benefit-risk balance of MS in patients with overweight and type 2 diabetes.**

Do you have any comments about the efficacy, safety, B/R balance of MS for these patients? If the B/R balance is positive, what would the indication be?

All the experts indicated that there is not enough data to reach a conclusion with respect to the B/R balance for MS for patients with overweight. In addition, some experts pointed out that the T2DM of these patients may not have the same characteristics as that of patients with class 1 or more severe obesity.

E4 **Answer to question 3 on the target population of MS.**

It is not possible to identify any factors predictive of the success or failure of MS in the target population of the assessment with the data available. Do you have any comments to make concerning this point?

Do you think that other criteria should be considered or specified to define the target population of MS and, if so, which? (Level of treatment for T2DM, duration, severity of T2DM; other biological markers, peptide C; other criteria: age, etc.).

Is the preoperative assessment, particularly with the anaesthetist, different for patients with moderate obesity potentially eligible for MS from that for patients already eligible for metabolic surgery (severe and morbid obesity)?

All the experts indicated that there are no validated factors predictive of the success or failure of MS within the population of T2DM patients with class 1 obesity.

The experts indicated that glycaemic targets are individualised, and failure of standard T2DM management may be defined as a patient who has not achieved this target despite "changing their lifestyle habits (diet, sedentarism, etc.) and optimised follow-up of pharmacological treatment by a diabetes specialist". Apart from BMI, the criteria for offering MS to a patient with T2DM and class 1 obesity are the same as for patients with T2DM and more severe obesity (class 2 and 3) according to the experts. They specified these criteria, indicating that MS may be offered to patients whose target is met but with a deterioration in quality of life (for example, the occurrence of AEs related to pharmacological treatments); as well as to patients who, despite optimised management by a diabetes specialist, do not achieve their individualised targets.

E5 **Answer to question 4 on the possibility of proposing a preferred technique.**

Data from randomised controlled trials meeting the assessment criteria is only available for three surgical techniques that are already recommended and included in the list of reimbursable treatments: LAGB, SG, RYGB. Based on the available data, it is not possible, however, to propose a preferred surgical technique among the three indicated with a sufficient level of certainty. No data meeting these criteria was found for OAGB, BPD-DS, SADI-Sleeve, SG-TB and Endosleeve. These techniques in the metabolic surgery indication may therefore only be performed currently in the context of clinical trials, after informing the patient, in accordance with article L.1122-1 of the French Public Health Code, enabling the freely-given, informed consent of patients. Do you have any comments to make concerning these points?

The experts consider that there are no elements enabling a preferred surgical technique to be chosen from among LAGB, SG or RYGB, for performance of MS in patients with T2DM and class 1 obesity. In their opinion, all three may be proposed for MS. However, several experts pointed out that there is only one study reporting results following SG and that the efficacy of LAGB in terms of effect size (number of remissions) and T2DM remission duration appears to be more limited than that of RYGB.

Several experts specified that in their routine practice, they look for gastroparesis in the preoperative assessment; and when it is present, they propose an RYGB rather than an SG.

The group indicated that LAGB is a procedure for which use is marginal in France today, primarily due to its limited efficacy in terms of weight loss and improvement of T2DM and the limited maintenance of these benefits over time. However, it specified that since the morbidity of this technique is lower than that for SG and RYBG, LAGB cannot be excluded and may be offered to patients with T2DM and class 1 obesity. It reiterated that ultimately it is up to the patient to choose which procedure they undergo after receiving information on the expected efficacy and risks of each technique.

If MS becomes part of routine care, the entire group recommended that a registry should be kept both to collate efficacy data (T2DM remission, improvement in glycaemic control, therapeutic de-escalation and, in the longer term, evolution of micro- and macro-angiopathic complications) and to carry out vigilance activities (collection of SAEs) for this indication extension and identify any potential factors predictive of a good or less good response to MS.

The experts were not aware of any studies meeting the PICOTS criteria concerning the OAGB, BPD-DS, SADI-Sleeve, SG-TB and Endosleeve techniques. The group agreed that currently these techniques can therefore only be performed in the context of clinical trials in the metabolic surgery indication.

Several experts pointed out that studies are ongoing and they encouraged the HAS to assess these new techniques in the BS or MS indications following publication of the results.

E6 What is the level of agreement with the proposed indication and non-indication for MS drafted at the meeting?

Since the positions of the different members of the group are consistent in terms of the MS indication and the other points covered during the discussion, a short text was drafted collectively during the meeting and submitted for their approval using a Lickert scale (1 strongly disagree to 9 strongly agree).

The text reads as follows: “In view of the data analysed, metabolic surgery may be offered to type 2 diabetes patients with class 1 obesity (BMI of 30 to 35 kg/m^2) when their individualised glycaemic targets have not been achieved despite well-managed medical care, in particular diabetes treatment and nutritional measures, in accordance with current good practice guidelines, for at least six months.

The decision is taken with the patient following discussion at a multidisciplinary team meeting including a diabetes specialist.

LAGB, SG and RYGB procedures may be proposed. At this stage there is no evidence making it possible to favour one of these three techniques over the others.

The contraindications for bariatric surgery and metabolic surgery are the same.”

The vote result is as follows: 13 / 13 votes; mean 8.8; median 9. The group “strongly agrees” with this indication.

Aspects relative to preparation for the procedure

P1 Does patient preparation for MS differ from that for BS? Do they have the same preoperative pathway? How do they differ?

What information does the patient need to make informed choices before the procedure in terms of preparation?

The experts indicated that preparation for MS is identical to that for BS. The group highlighted the need for all patients, irrespective of obesity class, to:

- perform an ophthalmoscopic exam to prevent worsening of retinopathy (which should be treated before surgery if necessary) for all patients with T2DM;
- control the T2DM diabetes during the surgery preparation phase to below an HBa_{1c} level of 9% if possible, in accordance with SFAR guidelines.[24]

The experts indicated that the preoperative assessment, including with the anaesthetist, presents no specificities for T2DM patients with class 1 obesity compared to T2DM patients with class 2 or 3 obesity.

[24] https://sfar.org/gestion-du-patient-diabetique/

However, they emphasised the need for vigilance, as is the case for all T2DM patients, in terms of the management of micro-angiopathy in situations of rapid correction[25] of a severe and chronic imbalance in diabetes (transient acute exacerbation of neuropathies and retinopathies) and, more generally, management of the cardiovascular risk.

It should be noted that, in their practice, for the preparation and follow-up of MS, several experts referred to a consensus conference of 170 French experts and the SOFFCOMM and SFD metabolic surgery study group, published in 2020 by Galtier *et al*. (36).

The group indicated that patients should be provided with information on:

- **the expected benefits** of MS in terms of improvement of T2DM and other comorbidities;
- **its risks**, differentiating these for each of the three techniques (LAGB, SG, RYGB);
- **and its constraints**, particularly in terms of postoperative follow-up, and lifelong follow-up, with nutritional supplements in the case of RYGB.

The group indicated that patients should be informed more specifically that:

- T2DM remissions are observed after three years in 30 to 40% of cases;
- the T2DM remission may not be definitive and patients may require antidiabetic drugs again after several months or years;
- monitoring to identify micro- and macro-angiopathic complications must be continued (although no data is available concerning the frequency of this screening);
- there are benefits other than T2DM remission, such as therapeutic de-escalation, weight loss, resolution of other comorbidities, etc.;
- they will have to undergo lifelong follow-up after surgery.

Overall, the group specified that, in addition to the specific points listed above, patients should receive the same information as that provided for BS.

Aspects relative to performance of the procedure

R1 Do the conditions for performance of the selected techniques present any specificities in the case of the "metabolic" indication compared to the "bariatric" indication? What information does the patient need to make informed choices before the procedure in terms of expected efficacy and the risk of adverse events?

The experts indicated that there are no specific conditions for the performance of these techniques in the metabolic indication compared to the bariatric indication. However, several experts state that, in the case of MS, they adapt the length of the intestinal loops in RYGB in order to reduce the risk of under-nutrition.

[25] "Rapid" glycaemic improvement.

Aspects relative to follow-up

S1 **Could you indicate whether follow-up after metabolic surgery presents any specificities compared to follow-up after bariatric surgery?**

Type of visits, frequency, vitamin supplementation, prevention/identification of adverse events, including under-nutrition, other, etc.

If any specificities emerge, could you indicate the specific place/role of each medical or paramedical player in the management of follow-up after metabolic surgery?

What information does the patient need to make informed choices before the procedure in terms of postoperative follow-up?

The experts indicated that the follow-up for MS is the same as that for BS, i.e. it is identical for patients with T2DM irrespective of their obesity class. They specified that this follow-up must involve a diabetes specialist, even if T2DM remission is obtained. It must include monitoring of HbA_{1c} every six months to one year in the event of T2DM remission or every three months in other cases. In addition, screening for micro- and macro-angiopathic complications must be continued (see answer P1).

Additional remarks

Some experts pointed out that the size of the "potential" target population (T2DM and class 1 obesity) is large, estimated to be around 800,000 people in France (scoping document). However, they specified that it is unlikely that such a large number of metabolic surgeries be performed in the short term. Firstly, they indicated that the healthcare system is not organised to enable both the performance of so many surgical procedures and the lifelong monitoring of these patients. They then indicated, without being able to specify further however, that of these 800,000 patients, only a minority would be eligible for MS (i.e. presenting failure of standard management, see indication above, or presenting AEs to antidiabetic treatments impairing their quality of life). Finally, they indicated that there is likely to be little demand from TDM2 patients with class 1 obesity for MS. They based this statement on their routine clinical practice with diabetic patients with class 2 and 3 obesity and observation of the patient recruitment difficulties encountered in the Diabsurg study.[26]

[26] French randomised study comparing conventional medical management for T2DM with RYGB, in which the primary outcome measure is overall mortality (NCT01501201).

Appendix 9. Lists of bodies consulted as stakeholders.

Table 8. Professional bodies and patient associations that were consulted.

Specialisations	Name of body to be consulted
General medicine	*Collège de la médecine générale*
Endocrinology, diabetology and nutrition	*Société francophone du diabète* (SFD) and *Association française d'étude , et de recherche sur l'obésité* (AFERO), with copy to the *Conseil national professionnel d'endocrinologie, diabétologie, nutrition* (CNP-EDN)
Gastrointestinal surgery	*Société française et francophone de chirurgie de l'obésité et des maladies métaboliques* (SOFFCOMM), with copy to the *Conseil national professionnel de chirurgie viscérale et digestive* (CNP-CVD)
Hepato-gastroenterology	*Conseil national professionnel d'hépato-gastroentérologie* (CNP-HGE)
Psychiatry / psychology	*Conseil national professionnel de psychiatrie* (CNPP) *Fédération française des psychologues et de psychologie* (FFPP)
Nutrition	*Association française des diététiciens nutritionnistes* (AFDN)
Patient and user associations	*Ligue contre l'obésité*, *Fédération française des diabétiques*, *Collectif national des associations d'obèses*

Appendix 10. Stakeholders' responses.

The stakeholders' responses are grouped together for each question.

General view on the provisional version of the assessment report

Q1 **Does your organisation have any comments regarding the clarity of the provisional report sent to it?**

SOFFCOMM *(Société française et francophone de chirurgie de l'obésité et des maladies métaboliques): No comment*

CNP EDN *(Conseil national professionnel d'endocrinologie, diabétologie, nutrition): This report is very clear. No remarks. The report is very clear, including analysis of the published data and obtaining of unpublished data more specifically targeting the population concerned.*

AFDN (*Association française des diététiciens nutritionnistes*)*: The AFDN highlights the clarity and quality of the provisional version of the assessment report.*

CNP HGE *(Conseil national professionnel d'hépato-gastroentérologie)*: None

AFERO *(Association française d'étude et de recherche sur l'obésité)*: *No, it is very clear.*

CMG (*Conseil national professionnel d'hépato-gastroentérologie*)*: The report is clear, particularly as concerns the limitations of the studies used.*

SFD *(Société francophone du diabète): No comments*

CNAO (*Collectif national des associations d'obèses*)*: No comments*

LCO (*Ligue contre l'obésité*)*: The report appears to be very clear in its conclusions: there is a clear trend supporting the use of metabolic surgery to treat T2DM.*

However, the target population to be studied by the mission (adult population without an upper age limit) is not exactly the same as that of the studies used to accomplish this mission, with this population being limited to 55, 60 or 65 years, depending on the study, to meet current criteria for surgery.

Hence, the conclusion should more explicitly include the proposed strategy for the population of T2DM patients over 60 or 65 years of age who are excluded from surgery by the current BS criteria. Since this population is not taken into account by the selected studies or meta-analyses, can we propose, on a case-by-case basis and depending on the clinical context, accepting the performance of metabolic surgery beyond the age of 60 or even 65 years, for example after a regional referral MDT meeting?

Furthermore, the selected studies referenced in this preliminary report concerning "metabolic" surgery generally mention secondary outcome measures, something that does not seem to us to be fully highlighted by the provisional version of the report. Given that these secondary outcome measures are related to the metabolic effects of the proposed surgery for T2DM (apart from the complications specific to diabetes), such as the effects on dyslipidaemia and thyroid disorders, on bone and muscle metabolism, on fatty liver disease, on cardiovascular

and renal functions, do they not require particular investigations specific to metabolic surgery, which the current bariatric surgery guidelines do not currently recommend?

For example, patients report that some teams routinely perform coronary calcium score screening, the value of which seems to be well documented in the current literature, as part of the preoperative assessment for macro-angiopathy. This test would make it possible to eliminate lipid-lowering treatments in patients with a disturbed lipid balance, thereby enabling an appreciable therapeutic de-escalation for the patients. In the context of authorising metabolic surgery, would this test not be necessary to better assess T2DM-related macro-angiopathy? To specify the role of lipid-lowering drugs associated with diabetes, both pre- and postoperatively, taking into account the hoped-for objectives of metabolic surgery which, in the eyes of the patients, cannot be limited to the management of T2DM without taking into account the overall health benefits of surgery?

Also, we will mention in the following questions proposals that did not appear in this preliminary report but which may also echo the latest work published by the HAS, firstly, and which respond to one of the desired objectives of the report, secondly, indicating in particular "the existence of elements of French practice not mentioned in the preliminary report" and that "the organisations consulted are responsible for bringing to the attention of the HAS", in accordance with its request (see scoping letter). We are aware that these additions are likely to raise new questions for the experts on certain points that the preliminary report does not explicitly mention (but which may have already been discussed in the collective working session).

Q2 **Are there, according to your organisation, any relevant publications that would meet the pre-determined selection criteria but have not been taken into account in the report?**

***SOFFCOMM**: No*

***CNP EDN**: No*

***AFDN**: To our knowledge, there are no other relevant publications that would meet the pre-determined selection criteria but have not been taken into account in the report.*

CNP HGE: *I would seem that there was a publication following drafting of the report concerning the efficacy of the EndoSleeve in type 2 diabetes and metabolic syndrome.*

Endoscopic sleeve gastroplasty for treatment of class 1 and 2 obesity (MERIT): a prospective, multicentre, randomised trial. Abu Dayyeh BK, Bazerbachi F, Vargas EJ, Sharaiha RZ, Thompson CC, Thaemert BC, Teixeira AF, Chapman CG, Kumbhari V, Ujiki MB, Ahrens J, Day C; MERIT Study Group, Galvao Neto M, Zundel N, Wilson EB. Lancet. 2022 Aug 6;400(10350):441-451. doi: 10.1016/S0140-6736(22)01280-6. Epub 2022 Jul 28.

AFERO: *No, nothing more in addition to those proposed by the experts.*

***CMG**: No*

SFD: *Not to my knowledge.*

CNAO: *No relevant publications to be added.*

LCO: *The deadline set by the HAS (one week) did not allow us to identify and produce the reference literature for the HAS at this stage.*

Metabolic surgery indication

Q3

The data collected by the report (meta-analysis of published and unpublished data, and individual experts' positions) has made it possible at this stage to propose an indication for metabolic surgery:

"Metabolic surgery may be offered to type 2 diabetes patients with class 1 obesity (BMI of 30 to 35 kg/m^2) when their individualised glycaemic targets have not been achieved despite well-managed medical care, in particular diabetes treatment and nutritional measures, in accordance with current good practice guidelines, for at least six months.

The decision is taken with the patient following discussion at a multidisciplinary team meeting including a diabetes specialist.

LAGB, SG and RYGB procedures may be proposed. At this stage there is no evidence making it possible to favour one of these three techniques over the others.

The contraindications for bariatric surgery and metabolic surgery are the same."

Does your organisation have any comments regarding this draft indication?

SOFFCOMM: *No comments.*

CNP EDN: *In agreement and support these recommendations for discussion at an MDT meeting with the presence of a diabetes specialist. Two comments, however: - There has been recent progress in terms of medical management thanks to the emergence of new therapeutic classes (GLP1 analogues or SGLT2 inhibitors), which should be assessed in this context. - The 6-month period of diabetic medical treatment seems short to me and I would suggest at least one year. The data in the literature does not seem to be sufficient to reach a conclusion. A drug treatment could never be given a favourable opinion with this type of data. What seems surprising is that the primary outcome measure evaluated is remission of diabetes, with the definition of this taking into account the absence of pharmacological treatment. By definition, pharmacological treatment cannot win since, because diabetes is a chronic disease, improvement in glycaemic control necessarily depends on taking the treatment, just as improvement following surgery depends on maintaining the surgical set-up (if the band is removed or the bypass reversed there is little chance that the benefits will persist). So the question is therefore not whether there is remission but whether surgical treatment can control diabetes in people whose diabetes could not be controlled by drug treatment alone, defined by the HbA1c target. However, this is still only an intermediate marker, since the ultimate goal is to reduce morbidity and mortality and not to control HbA1c*

per se. It should also be noted that, contrary to what is stated in the text, the patients in the published studies were not able to have "pharmacological treatment, including the antidiabetic drugs listed in the North American good practice guidelines" as defined in reference 24, this reference dating from 2021 whereas the publication years for the seven referenced studies are 2014, 2015, 2015, 2008, 2014, 2018 and 2019. This is important because there have been major changes in the drug treatments available and especially in their place in the guidelines, with GLP1 analogues and SGLT2 inhibitors having a prominent place in the 2021 guidelines, which was not the case when patients were enrolled in the studies. This is made even more important by the fact that these two classes of drugs have demonstrated significant efficacy in preventing cardiac and renal complications. Studies should therefore compare the efficacy of surgery versus these treatments. As for stating that at this stage there is no evidence making it possible to favour one of these three techniques (LAGB, SG, RYGB) over the others, to me it would seem more honest to say that only the RYGP has sufficient data and that the current data is not sufficient to make a judgement on the Sleeve and the LAGP techniques and that the latter appears to be less effective on weight and remission according to the available data.

***AFDN**: The AFDN proposes that the importance of patients having benefited from multi-professional and coordinated management of their type 2 diabetes (1) before considering metabolic surgery should be highlighted by the following formulation: "[…]* despite well-*managed multi-professional and coordinated medical* care, in particular diabetes *treatment and nutritional measures, in accordance with current good practice guidelines, for at least six months. […]." Reference: Haute Autorité de Santé. CARE PATHWAY GUIDE Type 2 diabetes in adults. March 2014.*

CNP HGE: *None*

AFERO: *- The decision must be taken with a diabetes specialist accustomed to managing diabetes following bariatric surgery. - The information about the effectiveness of SG and especially LAGB must be clear in terms of diabetes remission; even if the studies do not enable a difference to be made, clinical practice shows that these two techniques are less effective and it is very questionable to propose LAGB at present in France (high number of mechanical complications and lower benefit on diabetes than the other techniques).*

***CMG**: It would be pertinent to include patient education in the management.*

SFD: *Yes. It would have been useful to talk about the current GLP1 agonist context, and soon the double agonist context, for example: despite well-managed medical care, in particular diabetes treatment and nutritional measures, INCLUDING THE USE OF GLP1 RA drugs…*

CNAO: *- It is preferable that metabolic surgery be based on the provisions of the latest HAS guidelines on bariatric surgery, bearing in mind that these are currently being updated in 2022. - As a patient association, it seems to us to be indispensable and crucial that patients be properly informed so that they fully understand the surgical process, requiring complete compliance with "imperative lifelong follow-up", vitamin and trace element supplementation, as well as the contraindications. - To this end, patients will need to be followed up within a "community/hospital network", with healthcare professionals able to define the relevant follow-up for patients as close to their home as possible and to exchange information with the hospitals having performed the surgery. - The role and knowledge of the primary care physician is essential, with a specific consultation allocated for follow-up.*

LCO: *It seems to us that the terms "in particular" and "well-managed" are too vague. Following recent publications by the HAS concerning the management of a proportion of the population eligible for BS (class 2 and 3 obesity), pointing out the risks of a restrictive diet in particular and encouraging dietary management based on intuitive eating methods, we question the real superimposability of the nutritional guidelines for patients managed in a diabetic-type pathway and those implemented in BS.*

What are the risks of inconsistency for patients referred following a diabetes pathway to begin a bariatric surgery pathway, if the dietary recommendations are divergent, when moving from one pathway to the other? Bariatric surgery patients who have undergone repeated treatments over many years testify to the negative impact of these successive treatments, which the ANSES report has clearly demonstrated. The specificity of the target population seems to us to require further clarification of the starting point for the management of patients with a view to metabolic surgery: must a BS-type pathway be initiated in order to justify MS, or will the diabetes pathway be taken into account in the proposed delay of at least six months before accessing MS in an uncontrolled T2DM patient? In conclusion, the term "well-managed medical care" seems to us to be inadequate. Some patients mention certain teams using validated scores (Ricci-Gagnon, daily step score evaluated over prolonged periods (at least 14 days at six-month intervals for some teams), which would make it possible to better assess the "physical activity" factor during medical management, and its evolution, of this factor promoting failure or weight regain after BS or of a varying effect on the results of the different surgical techniques (with the latter not having the same repercussions on the patients' muscle mass, moreover). Yet, depending on the teams encountered, patients either do not receive any systematic protein supplementation at all, or they receive supplements whose tolerance (variable) and duration of prescription vary, with some teams, however, systematically supplementing all patients in the postoperative period for several months, regardless of the technique chosen. The mission does not make any specific recommendations for MS: is this a simple symmetry with BS when teams seem to be tending to move in this direction for many patients? An indication concerning this point would be desirable in the final report.

Furthermore, the report does not incorporate the notions of patient education or management using adapted physical education, nor evaluation of the emotional or suggestibility components governing the eating behaviour of patients and constituting the current bases of "well-managed care", as some recent HAS works available on its website have just reminded us (for a proportion of the target population at least). According to patients, different teams use scores such as Yales, TFEQ, GROS score (or others), which are useful for professionals, but also for patients, to identify eating disorders or alcohol use disorders (AUDIT score) These scores would provide data that would make it possible to compare the target population of MS with that of BS (by definition different) and to better identify the factors determining both a susceptibility to recidivism in terms of weight (particularly in the case of induced sarcopenia in a patient with moderate obesity) and that likely to increase the risk of recurrence of T2DM. Would there not be an advantage in making the preoperative assessment even more demanding in the context of metabolic surgery? Let us not forget that the "price to be paid for surgery" - for example in terms of comfort, or even dietary after-effects - tolerable for patients with class 2 and 3 obesity, is, by nature, likely to be more acceptable to these patients than to patients with class 1 obesity already being monitored for T2DM, who will be less tolerant of adverse effects and will therefore need to be very well-informed and carefully selected.

The evaluation of one of the publications taken into account to draft the report does not specify this management, and one of the studies (Courcoulas) actually compares low lifestyle intervention + surgery versus lifestyle intervention, which does not seem to correspond to "well-managed care" as understood by the experts.

However, this remark needs to be weighed up against the interest of this study, which is, in fact, very close to the real-world conditions frequently encountered in clinical practice. This could be mentioned without altering the report's conclusions.

Furthermore, as the methodological choice was based on BARIACT criteria, it is possible that some of the conclusions may be debatable in their current formulation. Only nine out of 35 criteria were retained when this American study was conducted. Yet this study aimed at establishing a minimum common core of data to facilitate the comparison of studies carried out in metabolic or bariatric surgery was conducted in such a way as to only incorporate the results of this surgery at two years. Hence the methodology excluded many warning signals that might appear beyond two years. For example, there not appear to be any particular risk of fracture that attracting the attention of the experts, since these are particularly late complications. And yet, the specificities of patients with class 2 and 3 obesity in terms of bone densitometry are well known and the risk of fracture in BS is well documented (as a result, there is specific vitamin D monitoring and reimbursement in BS, some studies have included measurement of PTH, and some experts have mentioned the possibility of adapting the loop length of some procedures in the context of MS). Thus, some patients mention teams requiring preoperative DEXA body densitometry assessments (superior to impedancemetry) for these reasons, both to avoid exposing future MS patients to a late bone complication, currently impossible to document for MS, and to assess the existence of sarcopenia or its future risk depending on the choice of surgical technique. These two risks cannot be formally excluded in the target population in the event of surgery, particularly in the case of malabsorptive surgery proposed in patients with class 1 obesity.

Moreover, this examination could contraindicate certain patients with osteopenia or sarcopenia, and makes it possible to evaluate the level of energy expenditure (and thus to guide the choice of technique?), and, finally, constitutes an important safety signal in the context of this surgery. This examination could subsequently provide more objective arguments to inform the choice of technique in an individualised manner in this indication, which is a priority for patients, and make them aware of the importance of lifelong follow-up thanks to more concrete information on the late effects of surgery, which the patients currently managed in BC avoid in part.

Moreover, this proposal seems to us to anticipate probable future recommendations for BS, particularly for revision surgery. However, not all T2DM patients will be excluded since the report indicates that the risk of recurrence of T2DM is 30 to 40%, which will eventually lead to a review for a fraction of them.

Thus, by supplementing the assessment required before metabolic surgery, this examination would differentiate between MS and BS in a way that we consider to be justified.

The same feedback from patients with T2DM undergoing a preoperative assessment of BS mentions teams that currently require a Doppler scan of the supra-aortic vessels with measurement of the media intima ratio (a marker of macro-angiopathy that is not unambiguous because it is also linked to smoking, but which makes it possible, in non-smoking patients, to guide the choice of proposed technique based on this marker of the

duration, severity and poor control of the T2DM), and sometimes require a Doppler scan of the renal arteries and assay of micro-albuminuria for example. The choice between ophthalmoscopy or retinal imaging does not appear to determine the choice of procedure, but it assesses micro-angiopathy and is already included in the current guidelines in BS. Other investigations may be required depending on the diabetes complications observed (Doppler scan of lower limbs, etc.).

We note that in cases of severe retinopathy, ophthalmological treatment and sometimes two-stage surgery are sometimes discussed in order not to induce too abrupt a change in blood glucose levels.

What is the opinion of the mission on the relevance of these investigations, or the specific situations in which they may be required? Numerous patients testify to the heterogeneity of current BS management, in particular the lack of information concerning ophthalmoscopy within 3 to 6 months postoperatively. This seems to us to be an opportunity to clarify these points on the occasion of a new authorisation in the context of T2DM. What does the mission think?

Finally, in the context of MS for the treatment of T2DM, it seems to us necessary to more explicitly specify the methods recommended for screening for NASH due to its association with situations of insulin resistance. In fact, the target population is not comparable to that for BS, since it only involves patients with T2DM. Since the severity of NASH has an impact on the choice of the proposed technique, we think it advisable to ask the experts again about the systematic recommendation of the NAFLD score, the FIB 4 score, and the place of a fibroscan or a percutaneous liver biopsy preoperatively depending on the context.

The contraindications for bariatric surgery and metabolic surgery are the same." If the previous comments are validated, body densitometry by DEXA could contraindicate (at least relatively) some patients, since we believe it can be a safety signal for patients.

Q4 **In the indication as formulated above, can your organisation propose an estimation of the size of the target population in France?**

As a reminder, the population of T2DM patients with class 1 obesity has been estimated to be 1.2 million people in France (see scoping document, page 5), but it has not been possible to estimate the proportion of patients meeting the above indication (Q3: individualised glycaemic targets not achieved, etc.)

***SOFFCOMM**: Difficult to estimate because beyond these recommendations based on scientific evidence, this proportion will also depend on the perception by the patients concerned, who are not severely obese, of the balance between the benefits of surgical treatment and the risks and constraints associated with this (see page 58).*

***CNP EDN**: Any answer could only be an estimation, not based on any concrete data. The expansion of the therapeutic arsenal in the management of type 2 diabetes in recent years will very probably reduce the number of patients who do not achieve their individualised glycaemic targets, especially in the early years of diabetes. We can emphasise that there is likely to be little demand for MS among the type 2 diabetes patients we treat in clinical practice*

(given the recruitment difficulties encountered in some interventional research protocols and the media coverage of surgery oriented towards severe obesity), with the possible exception of the BMI range closest to class 2 obesity, i.e. patients with BMIs between 34 and 35 kg/m^2 who are seeking to lose weight and/or patients with other complications of their obesity that may benefit from surgery such as OSA requiring appliance therapy, severe osteoarthritis of the knee, etc.

***AFDN**: The AFDN is unable to provide an estimate of the size of the target population in France.*

CNP HGE: *It is difficult for the CNP-HGE to provide such a proportional assessment, since it depends entirely on the indication, which in turn depends on the diabetic follow-up (de facto the diabetes specialist and not the gastroenterologist) and the response rate to well-managed care over the first six months. It is likely that 10 to 25% of the described population would be eligible but that after preoperative assessment and clear information, no more than 5 to 10% of this patient population would opt for metabolic surgery.*

AFERO: *No estimation currently possible for the number of T2DM patients with class 1 obesity in whom treatment has failed.*

***CMG**: No*

SFD: *Once again, the contribution of dual agonists will doubtless limit the size of the target population. Studies are ongoing…*

CNAO: *- According to the Ministry for Health and Prevention, in France in 2019, nearly 4 million people had type 2 diabetes. Published on 7 March 2022 by the Ministry. 93% of type 2 diabetics, all individuals having taken an antidiabetic drug, 3.720 million people affected. - Growth rate in type 2 diabetes of 3.5% per year.*

LCO: *This estimation is particularly complex, as it will depend, in particular, on the perception of surgery by the patients concerned, by endocrinologists and diabetes specialists, on the recent arrival of new medical therapies for T2DM, and on the extension of their use to certain types of obesity, which is likely to disrupt the decision tree for treatment using MS and BS. As approximately 5% of the BS target population actually undergo BS, an approximate sample size of candidates could be similar. However, the drawbacks of surgery could reduce this sample (price to pay for surgery considered to be too high for some patients). Or, on the contrary, the number of surgeries could be increased because the level of recognition by the authorities and the perception of the condition as a chronic progressive relapsing disease by patients, the general public AND by the medical profession is stronger for diabetes than for obesity. For this reason, the surgical option could appear to be a "naturally accepted" outcome in a diabetes decision tree, whereas recourse to BS is more complicated due to the lack of recognition of the disease and its reimbursement by the authorities. From the patient's perspective, therefore, the notion of fairness of treatment is a notion that will be weighed up between the need not to deprive certain uncontrolled T2DM patients of surgical treatment in a context of reimbursement of diabetes-related care, and, in parallel, difficulties in accessing the same type of treatment for patients with a much higher BMI who do not have T2DM. This essential element for patients must be highlighted.*

Q5 **In the indication as formulated above, can your organisation give an opinion on the capacity of the care system (bariatric/metabolic surgery), as currently organised in France, to enable the preparation, implementation and lifelong follow-up of patients with class 1 obesity and T2DM who undergo MS?**

It will be recalled that the experts estimated that only a fraction of patients meeting the indication would actually undergo the surgery in the short term (see page 58 of the report).

***SOFFCOMM**: The current care system will have the capacity to meet this new demand.*

***CNP EDN**: The current system is not organised to enable follow-up of the patients if there were to be a significant increase in the number of surgeries performed per year, taking into account MS in accordance with these guidelines. However, a significant increase seems unlikely. From 2007 to 2008, 93% of type 2 diabetes patients in France were cared for by general practitioners, very few of whom are trained in postoperative follow-up*. In the case of class 2 or 3 obesity complicated by diabetes, in clinical practice few general practitioners refer their patients for bariatric surgery with the potential improvement/remission of diabetes in mind but rather for the indication of weight loss. Hence, patients falling within the scope of the proposed MS indication would mainly be patients cared for by a diabetes specialist. Current endocrinology, diabetes and nutrition medical residents undergo training in nutrition as part of their programme, but this is recent. *Jaffiol C. Current management of type 2 diabetes in France. Bull Acad Natl Med 2009;193(7):1645-61.*

Current experience of the follow-up of patients who have undergone bariatric surgery shows the difficulties of long-term follow-up: few centres follow up patients beyond the second year after their surgery. Additional resources in terms of trained professionals will be necessary to ensure follow-up of these patients. Reference: French National Academy of Surgery report, Report following expert meeting on patient follow-up following bariatric surgery, 30 January 2015. Preparation and implementation should not be very different to what happens for obesity surgery. As far as follow-up is concerned, we can also suspect that the same thing will happen, with many people lost to follow-up, i.e. also not undergoing screening for complications (recommended even in case of remission), including in the event of recurrence. Drug treatment makes it necessary to maintain contact with the medical profession.

***AFDN**: In France, the number of bariatric surgeries performed per year increased from 12,800 in 2005 to 31,000 in 2011 (1) and has stabilised at around 45,000 since 2014 (47,084 in 2014 (2), 46,654 in 2018 (3)). In this context, the bariatric surgery care system could face difficulties for the preparation, implementation and, in particular, lifelong follow-up of patients. It is conceivable that these difficulties could also be encountered in the context of metabolic surgery. It seems necessary to anticipate the medium- and long-term care needs of these patients. For example, the system could rely more on the paramedical professions, particularly dieticians (4,5), to support patients and provide local care. References:*

1. *Lazzati A, Guy-Lachuer R, Delaunay V, Szwarcensztein K, Azoulay D. Bariatric surgery trends in France: 2005-2011. Surg Obes Relat Dis. 2014 Mar 1;10(2):328–34.*
2. *Debs T, Petrucciani N, Kassir R, Iannelli A, Amor I Ben, Gugenheim J. Trends of bariatric surgery in France during the last 10 years: analysis of 267,466 procedures from 2005–2014. Surg Obes Relat Dis. 2016 Sep 1;12(8):1602–9.*
3. *Angrisani L, Santonicola A, Iovino P, Ramos A, Shikora S, Kow L. Bariatric Surgery Survey 2018: Similarities and Disparities Among the 5 IFSO Chapters. Obes Surg. 2021 Jan 12;1–12.*

4. *Osland E, Powlesland H, Guthrie T, Lewis C-A, Memon MA. Micronutrient management following bariatric surgery: the role of the dietitian in the postoperative period. Ann Transl Med. 2020 Mar;8(S1):S9–S9.*
5. *Kulick D, Hark L, Deen D. The Bariatric Surgery Patient: A Growing Role for Registered Dietitians. J Am Diet Assoc. 2010 Apr;110(4):593–9.*

CNP HGE: *The CNP-HGE considers that the hepato-gastroenterology sector in France is capable of managing these patients, within the scope of its expertise (performance of endoscopic, hepatologic and other pre-treatment assessments). It cannot comment on the capacity of other sectors but it seems that nutritional care (physician, dietician, nutritional education) is likely to suffer from a lack of human resources due to the increase in the number of patients to be cared for.*

AFERO: *In fact, currently, the follow-up of bariatric surgery patients in France is very inadequate; it is difficult to see how this cohort of metabolic surgery patients can be properly followed up unless the care system is significantly reinforced...*

***CMG**: As with BS, the involvement of the primary care physician from the very start of the decision-making process and through to follow-up is essential.*

SFD: *The concern is long-term nutritional follow-up, which patients often give up on (data for patients undergoing surgery for class 2 and 3 obesity).*

CNAO: *- As indicated in the answer to Q3, it seems to me that the following aspects are essential: => excellent preparation for surgery, - => Obviously, the appropriate surgical procedure, with the patient's informed consent, - Full understanding by patients of the perioperative and medium- and long-term benefits/risks of their surgery, - Acceptance of patients regarding lifelong compliance, - the resources allocated for postoperative follow-up: community/hospital, with healthcare professionals with complete knowledge of the disease and bariatric/metabolic surgery, and with validated and relevant training in this specific patient follow-up. - In addition, the number of patients eligible for this surgical option is largely underestimated, given the damage done by the various COVID lockdowns, as well as the current economic crisis.*

LCO: *We believe that a reflection process on dissemination on a "case by case" or "centre by centre" basis is necessary to authorise surgery according to criteria that are more complex than those currently used in BS. It could be proposed that specialised obesity centres, regional diabetes reference centres and patient associations work together on a specific mission and propose a list of approved centres to regional health agencies in order to address the requirements of the population on the basis of its needs rather than on the basis of the available care provision. We also mention that certain BS teams have determined the figures for their activity from the outset based on a mathematical model which scales their care offer according to the medical team's capacity, in order to best guarantee the lifelong follow-up required in the context of BS. It would appear to be relevant to take into account this type of organisation (or others) with a view to authorisation of MS. In our opinion, the current observations concerning postoperative follow-up in BS strongly encourage this type of reflection, given the difficulty of estimating the size of the target population for MS.*

Performance conditions and patient information

Q6

The data collated by the report (meta-analysis of published and unpublished data, and individual experts' positions) has made it possible at this stage to propose the following conclusion:

"The preparation, performance and follow-up of MS for T2DM patients with class 1 obesity are the same as for BS for T2DM patients with class 2 or 3 obesity".

Does your organisation have any comments regarding preparation for MS, its performance and its follow-up, as proposed?

***SOFFCOMM**: No remarks.*

***CNP EDN**: It is probably necessary to add that the diabetes assessment should also be up to date, especially with regard to ophthalmological follow-up. Preparation should include diabetes-specific aspects, in particular information on potential complications. Follow-up should be specific to diabetes, with annual investigations to detect any microvascular complications.*

***AFDN**: The AFDN is in favour of this proposal and has no comments on the preparation, performance and follow-up of metabolic surgery insofar as it is proposed that it be the same as for bariatric surgery.*

CNP HGE: *None – The conclusion is well-founded, valid and essential. In agreement with this proposal. Emphasising, as did the expert group, the importance of screening and prior management of proliferative diabetic retinopathy.*

It is worth mentioning the possibility of adding investigation for gastroparesis (in the patient's history, in particular if diabetes has been diagnosed for more than 10 years and/or in the event of glycaemic variability; and if symptoms are evident by performing a radiological examination, i.e. scintigraphy) in order not to overlook it in the event of exacerbation. There is little data, and relative to small sample sizes only, in the literature concerning the performance of SG and RYGB in patients presenting diabetic gastroparesis. They seem to be relatively suggestive of an improvement in symptoms after RYGB. Only one study is available for SG**. To my knowledge there are none concerning LAGB which, conceptually, would not appear to be a good indication in this context.*

AFERO: *Yes, it should be the same as that for BS, but the diabetes complications assessment must be up-to-date, particularly at ophthalmological level, to avoid any potential exacerbation in the event of diabetic retinopathy.*

***CMG**: No comments.*

SFD: *No*

CNAO: *We agree entirely that metabolic surgery should be based on the HAS guidelines and on its guidelines for bariatric surgery, which are currently being updated. - Without forgetting, or not, the absolute necessity for local follow-up involving several healthcare professionals*

hinged around the patient, the primary care physician, the medical analysis laboratory, nutrition, physical activity, psychiatrist or psychologist, etc.

LCO: *All the above comments would encourage us to change these points, without compromising the interest of patients, in order to be able to access MS, in line with the conclusions of the report.*

We would like to question the mission, in view of the preceding remarks, about the relevance of densitometric follow-up at 2 and 5 years (which is carried out by certain teams in BS), with more frequent follow-up sometimes being observed (certain specialised obesity centres, mostly in the context of studies). We would like to question the mission about the relevance of identical follow-up, in particular concerning the endoscopic follow-up currently recommended for the detection of Barrett's oesophagus, which does not appear to be as relevant in patients with class 1 obesity: is it really necessary to propose the same type of follow-up to a target population which is different to that of BS in reality? We would like to question the mission about the relevance of the HOMA score and QUICKI test in the context of postoperative follow-up because the objective is T2DM remission for the majority of patients but the risk of diabetes recurrence is high (30-40%). Would these tools enable earlier detection of recurrences? A more effective modification of the therapeutic strategy for these patients? Are other tools available in this respect?

Q7 **The data collated by the report (meta-analysis of published and unpublished data, and individual experts' positions) has made it possible at this stage to propose the following conclusion:**

"Patients should be provided information on:

- **the expected benefits of MS in terms of improvement of T2DM and other comorbidities;**
- **its risks, differentiating these for each of the three techniques (LAGB, SG, RYGB);**
- **and its constraints, particularly in terms of postoperative follow-up, and lifelong follow-up, with nutritional supplements in the case of RYGB.**

Patients should be more specifically informed that:

- **T2DM remissions are observed after three years in 30 to 40% of cases;**
- **the T2DM remission may not be definitive and patients may require antidiabetic drugs again after several months or years;**
- **monitoring to identify micro- and macro-angiopathic complications must be continued (although no data is available concerning the frequency of this screening);**
- **there are benefits other than T2DM remission, such as therapeutic de-escalation, weight loss, resolution of other comorbidities, etc.;**
- **they will have to undergo and adhere to lifelong follow-up after surgery.**

In addition to the specific points listed above, patients should receive the same information as that provided for BS".

Does your organisation have any comments on the information to be communicated to patients, based on this proposal?

SOFFCOMM*: No comments concerning the points indicated above. A clarification, however, concerning information to be provided to patients about the three techniques: Although there are no specific studies comparing these three techniques in patients with class 1 obesity, several good-quality controlled studies in patients with class ≥2 obesity indicate that Roux-en-Y gastric bypass generally achieves superior and more prolonged metabolic results than sleeve gastrectomy and/or adjustable gastric banding, at the cost of a slightly higher risk of postoperative complications. Thereaux et al. JAMA Surg 2018. doi:10.1001/jamasurg.2017.6163 Thereaux et al. Lancet Diabetes Endocrinology 2019. doi.org/10.1016/S2213-8587(19)30191-3*

CNP EDN*: No particular remarks concerning the report. Reflection: There may be an unresolved question concerning informing the patient about the potential maintenance of SGLT2 inhibitors after the surgical procedure despite remission of diabetes when their indication lies mainly in their renal and cardiovascular protective effect.*

AFDN*: The AFDN is in favour of this proposal and has no comments on the information to be communicated to patients insofar as the patients will have to receive the information indicated below, including the same information as that given for bariatric surgery.*

CNP HGE: *None – The CNP-HGE is in full agreement with the information proposed above.*

AFERO: *- Nutritional supplements are not only reserved for RYGB; I would say nutritional supplements are essential after RYGB but also for other surgical techniques, with adaptation to postoperative nutritional laboratory assessments. - Details are missing here about the risks of operating on patients who do not have severe obesity and who do not necessarily want to lose weight: - Patients must be warned about the risk of eating difficulties after bariatric surgery, which can lead to excessive weight loss in patients whose obesity is not severe; - Patients must be warned about the possible repercussions of weight loss (psychological, skin effects, fatigue, etc.), especially if they do not want to lose weight, since the improvement in terms of glycaemic control may be cancelled out by a deterioration in their overall health.*

***CMG**: Indicate to patients that nutrition and physical activity remain essential treatments.*

SFD*: That dual agonists will soon be available and represent a possible alternative to MS.*

CNAO*: Patients should be provided information on: The expected benefits of metabolic surgery in relation to their type 2 diabetes, as well as the need for their commitment and compliance in terms of their future behaviour, in order to optimise their results.*

Patients must have a good understanding - and this must be achieved in several stages - of the specificities generated by the different bariatric surgery techniques, which they will potentially face during their lifetime. The duties and obligations of follow-up after surgery. Patients must be informed that surgery will not have a miraculous effect if they do not make a lifelong commitment.

LCO: *It seems to us that there is an error - "remission in 30 to 40%", whereas the report mentions 22 to 60% depending on the studies - and that this should be recurrences? Our remarks would follow on from all the comments made in the previous questions.*

FREE COMMENTS

Q8 Does your organisation have any remarks concerning the provisional version of the assessment report?

***SOFFCOMM**: No remarks.*

***CNP EDN**: While convinced of the value of metabolic surgery, it does not seem that the data presented in this report can enable clear conclusions to be drawn. Is the issue of remission the right one when it comes to diabetes management? The studies do not take into account current treatments and guidelines for diabetes. The data presented in the report is relatively short term, and new therapeutic classes for the management of diabetes are promising. Metabolic surgery could be an additional tool as long as it is properly supervised.*

***AFDN**: The study by Conte et. Al, (1) concerning data from the French National health data system (SNDS) appears to be interesting in the context of this assessment report, although it is does not meet the pre-defined selection criteria. This study is in line with the conclusions of the provisional report, demonstrating, in patients who have undergone bariatric surgery and who do not only have class 1 obesity, a diabetes remission rate of approximately 50% in the postoperative period, with 90% of patients discontinuing treatment within 9 to 13 months after surgery. It should be noted that this study indicates a relapse for 13 to 20% of patients*

within 10 years. The authors analysed the remission factors and demonstrated an advantage of gastric bypass over sleeve gastrectomy (more remissions and fewer relapses). Reference: Conte C, Lapeyre-Mestre M, Hanaire H, Ritz P. Diabetes Remission and Relapse After Bariatric Surgery: a Nationwide Population-Based Study. Obes Surg. 2020 Dec;30(12):4810-4820. doi: 10.1007/s11695-020-04924-3. Epub 2020 Aug 31. PMID: 32869127.

CNP HGE: None

AFERO: *This conclusion is based on data from the literature that does not use the new treatments that have become available in recent months and which are generally more effective in controlling blood glucose. In addition, the outcome measure of the studies is diabetes remission and not improvement of glycaemic control, which can be obtained, in particular, with the new treatments, hence the superiority of surgery compared to drug treatments each time. Finally, the risks of the impact of this surgery in patients whose obesity is not severe must be clearly detailed.*

***CMG**: No*

CNAO*: The opinion of the CNAO is favourable provided that the above-mentioned points are implemented in the interest of the population and patients. The need for management of food processing and production, as well as its advertising. - It is also important to highlight that at this time, obesity is still not part of the initial training of any healthcare professional, and we cannot help but question the quality and relevance of patient care provided by healthcare professionals who are not trained in our disease and even less in bariatric surgery. - It is also necessary to consider and put into perspective future drug projects in the field of type 2 diabetes. - In view of the unfortunate increase in obesity of all classes, we need to find solutions to protect the population as much as possible from chronic diseases, as well as epidemics such as COVID-19. As you know better than I do, obesity causes 18 associated diseases, COVID-19. We need to protect our young audiences as much as possible: children, adolescents and young adults, from the catastrophic increase in obesity and diabetes.*

LCO: *Concerning follow-up, we suggest that a genuine Personalized Care Plan, drawn up in accordance with models already tried and tested by some teams and intended for the primary care physician, the diabetes specialist and the patient, should be attached to MDT meeting conclusions, thus responding to the expected challenge of the management of a relapsing progressive chronic disease (T2DM). Following the example of oncology, a detailed care plan, which would be just as justified for BS as for MS, would seem to us to be a useful tool for patients and general practitioners to guide the management of patients in the post-operative period, and thus promote real and effective lifelong follow-up. The patients' perspective must guide the approach of supervisory bodies when taking into account the patients' interests: in terms of both geographical and financial access to care, the differentiated approach of supervisory bodies and the different perceptions of these two relapsing progressive chronic diseases - T2DM and obesity - despite the fact that they are interrelated, justifies an approach modulated by the representatives of patient associations, and would justify the support of supervisory bodies. MS seems to us to be an essential opportunity for access to a therapeutic proposal that patients should benefit from. It seems to us to be an opportunity to be pioneers in terms of proposals for future updates in BS.*

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- *Conseil national professionnel d'hépato-gastroentérologie* (CNP-HGE)
- *Association française des diététiciens nutritionnistes* (AFDN)
- *Conseil national professionnel de psychiatrie* (CNPP)
- *Fédération française des psychologues et de psychologie* (FFPP)
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Abbreviations and acronyms

BP-DS	*Biliopancreatic diversion with duodenal switch*
BS	Bariatric surgery
MS	Metabolic surgery
T2DM	Type 2 diabetes
HbA1c	Glycated haemoglobin
BMI	Body mass index
LAGB	Laparoscopic adjustable gastric banding
OAGB	One-anastomosis gastric bypass or omega-loop bypass
SADI-Sleeve	Single-anastomosis duodeno-ileal bypass with sleeve gastrectomy
SG-TB	Sleeve gastrectomy with transit bipartition

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