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Factors Influencing the Prescription of First-Line Treatment for Type 2 Diabetes Mellitus: A Systematic Review

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Abstract

Background/Objectives: Understanding prescribing patterns for type 2 diabetes mellitus, a complex condition affecting over 10% of the global adult population, can optimise prescribing practices, guide policymakers in promoting evidence-based medicine, and help tailor first-line treatments to individual characteristics or specific subgroups, improving patient outcomes. This study aimed to identify factors influencing the prescription and non-prescription of metformin, the recommended first-line therapy in Western guidelines, and to evaluate whether these prescribing patterns align with evidence-based recommendations. It also explores factors associated with initial combination therapy, a more recent and controversial approach compared to stepwise therapy. Methods: We conducted a systematic search in PubMed, Scopus, and Web of Science on 25 August 2023, without language or time restrictions, to identify observational analytical studies assessing factors associated with the initiation of metformin or combination therapy in adults with type 2 diabetes mellitus who were naïve to antidiabetic medications. Studies involving pregnant or breastfeeding women were excluded. A narrative synthesis was conducted. Study quality was assessed using the Joanna Briggs Institute critical appraisal checklists (PROSPERO registration number CRD42023438313). Results: Thirty studies were included, evaluating 105 variables, most of which (62%) were assessed in one study. The 25 variables using combination therapy as the outcome were mostly (72%) evaluated also in one study. Initial metformin prescription was strongly and positively associated with younger age, lower glycated haemoglobin levels, higher body mass index, and absence of renal impairment. Initial combination therapy was associated with higher HbA1c levels and a lower burden of comorbidities. Findings also highlighted a discrepancy between clinical practice and evidence-based recommendations. However, concerns were raised regarding both the internal and external validity of the included studies. Conclusions: Our systematic review, which offers insights into real-world clinical practices, indicated that there is a misalignment between clinical practices and evidence-based recommendations, supporting the need for interventions in this field.

Keywords: clinical decision-making; combination therapy; first line; metformin; prescribing; type 2 diabetes mellitus

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1. Introduction

More than 90% of people with diabetes have type 2 diabetes mellitus (T2DM), a chronic and complex condition requiring a multifactorial approach to prevent or delay microvascular and macrovascular complications [1]. With a global prevalence of 10.5% among adults aged 20 to 79 in 2021 [2], T2DM contributed to 11.3% of deaths worldwide [3]. It has led to a 315% increase in healthcare expenditures over 15 years (2007–2021) [2], significantly burdening healthcare systems and society. Given this impact, optimising initial treatment strategies is essential. Prescribing the most appropriate treatment from the beginning can influence long-term outcomes and reduce the overall burden on healthcare systems.

Several classes of antidiabetic drugs (ADs) are currently available, each with distinct profiles of effectiveness and safety [4]. The most commonly used ADs belong to seven drug classes: biguanides, sulfonylureas (SUs), thiazolidinediones (TZDs), dipeptidyl peptidase-4 inhibitors (DPP4i), sodium-glucose transporter-2 inhibitors (SGLT2i), glucagon-like peptidase-1 receptor agonists (GLP1-RA) and insulin [5]. Although metformin is widely endorsed as the preferred first-line therapy [6,7], data from Nicolucci et al. [7] show that approximately one-fifth of patients across 37 countries in six global regions did not receive metformin as their initial treatment. Additionally, prescribing patterns vary considerably, with sulfonylureas and DPP4i commonly used, while newer agents like SGLT2i and GLP1-RA remain underutilised in many regions. Evidence on the use of initial combination therapy is more limited. Current guidelines suggest this option when HbA1c exceeds target levels by 1.5% or more [4], although its benefits and risks remain under debate [8]. In the context of a complex condition with multiple therapeutic options, selecting the most appropriate initial treatment could pose a significant challenge for clinicians.

Variations in healthcare resource allocation and utilisation raise critical questions about quality, equity, and efficiency, with significant implications for health policies [9]. Such variation is particularly evident when multiple treatment options are available, contributing to uncertainty in clinical decision-making, a phenomenon known as "professional uncertainty" [10]. Furthermore, evidence from systematic reviews [11,12] suggests that prescribing decisions are influenced by a range of interconnected factors, including patients' clinical conditions, patient preferences, physician characteristics, medication costs, and pharmaceutical industry influence. Some variations in clinical practice may reflect legitimate differences in patient needs or preferences; however, any unwarranted prescribing must be identified and requires closer examination.

A systematic review addressing factors influencing first-line choice decisions in T2DM has yet to be found. Such a review addressing this gap would enhance our understanding of prescribing patterns and assess the robustness of existing scientific evidence. Furthermore, identifying key determinants of prescribing behaviour could help reduce unwarranted clinical variation, promote evidence-based practice, and enhance healthcare equity. Given that metformin is the recommended first-line treatment in guidelines [4,13] and that combination therapy, which may include metformin, is an emerging approach, this systematic review aims to identify the key factors influencing the choice of metformin or combination therapy as the first-line treatment for T2DM.

2. Materials and Methods

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [14] and was registered in the PROSPERO database in July 2023 under CRD42023438313. The registered protocol encompasses a broader systematic review, part of which is presented here.

2.1. Search Strategy

A search was conducted in Medline (PubMed), Scopus, and Web of Science on 25 August 2023, without restrictions on language or publication date.

The search strategy was based on the PECO-S framework: Population (individuals with T2DM drug-naïve to antidiabetic drugs), Exposure (predictive factors), Comparator (not applicable), Outcome (starting metformin or combination therapy), and Study type (observational analytical studies). Initial combination therapy was defined as the simultaneous initiation of two or more oral antidiabetic agents as the first-line treatment for T2DM. Sequential initiation (e.g., stepwise addition of a second drug after the initial prescription) was not classified as initial combination therapy.

The search strategy combined medical subject headings, free-text terms, and terms in the title/abstract and is available in Supplementary Tables S1–S3. Additional relevant studies were identified through manual reference screening and expert consultation. Grey literature was searched through ProQuest, the Networked Digital Library of These and Dissertations, Eldis, and targeted websites, including those of the World Health Organization (WHO), United Nations, International Diabetes Federation, New York Academy of Medicine, and National Institutes of Health.

2.2. Inclusion and Exclusion Criteria

The inclusion and exclusion criteria were selected based on the PECO-S elements, and all details are shown in Table 1.

Table 1. Study inclusion and exclusion criteria.

Category	Inclusion Criteria
Study population	Studies including ≥80% of adults (≥18 years) with T2DM naïve to antidiabetic treatment or those with relevant subgroup analyses.
Expose/Exhibit	Studies assessing factors influencing prescribing decisions (e.g., physician-, patient-, and system-related, pharmaceutical influence, cost).
Outcomes	Outcomes related to the initiation of metformin or oral combination therapy (two or more drugs initiated simultaneously).
Publication type	Observational analytical studies.
Category	**Exclusion criteria**
Study population	Studies on pregnant or breastfeeding women.

Pregnant and breastfeeding individuals were excluded due to significant differences in treatment approaches compared to the general adult population [15,16].

2.3. Study Selection Process

EndNote 20® was used to manage references and identify duplicates. After that, the Rayyan QCRI [17] tool was employed to support the blinded and independent screening of studies by two reviewers (SMH and MF or JA). Titles and abstracts were screened in the first stage, with any disagreements between researchers leading to studies being transferred to the second stage. In the second stage, the full text was analysed. During the initial screening, studies published in languages other than English, Portuguese, or Spanish were evaluated using an online translation tool. If eligibility criteria were met, the authors were contacted to provide a translated version. A follow-up was sent after 15 days, and if no response was received within 30 days, the study was excluded.

Disagreements were resolved by consensus; a third researcher was consulted if a consensus was not reached. This procedure was conducted for study selection, data extraction, and risk of bias analysis. The agreement proportion between the two reviewers was calculated for each stage.

2.4. Data Extraction

Data were extracted by one reviewer (SMH) and independently checked for accuracy and completeness by a second reviewer (MF or JA). The extraction followed a predefined set of variables, including (1) study identification (title, author(s), publication year, and country), (2) methods (sources and methods of participants selection, inclusion and exclusion criteria, sample size and its characteristics (sex and mean age), period(s) of data collection, follow-up, setting, analysis methods, and potential biases), (3) outcomes analysed and their prevalence, list of variables (factors), and degree of statistical significance associated with the outcomes.

2.5. Risk of Bias and Data Analysis

Two independent reviewers (SMH and MF or JA) assessed the quality of studies using the Joanna Briggs Institute (JBI) quality assessment checklist for cross-sectional and cohort studies [18]. Studies were not classified as "high", "moderate", or "low" quality due to the lack of a universally accepted categorisation. However, the appraisal informed the interpretation of findings, particularly when assessing the robustness of evidence.

Due to the expected and observed high heterogeneity of studies, a meta-analysis was not feasible. Instead, a narrative synthesis was conducted to explore the factors associated with metformin or combination therapy initiation. No formal methods were used to assess risk of reporting bias, such as small-study effects or publication bias, due to the heterogeneity in comparisons, outcomes, and the absence of statistical synthesis.

Given the nature of the narrative synthesis and the absence of a meta-analysis, the use of the GRADE system was not deemed appropriate, as the primary aim was to identify factors influencing physician prescribing, without the intention of providing direct clinical recommendations.

Data were summarised in cross-tabulated tables, grouped by treatment comparisons (e.g., metformin vs. sulfonylureas). Factors were organised according to categories commonly reported in the literature [11,12], including physician-related, healthcare system-related, patient-related, and disease-related factors. Furthermore, as patient-related factors were expected to constitute the largest group due to their availability in clinical records, these factors were subcategorised into sociodemographic, lifestyle and metabolic, cardiovascular, renal, and other clinical factors that did not fit into the previous categories. Each table included the study references and indicated whether the statistical results were significant, specifying if significance was found in univariate and/or multivariate analyses. The criterion for a statistically significant association between exposure and outcomes was p-value < 0.05, or a 95% confidence interval that did not include 1 in studies where the association was reported through risk measures (relative risk, odds ratio, or hazard ratio).

3. Results

3.1. Study Selection

Figure 1 presents the PRISMA 2020 flow diagram outlining the study selection process and main reasons for exclusion. Initially, 1645 studies were identified, and 4 additional studies were retrieved through citation searching. In the first stage, 1535 studies were excluded during the title and abstract screening. The main reason for exclusion was that studies presented different outcomes, with many studies researching adherence to first-line

treatment, investigating the effectiveness and side effects of first-line therapies, or performing cost-effectiveness analyses. In the second screening stage (full-text review), the main reason for exclusion remained outcome-related discrepancies. Several studies evaluated the initiation of different drug classes, such as sulfonylureas, or compared treatment initiation with non-initiation. The proportion of agreement between the independent reviewers from the first and second stages of screening studies was 51.4% and 69.5%, respectively.

3.2. Study Characteristics

Tables 2 and 3 summarise the characteristics of the included studies. Of the 30 studies, 9 (30%) were retrospective cohort studies [19–27] and 21 (70%) were cross-sectional studies [28–48]. A total of 12 studies (40%) were conducted in Europe, 11 (36.7%) in North America, 6 (20%) in Asia, and 1 (3.3%) in Australia. The number of participants ranged from 415 to 1,136,723, with a median of 27,138.

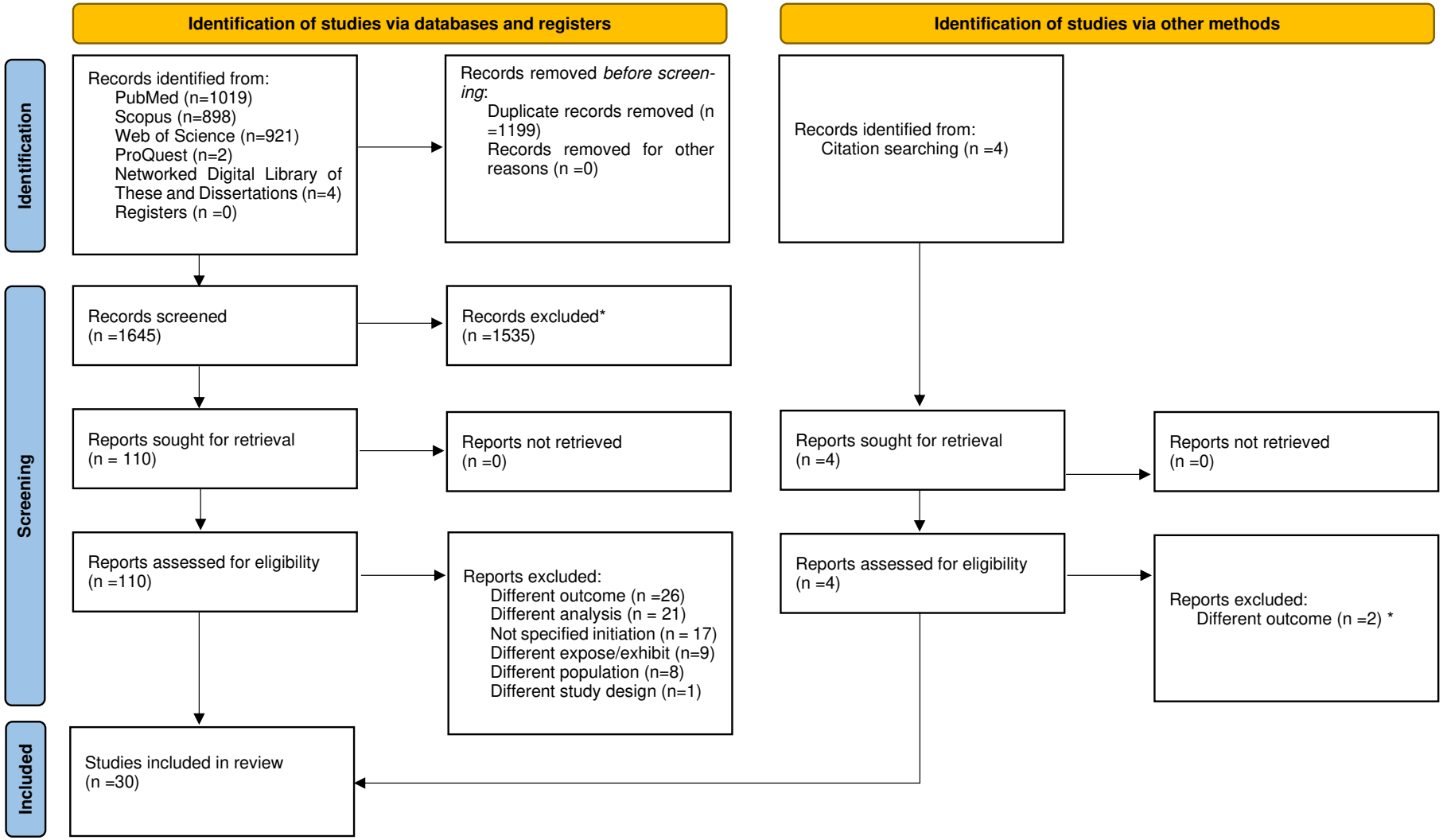

Figure 1. PRISMA 2020 flow diagram for study inclusion. * Automation tools were not used for the study inclusion/exclusion.

Table 2. Characteristics of the retrospective cohort studies which were eligible for inclusion.

Study and Country	Participants' Characteristics			Period to Identify Sample	Follow-Up (Months)	Source of Data	Setting	Antidiabetic Drug Studied	
	Sample Size	Male (%)	Mean Age (Years)						Prevalence Initiation (%)
Retrospective cohort studies									
Brouwer et al. (2012) [19], US	1972	48	>21	January 1998 to March 2009	Vary *	Vendor-based electronic health records (from BHCS and CCHS)	Primary care	Metf vs. SU (ref.) Metf vs. TZDs (ref.) Metf vs. CT (ref.) SU vs. CT (ref.)	66.63 (M) 10.60 (S) 5.22 (T) 13.74 (CT)
Zhang et al. (2012) [20], US	10,743	45	61	January 2003 to December 2005	24	General Electronic Healthcare's Clinical Data Services electronic medical record database	Multicentre	Metf	64 (M) (<65years) [1] 49 (M) (≥65years) [1]
Sinclair et al. (2012) [21], UK	9158	54	62	January 2003 to December 2005	24	International Medical Statistics (IMS) MediPlus database	Information from general practitioners.	Metf	76 (M) [1]
Raebel et al. (2013) [22], US	241,327	53	59	January 2005 to December 2010	6	Surveillance Prevention and Management of diabetes mellitus (SUPREME-DM)	Multicentre	SU vs. Metf (ref.)	19.17 (S) [1] 65.53 (M) [1]
Geier et al. (2014) [23], Germany	27,138	49	63	June 2003 to December 2009	Vary *	German Disease Management Programme for T2DM (DMP-DM2), funding by health insurance	Multicentre	Metf vs. SU (ref.)	33 (M) [2] 7 (S) [2]
Wright (2014) [24], UK	44,838	57	61	January 2005 to December 2009	Vary *	Clinical Practice Research Datalink	Primary care	SU vs. Metf (ref.)	10.4 (S) 87.8 (M)
Li (2019) [25], US	231,408	38	72	January 2007 to December 2017	12	Health insurance database (Medicare)	Multicentre	Metf Metf vs. SU (ref.)	68.4 (M) [1] 14.8 (S) [1]

Table 2. *Cont.*

Study and Country	Participants' Characteristics			Period to Identify Sample	Follow-Up (Months)	Source of Data	Setting	Antidiabetic Drug Studied	
	Sample Size	Male (%)	Mean Age (Years)						Prevalence Initiation (%)
Carrillo Balam (2020) [26], Scotland	154,660	56	61	January 2004 to December 2012	24	Scottish care information—diabetes	Multicentre	Metf	82.3 (M)
Ouchi et al. (2023) [27], Spain	86,854	58	59	January 2015 to December 2020	Vary *	Electronic medical records from SIDIAP	Primary care	CT vs. MT	78.3 (MT) 21.7 (CT)

Studies are listed in chronological order, from the oldest to the most recent. US, the United Stated of America; UK, the United Kingdom; BHCS, Baylor Health Care System; CCHS, Christiana Care Health System; SIDIAP, Information System for Research in Primary Care; Metf (M), metformin; SU (S), sulfonylureas; TZDs (T), thiazolidinediones; MT, monotherapy; CT, combination therapy, which means exposure to ≥2 or more drugs, CT in Brouwer et al. [19] includes only metformin, sulfonylureas, and thiazolidinedione; vs., versus, meaning that one drug was compared to another in statistical analysis; (ref.), category used as a dependent variable reference in statistical analysis. * Follow-up definitions: Brouwer et al. [19] followed patients until the first of the date of their last documented visit in the electronic health records plus 18 months or to 7 July 2009; In Geier et al. [23], the follow-up happened until individuals were started on antidiabetic drug therapy, death, or study end date, whichever came first; Wright [24] followed individuals from their identification (at any time during the sample identification period) until the end of the study (December 2012); Ouchi et al. [27] followed patients for at least 12 months or until death or end of data availability (transferred to another database or December 2020). [1] Prevalence among those who initiated therapy (not all of the sample initiated therapy). [2] The prevalence in Geier et al. [23] was calculated for the entire sample, among those who initiated therapy and those who did not.

Table 3. Characteristics of the cross-sectional studies which were eligible for inclusion.

Study and Country	Participants' Characteristics			Period to Identify Sample	Source of Data	Setting	Antidiabetic Drug Studied	
	Sample Size	Male (%)	Mean Age (Years)					Prevalence Initiation (%)
Cross-sectional studies								
Winkelmayer et al. (2011) [28], Austria	39,077	50	63	January 2006 to June 2008	Insurance claims data (public and non-for-profit health insurance company)	Multicentre	Metf vs. AHA (ref.)	71.7 (M)
Desai et al. (2012) [29], US	254,973	53	58	January 2006 to December 2008	Prescription claims data from CVS Caremark	Multicentre	Metf Metf vs. MT (ref.)	51 (M)
Grimes et al. (2014) [30], Ireland	20,947	58	>40	January 2008 to December 2009	National pharmacy claims databases in Ireland [1]	Multicentre	Metf vs. MT	76 (M)
Abdelmoneim et al. (2013) [31], Canada	39,276	NR	≥66	January 1998 to December 2010	Alberta Blue Cross provincial insurance programme	Multicentre	Metf vs. SU (ref.)	84.2 (M, 2010) 4.5 (S, 2010)

Table 3. *Cont.*

Study and Country	Participants' Characteristics			Period to Identify Sample	Source of Data	Setting	Antidiabetic Drug Studied	
	Sample Size	Male (%)	Mean Age (Years)					Prevalence Initiation (%)
Wang et al. (2013) [32], Canada	1279	49	≥18	January 2003 to December 2011	Electronic health record (MOXXI: Medical Office of the XXIst Century)	Primary care	SU vs. Metf * (ref.) TZDs vs. Metf * (ref.) Metf * vs. AHA (ref)	92 (M *)
Mitchell et al. (2013) [33], US	4627	48	53	January 2006 to June 2010	The i3 Invision Data Mart database (OptumInsight, Eden Prairie, MN, US)	Multicentre	CT, Metf	93.24 (MT)
Vashisht et al. (2016) [34], US	6121	51	NR	NR	Electronic medical records from Stanford Clinical Data Warehouse	Hospital	Glipizide vs. Metf (ref.) Pioglitazone vs. Metf (ref.)	NR
Fujihara et al. (2017) [35], Japan	2666	64	61	December 2009 to March 2015	The Japan Diabetes Clinical Data Management Study Group (JDDM)	Outpatient clinics (clinical diabetologists)	Metf vs. SU (ref.)	35.7 (M) 11.4 (S)
Tanabe et al. (2017) [36], Japan	7108	63	NR	April 2008 to April 2013	Electronic information systems constructed by Medical Data Vision (MDV)	Multicentre	SU vs. Metf	18.4 (S) 26.5 (M)
Liu et al. (2017) [37], Taiwan	28,640	53	57	January 2006 to December 2010	Taiwan National Insurance Research Database	Multicentre	AHA vs. Metf * (ref.)	43.8 (AHA, 2006) 26.2 (AHA, 2010)
Morita et al. (2019) [38], Japan	224,761	61	66	October 2012 to September 2016	Medical Data Vision database, a Diagnosis Procedure Combination database	Outpatient	DPP4i vs. Metf (ref.)	26.2 (D) 7.1(M)
Pinto et al. (2019) [39], Portugal	415	55	NR	January 2014 to December 2015	Portuguese Sentinel Practice Network	Multicentre	Metf, CT.	85.5 (M) 6.5 (CT)
Juste et al. (2019) [40], Italy	14,679	55	64	January 2016 to December 2016	Campania Regional Database for Medication Consumption	Primary care	MT vs. CT	86.9(MT) 13.1(CT)
Moreno-Juste et al. [41] (2020), Spain	4247	58	65	October 2013 to September 2014	Electronic health records and pharmacy billing records from health system (EpiChron Cohort)	Multicentre	Metf MT vs. CT	80.5 (M) 88.7(MT) 11.3 (CT)

Table 3. *Cont.*

Study and Country	Participants' Characteristics			Period to Identify Sample	Source of Data	Setting	Antidiabetic Drug Studied	
	Sample Size	Male (%)	Mean Age (Years)					Prevalence Initiation (%)
Yabe et al. (2020) [42], Japan	1485	62	60	June 2016 to May 2019	Real-world observational study on patient outcomes in diabetes (RESPOND)	Multicentre	Metf	16 (M)
Wood et al. (2020) [43], Australia	47,860	53	61	July 2013 to February 2018	Random sample from Australia's Pharmaceutical Benefits Scheme	Multicentre	SU vs. Metf (ref.) Non-Metf vs. Metf (ref.) CT vs. Metf (ref.)	85.8 (M) 4.6 (S) 1.9 (Non–M) 7.7 (CT)
Campbell et al.(2021) [44], Canada	17,932	55	56	April 2012 to March 2017	Multiple administrative health datasets from Alberta, Canada	Multicentre	AHA [2] vs. Metf (ref.)	89 (M)
Shin et al. (2021) [45], US	264,542 (Clinf.) 285,213 (Med.)	55 (Clinf.) 46 (Med.)	59 (Clinf.) 73 (Med.)	April 2013 to December 2019 (Clinf.) April 2013 to December 2017 (Med.)	Health insurance databases (Optum Clinformatics (Clinf.) and Medicare fee-for-service (Med.))	Multicentre	Metf Drugs without cardiovascular benefits vs. Metf (ref.) Drugs With cardiovascular benefits benefits vs. Metf (ref.)	Last data available: 83.1 (M, Clinf.) 80.6 (M, Med.)
Bonora et al. (2021) [46], Italy	65,932	51	NR	January 2018 to December 2018	Administrative data from National Health System (ARNO Diabetes Observatory database)	Multicentre	Metf, CT	71.9 (M) 3.8 (CT)
Barth et al. (2022) [47], Germany	16,006	57	61	January 2015 to December 2020	Health care database (Disease Analyzer database (IQVIA))	Multicentre	Metf	77 (M)
Bouchi et al. (2022) [48], Japan	1,136,723	58	>20	October 2014 to March 2018	National Database of health Insurance Claims and Specific Health Chek-ups in Japan	Outpatient clinic	Metf vs. MT (ref.)	15.9 (M)

Studies are listed in chronological order, from the oldest to the most recent; NR, not reported; US, the United Stated of America; [1] From the General Medical Services (GMS) scheme and the Long-Term Illness (LTI) scheme; Metf (M), metformin; Non-Metf (Non-M), non-metformin include acarbose, thiazolidinediones, dipeptidyl peptidase-4 inhibitors, glucagon-like peptidase receptor-1 agonists, or sodium-glucose transporter-2 inhibitors; SU (S), sulfonylureas; TZDs (T), thiazolidinediones; DPP4i (D), dipeptidyl peptidase-4 inhibitors; MT, monotherapy; CT, combination therapy, which means exposure to ≥2 or more drugs; AHA, other oral antihyperglycemic agents (it can include monotherapy and combination therapy); drugs without cardiovascular benefits include sulfonylureas, dipeptidyl peptidase-4 inhibitors, thiazolidinedione, and others (alpha-glucosidase inhibitors, amylin mimetics, dopamine receptor agonists, and meglitinides); drugs with cardiovascular benefits include sodium-glucose cotransporter-2 inhibitors and glucagon-like peptide-1; vs., versus, meaning that one drug was compared to another in statistical analysis; (ref.), category used as a dependent variable reference in statistical analysis; * alone or in combination therapy; [2] it included metformin in combination therapy.

Twenty studies employed data from multicentre settings [20,22,23,25,26,28–31,33,36,37,39,41–47] and six studies from primary care settings or general practitioners [19,21,24,27,32,40]. All studies relied on secondary data sources, defined as data collected by others for purposes different from the objectives of the research, such as medical records and healthcare billing files [49].

Twenty-eight studies [19–26,28–39,41–48] examined factors associated with metformin initiation. Nineteen of these [19,22–25,28–32,34–38,43–45,48] employed statistical models that examined factors linked to metformin initiation in direct comparison to initiation of other antidiabetic drug(s). The sulfonylureas group was the most frequently compared drugs, accounting for 36.7% (n = 11) of these studies [19,22–25,31,32,34–36,43]. A total of 8 studies [19,27,33,39–41,43,46] analysed factors influencing the initiation of combination therapy, and 6 studies [19,33,39,41,43,46] assessed both metformin and combination therapy in the same study.

3.3. Data Extracted and Analysed

The 105 variables extracted from the 30 studies are categorised into 4 main groups of factors: physician (Table 4), healthcare system (Table 5), patient (Tables 6–8), and disease factors (Table 9). The most extensive group of factors belongs to patient factors, with five subgroups of factors recognised: sociodemographic, lifestyle and metabolic, cardiovascular, renal, and other clinical factors. Sixty-five variables (62%) were evaluated by one study, and eleven (10.5%) were assessed by five or more studies.

Table 4. Strength of association between physician-related factors and the outcomes.

Physician-Related Factors	Outcomes					
		Metf.	**W/CVB**	**WCVB**	**AHA**	**CT**
Age (cat.)	**Metf.**				+++ [28] ++ [37]	
Years of experience (cont.)	**Metf.**				- - [32]	
Sex	**Metf.**				++ [37] ^{LR} - - - [28] - - [32,37] ^{ML}	
Medicine evidence questionnaire (cat.)	**Metf.**				- - [32]	
Physician Speciality	**Metf.**		++ [45]	++ [45]	+++ [28] ++ [37,44]	
	———	+ [42] - [39]				+ [39]

+++, variable with statistically significant association with the outcome in both univariable and multivariable analyses; ++, variable with statistically significant association with the outcome only in multivariable analysis; +, variable with statistically significant association with the outcome only in univariable analysis; - - -, variable with no statistically significant association with the outcome in both univariable and multivariable analyses; - -, variable with no statistically significant association with the outcome in multivariable analyses; -, variable with no statistically significant association with the outcome only in univariable analysis; Metf., metformin; W/CVB, drugs without cardiovascular benefits (sulfonylureas, dipeptidyl peptidase-4 inhibitor, thiazolidinediones, α-glucosidase inhibitors, amylin mimetics agents, dopamine receptor agonists, and meglitinides); WCVB, drugs with cardiovascular benefits (sodium glucose cotransporter 2 inhibitors, glucagon-like peptide-1 receptor agonists); AHA, other antidiabetic agents can include monotherapy or combination therapy; CT, combination therapy; cont., continuous; cat., categorical; statistical analysis used: ^{LR} data from logistic regression [37], ^{ML} data from multilevel model [37] (if unspecified, statistical result was the same for both).

Table 5. Strength of association between healthcare system-related factors and the outcomes.

Healthcare System-Related Factors		Outcomes						
		Metf.	**SU**	**DPP4i**	**W/CVB**	**WCVB**	**MT**	**AHA**
Guidelines (updates)	**Metf.**		- - [32]					++ [32]
	TZDs	++ [32]						
Time (cont.)	**Metf.**		++ [31]				++ [29]	
	———	+ [25,29, 45] [1] - [45] [2]						
Time (cat.)	**Metf.**		+++ [22] ++ [23,43] - - [19]				++ [43,48]	+++ [28] ++ [37]
	TZDs	++ [19]						
	CT	++ [43] - - [19]	- - [19]					
HbA1c tests (cat.)	**Metf.**				++ [45]	++ [45]		
Office visits (cont.)	**Metf.**		+++ [31]	+ [38]	- - [45]	++ [45] [ALX] - - [45] [2(TB)]		
Hospitalisation (cont.)	**Metf.**		+ [31] - - [31]					
Hospitalisation (cat.)	**Metf.**		++ [25]		++[45]	++ [45] [ALX] - -[45] [1(TB),2(TB)]		
Length of hospital stay (cont.)	**Metf.**				++ [45] [2(TB,TC)] - - [45] [ALX]	++ [45] [2(TA)] - - [45] [ALX]		
Length of hospital stay (cat.)	**Metf.**							+++ [28]
Emergency visits (cont.)	**Metf.**		+ [31] - - [31]					
Emergency visits (cat.)	**Metf.**				- - [45]	++ [45] [ALX] - - [45] [1(TA)]		
Preventive healthcare service	**Metf.**				++ [45]	++ [45] [2(TC)] - - [45] [ALX]		
Healthcare settings	**Metf.**						++ [48]	++ [37] [LR] - - [37] [ML]
Healthcare ownership	**Metf.**							++ [37]
Location urbanisation	**Metf.**							++ [37]
Hospital beds (cat.)	**Metf.**						++ [48]	
Health insurance	**Metf.**						++ [29]	+++ [28]
Co-payment (cat.)	**Metf.**							+++ [28]
Costs drugs (cat.)	**Metf.**		++ [25]					
Brand/generic ratio	**Metf.**				++ [45]	++ [45]		

+++, variable with statistically significant association with the outcome in both univariable and multivariable analyses; ++, variable with statistically significant association with the outcome only in multivariable analysis; +, variable with statistically significant association with the outcome only in univariable analysis; - -, variable with no statistically significant association with the outcome in multivariable analyses; -, variable with no statistically significant association with the outcome only in univariable analysis; Metf., metformin; SU, sulfonylureas; DPP4i, dipeptidyl peptidase-4 inhibitor; W/CVB, drugs without cardiovascular benefits (sulfonylureas, dipeptidyl peptidase-4 inhibitor, thiazolidinediones, α-glucosidase inhibitors, amylin mimetics agents, dopamine receptor agonists, and meglitinides); WCVB, drugs with cardiovascular benefits (sodium glucose cotransporter 2 inhibitors, glucagon-like peptide-1 receptor agonists); MT, monotherapy; AHA, other antidiabetic agents can include monotherapy or combination therapy; TZDs, thiazolidinediones; CT, combination therapy; HbA1c, glycated haemoglobin; cont., continuous; cat., categorical; databases: [1] data from USA Medicare; [2] data from Clinformatics; Period: [TA] Apr 13 to Sept 15; [TB] Oct 15 to Dec 17; [TC] Jan 18 to Dec 19; [ALX] all except references mentioned in the same space [45]; statistical analysis used: [LR] data from logistic regression [37], [ML] data from multilevel model [37]; (if unspecified, statistical result was the same for all).

Table 6. Strength of association between patient-related factors—sociodemographic, lifestyle, and metabolic—and the outcomes.

Patient-Related Factors: Sociodemographic		Outcomes						
		Metf.	**SU**	**W/CVB**	**WCVB**	**MT**	**AHA**	**CT**
Age (cont.)	**Metf.**		+++ [31] ++ [23,25,35] + [22,36]	++ [45]	++ [45]		++ [44]	
	DPP4i	+ [38]						
	CT					+ [40,41]		
Age (cat.)	**Metf.**		+++ [22] ++ [19,24,43]			++ [29,30,43]	+++ [28] ++ [32,37]	
	TZDs	++ [19]						
	CT	++ [19,43]	- - [19]					
	_____	+ [20,21,26]						
Age (cat.) and health insurance	**Metf.**					++ [48]		
Sex	**Metf.**		+++ [22] ++ [25] - - - [31] - - [19,23,35,43]	++ [45] ALX - - [45] 2(TC)	++ [45] ALX - - [45] 1(TA,TB)	++ [29,30,48] - - [43]	+++ [28] ++ [37] - - [32,44]	
	TZDs	- - [19]						
	DPP4i	+ [38]						
	CT	++ [19,43]	- - [19]			+ [40] - [41]		
	____	- [46]						+ [46] 3 - [46] 3
Race/Ethnicity	**Metf.**		+++ [22] ++ [19,25]	++ [45] 1(TA,TB)	++ [45] 1(TA,TB)			
	TZDs	- - [19]						
	CT	- - [19]	- - [19]					
Socioeconomic status	**Metf.**		++ [25] + [22]			++ [29]	++ [37] LR - - [37] ML	
	CT					- [41]		
Doctor or has a doctor in family	**Metf.**						++ [37] LR - - [37] ML	
Geographic region	**Metf.**		++ [25]	++ [45]	++ [45]			
	CT					+ [40,41]		
Immigrant status	**Metf.**					+ [41]		
Lifestyle and metabolic								
BMI (cont.)	**Metf.**		++ [23,35] + [22]					
	DPP4i	+ [38]						
BMI (cat.)	**Metf.**		++ [24]					
Obesity or overweight	**Metf.**			++ [45]	++ [45]			
Smoker (cat.)	**Metf.**			++ [45] 2(TA,TB) - - [45] ALX	++ [45] ALX - - [45] 1(TB),2(TC)			
Ex-smoker (cat.)	**Metf.**		+ [22] - - [22]					

Table 6. *Cont.*

Patient-Related Factors: Sociodemographic	Outcomes							
		Metf.	**SU**	**W/CVB**	**WCVB**	**MT**	**AHA**	**CT**
Current smoker (cat.)	**Metf.**		- - - [22] - - [23]					
Substance abuse (cat.)	**Metf.**			++ [45] 2(TA) - - [45] ALX	++ [45] ALX - - [45] 1(TA,TB)			
Liver disease	**Metf.**		+++ [31] ++ [24]					
	DPP4i	- [38]						
Hyperlipidaemia	**Metf.**		- [22]	++ [45] ALX - - [45] 1(TA),2(TA)	++ [45]			
Dyslipidaemia	**Metf.**		++ [43]			++ [43]		++ [43]
HDL (cont.)	**Metf.**		- [22]					
LDL (cont.)	**Metf.**		+ [22]					
Lipid-lowering meds	**Metf.**		+++ [31] - - [23]			++ [48]		
Statin use	**Metf.**			++ [45]	++ [45]			

+++, variable with statistically significant association with the outcome in both univariable and multivariable analyses; ++, variable with statistically significant association with the outcome only in multivariable analysis; +, variable with statistically significant association with the outcome only in univariable analysis; - - -, variable with no statistically significant association with the outcome in both univariable and multivariable analyses; - -, variable with no statistically significant association with the outcome in multivariable analyses; -, variable with no statistically significant association with the outcome only in univariable analysis; Metf., metformin; SU, sulfonylureas; W/CVB, drugs without cardiovascular benefits (sulfonylureas, dipeptidyl peptidase-4 inhibitor, thiazolidinediones, α-glucosidase inhibitors, amylin mimetics agents, dopamine receptor agonists, and meglitinides); WCVB, drugs with cardiovascular benefits (sodium glucose cotransporter 2 inhibitors, glucagon-like peptide-1 receptor agonists); MT, monotherapy; AHA, other antidiabetic agents can include monotherapy or combination therapy; CT, combination therapy; DPP4i, dipeptidyl peptidase-4 inhibitor; TZDs, thiazolidinediones; BMI, body mass index; HDL, high-density lipoprotein; LDL, low-density lipoprotein; cont., continuous; cat., categorical; databases: [1] data from USA Medicare; [2] data from Clinformatics; period: [TA] Apr 13 to Sept 15; [TB] Oct 15 to Dec 17; [TC] Jan 18 to Dec 19; [ALX] all except references mentioned in the same space [45]; statistical analysis used.: [LR] data from logistic regression [37], [ML] data from multilevel model [37]; (if unspecified, statistical result was the same for all); [3] combination therapy between metformin and DPP4i, metformin and SGLT2i, metformin and TZDs (pioglitazone) showed statistical significance, and combination therapy between metformin and sulfonylureas, TZDs (pioglitazone), and DPP4i (alogliptin) did not show statistical significance.

Table 7. Strength of association between patient-related cardiovascular and renal factors and the outcomes.

Patient-Related Factors: Cardiovascular	Outcomes								
		Metf.	**SU**	**DPP4i**	**W/CVB**	**WCVB**	**MT**	**AHA**	**CT**
Hypertension	**Metf.**		+++ [31] ++ [35] + [22] - - [43]		++ [45]	++ [45]	- - [43]		- - [43]
Coagulopathy	**Metf.**		+ [31] - - [31]						
Cardiovascular disease	**Metf.**		++ [25] + [22]		++ [45]	++ [45]		- - [32]	
	___	- [47]							
IHD	**Metf.**		+ [31] - - [31]				++ [48]		
IHD/angina	**Metf.**		- - [43]				- - [43]		- - [43]
IHD/hypertension	**Metf.**		- - [43]				- - [43]		- - [43]
IHD/Stroke	**Metf.**			+ [38]					

Table 7. *Cont.*

Patient-Related Factors: Cardiovascular		Outcomes							
		Metf.	**SU**	**DPP4i**	**W/CVB**	**WCVB**	**MT**	**AHA**	**CT**
Coronary atherosclerosis of native coronary artery	**Pio (TZDs)**	++ [34]							
Heart failure	**Metf.**		+++ [31] ++ [43] + [22]				- - [43]		++ [43]
Valvular disease	**Metf.**		+++ [31]						
Arrhythmia	**Metf.**		+ [31] - - [31]						
Atrial fibrillation	**Metf.**		++ [43]				- - [43]		- - [43]
Peripheral vascular disease	**Metf.**		+ [31] - - [31]						
Cerebrovascular disease	**Metf.**		++ [43] + [31] - - [31]				- - [43]		++ [43]
Micro/macrovascular complications	**CT**						+ [40]		
Microvascular complications	**Metf.**				++ [45]	++ [45] ALX - - [45] 2(TA)			
Diabetic retinopathy	**Metf.**		- - - [31] - - [24]	+ [38]					
Diabetic neuropathy	**Metf.**		- - - [31] - - [24]	- [38]					
Cardiovascular meds	**Metf.**		++ [24] [3] - - [24] [4]						
Antihypertensive meds	**Metf.**		- - [23]				++ [48]		
ACE inhibitors or ARBs	**Metf.**				++ [45]	++ [45]			
Beta-blockers	**Metf.**				++ [45] 1(TB) - - [45] ALX	- - [45]			
Calcium channel blockers	**Metf.**				++ [45] 1(TA)2(TC) - - [45] ALX	++ [45] 2(TA,TC) - - [45] ALX			
Loop diuretics	**Metf.**				++ [45]	++ [45] ALX - - [45] 2(TA)			
Thiazide diuretics	**Metf.**				++ [45]	++ [45] ALX - - [45] 1(TB)			
Anticoagulants meds	**Metf.**				++ [45] 2(TC) - - [45] ALX	++ [45] ALX - - [45] 1(TA)2(TC)			
Antiplatelet meds	**Metf.**				++ [45]	++ [45] ALX - - [45] 1(TB)2(TB)			
Renal									
Serum creatinine (cont.)	**Metf.**		+ [22]						

Table 7. *Cont.*

Patient-Related Factors: Cardiovascular		Outcomes							
		Metf.	**SU**	**DPP4i**	**W/CVB**	**WCVB**	**MT**	**AHA**	**CT**
Serum creatinine (cat.)	**Metf.**		+++ [22] ++ [19]						- - [19]
	TZDs	++ [19]							
	CT		++ [19]						
Renal disease	**Metf.**			+ [38]				++ [32]	
Chronic kidney disease	**Metf.**		+++ [22] ++ [24,25]		++ [45]	++ [45]	- - [48]		
	CT						+ [41]		
Renal failure	**Metf.**		+ [22]						
	Glip (SU)	++ [34]							
Diabetic nephropathy	**Metf.**		+++ [31]	- [38]					
	Glip (SU)	++ [34]							

+++, variable with statistically significant association with the outcome in both univariable and multivariable analyses; ++, variable with statistically significant association with the outcome only in multivariable analysis; +, variable with statistically significant association with the outcome only in univariable analysis; - - -, variable with no statistically significant association with the outcome in both univariable and multivariable analyses; - -, variable with no statistically significant association with the outcome in multivariable analyses; -, variable with no statistically significant association with the outcome only in univariable analysis; Metf., metformin; SU, sulfonylureas; DPP4i, dipeptidyl peptidase-4 inhibitor; W/CVB, drugs without cardiovascular benefits (SU, DPP4i, TZDs, α-glucosidase inhibitors, amylin mimetics agents, dopamine receptor agonists, and meglitinides); WCVB, drugs with cardiovascular benefits (sodium glucose cotransporter 2 inhibitors, glucagon-like peptide-1 receptor agonists); MT, monotherapy; AHA, other antidiabetic agents can include monotherapy or combination therapy; CT, combination therapy; Pio, pioglitazone; TZDs, thiazolidinediones; Glip, glipizide; IHD, ischemic heart disease; ACE, angiotensin-converting enzyme; ARBs, angiotensin receptor blockers; cont., continuous; cat., categorical; databases: [1] data from USA Medicare; [2] data from Clinformatics; period: [TA] Apr 13 to Sept 15; [TB] Oct 15 to Dec 17; [TC] Jan 18 to Dec 19; [ALX] all except references mentioned in the same space [45] (if unspecified, statistical result was the same for all); [3] current use; [4] previous use.

Table 8. Strength of association between patient-related factors: other clinical factors and the outcomes.

Patient-Related Factors: Other Clinical		Outcomes							
		Metf.	**SU**	**DPP4i**	**W/CVB**	**WCVB**	**MT**	**AHA**	**CT**
Esophageal varices, without bleeding, in disease classified elsewhere	**Glip (SU)**	++ [34]							
Fluid and electrolyte disorder	**Metf.**		+ [31] - - [31]						
Paracetamol	**Pio (TZDs)**	++ [34]							
COPD	**Metf.**		+ [31] - - [31]		++ [45] 1(TA)2(TA) - - [45] [ALX]	++ [45] 1(TC) - - [45] [ALX]			
Pulmonary collapse	**Pio (TZDs)**	++ [34]							
Dementia	**Metf.**		++ [24]						
Depression	**Metf.**		++ [43] + [22,31] - - [31]				- - [43]		++ [43]
Neuropsychiatric meds	**CT**						+ [40]		
Antipsychotic meds	**Metf.**		- - [24] [3,4]						
Cancer	**Metf.**		+++ [31]						

Table 8. *Cont.*

Patient-Related Factors: Other Clinical	Outcomes								
		Metf.	**SU**	**DPP4i**	**W/CVB**	**WCVB**	**MT**	**AHA**	**CT**
Lymphoma	**Metf.**		+ [31] - - [31]						
Hypothyroidism	**Metf.**		- - - [31]						
Rheumatoid arthritis	**Metf.**		+ [31] - - [31]						
Immune modulators/suppressants	**Metf.**		++ [24] [3] - - [24] [4]						
Oral corticosteroids	**Metf.**		++ [24] [3] - - [24] [4]						
Tacrolimus	**Glip (SU)**	++ [34]							
Cefepime	**Glip (SU)**	++ [34]							
Medication use (cont.)	**Metf.**		- - [25]				++ [29]		
	CT						+ [41]		
Medication use (cat.)	**Metf.**							+++ [28]	
	CT						+ [40]		
Comorbidities (cont.)	**Metf.**		++ [25]						
	CT						+ [41]		
Comorbidities (cat.)	**Metf.**		++ [43]				++ [43]	++ [44]	++ [43]
Quan Score (cont.)	**Metf.**		+ [22]						
Rx-Risk comorbidity index (cont.)	**CT**						+ [40]		

+++, variable with statistically significant association with the outcome in both univariable and multivariable analyses; ++, variable with statistically significant association with the outcome only in multivariable analysis; +, variable with statistically significant association with the outcome only in univariable analysis; - - -, variable with no statistically significant association with the outcome in both univariable and multivariable analyses; - -, variable with no statistically significant association with the outcome in multivariable analyses; Metf., metformin; SU, sulfonylureas; DPP4i, dipeptidyl peptidase-4 inhibitor; W/CVB, drugs without cardiovascular benefits (sulfonylureas, dipeptidyl peptidase-4 inhibitor, thiazolidinediones, α-glucosidase inhibitors, amylin mimetics agents, dopamine receptor agonists, and meglitinides); WCVB, drugs with cardiovascular benefits (sodium glucose cotransporter 2 inhibitors, glucagon-like peptide-1 receptor agonists); MT, monotherapy; AHA, other antidiabetic agents can include monotherapy or combination therapy; CT, combination therapy; Glip, glipizide; Pio; pioglitazone; TZDs, thiazolidinediones; COPD, chronic obstructive pulmonary disease; cont., continuous; cat., categorical; databases: [1] data from USA Medicare; [2] data from Clinformatics; period: [TA] Apr 13 to Sept 15; [TC] Jan 18 to Dec 19; [ALX] all except references mentioned in the same space [45]; [3] current use; [4] previous use.

Table 9. Strength of association between disease-related factors and the outcomes.

Disease-Related Factors	Outcomes									
		Metf.	**SU**	**TZDs**	**DPP4i**	**W/CVB**	**WCVB**	**MT**	**AHA**	**CT**
HbA1c (cont.)	**Metf.**		++ [23,35] + [22] - [36]		+ [38]				++ [44]	
HbA1c (cat.)	**Metf.**		+++ [22] ++ [19,24]	- - [19]						++ [19]
	CT		++[19]					+ [27]		
	_____	+ [33]								+ [33]
Fasting glucose (cont.)	**Metf.**		+ [22]							
Random glucose (cont.)	**Metf.**		+ [22]							
Glucose	**Pio (TZDs)**	++ [34]								

Table 9. *Cont.*

Disease-Related Factors		Outcomes								
		Metf.	**SU**	**TZDs**	**DPP4i**	**W/CVB**	**WCVB**	**MT**	**AHA**	**CT**
Diabetes duration (cont.)	**Metf.**		++ [23,35]							
Time to initiation (cont.)	**Metf.**		++ [23]							
	CT							+ [27]		
Number of antidiabetics at initiation (cat.)	**Metf**								- - [32]	
Diabetes without complications	**Pio (TZDs**	++ [34]								
Hypoglycaemic events (cat.)	**Metf.**					++ [45] ALX - - [45] 1(TB)2(TB)	++ [45]ALX - - [45] 1(TA,TB)			
DCSI (cat.)	**Metf.**								++ [37] LR - - [37] ML	

+++, variable with statistically significant association with the outcome in both univariable and multivariable analyses; ++, variable with statistically significant association with the outcome only in multivariable analysis; +, variable with statistically significant association with the outcome only in univariable analysis; - -, variable with no statistically significant association with the outcome in multivariable analyses; -, variable with no statistically significant association with the outcome only in univariable analysis; Metf., metformin; SU, sulfonylureas; TZDs, thiazolidinediones; DPP4i, dipeptidyl peptidase-4 inhibitor; W/CVB, drugs without cardiovascular benefits (sulfonylureas, dipeptidyl peptidase-4 inhibitor, thiazolidinediones, α-glucosidase inhibitors, amylin mimetics agents, dopamine receptor agonists, and meglitinides); WCVB, drugs with cardiovascular benefits (sodium glucose cotransporter 2 inhibitors, glucagon-like peptide-1 receptor agonists); MT, monotherapy; AHA, other antidiabetic agents can include monotherapy or combination therapy; CT, combination therapy; Pio; pioglitazone; HbA1c, glycated haemoglobin; DCSI, diabetes complication severity index; cont., continuous; cat., categorical; databases: [1] data from USA Medicare; [2] data from Clinformatics; period: [TA] Apr 13 to Sept 15; [TB] Oct 15 to Dec 17; [ALX] all except references mentioned in the same space [45]; statistical analysis used: [LR] data from logistic regression [37], [ML] data from multilevel model [37].

It is also important to highlight that one study [45] showed data analysis not as a single block but for different periods and two databases, and another [37] employed two statistical analyses: multivariable logistic regression and multilevel linear model.

3.3.1. Physician-Related Factors

Table 4 shows that physician age presented a statistical association with the prescription profile [28,37], with older physicians more frequently initiating non-metformin therapies compared to metformin. Three studies [28,32,37] reported a non-association between physician sex and initial therapy choice. However, Liu et al. [37], using logistic regression, reported that male physicians were more likely to prescribe non-metformin treatments than their female counterparts. Physician speciality was the most assessed variable in this category, with six studies [28,37,39,42,44,45] showing a statistically significant association. Campbell et al. [44] reported that specialists were more likely than general practitioners (GPs) to prescribe metformin in combination or other antidiabetic agents, rather than metformin monotherapy. Pinto et al. [39] also reported GPs had a lower prevalence of prescribing combination therapy compared to other specialists (4.2% vs. 33.3%, $p < 0.001$). However, no significant differences were observed between GPs and specialists in the prescription rates of metformin monotherapy or metformin in combination therapy. Another study [37] presented that GPs had a higher chance of prescribing non-metformin than metformin compared to endocrinologists. In contrast, Shin et al. [45] observed that individuals visiting endocrinologists had a lower chance of initiating metformin than other drugs indepen-

dently of their cardiovascular benefits; the opposite was found when visiting internists. Finally, the two additional variables, years of experience and the medical evidence questionnaire, assessed by Wang et al. [32], presented a non-statistically significant association.

3.3.2. Healthcare System-Related Factors

Eleven studies [19,22,23,25,28,29,31,37,43,45,48] demonstrated a statistically significant association between more recent time periods and the prescription profile. However, in two studies, statistical significance varied depending on the database analysed [45] or the specific drug and comparator used [19]. Studies reported that the most recent periods were positively associated with metformin initiation [25,45] and also when compared with sulfonylureas [22,23,31,43], other monotherapies [29,48], other antidiabetic agents (eventually in monotherapy or combination therapy) [28,37], or combination therapy [43]. Additionally, Wang et al. [32] studied how primary care physicians responded to a change in the Canadian Diabetes Association Guidelines, which significantly increased metformin initiation as a first line, except when compared to sulfonylureas.

One cross-sectional study [45] reported that individuals with three or more HbA1c tests within 365 days before the index date had higher odds of initiating any other medicine than metformin, irrespective of their cardiovascular benefits. Additionally, variables such as the number of office visits [31,38], hospitalisations [25,31], emergency visits [31], and the length of stay [28] were statistically significantly associated with lower odds of metformin prescriptions. However, Abdelmoneim et al. [31] and Shin et al. [45] reported no statistically significant association with some of these variables (see Table 5).

Two studies [28,29] reported an association between the health insurance and the initial therapy choice. Regarding the co-payment and cost of drugs, one study [28] indicated that individuals with a co-payment waiver had a lower chance of starting metformin than sulfonylureas, the same that Li [25] found for individuals in the top 10% of prescription drug expenses under Medicare Part D. Medicare is a health programme for individuals aged 65 and over and younger individuals with disabilities, with Medicare Part D being an optional plan that covers drug costs [50]. Shin et al. [45] stated that individuals with more brand-name experience also had a lower chance of starting metformin than drugs independently of their cardiovascular benefits.

3.3.3. Patient-Related Factors: Sociodemographic

Twenty-two studies [19–26,28–32,35–38,40,41,43–45] evaluated the association between age and initial therapy choice. Metformin initiation was associated with younger individuals when compared to sulfonylureas [19,22–25,31,35,36,43], other antidiabetic agents (including monotherapy (MT) and eventually MT or combination therapy (AHA)) [28,30,32,37,43,44], thiazolidinediones [19], DPP4i [38], and drugs without cardiovascular benefits [45]. Even when age was analysed in interaction with insurance type [48], metformin prescription decreased with advancing age compared to other monotherapies. On the other hand, when metformin is compared with drugs with cardiovascular benefits, the chance of prescribing increases with age [45]. Two studies [19,43] found a significant but inverse association between age and combination therapy. The other two studies [40,41] indicated that younger people were more prevalent in combination therapy than monotherapy. Moreover, one study [19] found no association between age and combination therapy compared to sulfonylureas.

Nineteen studies assessed the association between sex and prescribing patterns [19,22,23,25,28–32,35,37,38,40,41,43–46,48]. Nine studies [22,25,28–30,37,38,40,48] reported a statistically significant association, while six found no such association [23,32,35,41,44,46]. In the remaining four studies [19,43,45,46] several analyses were conducted within each study. This led to the report of statistically significant associations depending on the prescribing profile evaluated

(i.e., the same study analysed different prescribing profiles with sex) or the database analysed (i.e., the same study analysed two different databases). The statistical associations found that females were more likely to initiate metformin than men compared to sulfonylureas [22,25], other monotherapies [30,48], other antidiabetic agents [37], or DPP4i [38]. On the other hand, Winkelmayer et al. [28] identified a significant association, though its direction varied between univariate and multivariate analyses, and Desai et al. [29] noted that men had a higher chance of starting metformin than other monotherapies.

Regarding race/ethnicity, black individuals showed a lower chance of starting metformin than sulfonylureas compared to white individuals [19,22,25]. White individuals also showed more chance of starting drugs with cardiovascular benefits than metformin compared to non-white [45]. However, there was no statistically significant association between race/ethnicity and combination therapy compared to metformin or sulfonylureas [19].

Individuals with lower socioeconomic status were associated with more frequent non-metformin prescriptions [29,37] or sulfonylurea prescriptions [22,25] compared to metformin. Conversely, Liu et al. [37] also found the same for a higher socioeconomic status category, and statistical significance was lost in the multilevel linear model.

3.3.4. Patient-Related Factors: Lifestyle and Metabolic

Nine studies [22–24,31,35,38,43,45,48] evaluated at least one lifestyle or metabolic variable (Table 6). A higher body mass index (BMI) was significantly associated with increased chance of starting metformin compared to sulfonylureas [22–24,35], DPP4i [38], or drugs without cardiovascular benefits [45]. However, when compared with agents that provide cardiovascular benefits, the chance of prescribing metformin initiation decreased with increasing BMI [45]. Liver disease was associated with a decreased chance of starting metformin compared to sulfonylureas [24,31], although no statistically significant association was observed when compared with DPP4i [38]. Individuals with dyslipidaemia had higher odds of initiating combination therapy than metformin [43]. For other variables within this category, either no statistically significant associations were found or the direction of associations was inconsistent.

3.3.5. Patient-Related Factors: Cardiovascular

The impact of twenty-seven cardiovascular variables (the most extensively represented group) was assessed in fourteen studies [22–25,31,32,34,35,38,40,43,45,47,48]. Hypertension was evaluated with initial therapy choice in five studies [22,31,35,43,45]. Three studies [22,31,35] reported statistically significant results, although the findings were conflicting. Abdelmoneim et al. [31] found that hypertension increased the odds of starting metformin compared to sulfonylureas, while Fujihara et al. [35] reported the opposite. Shin et al. [45] also linked hypertension to a decreased chance of starting metformin compared to drugs with or without cardiovascular benefits. However, in the same study, the use of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers (both antihypertensive agents) increased the odds of initiating metformin. No significant association was found between hypertension and combination therapy compared to metformin [43].

Two studies [22,25] reported that cardiovascular disease was negatively associated with metformin initiation compared to sulfonylureas. Similarly, Shin et al. [45] found the same when comparing metformin to drugs with or without cardiovascular benefits. In contrast, no statistically significant association was found by Wang et al. [32].

Three studies [22,31,43] reported that heart failure was negatively associated with metformin compared to sulfonylureas. Additionally, Wood et al. [43] reported that individuals with heart failure had higher odds of initiating combination therapy rather than metformin. Similarly, cerebrovascular disease was associated with decreased odds of initiating metformin

compared to sulfonylureas or combination therapy, although no significant association was found when comparing metformin to non-metformin therapies for either heart failure or cerebrovascular disease [43]. A similar pattern was found for valvular disease, which was associated with lower odds of initiating metformin compared to sulfonylureas [31].

3.3.6. Patient-Related Factors: Renal

Eleven studies [19,22,24,25,31,32,34,38,41,45,48] evaluated renal-related variables. It is unanimously reported that renal impairment, such as elevated serum creatinine, renal disease, chronic renal disease (CKD), renal failure, and diabetes-related nephropathy, was consistently associated with a reduced chance of initiating metformin therapy [19,22,24,25,31,32,34,38,45,48]. For example, Raebel et al. [22] showed that individuals with serum creatinine levels between 1.4 and $\leq$2 mg/dl, compared to those with levels < 1.4 mg/dL (reference group), had a relative risk of 2.21 (95% CI: 2.05–2.39) of starting sulfonylureas instead of metformin. Similarly, Wang et al. [32] found that individuals with renal disease had significantly lower odds (OR 0.14; 95% CI: 0.05–0.40) of starting metformin than other antidiabetic agents.

Regarding combination therapy, Brouwer et al. [19] reported that elevated serum creatinine levels were associated with a decreased chance of beginning combination therapy compared to sulfonylureas. Another study [41] observed that individuals with CKD were less frequently prescribed combination therapy than monotherapies such as sulfonylureas or DPP4i.

3.3.7. Patient-Related Factors: Other Clinical Factors

Twenty-one other clinical variables were assessed with the prescription profile in twelve studies [22,24,25,28,29,31,34,40,41,43–45]. Of these, 81% (17) of the variables were examined in only one study. Dementia was negatively associated with metformin initiation compared to sulfonylureas [24]. Wood et al. [43] reported that depression was positively associated with metformin initiation compared to sulfonylureas, which aligned with Raebel et al.'s [22] findings. However, these associations differed in direction from the univariable analysis reported by Abdelmoneim et al. [31]. Wood et al. [43] also reported that depression was positively associated with metformin initiation compared with combination therapy, and statistical significance was not found comparing non-metformin monotherapies with metformin. Juste et al. [40] reported that the prevalence of neuropsychiatric medication was higher among monotherapy initiators than among combination therapy initiators.

Regarding medication use, Desai et al. [29] reported that the chances of starting metformin rather than other monotherapies decreased for each additional prescription. However, Li [25] found no statistical association, and Winkelmayer et al. [28] observed that the odds of initiating metformin increased with a higher number of therapeutic class prescriptions compared to other antidiabetic agents. However, this pattern shifted in the univariable analysis, where individuals taking $\geq$9 medications had reduced odds of initiating metformin compared to those taking none. Two studies [40,41] observed that the prevalence of other types of medication use was higher among monotherapy initiators than among combination therapy initiators.

Wood et al. [43] presented that individuals with one to three comorbidities had a lower chance of starting sulfonylureas than metformin compared to those with no comorbidities. No statistically significant association was found when comparing four or more comorbidities to zero. Additionally, individuals with one to six comorbidities had lower odds of initiating non-metformin monotherapy compared to metformin, though this was not statistically significant when comparing seven or more comorbidities to zero. Nevertheless, compared to zero, one or more comorbidities reduced the odds of initiating combination therapy rather than metformin. Similarly, Campbell et al. [44] also reported that individuals with one or more comorbidities were less likely to start metformin in combination therapy

or other drug therapies instead of metformin alone compared to those with no comorbidities. Additionally, Juste et al. [40] noted that individuals who initiated combination therapy had a lower comorbidity score compared to those initiating monotherapy.

3.3.8. Disease-Related Factors

Data were extracted from fourteen studies [19,22–24,27,32–38,44,45] with ten variables collected. HbA1c was the most studied variable, being addressed in ten studies [19,22–24,27,33,35,36,38,44]. Five studies [19,22–24,35] stated that higher HbA1c levels were statistically associated with the initial sulfonylureas therapy instead of metformin, but one study did not find statistical significance [36]. Campbell et al. [44] also indicated that individuals with a higher HbA1c level were more likely to start non-metformin and combination therapy than metformin alone. On the other hand, Morita et al. [38] reported the opposite when comparing metformin to DPP4i, and no statistically significant association was noted when comparing metformin to thiazolidinediones [19]. Combination therapy was statistically associated with higher levels of HbA1c compared to metformin, sulfonylureas [19], or monotherapy [27].

Raebel et al. [22] also assessed fasting and random glucose levels and reported that both levels were higher among those who initiated sulfonylureas than those who initiated metformin in univariable analysis. Vashisht et al. [34] identified glucose and diabetes without complications as variables statistically associated with pioglitazone (TZD) choice instead of metformin. However, the study did not specify how glucose was measured, nor whether the association with pioglitazone was positive or negative.

Shorter diabetes duration [23,35] and earlier treatment initiation [23] were statistically associated with metformin initiation compared to sulfonylureas. Ouchi et al. [27] also found that combination therapy (89.62 days, SD 279.1) was prescribed significantly earlier ($p < 0.001$) than monotherapy (190.7 days, SD 366.2).

3.4. Quality Assessment

The quality assessment results for observational cohort studies are presented in Table 10. None of the studies ensured the similarity between compared groups (exposed vs. unexposed). It was also not possible to confirm the exposure measured similarly between groups and their validity and reliability, as all studies relied on secondary data without detailing the method of exposure measurement. None of the studies identified potential confounders or strategies to address them. Five studies [19,22,23,25,27] raised concerns regarding outcome validity and reliability, as the data sources might have reflected treatment adherence (e.g., pharmacy dispensing records) rather than prescriptions. Follow-up loss was either ignored [23] or avoided through inclusion/exclusion criteria [19–22,24–27] without strategies being expected to address it. Although five studies [19,22–25] used multivariable analysis (appropriate statistical analysis considered), none reported on the assumptions underlying the statistical models. Additionally, one study [27] did not report the statistical methods used.

Table 11 presents the results of quality assessment for observational cross-sectional studies. Eight studies [33–36,38,42,44,46] did not provide clear inclusion criteria, and eight studies [29,30,34–36,39,46,47] lacked information to infer the health status of the sample. It was also not possible to confirm the exposure measured validity and reliability. However, four studies [29,30,39,46] reported exposures without a gold standard measurement (e.g., age, sex, type of insurance), suggesting no risk of bias. Only two studies [32,44] identified potential confounding factors, but the associated statistical models also included these variables as outcomes of interest, raising concerns about whether they were exclusively used for confounding control. Therefore, only two other studies [42,47] addressed confounding through matching or stratification. Twelve studies [28–33,37,40,41,43–45] relied on pharmacy dispensing data or lacked clarity on data sources, undermining outcome

validity and reliability. None used appropriate statistical analyses due either to the absence of multivariable analysis [33,36,38–42,46,47], unreported statistical model assumptions [28–32,35,37,43–45,48], or omission of *p*-value results [34]. Overall, the quality assessment underscores multiple issues across the studies, pointing to a high risk of bias.

Table 10. Quality assessment and risk of bias of cohort studies included.

	Topics Assessed										
Retrospective Cohort Studies	**D1**	**D2**	**D3**	**D4**	**D5**	**D6**	**D7**	**D8**	**D9**	**D10**	**D11**
Brouwer et al. [19]	Unclear	Unclear	Unclear	No	No	Unclear	Unclear	Yes	Unclear	N/A	Unclear
Zhang et al. [20]	Unclear	Unclear	Unclear	No	No	Yes	Yes	Yes	Unclear	N/A	No
Sinclair et al. [21]	Unclear	Unclear	Unclear	No	No	Yes	Yes	Yes	Unclear	N/A	No
Raebel et al. [22]	Unclear	Unclear	Unclear	No	No	Yes	Unclear	Yes	Unclear	N/A	Unclear
Geier et al. [23]	Unclear	Unclear	Unclear	No	No	Yes	Unclear	Yes	Unclear	N/A	Unclear
Wright [24]	Unclear	Unclear	Unclear	No	No	Yes	Yes	Yes	Unclear	N/A	Unclear
Li [25]	Unclear	Unclear	Unclear	No	No	Yes	Unclear	Yes	Unclear	N/A	Unclear
Carrillo Balam [26]	Unclear	Unclear	Unclear	No	No	Yes	Yes	Yes	Unclear	N/A	No
Ouchi et al. [27]	Unclear	Unclear	Unclear	No	No	Unclear	Unclear	Yes	Unclear	N/A	Unclear

D1. Were the two groups similar and recruited from the same population? D2. Were the exposures measured similarly to assign people to both exposed and unposed groups? D3. Was the exposure measured in a valid and reliable way? D4. Were confounding factors identified? D5. Were strategies to deal with confounding factors stated? D6. Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)? D7. Were the outcomes measured in a valid and reliable way? D8. Was the follow up time reported and sufficient to be long enough for outcomes to occur? D9. Was follow up complete, and if not, were the reasons for loss of follow up described and explored? D10. Were strategies to address incomplete follow up utilised? D11. Was appropriate statistical analysis used? N/A, not applicable.

Table 11. Quality assessment and risk of bias of cross-sectional studies included.

	Topics Assessed							
Cross-Sectional Studies	**D1**	**D2**	**D3**	**D4**	**D5**	**D6**	**D7**	**D8**
Winkelmayer et al. [28]	Yes	Yes	Unclear	Yes	No	No	Unclear	Unclear
Desai et al. [29]	Yes	No	N/A	Yes	No	No	Unclear	Unclear
Grimes et al. [30]	Yes	No	N/A	Yes	No	No	Unclear	Unclear
Abdelmoneim et al. [31]	Yes	Yes	Unclear	Yes	No	No	Unclear	Unclear
Wang et al. (2013) [32]	Yes	Yes	Unclear	Yes	Yes	Unclear	Unclear	Unclear
Mitchell et al. [33]	No	Yes	Unclear	Unclear	No	No	Unclear	No
Vashisht et al. [34]	No	No	Unclear	Yes	No	No	Yes	Unclear
Fujihara et al. [35]	No	No	Unclear	Unclear	No	No	Yes	Unclear
Tanabe et al. [36]	No	No	Unclear	Unclear	No	No	Yes	No
Liu et al. [37]	Yes	Yes	Unclear	Yes	No	No	Unclear	Unclear
Morita et al. [38]	No	Yes	Unclear	Yes	No	No	Yes	No
Pinto et al. [39]	Yes	No	N/A	Yes	No	No	Yes	No
Juste et al. [40]	Yes	Yes	Unclear	Yes	No	No	Unclear	No
Moreno-Juste et al. [41]	Yes	Yes	Unclear	Yes	No	No	Unclear	No
Yabe et al. [42]	No	Yes	Unclear	Unclear	No	Yes	Yes	No
Wood et al. [43]	Yes	Yes	Unclear	Yes	No	No	Unclear	Unclear
Campbell et al. [44]	No	Yes	Unclear	Yes	Yes	Unclear	Unclear	Unclear
Shin et al. (2021) [45]	Yes	Yes	Unclear	Yes	No	No	Unclear	Unclear
Bonora et al. [46]	No	No	N/A	No	No	No	Yes	No
Barth et al. [47]	Yes	No	Unclear	Yes	No	Yes	Yes	No
Bouchi et al. [48]	Yes	Yes	Unclear	Yes	Unclear	Unclear	Yes	Unclear

D1. Were the criteria for inclusion in the sample clearly defined? D2. Were the study subjects and the setting described in detail? D3. Was the exposure measured in a valid and reliable way? D4. Were objective, standard criteria used for measurement of the condition? D5. Were confounding factors identified? D6. Were strategies to deal with confounding factors stated? D7. Were the outcomes measured in a valid and reliable way? D8. Was appropriate statistical analysis used? N/A, not applicable.

4. Discussion

This systematic review identified 30 studies exploring factors influencing first-line treatment decisions in T2DM, focusing on metformin and combination therapy. Although clinical decision-making can be inherently complex, the identification of key factors serves two main purposes: first, it enables the alignment of clinical practice with evidence-based guidelines by addressing gaps in knowledge and practice patterns; second, it aids in

tailoring treatment decisions to individual characteristics, thereby improving the quality of care and patient outcomes [51].

The prevalence of the two initial therapies analysed varied widely across studies, with the greatest variation observed in metformin initiation. For instance, Morita et al. [38] reported that 7.1% of their sample started metformin monotherapy, while Campbell et al. [44] found that 89% of participants initiated metformin monotherapy. This discrepancy may be attributed to differences in national clinical guidelines: Canadian guidelines recommend metformin as the first-line treatment unless contraindicated [52], while Japanese guidelines do not specify a preferred drug for initiation [53]. However, it is important to consider access to medicines and their relationship with cost and insurance coverage. Although newer oral agents have increased medication-related costs [54], in Japan, certain social security systems help reduce the burden of out-of-pocket expenses for individuals with low income [55]. Conversely, a 2016 report by Innovative Medicines Canada indicated that only 37% of new medicines received public reimbursement in Canada, and 90% of those included in public drug plans were subject to reimbursement restrictions [56]. These differences in access and coverage may contribute to the variation observed across studies, a notion supported by three studies [25,28,29] that analysed the impact of those factors on prescription patterns.

One hundred and five variables were evaluated as potential predictive factors influencing initial therapy decisions, with only 9.5% (10) showing no association with initial therapy choice. Among these, 25 variables were assessed with combination therapy, with 18 (72%) evaluated in just one study. Notably, only 11 of the 105 variables were assessed in five or more studies, indicating limited replication and, consequently, reduced robustness for most findings.

Age and sex were the most frequently assessed variables, reflecting the accessibility of demographic data. On the other hand, physician-related factors were the group with the least variables evaluated, perhaps due to challenges in extracting this information from secondary data sources. In contrast, the subgroup of cardiovascular factors included the highest number of assessed variables, which may reflect researchers' interest in studying these factors and the emphasis of guidelines on cardiovascular diseases in individuals with T2DM [57,58]. Among the 21 variables categorised as other clinical factors, several raised concerns regarding their clinical relevance, suggesting that data availability may have driven their inclusion.

Interestingly, while physician age was associated with initial therapy choice, years of experience were not, yielding contradictory results since age is typically linked to years of experience. Moreover, a survey study [59] found that years of experience influenced the factors considered when selecting first-line treatment, and a chart review study [60] revealed that more experienced physicians were less likely to follow guidelines. These findings highlight the complexity of physician-related factors and their interplay with clinical decision-making. Additionally, regarding associations found with physician specialties, it is important to consider that access to these specialties is strongly influenced by the patient's health status and the severity of the disease [61]. Healthcare utilisation is also significantly affected by the patient's socioeconomic status [62], and both socioeconomic status and health insurance were associated with prescription profile.

Patient-related factors, particularly age, also play a significant role in influencing therapy decisions, with metformin consistently linked to a younger age. A survey study [63] also reported that reasons cited by physicians to avoid initial dual therapy were often associated with patient age. Additionally, metformin initiation was negatively associated with several cardiovascular conditions and healthcare utilisation, indicating a tendency to

avoid metformin in individuals with poorer health status. This trend is surprising given its well-established safety profile [64] and its benefits for various conditions [65].

Concerns about these findings are heightened when comparing metformin to sulfonylureas, which are associated with an increased risk of hypoglycaemia [66]. Guidelines recommend a conservative approach to sulfonylureas, particularly in older individuals [4,67,68], and the scientific literature highlights their potential harm in those at high risk for cardiovascular disease [69]. The preference for sulfonylureas over metformin at high HbA1c levels is also not supported by guideline recommendations [4] or the scientific literature [70,71]. This observed preference for sulfonylureas, despite the presence of factors that would favour metformin use, underscores a misalignment between clinical practice and established guideline recommendations. However, this finding has already been reported by Giorda et al. [72], who, in their cross-sectional observational study, found that 70.6% of their sample presented characteristics that increased the risk of inappropriate sulfonylurea prescription. This tendency may be partially explained by the fact that sulfonylureas are the oldest class of oral antidiabetic agents, which may contribute to a sense of familiarity and perceived reliability among some physicians [73].

On the other hand, renal-related factors present a valid reason for avoiding metformin, as it should not be used in individuals with an estimated glomerular filtration rate < 30 mL/min per 1.73 m^2 [74]. This may explain why studies report that physicians are cautious about prescribing it to individuals with renal problems. Similarly, for BMI, the findings also align with guideline recommendations [4,67].

The positive association between high HbA1c levels and combination therapy is consistent with recommendations, particularly the consensus report from the ADA and EASD [4], which advocates for considering initial combination therapy in individuals with elevated HbA1c at diagnosis. Additionally, the tendency to avoid combination therapy in individuals with a high number of comorbidities aligns with Ismail-Beigi et al. [75], who highlighted the importance of less intensive treatment for those with multiple or severe comorbidities.

While these findings are noteworthy, it is important to recognise the significant methodological limitations and weaknesses that affect their validity and reliability. There is a lack of clear definitions for the medications included in combination therapy and those used as the reference category for comparison. Many studies simply refer to "combination therapy" and "other antidiabetic drugs," leading to ambiguity. Moreover, different reference categories were used for comparison with metformin or combination therapy. For instance, one study compared metformin alone or in combination with other antidiabetic medications that did not include metformin [32], while another compared metformin alone to other antihyperglycemic agents, including metformin used in combination therapy [44]. Adding to this are the inconsistent definitions of independent variables and the variation in the timing of their collection across studies. These inconsistencies not only hinder comparisons between studies but also undermine the external validity of the findings, limiting their generalisability.

The lack of efforts to ensure the similarity of groups and to identify and address potential confounder factors brought possible biases. For example, Zhang et al. [20] divided their sample into individuals <65 years and ≥65 years and reported twenty-five statistically significant differences between the two groups in twenty-nine variables analysed. This aligns with the scientific literature that has shown that the prevalence of cardiovascular disease increases with age [76], CKD is more common among older individuals [77], and multimorbidity is also more prevalent in older adults, strongly associated with increased healthcare utilisation and costs [78,79]. This information, along with the quality assessment results, raises concerns about the internal validity of the studies and suggests a high risk of bias in the findings.

Despite these internal and external validity concerns, some observed clinical practices deviate from established guidelines and the scientific literature. This misalignment highlights an urgent need to bridge the gap between clinical practice and evidence-based recommendations. Furthermore, more robust studies are essential, particularly those that emphasise external validation and minimise the risk of bias. These studies should facilitate direct comparisons across research, providing a more reliable basis for developing evidence-based recommendations grounded in high-quality data.

Strengths and Limitations

As far as we know, this is the first systematic review to map all factors driving physicians to choose metformin or combination therapy as first-line treatment. This review offers an exhaustive overview of the scientific literature, as no time or language restrictions were imposed, and grey literature was also included. Furthermore, compared to Mahmoud et al. [80], who conducted a meta-analysis of factors influencing antidiabetic drug prescribing for T2DM, including initiation therapy, this review expands the scope by incorporating nineteen additional studies.

All studies assessing the outcomes of interest were included, regardless of the reference group used for comparison. This inclusive approach enabled a broader range of comparisons but also introduced heterogeneity into the analysis. Additionally, due to the diversity in study designs, outcome measures, and treatment comparisons, it was not possible to assess the potential for reporting bias using standard tools such as funnel plots. This limits our ability to determine whether the published literature may overrepresent statistically significant findings. Moreover, the weak evidence in the main findings due to the low quality of the studies, which integrated this systematic review, should not be overlooked.

5. Conclusions

This systematic review identified several factors associated with metformin and combination therapy as first-line therapies in T2DM, revealing clinical practices not aligned with evidence-based medicine. However, few studies have focused on combination therapy, assessing physician-related factors, and even fewer have compared metformin with newer drugs, such as SGLT2i. Additionally, the studies included in this review exhibited low certainty evidence. Therefore, a robust methodology is needed to bring scientific evidence. As a result, further research is required to address these weaknesses and potential biases, provide stronger evidence, and ultimately support the findings reported in this review.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/diabetology6100114/s1, Table S1: Search query on PubMed (Medline); Table S2: Search query on Scopus; Table S3: Search on Web of Science.

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Abbreviations

The following abbreviations are used in this manuscript:

ACE	Angiotensin-converting enzyme
ADA	American Diabetes Association
ADs	Antidiabetic drugs
AHA	Other oral antihyperglycemic agents
ARBs	Angiotensin receptor blockers
BMI	Body mass index
Cat.	Categorical
CKD	Chronic kidney disease
Cont.	Continuous
COPD	Chronic obstructive pulmonary disease
CT	Combination therapy
DCSI	Diabetes complication severity index
DPP4i	Dipeptidyl peptidase-4 inhibitors
EASD	European Association for the Study of Diabetes
GLP1-RA	Glucagon-like peptidase-1 receptor agonists
Glip	Glipizide
GPs	General practitioners
HbA1c	Glycated haemoglobin
HDL	High-density lipoprotein
IHD	Ischemic heart disease
JBI	Joanna Briggs Institute
LDL	Low-density lipoprotein
Metf.	Metformin
MT	Monotherapy
Non-Metf	Non-metformin
PECO-S	Population, Exposure, Comparator, Outcomes, Study type
Pio	Pioglitazone
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
SGLT2i	Sodium-glucose transporter-2 inhibitors
SU	Sulfonylureas
TZDs	Thiazolidinediones
W/CVB	Drugs without cardiovascular benefits
WCVB	Drugs with cardiovascular benefits
WHO	World Health Organization

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