Quantifying heterogeneity within and between treatment guidelines for type 2 diabetes: Potential implications for EU-wide health technology assessment

Nick Fabrin Nielsen[1]; Barnaby Hunt[2]; Samuel JP Malkin[2]; Sanaz Gabery[1]; Annabel Acs[1]

HTA57

Aim

- By 2030, the European Union (EU) will require manufacturers to submit a Joint Clinical Assessment (JCA) dossier for new therapies, aiming to harmonize health technology assessment (HTA) across the EU.
- This will require all 27 member states to define relevant PICO (population, intervention, comparator, outcome) requirements.
- In type 2 diabetes, step-wise intensification is often required to maintain glycemic control, with recommendations at each therapy line creating branched treatment pathways.
- This review seeks to quantify the heterogeneity in managing type 2 diabetes in EU guidelines and the implications for the JCA process.

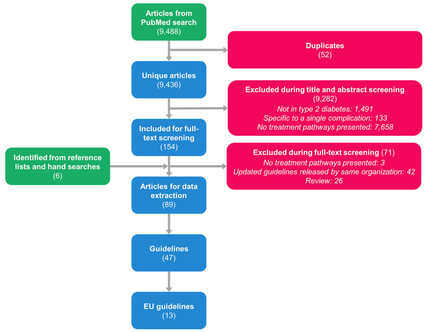
Introduction

- Healthcare systems worldwide are coming under increasing pressure, with budgets becoming tightened due to global economic factors and as populations grow and become more elderly.[1]
- HTA of novel interventions is therefore useful and often mandatory to evaluate whether a new medication or medical device is considered value for money.
- The EU JCA is designed to capture different member states' requirements such as the definition of standard of care (comparator treatments) and clinical outcome preferences, thereby mitigating redundant activities and benefitting countries which do not have established HTA expertise or infrastructure.[2]
- However, the joint process could result in a mandated increase in clinical evidence generation due to differences between EU-level and member-state-level requirements, which could lead to delays in accessing novel interventions, particularly for diseases with a wide range of therapy options.
- Type 2 diabetes is a complex and progressive disease with a variety of available treatment options, with more traditional therapies such as metformin, sulfonylureas and insulins supplemented with modern medication classes, including dipeptidyl peptidase-4 (DPP-4) inhibitors, sodium-glucose cotransporter-2 (SGLT-2) inhibitors, and glucagon-like peptide-1 (GLP-1) receptor agonists, which are all associated with different benefits.[3]
- To simplify and collate these options, countries and diabetes organizations often publish treatment guidelines to help guide decision making for physicians, patients, and healthcare payers.
- These guidelines often recommend classes of therapies in specific populations and sequences and/or places in the treatment algorithm, which can indicate relevant subgroups and comparator therapies for EU member states.
- This review of published guidelines across the EU seeks to quantify the potential complexity of evaluating a novel intervention for type 2 diabetes under the new JCA process.

Methods

- A systematic literature review was performed in the PubMed and guideline-specific databases, designed to identify clinical guidelines that described sequential treatment pathways worldwide.
- Searches were performed in May 2021 and limited to publications published from 2016 onwards, to ensure that all publications reflected modern treatment guidelines of type 2 diabetes.
- Publications were excluded if they were not in populations with type 2 diabetes, if they were specific to a single diabetes-related complication, or if no sequential treatment pathways were presented.
- Data extraction was based on pre-defined criteria to capture each treatment pathway (including treatments initiated and discontinued at each step and reasons for treatment intensification), the agency/body recommending the pathway, and the characteristics of the population or subgroup.
- A treatment pathway was defined as two or more sequential recommendations of therapy (e.g., metformin followed by sulfonylurea), while guidelines were defined through the utilized search terms and whether they contained clear sequential treatment pathways.
- Extracted pathways were screened for uniqueness, with duplicates combined and the number of guidelines recommending each pathway noted – a unique pathway was defined as containing a unique sequence of therapies at each line.
- Following data extraction, pathways were limited to those from guidelines published for member countries of the EU.

Figure 1: Literature search flow diagram

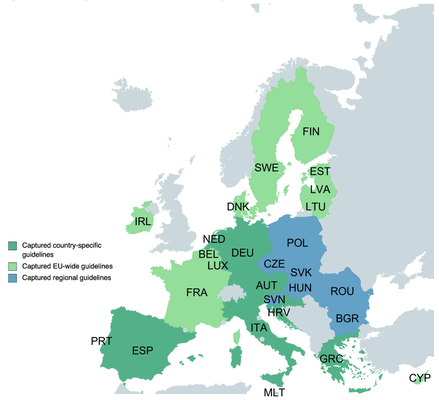


EU, European Union.

Results

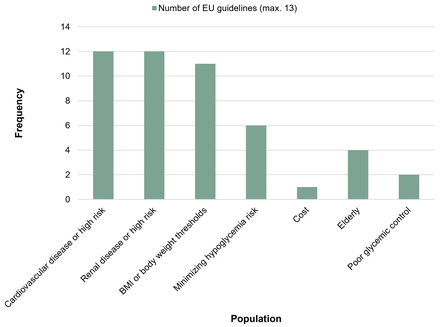
- A total of 47 publications were taken forward for data extraction, of which 13 EU-specific guidelines were identified (Figure 1).
- Country-specific guidelines were identified for eight EU countries, with captured regional guidelines published by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD), the Central and Eastern European Diabetes Expert Group (CEE DEG), the European Renal Association (ERA) and the European Dialysis and Transplantation Association (EDTA), the European Society of Cardiology (ESC) and the EASD, and Primary Care Diabetes Europe (Figure 2).
- Captured guidelines recommended treatment pathways for seven subgroups of people with type 2 diabetes (Figure 3).
- A total of 463 non-unique pathways were identified from EU-specific clinical guidelines, of which 427 were evaluated as unique, covering up to seven lines of therapy (Figure 4).
- The most common pathway, specified in five EU guidelines, was first-line therapy with metformin, followed by second-line therapy with an SGLT-2 inhibitor, third-line therapy with a GLP-1 receptor agonist, and fourth-line therapy with basal insulin.

Figure 2: Map of EU countries captured in the review



Countries are colored hierarchically: light green applies to all EU countries, based on EU-wide guidelines; blue applies to countries that also had published regional-specific guidelines; dark green applies to countries that also had published country-specific guidelines. EU, European Union.

Figure 3: Guideline-reported populations



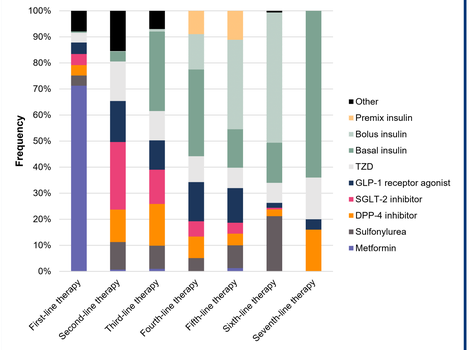
BMI, body mass index; EU, European Union.

- Recommendations were consistent for first-line therapy, with metformin specified in over 70% of pathways, while second- and third-line therapy varied more, with no single treatment option recommended in more than 26% of pathways (Figure 4).
- The diversity of recommendations led to several medications, including GLP-1 receptor agonists, DPP-4 inhibitors, TZDs, and basal insulin, being indicated at every position in the pathway.
- However, overlap between guidelines in terms of unique pathways was minimal, with the largest number of shared pathways (16) found in guidelines published by the ADA/EASD and the ESC/EASD, and most guidelines sharing no unique pathways.

Discussion

- Clinical guidelines for type 2 diabetes in the EU have overlap, but present substantial differences to overcome when defining the scope of a JCA.
- More than six specialized populations were specified across the captured EU guidelines (Figure 3).
- Guidelines differed substantially in the recommended pathways, with 427 unique pathways extracted and some medications recommended at almost every line of therapy (Figure 4).
- This indicates the potential for different comparisons in terms of comparators and patient populations, as prior type 2 diabetes medications and different baseline characteristics can influence outcomes when receiving a new intervention.
- Generation of appropriate clinical evidence satisfying each member state's criteria under the JCA process therefore currently appears challenging.

Figure 4: Proportion of therapy use by treatment line



The number of unique pathways decreased as lines of therapy increased: first- and second-line captured 427 pathways, third-line 426, fourth-line 412, fifth-line 332, sixth-line 156, and seventh-line 25. DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; SGLT-2, sodium-glucose cotransporter-2.

- Country-specific requirements for health economic analyses of type 2 diabetes interventions should also be considered.
- Healthcare budgets and willingness-to-pay thresholds in each member state vary, and the JCA may have to balance these aspects without going over scope.
- Harmonizing relevant PICO criteria as part of clinical evidence generation for multiple countries or a unified HTA process could be difficult, given that each member state has different criteria for reimbursement and populations where specific medications are recommended (Figure 3).

Conclusion

- Consolidating country-specific clinical evidence requirements for evaluation of novel interventions for type 2 diabetes could be challenging in an EU-wide JCA, evidenced by the current heterogeneity in treatment guidelines.
- This could lead to potentially complex evidence generation needs and delays in reimbursement of efficacious medications.
- Collaboration between regulators, healthcare professional associations and patient organizations to mitigate complexity could represent a strategy to successfully implement the JCA process for type 2 diabetes interventions.

[1]Novo Nordisk A/S, Søborg, Denmark; [2]Ossian Health Economics and Communications, Basel, Switzerland
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References:
(**1**) Verelst et al. Eurosurveillance. 2020; (**2**) EUnetHTA. Joint Clinical Assessment (JCA). 2021. Available at: https://www.eunethta.eu/jca/; (**3**) Davies et al. Diabetes Care. 2022;45(11):2753–86