

Cardiovascular Outcome Evidence in ANVISA Approved Professional Prescribing Information for SGLT2 Inhibitors

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Abstract

Background

Sodium–glucose cotransporter-2 (SGLT2) inhibitors have demonstrated cardiovascular and renal benefits in cardiovascular outcome trials (CVOTs), but the extent to which these findings are represented in official regulatory prescribing information is unclear. Objective: To characterize the cardiovascular outcome information reported in ANVISA-approved professional prescribing information for SGLT2 inhibitors and examine its correspondence with evidence from landmark CVOTs.

Methods

A descriptive document analysis evaluated the most recent ANVISA-approved professional prescribing information available on 25 April 2026 for empagliflozin, dapagliflozin, and canagliflozin. Cardiovascular information was assessed using a predefined framework covering three-point major adverse cardiovascular events (MACE), quantitative reporting, clarity, correspondence with relevant CVOT evidence, and therapeutic context.

Results

Cardiovascular outcome reporting varied across the three documents. The empagliflozin document included quantitative cardiovascular outcome information and all three components of three-point MACE. The dapagliflozin document emphasized heart-failure and renal outcomes and provided limited information on individual MACE components. The canagliflozin document did not provide quantitative cardiovascular outcome estimates.

Conclusion

The evaluated ANVISA-approved professional prescribing information differed in the extent and type of cardiovascular outcome evidence communicated. These findings support further evaluation of how clinically relevant evidence is translated into regulatory drug information.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is one of the most prevalent chronic diseases worldwide and represents a major public health challenge because of its rising prevalence, substantial healthcare costs, and long-term complications (GBD 2021 Diabetes Collaborators, 2023). Individuals with T2DM are at markedly increased risk of cardiovascular disease (CVD), including coronary artery disease, stroke, heart failure, and cardiovascular death, making CVD a major determinant of morbidity and premature mortality in this population (Marx et al., 2023; Joseph et al., 2022). Consequently, the management of T2DM has

evolved beyond glycaemic control to encompass cardiovascular and renal risk reduction, with the aim of improving long-term clinical outcomes, quality of life, and survival (Chan et al., 2026).

This paradigm shift was driven by growing recognition that improvements in glycaemic control alone did not consistently translate into reductions in major cardiovascular events. While the United Kingdom Prospective Diabetes Study (UKPDS) demonstrated the long-term benefits of intensive glycaemic control, subsequent large randomized trials, including ACCORD and ADVANCE, highlighted the limitations of glycated haemoglobin (HbA1c) reduction as a surrogate for cardiovascular protection and underscored the need to evaluate clinically meaningful cardiovascular outcomes directly (UKPDS Group, 1998; ACCORD Study Group, 2008; ADVANCE Collaborative Group, 2008). Concerns regarding the cardiovascular safety of rosiglitazone further intensified scrutiny of glucose-lowering therapies and prompted a major shift in regulatory expectations. As discussed by Goldfine (2008), these developments emphasized the need for dedicated assessment of cardiovascular safety rather than relying solely on glycaemic efficacy. In response, the U.S. Food and Drug Administration (FDA) issued its December 2008 Guidance for Industry, requiring that new glucose-lowering therapies demonstrate cardiovascular safety through dedicated cardiovascular outcome trials (CVOTs), initially to establish cardiovascular non-inferiority before approval (U.S. Food and Drug Administration, 2008; Goldfine, 2008). Similar regulatory expectations were subsequently adopted by other agencies, including the European Medicines Agency (EMA) and the Brazilian Health Regulatory Agency (ANVISA). Consequently, the evaluation of glucose-lowering therapies evolved from an exclusive focus on HbA1c reduction toward the assessment of clinically meaningful outcomes such as cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, hospitalization for heart failure, and progression of chronic kidney disease (Cefalu et al., 2018).

Among the therapeutic advances emerging from this regulatory framework, sodium–glucose cotransporter-2 (SGLT2) inhibitors have become important agents in the management of T2DM. Beyond their glucose-lowering effects through inhibition of renal glucose reabsorption (Vallon, 2015), these agents exert multiple effects involving hemodynamic status, cardiac metabolism, inflammation, and renal function that may contribute to cardiovascular and kidney benefits (Cowie & Fisher, 2020).

However, the cardiovascular effects of SGLT2 inhibitors vary according to the specific clinical outcome evaluated. The EMPA-REG OUTCOME trial demonstrated that empagliflozin reduced cardiovascular mortality, all-cause mortality, and hospitalization for heart failure in patients with T2DM and established cardiovascular disease (Zinman et al., 2015). Similarly, the CANVAS Program showed a significant reduction in major adverse cardiovascular events (MACE) with canagliflozin among patients with T2DM at high cardiovascular risk (Neal et al., 2017). In contrast, the DECLARE–TIMI 58 trial confirmed the cardiovascular safety of dapagliflozin but did not demonstrate a statistically significant reduction in MACE; its main cardiovascular benefit was a reduction in hospitalization for heart failure, together with favorable effects on renal outcomes (Wiviott et al., 2019).

Subsequent meta-analyses have demonstrated that, although effects on atherosclerotic cardiovascular outcomes such as MACE differ according to trial population and baseline cardiovascular risk, SGLT2

inhibitors consistently reduce hospitalization for heart failure and slow chronic kidney disease progression (Zelniker et al., 2019). Accordingly, contemporary guidelines, including the American Diabetes Association Standards of Care in Diabetes 2026 and the European Society of Cardiology Guidelines for the Management of Cardiovascular Disease in Patients with Diabetes (2023), recommend the use of SGLT2 inhibitors in individuals with T2DM and established cardiovascular disease, heart failure, chronic kidney disease, or elevated cardiovascular risk, independent of baseline HbA1c when clinically appropriate (ADA, 2026; Marx et al., 2023).

The rapid expansion of evidence supporting cardiovascular and renal benefits has broadened the therapeutic role of SGLT2 inhibitors beyond glycaemic control. However, the clinical usefulness of this evidence also depends on how relevant findings are communicated in official regulatory prescribing information. Professional prescribing information approved by national regulatory authorities is an important source of standardized technical information for healthcare professionals and supports prescribing, dispensing, counselling, and pharmacovigilance (Raynor et al., 2007; Ramírez-Telles & Argotti-Rodríguez, 2022). In Brazil, ANVISA regulates the content and updating of medicine package inserts. Consequently, characterization of the cardiovascular evidence communicated in these documents is relevant to regulatory science and evidence translation.

Despite the growing body of evidence supporting cardiovascular effects of SGLT2 inhibitors, limited attention has been directed toward how these findings are represented in regulatory prescribing documents. Previous studies of medicine information documents have frequently focused on readability, comprehensibility, and usability rather than on the correspondence between high-quality clinical evidence and official regulatory information (Pires et al., 2015). It therefore remains relevant to examine whether professional prescribing information reports major cardiovascular outcomes, describes cardiovascular benefits with sufficient clinical context, and reflects the principal findings of landmark CVOTs. This study addresses that question through a focused analysis of the professional prescribing information available from ANVISA for three SGLT2 inhibitors.

The study was designed to characterize how cardiovascular evidence from landmark CVOTs is represented in ANVISA-approved professional prescribing information for SGLT2 inhibitors, using three-point MACE as a standardized reference framework while also considering other clinically relevant cardiovascular and renal outcomes.

OBJECTIVE

To characterize the presence, completeness, quantitative detail, clinical context, and correspondence with landmark cardiovascular outcome trial evidence of cardiovascular information reported in ANVISA-approved professional prescribing information for SGLT2 inhibitors, using three-point MACE as a standardized evaluation framework.

MATERIALS AND METHODS

Study Design

This is a descriptive, document-based cross-sectional study of ANVISA-approved professional prescribing information for SGLT2 inhibitors. The study did not evaluate the clinical efficacy or comparative effectiveness of the medicines themselves. Instead, it examined how cardiovascular outcome evidence was represented in official regulatory documents. A predefined framework was used to assess reporting of major adverse cardiovascular events (MACE), quantitative detail, clarity, correspondence with relevant CVOT evidence, and therapeutic context.

Data Source and Study Sample

The data source consisted of ANVISA-approved professional prescribing information available through the official ANVISA Electronic Drug Information Database (Bulário Eletrônico: <https://consultas.anvisa.gov.br/#/bulario/>). Documents were retrieved on 25 April 2026 using the Portuguese generic names of SGLT2 inhibitors with active marketing authorization in Brazil.

The database was searched using the “Nome do Princípio Ativo” field. The search terms were “empagliflozina”, “dapagliflozina”, and “canagliflozina”. No additional filters were applied during the initial retrieval. Retrieved records were manually screened to confirm the active ingredient, document type, ANVISA approval status, and availability of professional prescribing information. For each active ingredient, the most recent ANVISA-approved version available on the date of data collection was selected. Each selected document was downloaded in PDF format and archived for extraction and verification.

The marketing authorization status of each active ingredient was verified through the ANVISA database on 25 April 2026. The unit of analysis was the most recent professional prescribing information available for each active ingredient. Three documents were therefore included: empagliflozin, dapagliflozin, and canagliflozin. Their revision dates were 26 March 2026, 12 December 2025, and 27 October 2025, respectively.

Because the analysis selected one current professional prescribing document for each eligible active ingredient, the study should be interpreted as an analysis of the selected regulatory documents rather than a census of every commercial product or every professional prescribing information containing these active ingredients. Duplicate records, obsolete or superseded versions, documents that did not correspond to ANVISA-approved professional prescribing information, and documents associated with products without active marketing authorization were excluded.

Data Extraction

A structured extraction form was developed specifically for the study. For each professional prescribing document, the following information was systematically recorded:

1. presence of cardiovascular outcome information;
2. reporting of individual components of major adverse cardiovascular events (MACE);
3. depth of cardiovascular outcome reporting (qualitative or quantitative);
4. clarity and accessibility of the information presented;
5. consistency between professional prescribing information and evidence generated by landmark CVOTs; and
6. therapeutic context in which cardiovascular benefits were described (e.g., type 2 diabetes mellitus, established cardiovascular disease, heart failure, or chronic kidney disease).

The predefined extraction domains and scoring criteria were applied consistently across the three documents. Correspondence with landmark CVOTs was assessed by comparing statements and outcome information in the regulatory documents with the published results of the relevant trials. The extraction variables are summarized in Table 2, and the operational definitions and point allocation for each scoring domain are presented in Table 1.

Table 1
Structured evaluation framework (0–10 points)

Domain	Evaluation criteria	Score
Three-point MACE components	None (0); one component (1); two components (2); all three components (3)	0–3
Depth of information	None (0); qualitative description (1); quantitative reporting of cardiovascular outcomes (2)	0–2
Clarity and accessibility	Unclear (0); partially clear (1); clear and easily interpretable (2)	0–2
Evidence alignment with landmark CVOTs	No evidence of alignment in the reported information (0); partially aligned (1); fully aligned (2)	0–2
Therapeutic context	Cardiovascular benefits appropriately contextualized (1); absent or insufficient (0)	0–1

Table 2
Data Extraction Variables

Domain	Description
Presence of cardiovascular outcome information	Whether cardiovascular outcomes, including individual three-point MACE components, are reported
Depth of reporting	Qualitative versus quantitative reporting of cardiovascular outcomes
Clarity	Ease of interpretation and accessibility of the reported information
Evidence alignment	Correspondence between the reported information and relevant cardiovascular outcome trials
Clinical context	Therapeutic population and clinical context in which cardiovascular outcomes are presented (e.g., high cardiovascular risk, heart failure, CKD)

As the study used only publicly available regulatory documents and did not involve human participants, identifiable personal data, or interaction with individuals, ethical approval was not required.

Justification for the MACE Framework

Three-point major adverse cardiovascular events (MACE) cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke were selected as the principal standardized framework because this composite endpoint has been widely used in regulatory cardiovascular outcome trials of glucose-lowering therapies. The framework provides a consistent basis for examining whether these three outcomes are explicitly represented in professional prescribing information.

However, MACE does not encompass the full spectrum of cardiovascular and renal benefits associated with SGLT2 inhibitors. In particular, the major SGLT2 inhibitor trials differed in populations, primary endpoints, and treatment effects, and several clinically important findings concern hospitalization for heart failure and renal outcomes rather than three-point MACE. Therefore, MACE was used as an analytical reference rather than as a definition of overall therapeutic benefit or regulatory adequacy.

Development of the Scoring Framework

Because no validated instrument was identified for assessing the translation of cardiovascular outcome evidence into regulatory prescribing information, a structured evaluation framework was developed specifically for this exploratory document analysis. The framework was intended to make the assessment transparent and reproducible; it was not presented as a psychometrically validated quality instrument.

The scoring domains were specified a priori from characteristics considered relevant to evidence-based regulatory communication and informed by landmark CVOT evidence, regulatory prescribing principles, and clinical decision-making. Five complementary domains were evaluated:

1. completeness of reporting of the three MACE components;
2. depth of cardiovascular information provided;
3. clarity and accessibility of the information;
4. consistency with evidence generated by landmark CVOTs; and
5. description of the therapeutic context in which cardiovascular benefits were presented.

Each domain reflects a distinct dimension of information quality considered relevant for clinicians interpreting official prescribing information.

Scoring Procedure

Each professional prescribing document received an overall score from 0 to 10 points according to the predefined criteria shown in Table 1. Higher scores indicate that more of the predefined reporting criteria were met; the score should not be interpreted as a validated measure of overall regulatory quality.

Table 1. **Structured evaluation framework for cardiovascular outcome reporting in ANVISA-approved professional prescribing information (0–10 points).**

Note

The score is a study-specific descriptive measure of the predefined reporting criteria and is not a validated measure of overall regulatory quality or clinical efficacy/safety.

The maximum possible score was 10 points. Scores were used descriptively to summarize the extent to which each document met the study-specific reporting criteria.

DATA ANALYSIS

Descriptive analysis was performed using frequencies, percentages, and the study-specific overall scores. Because only three documents were evaluated, no inferential statistical analysis was undertaken.

A structured evaluation framework based on three-point MACE was used as the primary reference standard. Cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke were assessed individually and collectively. Each document was then evaluated against the predefined five-domain scoring framework described in Table 1. Data extraction variables are described in Table 2, while the characteristics of the evaluated documents and the domain-level results are presented in Tables 3 and 4.

Table 3
Characteristics of the evaluated professional prescribing documents and cardiovascular outcome reporting

Characteristic	Result
Number of professional prescribing documents evaluated	3
SGLT2 inhibitors	empagliflozin, dapagliflozin, canagliflozin
Professional prescribing documents reporting any cardiovascular outcome	2 (66.7%)
Professional prescribing documents reporting all three three-point MACE components (cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke)	1 (33.3%)
Professional prescribing documents providing quantitative cardiovascular outcome data	1 (33.3%)
Professional prescribing documents with no cardiovascular outcome information	1 (33.3%)

Table 4
Domain-level evaluation of cardiovascular outcome reporting in the evaluated professional prescribing documents

Professional prescribing information	MACE components reported	Depth	Clarity	Evidence alignment with CVOTs	Therapeutic context	Total score (0–10)
empagliflozin	Complete (3/3)	Quantitative	Clear	Full	Present	10
dapagliflozin	Partial (1/3)	Qualitative	Clear	Partial	Present	6
canagliflozin	None	None	Clear	No evidence of alignment	Absent	2

Table 2. Data extraction variables used to assess cardiovascular outcome information in ANVISA-approved professional prescribing information.

Study workflow

Figure 1

RESULTS

Three ANVISA-approved professional prescribing documents corresponding to empagliflozin, dapagliflozin, and canagliflozin were included. These represented the most recent available document

for each active ingredient on 25 April 2026.

Cardiovascular outcome reporting varied across the three professional prescribing documents (Tables 3 and 4). Two documents (66.7%) reported at least one cardiovascular outcome, whereas one (33.3%) reported all three components of three-point MACE. Quantitative cardiovascular outcome estimates were identified in one document, while the canagliflozin document did not provide quantitative cardiovascular outcome estimates.

Table 3. Characteristics of the evaluated ANVISA-approved professional prescribing documents and cardiovascular outcome information identified.

Table 4. Domain-level evaluation of cardiovascular outcome reporting in the evaluated professional prescribing documents

Note

A score of 0 for evidence alignment indicates that no evidence of alignment could be established from the reported content; it does not imply that the underlying clinical evidence was contradicted.

The empagliflozin professional prescribing information included quantitative cardiovascular outcome information and reported the three components of three-point MACE. Its cardiovascular outcome information was broadly consistent with the principal findings of EMPA-REG OUTCOME, including reductions in cardiovascular death and hospitalization for heart failure (Zinman et al., 2015).

The dapagliflozin professional prescribing information emphasized heart-failure and renal outcomes and provided limited reporting of the individual components of three-point MACE. This pattern is compatible with the outcome profile of DECLARE–TIMI 58, in which dapagliflozin demonstrated cardiovascular safety and reduced the composite of cardiovascular death or hospitalization for heart failure, without a statistically significant reduction in three-point MACE (Wiviott et al., 2019).

The canagliflozin professional prescribing information did not provide quantitative cardiovascular outcome estimates. The absence of quantitative reporting was classified as non-reporting rather than as evidence of contradiction with the CANVAS Program.

Overall, one document (33.3%) reported all three components of three-point MACE, while two documents (66.7%) reported cardiovascular outcomes incompletely or did not provide quantitative cardiovascular outcome estimates. The differences concerned not only whether cardiovascular outcomes were mentioned, but also the level of quantitative detail, the outcomes emphasized, and the clinical context in which benefits were presented.

The comparative description indicates substantial variation in how cardiovascular outcome evidence was represented in the three ANVISA-approved professional prescribing documents. These differences

should be interpreted as variation in regulatory information content and emphasis, rather than as a ranking of the clinical efficacy or safety of the medicines.

DISCUSSION

This study identified substantial variation in the representation of cardiovascular outcome evidence in ANVISA-approved professional prescribing information for empagliflozin, dapagliflozin, and canagliflozin. The differences involved the completeness of three-point MACE reporting, quantitative presentation, the cardiovascular outcomes emphasized, and the clinical context provided. Because the analysis concerned regulatory documents rather than patient outcomes, the findings describe information translation and should not be interpreted as evidence that one SGLT2 inhibitor is clinically superior to another.

The empagliflozin document contained quantitative cardiovascular outcome information and all three components of three-point MACE, corresponding closely to the principal cardiovascular findings of EMPA-REG OUTCOME (Zinman et al., 2015). The dapagliflozin document placed greater emphasis on heart-failure and renal outcomes and contained limited information on individual MACE components. This is not necessarily a deficiency, because DECLARE–TIMI 58 did not demonstrate a statistically significant reduction in three-point MACE; its clinically important findings included cardiovascular safety and reductions in heart-failure-related outcomes (Wiviott et al., 2019). The canagliflozin document did not provide quantitative cardiovascular outcome estimates. Importantly, absence of an outcome from a regulatory document should be distinguished from a statement that contradicts the corresponding clinical trial.

The therapeutic role of SGLT2 inhibitors has also evolved since the publication of the first diabetes-focused CVOTs. Subsequent trials demonstrated benefits of dapagliflozin and empagliflozin in patients with heart failure, including populations with and without diabetes (McMurray et al., 2019; Packer et al., 2020). Meta-analytic evidence has further supported cardiovascular and renal benefits across the class, although the magnitude and composition of benefit vary by population and endpoint (Zelniker et al., 2019; Vaduganathan et al., 2022). These developments reinforce the importance of describing cardiovascular evidence in its appropriate clinical context rather than relying on a single composite endpoint.

The findings are relevant to regulatory science because professional prescribing information is an official source of technical information for healthcare professionals. However, regulatory prescribing documents are not intended to reproduce the complete clinical evidence base. The appropriate question is therefore not whether a leaflet contains every result from a CVOT, but whether the information it provides is accurate, clinically contextualized, and sufficient for the regulatory purpose for which it is intended. Future assessments should consider both the completeness of reporting and the appropriateness of the outcomes selected for inclusion.

Interpretation of differences among the three documents requires caution because the pivotal CVOTs enrolled different populations and evaluated different primary and secondary endpoints. Consequently, direct comparison of the amount or type of cardiovascular information across medicines does not constitute a comparison of their clinical effectiveness. The present study instead compares the characteristics of the regulatory information itself.

An important strength of the study is the use of a transparent, predefined framework to examine the translation of cardiovascular outcome evidence into regulatory prescribing information. The analysis also used the most recent documents available on a specified date and compared them with published landmark CVOT results. Nevertheless, the scoring framework was developed for this study and has not been externally validated. Its value is therefore primarily exploratory and descriptive.

The findings may inform future research and regulatory discussions about the communication of clinically meaningful cardiovascular evidence. Rather than implying that every regulatory document should reproduce the full CVOT evidence base, the results support consideration of consistent principles for reporting clinically important outcomes, quantitative estimates when appropriate, and sufficient therapeutic context. Such principles could improve transparency and facilitate interpretation of regulatory information by healthcare professionals.

Several limitations should be considered. First, the analysis included only three SGLT2 inhibitor active ingredients available in Brazil on the data-collection date, limiting the breadth of generalization. Second, one current professional prescribing document was analyzed for each active ingredient; the study therefore does not describe variation among all commercial products or historical versions. Third, the scoring framework was developed specifically for this study and was not a validated measurement instrument. Fourth, the original extraction and scoring were performed by one reviewer, which may have introduced subjectivity, particularly for domains such as clarity and correspondence with clinical evidence. Finally, regulatory documents and clinical evidence are time-dependent; subsequent revisions or new trials may change the observed correspondence. These limitations support interpreting the findings as an exploratory regulatory document analysis rather than as evidence of systematic inadequacy across ANVISA prescribing information.

CONCLUSION

This study identified substantial variation in the cardiovascular outcome information communicated in the evaluated ANVISA-approved professional prescribing documents for SGLT2 inhibitors. The documents differed in the completeness of three-point MACE reporting, quantitative detail, outcomes emphasized, and therapeutic context. The findings illustrate how evidence from landmark CVOTs may be represented differently in regulatory prescribing information.

Because the study evaluated regulatory documents rather than clinical outcomes, the observed differences should not be interpreted as differences in the clinical efficacy or safety of the medicines. In particular, non-reporting of a specific outcome was distinguished from contradiction of clinical evidence.

Future regulatory-science studies could evaluate broader therapeutic classes, multiple regulatory jurisdictions, successive versions of prescribing information, and independently assessed reporting frameworks. Systematic approaches to communicating clinically relevant cardiovascular and renal outcomes may improve the transparency and clinical usefulness of regulatory drug information while preserving the specific purpose and scope of official prescribing documents.

Declarations

1. Clinical Trial Number

Clinical trial number: not applicable.

This study was a descriptive, document-based analysis of publicly available regulatory prescribing information and did not constitute a clinical trial.

2. Ethics and Consent to Participate

Ethics and Consent to Participate declarations: not applicable.

The study used only publicly available regulatory documents and did not involve human participants, identifiable personal data, participant interaction, or intervention.

3. Consent to Publish

Consent to Publish declaration: not applicable.

The study did not involve individual participant data or identifiable individual information requiring consent for publication.

4. Data Availability Statement

The data supporting the findings of this study were obtained from the publicly accessible ANVISA Electronic Drug Information Database (Bulário Eletrônico). The healthcare professional electronic package inserts analyzed in this study are available on the official ANVISA website at: <https://consultas.anvisa.gov.br/#/bulario/>.

The extracted data and structured evaluation framework used in the analysis are available from the corresponding author upon reasonable request.

5. Author Contributions

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All authors reviewed and approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

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7. Competing Interests

The authors declare that they have no competing interests.

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Figures

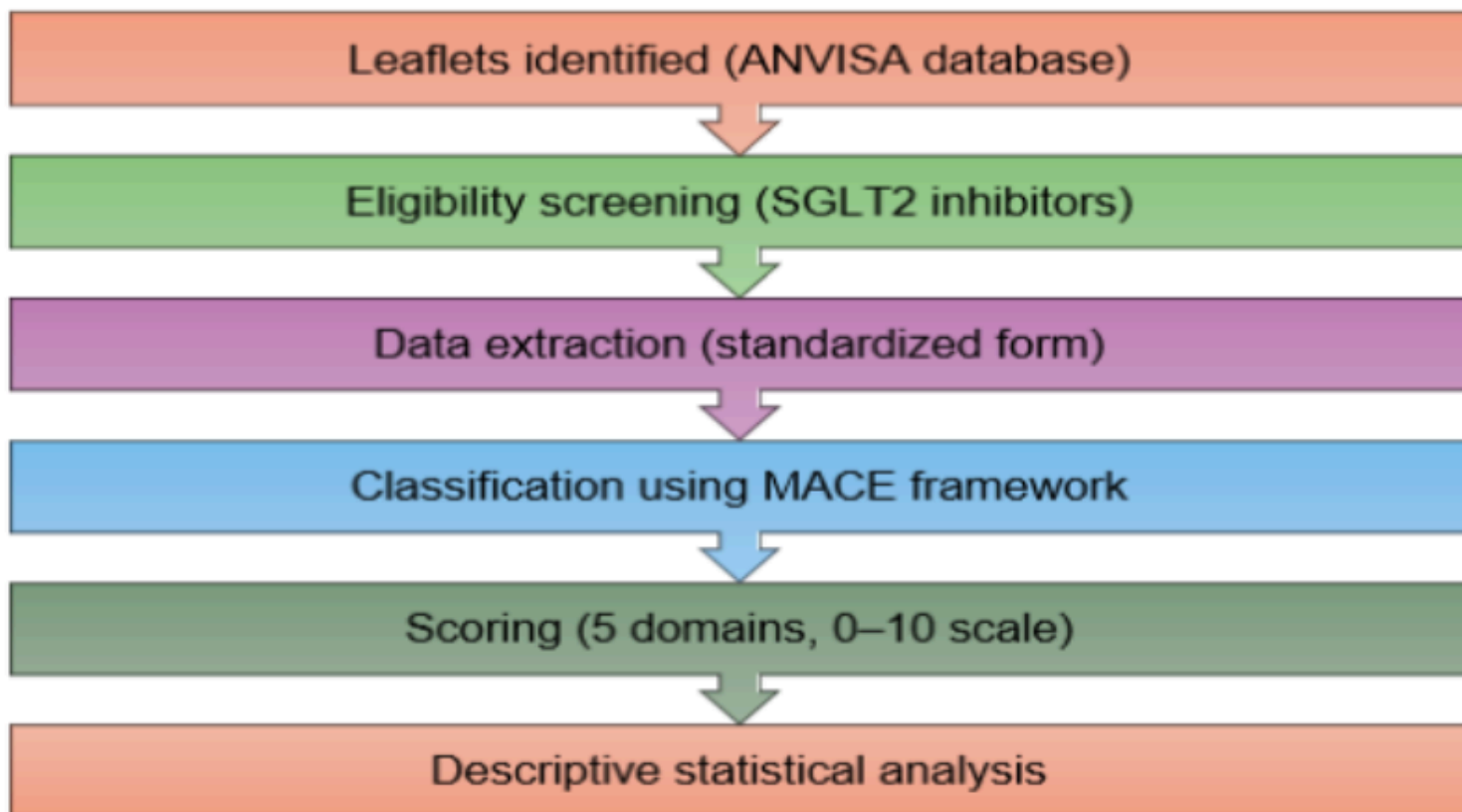


Figure 1

Study workflow for identification, selection, and evaluation of ANVISA-approved professional prescribing information.