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Applying a "Big Data" Literature System to Recommend Antihypertensive Drugs for Hypertension Patients with Diabetes Mellitus

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Data Interpretation D
Manuscript Preparation E
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Background: The explosive increase in medical literature has changed therapeutic strategies, but it is challenging for physicians to keep up-to-date on the medical literature. Scientific literature data mining on a large-scale of can be used to refresh physician knowledge and better improve the quality of disease treatment.

Material/Methods: This paper reports on a reformulated version of a data mining method called MedRank, which is a network-based algorithm that ranks therapy for a target disease based on the MEDLINE literature database. MedRank algorithm input for this study was a clear definition of the disease model; the algorithm output was the accurate recommendation of antihypertensive drugs. Hypertension with diabetes mellitus was chosen as the input disease model. The ranking output of antihypertensive drugs are based on the Joint National Committee (JNC) guidelines, one through eight, and the publication dates, ≤1977, ≤1980, ≤1984, ≤1988, ≤1993, ≤1997, ≤2003, and ≤2013. The McNemar's test was used to evaluate the efficacy of MedRank based on specific JNC guidelines.

Results: The ranking order of antihypertensive drugs changed with the date of the published literature, and the MedRank algorithm drug recommendations had excellent consistency with the JNC guidelines in 2013 (P=1.00 from McNemar's test, Kappa=0.78, P=1.00). Moreover, the Kappa index increased over time. Sensitivity was better than specificity for MedRank; in addition, sensitivity was maintained at a high level, and specificity increased from 1997 to 2013.

Conclusions: The use of MedRank in ranking medical literature on hypertension with diabetes mellitus in our study suggests possible application in clinical practice; it is a potential method for supporting antihypertensive drug-prescription decisions.

MeSH Keywords: Antihypertensive Agents • Data Mining • Diabetes Mellitus • Hypertension

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Background

The vast body of medical literature continues to grow rapidly. MEDLINE is the premier bibliographic database of the world's largest medical library. There were over 22,000,000 references from 5,600 journals in MEDLINE in 2015. More than 869,000 new citations were added to MEDLINE in 2016. As the quantity of medical literature rapidly expands, keeping medical knowledge up-to-date has become a serious challenge for physicians. Thus, the ability to utilize the MEDLINE system effectively and rapidly is essential for medical professionals.

The explosion of data in the last decade is revolutionizing all aspects of human life. Advances in storage and analysis of healthcare data have offered both opportunities and challenges. Data mining is considered a promising tool that could inform personalized medicine and prescriptive analytics as well as clinical risk interventions [1]. In 2009, Google used data from billions of Google search queries to estimate the current level of weekly influenza activity in each region of the United States [2]. In addition to Google search data, a number of "big data" medical sources exist today, including electronic health records (EHR), genetic information, health insurance, registries, clinical trials, and literature databases [3]. One study detected thousands of associations between Mendelian and complex diseases by mining the medical records of over 110 million patients. Such work is meaningful for studies of the etiologies of rare diseases and also highlights the importance of data mining in a very large human population [4]. Data mining is also used for clinical pharmacology. Wu et al. established an ontology and a corpus of information to identified drug interactions by searching abstracts of publications in PubMed using text-mining techniques [5]. Network medicine is a data mining approach used to understand disease and discover therapeutics looking at molecules and molecular interactions [6]. Herskovic et al. applied graph-based ranking algorithm MedRank using concepts extracted from the text to identify the good indexing terms [7]. In 2013, Chen, Li and Han proposed that MedRank, a new network-based ranking algorithm, could be used to recommend medical treatments for a given disease based on data extracted from the MEDLINE system [8]. Thus, utilization of the increasing volume of medical data to explore accurate pathogenic research and provide therapeutic strategies by data mining is becoming a trend.

The innovation of data mining has made it possible to analyze and utilize mass publications. Network-based ranking, which use a graph structure, is a good tool for utilizing mass literature to discover new knowledge [9]. The concept was first referred to as PageRank. But PageRank was not applicable to medical ranking problems, because it was designed for one type only [10,11]. Chen et al. proposed using MedRank to recommend medical treatments for a given disease based upon the MEDLINE database [8]. MedRank uses the MEDLINE database to construct a medical information network [12] that is abstracted as a graph with referential relationships amongst different types of indirect objects extracted from MEDLINE. In their research, five types of diseases, including acquired immune deficiency syndrome, type 2 diabetes mellitus (DM2), amyotrophic lateral sclerosis (ALS), rheumatoid arthritis, and type B hepatitis, were analyzed by MedRank, and the output results was evaluated by physicians. The results demonstrated that the efficacy of MedRank was acceptable, but agreement with expert rankings for DM2 was worse compared with other diseases. This algorithm suggests that data mining may be a useful methodology for drug recommendations based on the medical literature.

Data mining professionals without medical backgrounds designed the formulas of the MedRank algorithm. Three key points about medical knowledge were ignored by MedRank algorithm. First, only simple and independent diseases without complications are suitable for the algorithm. Drug therapy strategies for DM2 patients are dependent on the personal characteristic related to the illness, such as age, obesity, insulin resistance, history of therapy, blood glucose levels, and other factors. Second, the drug outputs were not classified. Hypoglycemic agents were the most frequently recommended drugs, but the data included insulin, metformin, thiazolidinediones, and other agents. The results weren't specific to the drug category. Third, the weight of the publications, including time of publication and research type, was not considered. For these reasons, our medical team reformulated the MedRank algorithm. We made three major improvements in MedRank algorithm, including disease model input, drug recommendation output, and weight of the literature.

Cardiovascular and cerebrovascular diseases are responsible for most deaths in the world [13]. As the major risk factor for cardiovascular disease, hypertension is prevalent throughout the world [14]. A large body of evidence has demonstrated that antihypertensive therapy prevents the complications of hypertension, such as stroke, heart failure, and myocardial infarction, and decreases the mortality rate from cardiovascular disease [15]. Given the rapid discovery and development of the antihypertensive pharmaceutical industry and an increasing amount of evidence from clinical studies, antihypertensive strategies are frequently updated. Thus, it is helpful to establish a real-time antihypertensive recommendation system for physicians, especially those specializing in non-cardiovascular disease and family physicians. Hypertension with diabetes mellitus was chosen as the target disease model due to the large number of patients with this diagnosis and the abundance of clinical studies. All types of individual antihypertensive drugs were ranked, and the results were compared with existing guidelines to evaluate the efficacy of our reformulated MedRank algorithm.

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This study was an attempt to develop an advantageous data mining service for clinical strategies based on "big data" literature. The cooperation between data mining and medical groups may lead to potential successes in other medical domains.

Material and Methods

Data source

The literature analyzed in this study was present in the MEDLINE database maintained by the United States National Library of Medicine (NLM), which consists of more than 22 million journal citations and abstracts. MEDLINE (2015) corpus can be acquired in XML format (109 GB) from *http://www.nlm.nih.gov/bsd/licensee/access/medline_pubmed.html*. Permission to access the data was acquired by the Third Xiangya Hospital in China in June 2015. Each citation contains the bibliographical information of an article, such as article ID (PMID), title, author list, journal title, venue, publication type, and indexed Medical Subject Headings (MeSH) terms.

Search strategy

The MEDLINE database is indexed by NLM MeSH to produce a hierarchically structured medical thesaurus and to facilitate searching. MeSH is a comprehensive controlled vocabulary for the purpose of indexing journal articles and books in the life sciences, including the disease and drugs used in the current study. MeSH is widely used in medical areas such as the NLM catalog of book holdings and the ClinicalTrials.gov registry system. Therefore, a search strategy based on MeSH is responsible and efficient.

Improvement of MedRank and search details

Three major improvements were made to the current MedRank algorithm [8] as follows: disease model input, drug recommendation output, and weight of the literature.

Disease model input

Considering that it is easier to obtain a better recommendation ranking with a higher level of homogeneity in patients, a detailed diagnosis such as "hypertension combined with diabetes mellitus" but not "hypertension" was chosen as the input disease model. Therefore, the required criteria were as follows. First, the indexed MeSH terms must include "Humans" and "Hypertension. Second, an included article was required to be indexed by "Diabetes Mellitus". In the sub-analysis, hypertension with diabetic nephropathy was ranked by MedRank. "Kidney Failure, Chronic" or "Kidney Insufficiency, Chronic" was added as the input disease model, and the disease model also was selected based on different countries and areas, including the United States, Europe, Japan, and China according to MeSH terms. Supplementary Table 1 shows detailed information on the toponymy MeSH terms.

Drug recommendation output

As the therapeutic strategy for cardiovascular disease is comprehensive, the output should focus on only one kind of therapy. For example, patients suffering from myocardial infarction should receive aspirin, statins, angiotensin-converting enzyme inhibitors (ACEIs), calcium channel blockers (CCBs), nitroglycerin, and so on. It is not reasonable to rank all types of drugs recommended in the literature. Thus, only "antihypertensive drug" was ranked for "hypertension with diabetes mellitus" patients. In addition, the category of drugs in the past MedRank output was revised. Only the chemical drug name and category were defined as the output for the new reformulated MedRank. Therefore, articles on nine major categories of antihypertensive drugs were identified via MeSH indexed terms in the current study. The MeSH terms belonging to the nine major categories included 95 heading terms and 121 supplementary concepts. To build a model for antihypertensive treatment recommendations, only the index MeSH terms/concepts of the aforementioned antihypertensive agents that were labeled with the qualifiers "therapeutic use", "drug therapy", or "administration & dosage" were extracted for modeling.

Weight of the literature

Our model considered the publication date, publication type, institutions and design methods of literature. To ensure the quality of the included articles, the publication type information of an article was taken into consideration, which included the following indexed MeSH terms: "meta-analysis", "randomized controlled trial", "pragmatic clinical trial", "twin study", "controlled clinical trial", "observational study", "comparative study", and "case report". The type of publication, publication date, institutions and design methods were weighted, and the details are discussed below.

The edge weight of the graph was calculated based on 1) time factor (T), publication type (P) and institutions and design methods of clinical trials (I). For T information was extracted from the publication year of the article. If the article was published in the current year, weight=0; if it was published in the past 10 years, weight=1; otherwise, weight=−1. For P, according to the evidence grade of evidence-based medicine (EBM), good articles are associated with good publication types: "meta-analysis", "randomized controlled trial", "prospective studies" and "multicenter study", weight=1; otherwise, weight=0. For I, good articles use good clinical trial methods to control bias. For the list of prospective studies, random allocation,

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matched-pair analysis, multicenter studies, double-blind method\single-blind method, government financing, academies and institutes, government, nonprofit organizations, weight=1; otherwise, weight=0. The formula for the final weight was, weight=0.7+(T+P+I)/10.

From the viewpoint of EBM, we define "good articles" according to the evidence grade of EBM and the Cochrane Collaboration's risk of bias (RoB) tool. To control selection bias, good articles were indexed by "random allocation" and "prospective studies", rather than "loss to follow up" and "volunteers". To control information bias, good articles used good methods of "single-blind method" and "double-blind method", and were supported by government or reliable health institutes (e.g., "Financing, Government", "Academies and Institutes", "Government", and "Organizations, Nonprofit") rather than by drug manufacturers. To control confounding bias, good articles used good methods of "random allocation" and "matched-pair analysis".

Heterogeneous graph extraction

We constructed a star network graph (Figure 1) of five types of objects extracted from the MEDLINE corpus, including *Article*, *Author*, *Journal*, *Publication Type*, and *Antihypertensive Drug*. Every MEDLINE citation record that satisfied the "Human", "Hypertension" and "Diabetes Mellitus" selection criteria was disease modeled as an instance of the *Article* type object on the graph. For each article, authors, publishing journal, type of publication, and main antihypertensive drugs discussed in the article were modeled as instances of the *Author*, *Journal*, *Publication Type*, and *Antihypertensive Drug* object types, respectively, with an edge of the *Article* object on the heterogeneous graph.

Ranking on the heterogeneous graph

We applied MedRank to the heterogeneous graph produced in the graph extraction phase, which included the *Article*, *Author*, *Journal*, *Publication Type*, and *Antihypertensive Drug* object types, with *Article* as the center type. The algorithm iteratively computes the ranks of objects of the same type until convergence occurs based on the following updating function:

$$Rx_1 \leftarrow (a\left(\prod_{t=1}^{n-1} Wx_t C D^{-1}_{CX_{t+1}} Wcx_{t+1}\right) Wx_n c D^{-1}_{CX_1} Wcx_1 + (1-a)U/|X_1|)Rx_2$$

where t∈{1,...,n–1}, n is a positive integer greater than 1; X_t denotes the object type and X_1 is the target type, i.e., the antihypertensive drug in our case; R_(X_1)is a vector for the rank of X_1-type objects; C is the center type, i.e., the article in our case; U is an |X_1 |×|X_1 | unit matrix; |X_1| is the total number of objects of type X_1; α determines the weight of U/|X_1|; W_AB is a weighted adjacency matrix of type A and type B objects that stores the weighted links between the objects; and D_AB^(–1) is a diagonal matrix in which the diagonal value is equivalent to the sum of the W_AB row for the purposes of row normalization.

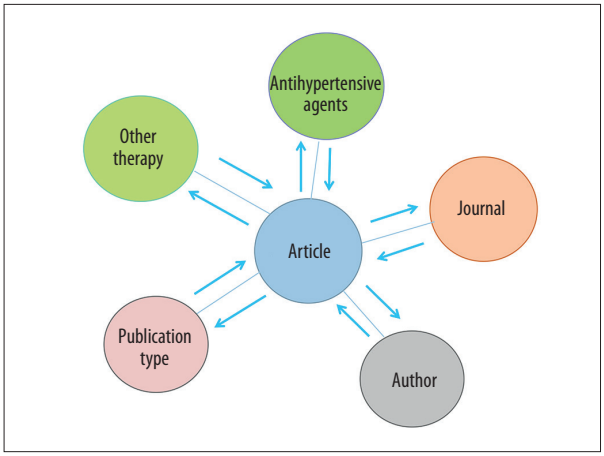

Figure 1. The star network graph of five objects extracted from the MEDLINE corpus.

Ranking results compared with Joint National Committee (JNC) guidelines

The Joint National Committee (JNC) guidelines are issued by American Heart Association and focus on detection, evaluation, and treatment of high blood pressure. JNC guidelines are one of the most authoritative hypertension guidelines and have played a leading role in the field of hypertension [16]. The efficacy of MedRank was compared with the JNC guidelines. The individual drugs were ranked based on the JNC guidelines one through eight, for publishing times ≤1977, ≤1980, ≤1984, ≤1988, ≤1993, ≤1997, ≤2003, and ≤2013 [16–22]. A ranking result indicated that the MedRank algorithm cannot analyze drug efficacy without support from a sufficiently credible or authoritative author and/or journal and/or a poor publication type. Thus, the drugs ranked in the top 20% according to MedRank were defined as preferred drugs, and those ranked in the bottom 20% with a score (not 0) were defined as contraindication drugs. The difference between countries was evaluated through a sub-analysis for publishing year ≤2013, and the results were compared with guidelines from different countries. Furthermore, each individual antihypertensive drug was divided into nine major antihypertensive drug categories: diuretics, adrenergic β-antagonists, adrenergic α-antagonists, adrenergic α, and β-antagonists, ACEIs, angiotensin receptor blockers (ARBs), CCBs, and ganglionic blockers. For the analysis, first the present antihypertensive category types were ranked based on the MedRank results. The ranking results were based on category at seven different time points, namely ≤1984, ≤1988, ≤1993, ≤1997, ≤2003, ≤2013 and ≤2015, are summarized.

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Table 1. Numbers of papers, authors and journals over time.

	Papers	Authors	Journals
≤1977	0	0	0
≤1980	0	0	0
≤1984	21	57	19
≤1988	165	553	101
≤1993	601	1,724	217
≤1997	1,017	3,044	313
≤2003	2,298	6,413	556
≤2013	5,363	17,399	1,144
≤2015	5,424	17,632	1,152

Statistical analysis

McNemar's test was used to evaluate the efficacy of MedRank with guidelines. The consistency between MedRank and guidelines was determined based on the Kappa index. The sensitivity and specificity of the algorithm were also measured. All analyses were performed using the SPSS (version 17.0) statistical software.

Results

The characteristic of extracted literature

The literature meeting the inclusion criterion of being published in the years ≤1977, ≤1980, ≤1984, ≤1988, ≤1993, ≤1997, ≤2003, ≤2013, and ≤2015 is shown in Table 1. The first manuscript that focused on hypertension with diabetes mellitus, was published in 1983. A total of 5,424 manuscripts, 17,632 authors, and 1,152 journals were extracted from the MEDLINE dataset based on the aforementioned inclusion criterion by October 2015. The total number of manuscripts clearly showed explosive growth. In addition, the number of authors and journals that focus on drug strategies for hypertension with diabetes mellitus increased.

The ranking results of MedRank

Although 21 papers met the inclusion criteria of ≤1984, only four papers mentioned a drug therapy strategy. Five individual antihypertensive drugs (clonidine, indapamide, atenolol, chlorthalidone, and metoprolol) were discussed in those four papers. Finally, metoprolol and clonidine were ranked number 1 and number 2. Indapamide, atenolol, and chlorthalidone were not entered into the ranking system because the authors were not authoritative. The whole individual antihypertensive drug ranking results determined by the MedRank algorithm at ≤1984, ≤1988, ≤1993, ≤1997, ≤2003, ≤2013, and ≤2015 are shown in Supplementary Tables 2–8. According to the recommendations of our model, 206 antihypertensive agents were included in our study, and the most influential antihypertensive drugs for hypertension with diabetes mellitus were ranked as follows: irbesartan, indapamide, amlodipine, losartan, candesartan, enalapril, olmesartan, hydrochlorothiazide, carvedilol, trandolapril, and ramipril by Oct 2015. The numbers of citations that supported the antihypertensive drugs irbesartan, indapamide, and amlodipine were 66 papers, 42 papers, and 52 papers, respectively. If necessary, MedRank can offer supporting literatures for individual drugs to allow further study (Supplementary Table 9). From the overall ranking results, the recommendation sequence was: ARBs, diuretics, CCBs ACEIs, adrenergic α and β-antagonists, adrenergic β-antagonists, adrenergic α antagonists, others and ganglionic blockers by Oct 2015. Moreover, the therapeutic strategy based on the category changed over time, as shown in Figure 2. As Figure 2 illustrates, ARBs, newly developed antihypertensive drugs, and diuretics, as well as traditional antihypertensive drugs, were shown to benefit hypertension with diabetes mellitus, based on the MedRank algorithm.

The efficacy evaluation of MedRank

The total number of individual drugs ranked were 2, 13, 27, 41, 48, 52, and 52 during the time periods ≤1984, ≤1988, ≤1993, ≤1997, ≤2003, ≤2013, and ≤2015, respectively. Finally, the results, including ≤1997, ≤2003, and ≤2013, were compared with JNC guidelines six through eight [16–18], because a sufficient number of drugs were available for analysis. According to JNC guideline six, ACEIs, α-blockers, calcium antagonists, and diuretics in low doses "are preferred" for diabetic hypertensive patients [16]. Thiazide diuretics, β-blockers, ACEIs, ARBs and CCBs were preferred according to JNC guideline seven [17] in a different subtype of diabetic hypertension. The initiation of a thiazide-type diuretic or ACEI or ARB or CCB, alone or in

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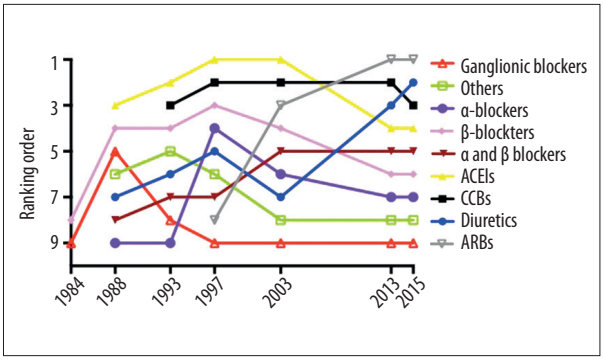

Figure 2. The ranking order of antihypertensive drug types over time.

combination, was recommended for non-black patients, whereas the initiation of thiazide-type diuretic or CCB, alone or in combination, was preferred for black patients in the updated JNC guideline eight [18]. Table 2 lists the recommendations and contraindications for drugs over time. Drugs marked with a star were not in accordance with the current JNC guidelines. To compare the consistency of MedRank and JNC guidelines, 18, 20, and 22 drugs were tested by McNemar's test and Kappa index. The consistency results are shown in Table 2 and Figure 3. The MedRank algorithm had excellent consistency with the guidelines in 2013 (P=1.00 from McNemar's test, Kappa=0.78, P=1.00). Moreover, the Kappa index increased over time. Sensitivity was better than specificity for MedRank. The sensitivity was 88.9% in 1997, 100% in 2003, and 90.9% in 2013. And the specificity was 55.6% in 1997, 60% in 2003, and 81.8% in 2013. Sensitivity was maintained a high level, and specificity increased from 1997 to 2013.

In the sub-analysis, irbesartan, losartan, olmesartan, benazepril, hydrochlorothiazide, and trandolapril were identified as ranked

Table 2. List of recommended and contraindicated drugs by MedRank and McNemar's test results compared with guidelines over time.

	Ranking order	≤1997	≤2003	≤2013
Recommendation	1	Captopril	Enalapril	Irbesartan
	2	Enalapril	Captopril	Amlodipine
	3	Felodipine	Nitrendipine	Losartan
	4	Nitrendipine	Irbesartan	Candesartan
	5	Atenolol*	Lisinopril	Indapamide
	6	Lisinopril	Candesartan	Enalapril
	7	Ramipril	Felodipine	Olmesartan
	8	Doxazosin	Atenolol	Hydrochlorothiazide
	9	Cilazapril	Ramipril	Carvedilol*
	10	–	Losartan	Trandolapril
	11	–	–	Ramipril
Contraindication	1	Guanfacine	Guanfacine	Guanfacine
	2	Moxonidine	Amosulalol*	Clonidine
	3	Acebutolol	Acebutolol*	Acebutolol
	4	Amosulalol	Spirapril*	Bisoprolol
	5	Manidipine*	Clonidine	Rilmenidine
	6	Delapril*	Cyclopenthiazide*	Spirapril*
	7	Nilvadipine*	Moxonidine	Indoramin
	8	Prazosin*	Prazosin	Amosulalol
	9	Clonidine	Indoramin	Prazosin
	10	–	Rilmenidine	Propranolol
	11	–	–	Cyclopenthiazide*
McNemar's Test		P=0.375	P=0.125	P=1.000

* Not consistent with the guideline.

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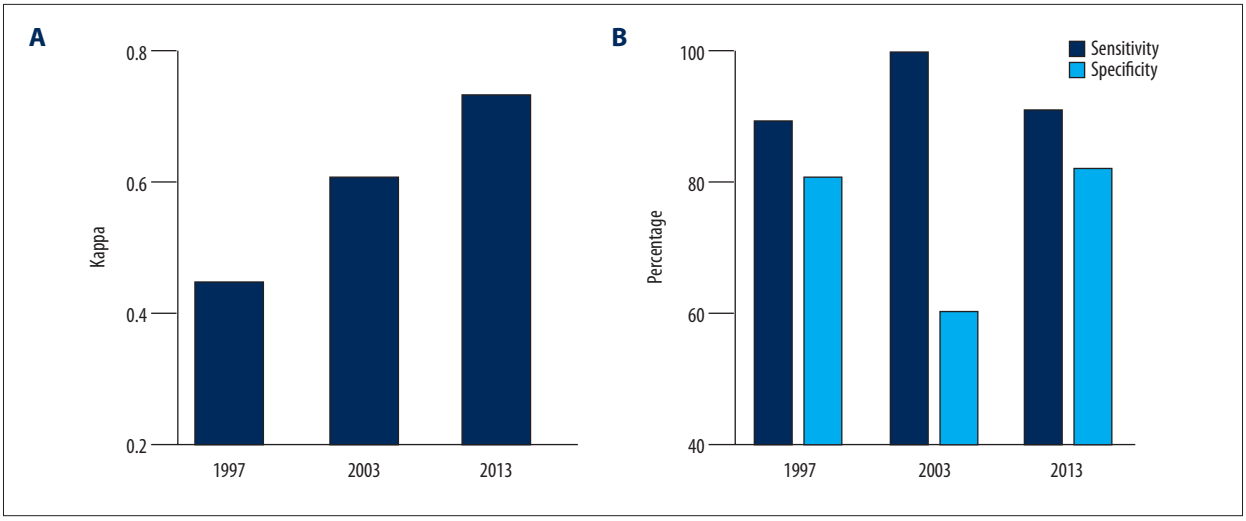

Figure 3. The concordance evaluation of MedRank compared with guidelines and over time. (**A**) The Kappa index of MedRank compared with guidelines over time. (**B**) The sensitivity and specificity of MedRank compared with guidelines over time.

Table 3. List of ranking results based on different countries or areas in 2013.

Ranking order	The United States	Europe	Japan	China
1	Olmesartan	Irbesartan	Candesartan	Enalapril
2	Irbesartan	Ramipril	Amlodipine	Felodipine
3	Amlodipine	Olmesartan	Olmesartan	Hydrochlorothiazide
4	Benazepril	Amlodipine	Losartan	Benazepril
5	Hydrochlorothiazide	Felodipine	Hydrochlorothiazide	Amlodipine
6	Carvedilol	Benazepril	Enalapril	–
7	Metoprolol	Enalapril	–	–
8	–	Trandolapril	–	–
9	–	Hydrochlorothiazide	–	–
10	–	Quinapril	–	–
11	–	Candesartan	–	–

results for hypertension with diabetic nephropathy in 2013. The results were consistent with guidelines. ARBs and ACEIs were recommended to be included in regiments to improve kidney function based on the available guidelines. Diuretics were recommended to be used combination with ARBs or ACEIs. In addition, the use of hydrochlorothiazide was supported by the literature, which evaluated the efficacy of a combination of losartan and hydrochlorothiazide compared with that of a maximum dose of losartan for the treatment of hypertensive patients [19].

Furthermore, a sub-analysis of the MedRank algorithm for different countries or areas, including the United States, Europe, Japan, and China (the mainland and Taiwan), was performed. ARBs, CCBs, ACEIs, and diuretics were on top of the ranking list, and adrenergic β-antagonists were on the bottom in the United States. The American ranking results of MedRank were consistent with the JNC guideline eight that recommends the thiazide-type diuretic, ACEI, ARB, or CCB for hypertension patients with diabetes. ARBs, CCBs, ACEIs, and diuretics were in the ranking list of Europe and Japan. A total of 8/11 and 4/6 individual drugs belong to the ACEI/ARB categories in the ranking list of Europe and Japan respectively. The 2013 European Society of Hypertension and the European Society of Cardiology guidelines (2013 ESH/ESC guidelines) [20] and 2014 Japanese guidelines [21] all recommend ACEI and ARB for hypertension with diabetes. ACEIs, CCB, and diuretics were on the ranking list based on Chinese literature. As was the case with the ESH/ESC and Japanese guidelines, Chinese guidelines [22] preferred ACEIs and ARBs, while CCBs and diuretics were considered second choices. The detailed results are shown in Table 3.

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Discussion

To the best of our knowledge, MedRank, proposed and named by Chen et al., is the first network-based ranking algorithm to rank the most influential treatments based on the medical literature [8]. Here, we reformulated the MedRank algorithm from a medical point of view. Input was a clear definition of the disease, while output was the accurate classification of antihypertensive drugs. More importantly, the weight of the logical chain was redefined based on publication type in the current MedRank algorithm. The efficacy of the new MedRank was compared with the corresponding guidelines, including publication time and country. The consistency increased over time, and excellent consistency was found in the 2013 worldwide ranking results (P=1.00 from McNemar's test, Kappa=0.78, P=1.00). Sensitivity was better than specificity for MedRank; meanwhile, sensitivity maintained a high level, and specificity increased from 1997 to 2013. Moreover, the ranking results were consistent with the guidelines from the corresponding countries and reflected the differences among countries. Thus, the new MedRank algorithm is beneficial for the selection of therapeutic strategies based on medical literature, which is growing in number at an ever-increasing speed. It is advantageous to explore text mining of "big data" from the MEDLINE database through cooperation between medical and data mining groups, and this endeavor may lead to potential success in other medical domains.

The MedRank is a new network-based algorithm that ranks heterogeneous objects in a medical information network [8]. The network-based algorithm was first referred to as the PageRank [9]. The idea behind it was essentially the eigenvector centrality that finds those "center" or important nodes such that their neighbors are themselves important. The key idea of PageRank was the rank propagation through links, i.e., ranks were propagated from one webpage to another through the hyperlinks. The PageRank has not only been used in the search engine of Google, but also in identifying the spatial concentration of human movement [23]. Nie et al. proposed a new strategy PopRank that extends the PageRank model from the webpage level to the web object level and from ranking homogeneous objects to heterogeneous ones [24]. Web object belong to different types, such as article or people, and can be related to each other in different ways. Sun et al. extended the ranking mechanism of PopRank from the Web objects to a network of heterogeneous objects. They established the RankClus, a ranking-based clustering algorithm that ranks bi-type objects in its own type within clusters [25]. The MedRank was the first work that introduced the network-based ranking approach to the medical domain that recommends treatments for a given disease based on data extracted from the MEDLINE system [8]. PageRank and PopRank are not applicable to the medical ranking problem, because PageRank is designed for one type only, i.e., webpage, and both of them are directly applicable only to directed graphs. MedRank's main difference from RankClus is that it is based on the available category labels and no clustering mechanism is involved. Data mining professionals without a medical background designed the formulas of the MedRank algorithm. There are three key points about medical knowledge that were ignored by the MedRank algorithm. Hence, we reformulated MedRank using text-mining techniques in MEDLINE to recommend the most influential treatment for a given disease; the results were specific to drug names and accounted for the level and time of the study.

The quantity of the literature that contained "hypertension combined with diabetes mellitus", and the numbers of categories and individual drugs dramatically increased from 1983 to 2015. This observation demonstrates the rapid discovery and development of the antihypertensive pharmaceutical industry, and the increasing number of clinical studies that were carried out. Thus, it is a big challenge for physicians to stay up-to-date with new medical knowledge, especially for non-cardiovascular physicians and family physicians.

Adverse effects, especially on glucose homeostasis, lipid profiles, renal function, and benefits for cardiovascular events were evaluated in a large number of clinical studies. Based on new evidence, the therapeutic strategy for "diabetic hypertension" have changed from the JNC guidelines one through eight. Based on the JNC guidelines one through five, no preferred antihypertensive drugs were recommended, and thiazides and related sulfonamide diuretics and β-blockers should be used with caution for diabetic hypertension [26–30]. ACEIs, α-blockers, CCBs, and diuretics were preferred in JNC guideline six [16]. Thiazide diuretics, β-blockers, ACEs, ARBs, and CCBs were preferred in JNC guideline seven [17], and β-blockers were excluded as an initial therapy in JNC guideline eight [18]. The therapeutic strategy evaluated by the current MedRank also changed. The ranking order of diuretics varied. Diuretics are the traditional antihypertensive drugs. The adverse effect on glucose and lipid metabolism limits their application, but new types of diuretics have improved the status on diabetic hypertension. ARBs, a relative new category of antihypertensive drugs, was ranked ninth in 1997. According to the updated clinical evidence, the recommendation of ARB has been strengthened. Meanwhile, the ranking order of ganglionic blockers decreased over time in the current MedRank algorithm. To evaluate the consistency of MedRank compared with existing guidelines, a statistical analysis using McNemar's test and the Kappa index were performed. The results demonstrated that the efficacy of MedRank was good in general, and improved over time. Furthermore, it is worth noting that the sensitivity was superior to the specificity. Because the primary purpose was drug recommendations for the target disease, the accuracy of ranking the top 10 results was more important. Beside

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recommendations, MedRank can offer the supporting literatures for individual drugs. These target publications will help physicians to update their knowledge and aid in medicine decisions. Thus, the new MedRank will be a useful tool to provide drug therapy recommendations for physicians.

It is attractive to recommend the therapy strategy for individual patient based on the personal characteristics. The alternative input of MedRank makes it possible to provide the precision medicine for individual patient. In our study, MedRank recommended ARBs and ACEIs for hypertension with diabetic nephropathy patients. Meanwhile, we attempted to analyze the subgroup results based on ethnic factors, but given that few indications of race were made in the literature, MedRank failed to rank drugs based on ethnic groups. More literature on various ethnic groups will make a MedRank ranking of drugs based on ethnic groups possible. In fact, more specific disease models, such as "female, black, diabetes mellitus, hypertension" could be used for input along with the increase of medical literature, and more accurate recommendations will be given by MedRank for an individual patient.

Furthermore, we also ranked the drugs based on literature from different countries or areas. In consideration of the quantity of literature and guidelines, analysis was not implemented in 1997 and 2003. In general, ranking results were consistent with the corresponding guidelines. The differences in therapeutic strategies among different countries reflected medication-taking behaviors and economies to some extent. On the whole, the prices of drugs on the Chinese rank list were cheaper than those in other countries. More importantly, recommendations of individual drugs may be more suitable for patients in a specific country, which is supported by the presence of relatively similar ethnic group and by the ease of obtaining a drug based on the country.

There are two limitations of this study MedRank algorithm. First, MedRank cannot recommend combinations of drugs. The combination of two drugs was viewed as two individual drugs for the purpose of ranking. The rational combination of antihypertensive drugs is a big challenge for MedRank. Second, assigning a weight based on publication time and type may not be suitable for other disease models. Thus, we need to adjust and test the assigned weight according to different disease models. The development of MedRank is a process that improves step by step. Advances in data mining and data sources will continue improve it.

Conclusions

In summary, we improved on an algorithm based on MEDLINE literature searching, named MedRank, using a data mining group. The proposed algorithm was evaluated according to different guidelines, including different countries and publication time. It has been shown that MedRank is effective and efficient. MedRank research suggests the possibility of establishing a real-time recommendation system for physicians to guide their clinical practice decisions for individual patients. For future research, we will extend this network-based ranking approach to other medical domains. Investigations into ranking medical treatments based on EHR databases, medical literature, genetic information, and health insurance will also be considered.

Conflicts of interest

None.

Supplementary Tables

Supplementary Table 1. Category of different countries and area based on MeSH.

Country or area	MeSH
China	China
	Hong Kong
	Macau
	Tibet
	Taiwan
Japan	Japan
	Tokyo
Europe	Europe
	Andorra
	Austria
	Balkan Peninsula
	Belgium
	Europe, Eastern
	Albania
	Baltic States
	Estonia
	Latvia
	Lithuania

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Country or area	MeSH
	Bosnia-Herzegovina
	Bulgaria
	Croatia
	Czech Republic
	Hungary
	Kosovo
	Macedonia (Republic)
	Moldova
	Montenegro
	Poland
	Republic of Belarus
	Romania
	Russia
	Bashkiria
	Dagestan
	Moscow
	Siberia
	Tatarstan
	Serbia
	Slovakia
	Slovenia
	Ukraine
	France
	Paris
	Germany
	Berlin
	Germany, East
	Germany, West
	Gibraltar
	Great Britain
	Channel Islands
	Guernsey
	England
	London
	Northern Ireland
	Scotland
	Hebrides
	Wales
	Greece
	Ireland
	Italy
	Rome
	Sicily
	Liechtenstein
	Luxembourg
	Mediterranean Region
	Mediterranean Islands
	Cyprus
	Malta
	Sicily
	Monaco
	Netherlands
	Portugal
	San Marino
	Scandinavian and Nordic Countries
	Denmark
	Greenland
	Finland
	Iceland
	Norway
	Svalbard
	Sweden
	Spain
	Switzerland
	Transcaucasia
	Armenia
	Azerbaijan
	Georgia (Republic)
	Vatican City
The United States	United States
	Appalachian Region
	Alabama
	Georgia
	Kentucky
	Maryland
	New York
	North Carolina
	Ohio
	Pennsylvania
	South Carolina
	Tennessee
	Virginia
	West Virginia
	Great Lakes Region
	Illinois
	Chicago

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Country or area	MeSH
	Indiana
	Michigan
	Minnesota
	New York
	New York City
	Ohio
	Pennsylvania
	Wisconsin
	Mid-Atlantic Region
	Delaware
	District of Columbia
	Maryland
	Baltimore
	New Jersey
	New York
	New York City
	Pennsylvania
	Philadelphia
	Midwestern United States
	Illinois
	Chicago
	Indiana
	Iowa
	Kansas
	Kentucky
	Michigan
	Minnesota
	Missouri
	Nebraska
	North Dakota
	Ohio
	Oklahoma
	South Dakota
	Wisconsin
	New England
	Connecticut
	Maine
	Massachusetts
	Boston

Country or area	MeSH
	New Hampshire
	Rhode Island
	Vermont
	Northwestern United States
	Idaho
	Montana
	Oregon
	Washington
	Wyoming
	Pacific States
	Alaska
	California
	Los Angeles
	San Francisco
	Hawaii
	Oregon
	Washington
	Southeastern United States
	Alabama
	Arkansas
	Florida
	Georgia
	Louisiana
	New Orleans
	Mississippi
	North Carolina
	South Carolina
	Virginia
	West Virginia
	Southwestern United States
	Arizona
	California
	Los Angeles
	San Francisco
	Colorado
	Nevada
	New Mexico
	Texas
	Utah

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Supplementary Table 2. List of ranking results in 1984.

Ranking order	Drug name	Medrank result
1	Metoprolol	0.759174311926605
2	Clonidine	0.240825688073394
3	Tocopherylquinone	0
4	Travoprost	0
5	Tibolone	0
6	Theodrenaline	0
7	Tetrahydropalmatine	0
8	Treprostinil	0
9	L-Proline, N2-((1S)-1-Carboxy-3-Phenylpropyl)-N6-((4-Hydroxyphenyl) Iminomethyl)-L-Lysyl-	0
10	Ryodipine	0
11	Cyclo(Methyltyrosyl-Isoleucyl-Prolyl-Leucyl)	0
12	Viprostol	0
13	Bis(P-Chlorophenyl)Acetic Acid	0
14	Chlorthalidone	0
15	Cyclopenthiazide	0
16	Nip 121	0
17	Cyclothiazide	0
18	N(1),N(11)-Diethylnorspermine	0
19	N(1),N(14)-Bis(Ethyl) Homospermine	0
20	Hydroflumethiazide	0
21	Scoparone	0
22	Sesamin	0
23	Terlipressin	0
24	Parathyroid Hormone-Related Protein (1-34)	0
25	Remikiren	0
26	Rilmenidine	0
27	Pempidine	0
28	Pentolinium Tartrate	0
29	Pinacidil	0
30	Mecamylamine	0
31	Minoxidil	0
32	Pargyline	0
33	Protoveratrines	0
34	Amlodipine	0
35	Todralazine	0
36	Bq 22-708	0
37	Lercanidipine	0
38	Veratrum Alkaloids	0
39	Magnesium Sulfate	0
40	Bretylium Tosylate	0
41	Diltiazem	0
42	Cromakalim	0
43	3,4-Dichloro-N-Methyl-N-(2-(1-Pyrrolidinyl)-Cyclohexyl)-Benzeneacetamide, (Trans)-Isomer	0
44	Adrenomedullin	0
45	Bethanidine	0
46	Debrisoquin	0
47	Kallidin	0
48	Ketanserin	0
49	Proline	0
50	Epoprostenol	0
51	Fenoldopam	0
52	Hexamethonium	0
53	Monatepil	0
54	Moxonidine	0
55	1-0-Octadecyl 2-0-Acetyl Sn-Glycero-3-Phosphorylcholine	0
56	Ferulic Acid	0
57	Moexipril	0
58	Nitroprusside	0
59	Nipradilol	0
60	Angiotensin I (1-7)	0
61	Aprikalim	0
62	Atrial Natriuretic Factor Prohormone (103-126)	0
63	2-(4-(2-Carboxyethyl) Phenethylamino)-5'-N-Ethylcarboxamidoadenosine	0
64	3-Nitropropionic Acid	0
65	5-(Dimethylamino)-N-(3,4-Dimethyl-5-Isoxazolyl)-1-Naphthalenesulfonamide	0
66	Lacidipine	0
67	Propranolol	0
68	Timolol	0

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Ranking order	Drug name	Medrank result
69	Essential 303 Forte	0
70	Oxprenolol	0
71	Penbutolol	0
72	Pindolol	0
73	N-Cyano-N'-(2-Nitroxyethyl)-3-Pyridinecarboximidamide Methanesulfonate	0
74	Diazoxide	0
75	Cicletanine	0
76	N,N-Di-N-Propyldopamine	0
77	Telmisartan	0
78	Clentiazem	0
79	Azepexole	0
80	Fk 409	0
81	Flesinoxan	0
82	Grayanotoxin I	0
83	Dihydralazine	0
84	Exp3174	0
85	Nicorandil	0
86	Latanoprost	0
87	Linsidomine	0
88	Lofexidine	0
89	Indorenate	0
90	Isopropyl Unoprostone	0
91	L 158809	0
92	Dorzolamide	0
93	Bimatoprost	0
94	Bosentan	0
95	Bq 788	0
96	Bendazole	0
97	Berbamine	0
98	Bimakalim	0
99	Budralazine	0
100	Dauricine	0
101	Diallyl Disulfide	0
102	Brimonidine	0
103	Cafedrine	0
104	Candoxatril	0
105	Teprotide	0
106	Nicardipine	0
107	Nimodipine	0
108	Cilazapril	0

Ranking order	Drug name	Medrank result
109	Fosinopril	0
110	Lisinopril	0
111	Bietaserpine	0
112	Guanadrel	0
113	Guanabenz	0
114	Nisoldipine	0
115	Nitrendipine	0
116	Felodipine	0
117	Captopril	0
118	Alacepril	0
119	Ceronapril	0
120	Imidapril	0
121	Trimethaphan	0
122	Niguldipine	0
123	Hydrochlorothiazide	0
124	Spirapril	0
125	Temocapril Hydrochloride	0
126	Zofenopril	0
127	Libenzapril	0
128	Efonidipine	0
129	Omapatrilat	0
130	Guanethidine	0
131	Amosulalol	0
132	Talinolol	0
133	Tobanum	0
134	Medroxalol	0
135	Trichlormethiazide	0
136	Mibefradil	0
137	Dihydroalprenolol	0
138	Metipranolol	0
139	Nadolol	0
140	Alprenolol	0
141	Bupranolol	0
142	Carteolol	0
143	Vincamine	0
144	1-Hexadecyl-2-Acetyl-Glycero-3-Phosphocholine	0
145	Candesartan	0
146	Eprosartan	0
147	Guanfacine	0
148	Methyldopa	0
149	Reserpine	0
150	Indapamide	0

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Ranking order	Drug name	Medrank result
151	Indoramin	0
152	Xipamide	0
153	Irbesartan	0
154	Olmesartan	0
155	Saprisartan Potassium	0
156	Phenoxybenzamine	0
157	Phentolamine	0
158	Piperoxan	0
159	Trimazosin	0
160	Urapidil	0
161	Doxazosin	0
162	Epanolol	0
163	Indenolol	0
164	Nebivolol	0
165	Prazosin	0
166	Tolazoline	0
167	Losartan	0
168	Naftopidil	0
169	Torsemide	0
170	Muzolimine	0
171	Ticrynafen	0
172	Chlorothiazide	0
173	Labetalol	0
174	Nilvadipine	0
175	Oleuropein	0
176	Metolazone	0
177	Benoxathian	0
178	Furosemide	0
179	Bumetanide	0

Ranking order	Drug name	Medrank result
180	Ethacrynic Acid	0
181	Atenolol	0
182	Valsartan	0
183	Cadralazine	0
184	Etozolin	0
185	Ae0047	0
186	Hydralazine	0
187	Carvedilol	0
188	Chlorisondamine	0
189	Acebutolol	0
190	Bisoprolol	0
191	Polythiazide	0
192	Isradipine	0
193	Bendroflumethiazide	0
194	Ramipril	0
195	1-Sarcosine-8-Isoleucine Angiotensin Ii	0
196	Benazepril	0
197	Delapril	0
198	Betaxolol	0
199	Celiprolol	0
200	Manidipine	0
201	Trandolapril	0
202	Enalapril	0
203	Perindopril	0
204	Quinapril	0
205	Buthiazide	0
206	Rentiapril	0

Supplementary Table 3. List of ranking results in 1988.

Ranking order	Drug name	Medrank result
1	Captopril	0.473355849953823
2	Metoprolol	0.158180154454512
3	Clonidine	0.0863908068126228
4	Acebutolol	0.0553206961592188
5	Atenolol	0.0367689007022248
6	Ketanserin	0.0367407357012854
7	Hydrochlorothiazide	0.0361650151920702
8	Carvedilol	0.02832419643352
9	Propranolol	0.0276603480796094

Ranking order	Drug name	Medrank result
10	Furosemide	0.026553934156425
11	Indapamide	0.0164606460241176
12	Enalapril	0.0123454845180882
13	Indoramin	0.00573323181248179
14	Veratrum Alkaloids	0
15	Theodrenaline	0
16	Tetrahydropalmatine	0
17	Tocopherylquinone	0
18	Travoprost	0

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Ranking order	Drug name	Medrank result
19	Tibolone	0
20	Lercanidipine	0
21	Treprostinil	0
22	Terlipressin	0
23	Chlorthalidone	0
24	Cyclopenthiazide	0
25	Chlorothiazide	0
26	Cyclothiazide	0
27	Bendroflumethiazide	0
28	Medroxalol	0
29	Scoparone	0
30	Sesamin	0
31	Trichlormethiazide	0
32	Metolazone	0
33	Labetalol	0
34	Kallidin	0
35	Proline	0
36	Mecamylamine	0
37	Epoprostenol	0
38	Fenoldopam	0
39	Hexamethonium	0
40	Pentolinium Tartrate	0
41	Pinacidil	0
42	Protoveratrines	0
43	Minoxidil	0
44	Pargyline	0
45	Pempidine	0
46	L-Proline, N2-((1S)-1-Carboxy-3-Phenylpropyl)-N6-((4-Hydroxyphenyl) Iminomethyl)-L-Lysyl-	0
47	Ryodipine	0
48	3,4-Dichloro-N-Methyl-N-(2-(1-Pyrrolidinyl)-Cyclohexyl)-Benzeneacetamide, (Trans)-Isomer	0
49	Viprostol	0
50	Bis(P-Chlorophenyl) Acetic Acid	0
51	Cyclo(Methyltyrosyl-Isoleucyl-Prolyl-Leucyl)	0
52	Diltiazem	0
53	Cromakalim	0
54	Debrisoquin	0
55	Adrenomedullin	0
56	Bethanidine	0
57	Bretylium Tosylate	0
58	1-Hexadecyl-2-Acetyl-Glycero-3-Phosphocholine	0
59	2-(4-(2-Carboxyethyl) Phenethylamino)-5'-N-Ethylcarboxa-midoadenosine	0
60	3-Nitropropionic Acid	0
61	Nipradilol	0
62	Moxonidine	0
63	1-0-Octadecyl 2-0-Acetyl Sn-Glycero-3-Phosphorylcholine	0
64	Atrial Natriuretic Factor Prohormone (103-126)	0
65	Azepexole	0
66	Bendazole	0
67	5-(Dimethylamino)-N-(3,4-Dimethyl-5-Isoxazolyl)-1-Naphthalenesu-lfonamide	0
68	Angiotensin I (1-7)	0
69	Aprikalim	0
70	Nitroprusside	0
71	Essential 303 Forte	0
72	Nilvadipine	0
73	Amlodipine	0
74	Penbutolol	0
75	Pindolol	0
76	Timolol	0
77	Cicletanine	0
78	Lacidipine	0
79	Moexipril	0
80	Clentiazem	0
81	N-Cyano-N'-(2-Nitroxyethyl)-3-Pyridinecarbo-ximidamide Methanesulfonate	0

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Ranking order	Drug name	Medrank result
82	Diazoxide	0
83	Vincamine	0
84	Indorenate	0
85	Isopropyl Unoprostone	0
86	Ferulic Acid	0
87	Fk 409	0
88	Todralazine	0
89	Linsidomine	0
90	Lofexidine	0
91	Buthiazide	0
92	L 158809	0
93	Latanoprost	0
94	Oxprenolol	0
95	Hydralazine	0
96	Bosentan	0
97	Bq 788	0
98	Brimonidine	0
99	Berbamine	0
100	Bimakalim	0
101	Bimatoprost	0
102	Cadralazine	0
103	Dorzolamide	0
104	Dihydralazine	0
105	Cafedrine	0
106	Bq 22-708	0
107	Budralazine	0
108	Magnesium Sulfate	0
109	Isradipine	0
110	Teprotide	0
111	Nicardipine	0
112	Zofenopril	0
113	Cilazapril	0
114	Felodipine	0
115	Bietaserpine	0
116	Guanadrel	0
117	Guanabenz	0
118	Nimodipine	0
119	Nisoldipine	0
120	Nitrendipine	0
121	Niguldipine	0
122	Alacepril	0
123	Ceronapril	0

Ranking order	Drug name	Medrank result
124	Bisoprolol	0
125	Parathyroid Hormone-Related Protein (1-34)	0
126	Trimethaphan	0
127	Omapatrilat	0
128	Spirapril	0
129	Temocapril Hydrochloride	0
130	Imidapril	0
131	Libenzapril	0
132	Efonidipine	0
133	Guanethidine	0
134	Amosulalol	0
135	Talinolol	0
136	Tobanum	0
137	Mibefradil	0
138	Lisinopril	0
139	Nebivolol	0
140	Dihydroalprenolol	0
141	Metipranolol	0
142	Nadolol	0
143	Alprenolol	0
144	Bupranolol	0
145	Carteolol	0
146	Monatepil	0
147	Candesartan	0
148	Eprosartan	0
149	Guanfacine	0
150	Methyldopa	0
151	Reserpine	0
152	Xipamide	0
153	Diallyl Disulfide	0
154	Flesinoxan	0
155	Irbesartan	0
156	Olmesartan	0
157	Saprisartan Potassium	0
158	Trimazosin	0
159	Urapidil	0
160	Doxazosin	0
161	Dauricine	0
162	Benoxathian	0
163	Naftopidil	0

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Ranking order	Drug name	Medrank result
164	Prazosin	0
165	Tolazoline	0
166	Losartan	0
167	Phenoxybenzamine	0
168	Phentolamine	0
169	Piperoxan	0
170	N(1),N(11)-Diethylnorspermine	0
171	Hydroflumethiazide	0
172	Nip 121	0
173	Rilmenidine	0
174	Grayanotoxin I	0
175	Exp3174	0
176	Ticrynafen	0
177	Bumetanide	0
178	Ethacrynic Acid	0
179	N,N-Di-N-Propyldopamine	0
180	Torsemide	0
181	Muzolimine	0
182	Candoxatril	0
183	Perindopril	0
184	Ramipril	0
185	Ae0047	0
186	N(1),N(14)-Bis(Ethyl) Homospermine	0
187	Rentiapril	0
188	Trandolapril	0
189	Telmisartan	0
190	Fosinopril	0
191	Chlorisondamine	0
192	Valsartan	0
193	Etozolin	0
194	Polythiazide	0
195	Oleuropein	0
196	Betaxolol	0
197	Celiprolol	0
198	Nicorandil	0
199	Epanolol	0
200	Indenolol	0
201	Benazepril	0
202	Delapril	0
203	Quinapril	0
204	Manidipine	0
205	Remikiren	0
206	1-Sarcosine-8-Isoleucine Angiotensin Ii	0

Supplementary Table 4. List of ranking results in 1993.

Ranking order	Drug name	Medrank result
1	Captopril	0.254264008122187
2	Felodipine	0.159737532387746
3	Enalapril	0.0960388207449173
4	Nitrendipine	0.0775724737693584
5	Metoprolol	0.0591895150356183
6	Ketanserin	0.0459614758275924
7	Atenolol	0.0458814394661039
8	Nicardipine	0.043577140678444
9	Indapamide	0.0365568297365585
10	Hydrochlorothiazide	0.0298915439942781
11	Isradipine	0.0290720690747235
12	Carvedilol	0.0248799715762873
13	Cilazapril	0.0192747528894099
14	Diltiazem	0.0130929255289666
15	Indoramin	0.0129022958200223
16	Furosemide	0.0125735816951632
17	Clonidine	0.00935996490308347
18	Propranolol	0.00888936696517029
19	Cyclopenthiazide	0.00513388423185767
20	Acebutolol	0.00331304295467089
21	Prazosin	0.00328568590838891
22	Amosulalol	0.00261771295183873
23	Nilvadipine	0.00177584332465582
24	Nisoldipine	0.00165652147733544
25	Delapril	0.00165652147733544
26	Manidipine	0.00165652147733544
27	Guanfacine	0.000188557980950717
28	Rilmenidine	0
29	Remikiren	0
30	Sesamin	0

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Ranking order	Drug name	Medrank result
31	Minoxidil	0
32	Lofexidine	0
33	Scoparone	0
34	Monatepil	0
35	N(1),N(14)-Bis(Ethyl) Homospermine	0
36	Nip 121	0
37	Chlorthalidone	0
38	N(1),N(11)-Diethylnorspermine	0
39	Parathyroid Hormone-Related Protein (1-34)	0
40	Cyclothiazide	0
41	Hydroflumethiazide	0
42	Bretylium Tosylate	0
43	Cromakalim	0
44	Debrisoquin	0
45	3,4-Dichloro-N-Methyl-N-(2-(1-Pyrrolidinyl)-Cyclohexyl)-Benzeneacetamide, (Trans)-Isomer	0
46	Adrenomedullin	0
47	Bethanidine	0
48	Kallidin	0
49	Proline	0
50	Mecamylamine	0
51	Epoprostenol	0
52	Fenoldopam	0
53	Hexamethonium	0
54	Tibolone	0
55	Tocopherylquinone	0
56	Travoprost	0
57	Terlipressin	0
58	Tetrahydropalmatine	0
59	Theodrenaline	0
60	Cyclo(Methyltyrosyl-Isoleucyl-Prolyl-Leucyl)	0
61	L-Proline, N2-((1S)-1-Carboxy-3-Phenylpropyl)-N6-((4-Hydroxyphenyl) Iminomethyl)-L-Lysyl-	0
62	Ryodipine	0
63	Treprostinil	0
64	Viprostol	0
65	Bis(P-Chlorophenyl) Acetic Acid	0
66	Moxonidine	0
67	1-0-Octadecyl 2-0-Acetyl Sn-Glycero-3-Phosphorylcholine	0
68	Ferulic Acid	0
69	Moexipril	0
70	Nitroprusside	0
71	Nipradilol	0
72	Angiotensin I (1-7)	0
73	Aprikalim	0
74	Atrial Natriuretic Factor Prohormone (103-126)	0
75	2-(4-(2-Carboxyethyl) Phenethylamino)-5'-N-Ethylcarboxam-idoadenosine	0
76	3-Nitropropionic Acid	0
77	5-(Dimethylamino)-N-(3,4-Dimethyl-5-Isoxazolyl)-1-Naphthalene-sulfonamide	0
78	Timolol	0
79	Essential 303 Forte	0
80	N,N-Di-N-Propyldopamine	0
81	Oxprenolol	0
82	Penbutolol	0
83	Pindolol	0
84	Diazoxide	0
85	Cicletanine	0
86	Lacidipine	0
87	Telmisartan	0
88	1-Hexadecyl-2-Acetyl-Glycero-3-Phosphocholine	0
89	N-Cyano-N'-(2-Nitroxyethyl)-3-Pyridinecarboxi-midamide Methanesulfonate	0
90	Azepexole	0

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Ranking order	Drug name	Medrank result
91	Nicorandil	0
92	Fk 409	0
93	Flesinoxan	0
94	Dorzolamide	0
95	Dihydralazine	0
96	Exp3174	0
97	L 158809	0
98	Latanoprost	0
99	Linsidomine	0
100	Grayanotoxin I	0
101	Indorenate	0
102	Isopropyl Unoprostone	0
103	Bimatoprost	0
104	Bosentan	0
105	Bq 788	0
106	Bendazole	0
107	Berbamine	0
108	Bimakalim	0
109	Budralazine	0
110	Dauricine	0
111	Diallyl Disulfide	0
112	Brimonidine	0
113	Cafedrine	0
114	Candoxatril	0
115	Pargyline	0
116	Spirapril	0
117	Temocapril Hydrochloride	0
118	Omapatrilat	0
119	Libenzapril	0
120	Efonidipine	0
121	Zofenopril	0
122	Nimodipine	0
123	Bietaserpine	0
124	Teprotide	0
125	Fosinopril	0
126	Lisinopril	0
127	Bendroflumethiazide	0
128	Chlorisondamine	0
129	Polythiazide	0
130	Cadralazine	0
131	Etozolin	0

Ranking order	Drug name	Medrank result
132	Bisoprolol	0
133	Ceronapril	0
134	Imidapril	0
135	Alacepril	0
136	Trimethaphan	0
137	Niguldipine	0
138	Guanadrel	0
139	Talinolol	0
140	Tobanum	0
141	Mibefradil	0
142	Medroxalol	0
143	Trichlormethiazide	0
144	Alprenolol	0
145	Metipranolol	0
146	Nadolol	0
147	Dihydroalprenolol	0
148	Bupranolol	0
149	Carteolol	0
150	Reserpine	0
151	Candesartan	0
152	Methyldopa	0
153	Guanabenz	0
154	Guanethidine	0
155	Eprosartan	0
156	Xipamide	0
157	Vincamine	0
158	Saprisartan Potassium	0
159	Irbesartan	0
160	Olmesartan	0
161	Valsartan	0
162	Muzolimine	0
163	Ticrynafen	0
164	Torsemide	0
165	Chlorothiazide	0
166	Labetalol	0
167	Bumetanide	0
168	Benoxathian	0
169	Naftopidil	0
170	Metolazone	0
171	Ethacrynic Acid	0
172	Oleuropein	0
173	Protoveratrines	0

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Ranking order	Drug name	Medrank result
174	Lercanidipine	0
175	Pinacidil	0
176	Pempidine	0
177	Pentolinium Tartrate	0
178	Veratrum Alkaloids	0
179	Bq 22-708	0
180	Clentiazem	0
181	Todralazine	0
182	Magnesium Sulfate	0
183	Amlodipine	0
184	Trimazosin	0
185	Quinapril	0
186	Buthiazide	0
187	Benazepril	0
188	Celiprolol	0
189	1-Sarcosine-8-Isoleucine Angiotensin Ii	0

Ranking order	Drug name	Medrank result
190	Rentiapril	0
191	Ae0047	0
192	Hydralazine	0
193	Ramipril	0
194	Trandolapril	0
195	Perindopril	0
196	Phentolamine	0
197	Piperoxan	0
198	Phenoxybenzamine	0
199	Urapidil	0
200	Doxazosin	0
201	Tolazoline	0
202	Nebivolol	0
203	Betaxolol	0
204	Indenolol	0
205	Losartan	0
206	Epanolol	0

Supplementary Table 5. List of ranking results in 1997.

Ranking order	Drug name	Medrank result
1	Captopril	0.150919484172668
2	Enalapril	0.140683321805829
3	Felodipine	0.0885911222743347
4	Nitrendipine	0.0841835323060517
5	Atenolol	0.0560408050272954
6	Lisinopril	0.0549804336677904
7	Ramipril	0.052858790304965
8	Doxazosin	0.0411374114452941
9	Cilazapril	0.0326428741457401
10	Furosemide	0.0269474477000088
11	Bendroflumethiazide	0.0231731248150525
12	Ketanserin	0.0228192110770944
13	Quinapril	0.0193671677877005
14	Lacidipine	0.0178953407794078
15	Metoprolol	0.0172294964377578
16	Fosinopril	0.0168287698288791
17	Indapamide	0.0167835795361915
18	Nicardipine	0.0164998283395523
19	Isradipine	0.0142915640604658
20	Carvedilol	0.0135320710998319
21	Nebivolol	0.0109132668566996

Ranking order	Drug name	Medrank result
22	Hydrochlorothiazide	0.0108346392732554
23	Amlodipine	0.00964555634832749
24	Diltiazem	0.00918714660265147
25	Chlorthalidone	0.00767246617196031
26	Candesartan	0.00733322970946846
27	Nisoldipine	0.00702487755993045
28	Trandolapril	0.00665928049873496
29	Benazepril	0.00487972395800254
30	Propranolol	0.00438836038886944
31	Indoramin	0.0035127168378336
32	Cyclopenthiazide	0.00222016977441181
33	Clonidine	0.002006780992633
34	Prazosin	0.00151577589792511
35	Nilvadipine	0.0013008603788335
36	Delapril	0.00098721605412767
37	Manidipine	0.00098721605412767
38	Amosulalol	0.000679289914480195
39	Acebutolol	0.000679289914480195
40	Moxonidine	0.000113700137274801
41	Guanfacine	5.3060064061574E-05

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Ranking order	Drug name	Medrank result
42	N-Cyano-N'-(2-Nitroxyethyl)-3-Pyridinecarboxi-midamide Methanesulfonate	0
43	Oxprenolol	0
44	Bretylium Tosylate	0
45	Metolazone	0
46	Theodrenaline	0
47	Medroxalol	0
48	Cyclothiazide	0
49	Kallidin	0
50	N(1),N(11)-Diethylnorspermine	0
51	Bethanidine	0
52	Adrenomedullin	0
53	N,N-Di-N-Propyldopamine	0
54	Hexamethonium	0
55	Chlorothiazide	0
56	Labetalol	0
57	Cyclo(Methyltyrosyl-Isoleucyl-Prolyl-Leucyl)	0
58	Debrisoquin	0
59	L-Proline, N2-((1S)-1-Carboxy-3-Phenylpropyl)-N6-((4-Hydroxyphenyl) Iminomethyl)-L-Lysyl-	0
60	Epoprostenol	0
61	Travoprost	0
62	Cromakalim	0
63	Viprostol	0
64	Treprostinil	0
65	Bis(P-Chlorophenyl) Acetic Acid	0
66	Tocopherylquinone	0
67	Fenoldopam	0
68	Scoparone	0
69	Trichlormethiazide	0
70	3,4-Dichloro-N-Methyl-N-(2-(1-Pyrrolidinyl)-Cyclohexyl)-Benzeneacetamide, (Trans)-Isomer	0
71	Sesamin	0
72	Ryodipine	0
73	Tibolone	0
74	Terlipressin	0
75	Tetrahydropalmatine	0
76	Buthiazide	0
77	5-(Dimethylamino)-N-(3,4-Dimethyl-5-Isoxazolyl) -1-Naphthalene-sulfonamide	0
78	Angiotensin I (1-7)	0
79	3-Nitropropionic Acid	0
80	1-Hexadecyl-2-Acetyl-Glycero-3-Phosphocholine	0
81	2-(4-(2-Carboxyethyl) Phenethylamino)-5'-N-Ethylcarboxa-midoadenosine	0
82	Oleuropein	0
83	Berbamine	0
84	Azepexole	0
85	Aprikalim	0
86	Atrial Natriuretic Factor Prohormone (103-126)	0
87	1-0-Octadecyl 2-0-Acetyl Sn-Glycero-3-Phosphorylcholine	0
88	Essential 303 Forte	0
89	Clentiazem	0
90	Timolol	0
91	Penbutolol	0
92	Pindolol	0
93	Nitroprusside	0
94	Nipradilol	0
95	Moexipril	0
96	Diazoxide	0
97	Cicletanine	0
98	Vincamine	0
99	Indorenate	0
100	Todralazine	0
101	Ferulic Acid	0
102	Fk 409	0
103	Linsidomine	0

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Ranking order	Drug name	Medrank result
104	Lofexidine	0
105	Latanoprost	0
106	Isopropyl Unoprostone	0
107	L 158809	0
108	Hydralazine	0
109	Bq 788	0
110	Brimonidine	0
111	Bosentan	0
112	Bimakalim	0
113	Bimatoprost	0
114	Dorzolamide	0
115	Dihydralazine	0
116	Budralazine	0
117	Cafedrine	0
118	Bq 22-708	0
119	Omapatrilat	0
120	Spirapril	0
121	Efonidipine	0
122	Imidapril	0
123	Libenzapril	0
124	Temocapril Hydrochloride	0
125	Bietaserpine	0
126	Guanadrel	0
127	Nimodipine	0
128	Zofenopril	0
129	Teprotide	0
130	Telmisartan	0
131	Chlorisondamine	0
132	Polythiazide	0
133	Cadralazine	0
134	Etozolin	0
135	Bisoprolol	0
136	Alacepril	0
137	Ceronapril	0
138	Niguldipine	0
139	Parathyroid Hormone-Related Protein (1-34)	0
140	Trimethaphan	0
141	Talinolol	0
142	Tobanum	0
143	Mibefradil	0
144	Bendazole	0
145	Flesinoxan	0
146	Alprenolol	0
147	Metipranolol	0
148	Nadolol	0
149	Dihydroalprenolol	0
150	Bupranolol	0
151	Carteolol	0
152	Reserpine	0
153	Monatepil	0
154	Methyldopa	0
155	Guanabenz	0
156	Guanethidine	0
157	Eprosartan	0
158	Xipamide	0
159	Diallyl Disulfide	0
160	Saprisartan Potassium	0
161	Irbesartan	0
162	Olmesartan	0
163	Exp3174	0
164	Nip 121	0
165	Rilmenidine	0
166	Hydroflumethiazide	0
167	Grayanotoxin I	0
168	Torsemide	0
169	Ethacrynic Acid	0
170	Dauricine	0
171	Bumetanide	0
172	Muzolimine	0
173	Ticrynafen	0
174	Pargyline	0
175	Pempidine	0
176	Minoxidil	0
177	Proline	0
178	Mecamylamine	0
179	Pentolinium Tartrate	0
180	Veratrum Alkaloids	0
181	Magnesium Sulfate	0
182	Lercanidipine	0
183	Pinacidil	0
184	Protoveratrines	0

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Ranking order	Drug name	Medrank result
185	Celiprolol	0
186	Remikiren	0
187	Betaxolol	0
188	Epanolol	0
189	Indenolol	0
190	1-Sarcosine-8-Isoleucine Angiotensin Ii	0
191	Ae0047	0
192	Valsartan	0
193	Perindopril	0
194	N(1),N(14)-Bis(Ethyl) Homospermine	0
195	Rentiapril	0
196	Urapidil	0
197	Phenoxybenzamine	0
198	Trimazosin	0
199	Benoxathian	0
200	Naftopidil	0
201	Phentolamine	0
202	Candoxatril	0
203	Nicorandil	0
204	Losartan	0
205	Piperoxan	0
206	Tolazoline	0

Supplementary Table 6. List of ranking results in 2003.

Ranking order	Drug name	Medrank result
1	Enalapril	0.15002054465503
2	Captopril	0.0831136513337003
3	Nitrendipine	0.0556465015370699
4	Irbesartan	0.0505136940106168
5	Lisinopril	0.0463526819550658
6	Candesartan	0.0461026713657262
7	Felodipine	0.0449235870606363
8	Atenolol	0.0396698261439649
9	Ramipril	0.0368999585891977
10	Losartan	0.0344250843122766
11	Fosinopril	0.0326933384043416
12	Amlodipine	0.0326600377088823
13	Trandolapril	0.0312454974470637
14	Carvedilol	0.030393180874849
15	Doxazosin	0.0294592664662446
16	Nisoldipine	0.0292962658125306
17	Indapamide	0.0256378916582746
18	Cilazapril	0.0172709364631387
19	Isradipine	0.0167425324873232
20	Hydrochlorothiazide	0.0161599577218082
21	Quinapril	0.0143129570990151
22	Ketanserin	0.0141511375769114
23	Bendroflumethiazide	0.0141345587430979
24	Metoprolol	0.0139582284191943
25	Benazepril	0.0133456627217982
26	Furosemide	0.0120792150904337
27	Nebivolol	0.00895131620604635
28	Temocapril Hydrochloride	0.00831937752403704
29	Chlorthalidone	0.00784688238365008
30	Manidipine	0.0074983971155167
31	Lercanidipine	0.00715587268459299
32	Diltiazem	0.00553725034288513
33	Nicardipine	0.00509280804821371
34	Lacidipine	0.00434654723799898
35	Nilvadipine	0.00253691327760803
36	Delapril	0.0024087715515065
37	Propranolol	0.00177971886700227
38	Alacepril	0.00152663497757573
39	Rilmenidine	0.00138332235760662
40	Indoramin	0.00113083621370959
41	Prazosin	0.000998686428163052
42	Moxonidine	0.000747822537235915
43	Cyclopenthiazide	0.000535240897742833
44	Clonidine	0.000391181616635442
45	Spirapril	0.000249522826613601
46	Acebutolol	0.000169480926824553
47	Amosulalol	0.000168884391747055
48	Guanfacine	1.56659288959006E-05
49	Lofexidine	0
50	Chlorothiazide	0
51	Medroxalol	0

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Ranking order	Drug name	Medrank result
52	Cyclothiazide	0
53	Buthiazide	0
54	N(1),N(11)-Diethylnorspermine	0
55	N-Cyano-N'-(2-Nitroxyethyl)-3-Pyridinecarboxi-midamide Methanesulfonate	0
56	N,N-Di-N-Propyldopamine	0
57	Cyclo(Methyltyrosyl-Isoleucyl-Prolyl-Leucyl)	0
58	L-Proline, N2-((1S)-1-Carboxy-3-Phenylpropyl)-N6-((4-Hydroxyphenyl) Iminomethyl)-L-Lysyl-	0
59	Ryodipine	0
60	Treprostinil	0
61	Viprostol	0
62	Bis(P-Chlorophenyl) Acetic Acid	0
63	Bretylium Tosylate	0
64	Cromakalim	0
65	Debrisoquin	0
66	3,4-Dichloro-N-Methyl-N-(2-(1-Pyrrolidinyl)-Cyclohexyl)-Benzeneacetamide, (Trans)-Isomer	0
67	Adrenomedullin	0
68	Bethanidine	0
69	Scoparone	0
70	Sesamin	0
71	Terlipressin	0
72	Metolazone	0
73	Labetalol	0
74	Trichlormethiazide	0
75	Epoprostenol	0
76	Tocopherylquinone	0
77	Travoprost	0
78	Tetrahydropalmatine	0
79	Theodrenaline	0
80	Tibolone	0

Ranking order	Drug name	Medrank result
81	3-Nitropropionic Acid	0
82	5-(Dimethylamino)-N-(3,4-Dimethyl-5-Isoxazolyl)-1-Naphthalene-sulfonamide	0
83	2-(4-(2-Carboxyethyl) Phenethylamino)-5'-N-Ethylcarboxa-midoadenosine	0
84	1-0-Octadecyl 2-0-Acetyl Sn-Glycero-3-Phosphorylcholine	0
85	1-Hexadecyl-2-Acetyl-Glycero-3-Phosphocholine	0
86	Azepexole	0
87	Oleuropein	0
88	Atrial Natriuretic Factor Prohormone (103-126)	0
89	Angiotensin I (1-7)	0
90	Aprikalim	0
91	Nipradilol	0
92	Timolol	0
93	Essential 303 Forte	0
94	Pindolol	0
95	Oxprenolol	0
96	Penbutolol	0
97	Moexipril	0
98	Nitroprusside	0
99	Cicletanine	0
100	Clentiazem	0
101	Diazoxide	0
102	Todralazine	0
103	Vincamine	0
104	Fk 409	0
105	Hydralazine	0
106	Ferulic Acid	0
107	Latanoprost	0
108	Linsidomine	0
109	L 158809	0
110	Indorenate	0
111	Isopropyl Unoprostone	0
112	Dihydralazine	0

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Ranking order	Drug name	Medrank result
113	Bosentan	0
114	Bq 788	0
115	Bimatoprost	0
116	Berbamine	0
117	Bimakalim	0
118	Budralazine	0
119	Dorzolamide	0
120	Bq 22-708	0
121	Brimonidine	0
122	Cafedrine	0
123	Efonidipine	0
124	Omapatrilat	0
125	Libenzapril	0
126	Ceronapril	0
127	Imidapril	0
128	Bietaserpine	0
129	Guanadrel	0
130	Nimodipine	0
131	Zofenopril	0
132	Teprotide	0
133	Niguldipine	0
134	Etozolin	0
135	Polythiazide	0
136	Cadralazine	0
137	Ae0047	0
138	Valsartan	0
139	Parathyroid Hormone-Related Protein (1-34)	0
140	Trimethaphan	0
141	Bisoprolol	0
142	Telmisartan	0
143	Chlorisondamine	0
144	Tobanum	0
145	Alprenolol	0
146	Talinolol	0
147	Flesinoxan	0
148	Mibefradil	0
149	Metipranolol	0
150	Nadolol	0
151	Dihydroalprenolol	0
152	Bupranolol	0
153	Carteolol	0
154	Bendazole	0

Ranking order	Drug name	Medrank result
155	Reserpine	0
156	Monatepil	0
157	Methyldopa	0
158	Guanabenz	0
159	Guanethidine	0
160	Xipamide	0
161	Diallyl Disulfide	0
162	Saprisartan Potassium	0
163	Eprosartan	0
164	Olmesartan	0
165	Grayanotoxin I	0
166	Exp3174	0
167	Hydroflumethiazide	0
168	Veratrum Alkaloids	0
169	Magnesium Sulfate	0
170	Ticrynafen	0
171	Bumetanide	0
172	Muzolimine	0
173	Nip 121	0
174	Torsemide	0
175	Protoveratrines	0
176	Proline	0
177	Mecamylamine	0
178	Kallidin	0
179	Fenoldopam	0
180	Hexamethonium	0
181	Pentolinium Tartrate	0
182	Pinacidil	0
183	Pempidine	0
184	Minoxidil	0
185	Pargyline	0
186	Betaxolol	0
187	Celiprolol	0
188	Indenolol	0
189	Nicorandil	0
190	Epanolol	0
191	Rentiapril	0
192	Perindopril	0
193	N(1),N(14)-Bis(Ethyl) Homospermine	0
194	Remikiren	0

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Ranking order	Drug name	Medrank result
195	1-Sarcosine-8-Isoleucine Angiotensin Ii	0
196	Candoxatril	0
197	Naftopidil	0
198	Trimazosin	0
199	Benoxathian	0
200	Ethacrynic Acid	0
201	Dauricine	0
202	Piperoxan	0
203	Tolazoline	0
204	Phentolamine	0
205	Urapidil	0
206	Phenoxybenzamine	0

Supplementary Table 7. List of ranking results in 2013.

Ranking order	Drug name	Medrank result
1	Irbesartan	0.105587165273498
2	Amlodipine	0.0921097605746109
3	Losartan	0.0775967619717653
4	Candesartan	0.0767171502650149
5	Indapamide	0.0671395688299851
6	Enalapril	0.0537448309009243
7	Olmesartan	0.0517849207499419
8	Hydrochlorothiazide	0.0432273102851592
9	Carvedilol	0.0424389410761461
10	Trandolapril	0.0357779048569068
11	Ramipril	0.0341874541578334
12	Manidipine	0.0325614530925225
13	Atenolol	0.0310179234899641
14	Benazepril	0.0306262271893328
15	Lisinopril	0.0267443766440223
16	Captopril	0.0256427038526556
17	Metoprolol	0.0242474489424228
18	Nitrendipine	0.0174136828486803
19	Delapril	0.0143179726241133
20	Doxazosin	0.0141556627073222
21	Felodipine	0.0116404881367631
22	Nebivolol	0.0110244385614901
23	Fosinopril	0.0085673496363659
24	Eprosartan	0.00772730410625312
25	Nisoldipine	0.00707071015115492
26	Quinapril	0.00666262560995991
27	Isradipine	0.00596632478493657
28	Ketanserin	0.00581346469020174
29	Cilazapril	0.005724007745483
30	Imidapril	0.00475211362938649
31	Moxonidine	0.0042267350183598
32	Bendroflumethiazide	0.00369595832562386
33	Diltiazem	0.00363708728397857
34	Furosemide	0.00314395268074787
35	Lercanidipine	0.00248043396115954
36	Temocapril Hydrochloride	0.00243211089271443
37	Chlorthalidone	0.00214394551331935
38	Nicardipine	0.00135235124519355
39	Lacidipine	0.000778006368820013
40	Nilvadipine	0.000585580464206557
41	Alacepril	0.000558796782863386
42	Cyclopenthiazide	0.000557558817343545
43	Propranolol	0.000487749089155929
44	Prazosin	0.000397098402886241
45	Amosulalol	0.000318778278874468
46	Indoramin	0.000262591422978599
47	Spirapril	0.000250286402132348
48	Rilmenidine	0.000235995560933647
49	Bisoprolol	0.000220154546314218
50	Acebutolol	0.000128198338794862
51	Clonidine	0.000116741812596155
52	Guanfacine	1.84140618641404E-06
53	Monatepil	0
54	Ryodipine	0
55	L-Proline, N2-((1S)-1-Carboxy-3-Phenylpropyl)-N6-((4-Hydroxyphenyl) Iminomethyl)-L-Lysyl-	0
56	N(1),N(11)-Diethylnorspermine	0
57	Cyclothiazide	0

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Ranking order	Drug name	Medrank result
58	3,4-Dichloro-N-Methyl-N-(2-(1-Pyrrolidinyl)-Cyclohexyl)-Benzeneacetamide, (Trans)-Isomer	0
59	Oxprenolol	0
60	Latanoprost	0
61	Tetrahydropalmatine	0
62	L 158809	0
63	Bretylium Tosylate	0
64	Linsidomine	0
65	Lofexidine	0
66	Bethanidine	0
67	Adrenomedullin	0
68	Remikiren	0
69	Scoparone	0
70	Parathyroid Hormone-Related Protein (1-34)	0
71	Tocopherylquinone	0
72	Sesamin	0
73	Terlipressin	0
74	Tibolone	0
75	Theodrenaline	0
76	Oleuropein	0
77	N(1),N(14)-Bis(Ethyl) Homospermine	0
78	Viprostol	0
79	Cyclo(Methyltyrosyl-Isoleucyl-Prolyl-Leucyl)	0
80	Bis(P-Chlorophenyl) Acetic Acid	0
81	Nip 121	0
82	Travoprost	0
83	N,N-Di-N-Propyldopamine	0
84	Treprostinil	0
85	Isopropyl Unoprostone	0
86	1-Hexadecyl-2-Acetyl-Glycero-3-Phosphocholine	0
87	2-(4-(2-Carboxyethyl) Phenethylamino)-5'-N-Ethylcarboxa-midoadenosine	0
88	Nipradilol	0
89	1-0-Octadecyl 2-0-Acetyl Sn-Glycero-3-Phosphorylcholine	0
90	3-Nitropropionic Acid	0
91	Aprikalim	0
92	Atrial Natriuretic Factor Prohormone (103-126)	0
93	5-(Dimethylamino)-N-(3,4-Dimethyl-5-Isoxazolyl)-1-Naphthalene-sulfonamide	0
94	Angiotensin I (1-7)	0
95	Nitroprusside	0
96	Timolol	0
97	Essential 303 Forte	0
98	Penbutolol	0
99	Pindolol	0
100	Telmisartan	0
101	Cicletanine	0
102	Moexipril	0
103	Clentiazem	0
104	Diazoxide	0
105	Azepexole	0
106	Dihydralazine	0
107	Exp3174	0
108	Diallyl Disulfide	0
109	Dorzolamide	0
110	Nicorandil	0
111	Grayanotoxin I	0
112	Indorenate	0
113	Fk 409	0
114	Flesinoxan	0
115	Dauricine	0
116	Bimakalim	0
117	Bimatoprost	0
118	Bendazole	0
119	Berbamine	0
120	Bosentan	0
121	Candoxatril	0
122	Budralazine	0
123	Bq 788	0
124	Cafedrine	0
125	Cromakalim	0

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Ranking order	Drug name	Medrank result
126	Ceronapril	0
127	Libenzapril	0
128	Niguldipine	0
129	Chlorisondamine	0
130	Trimethaphan	0
131	Teprotide	0
132	Nimodipine	0
133	Zofenopril	0
134	Efonidipine	0
135	Omapatrilat	0
136	Ae0047	0
137	Hydralazine	0
138	Perindopril	0
139	Buthiazide	0
140	Rentiapril	0
141	Polythiazide	0
142	N-Cyano-N'-(2-Nitroxyethyl)-3-Pyridinecarboximidamide Methanesulfonate	0
143	Etozolin	0
144	Valsartan	0
145	Cadralazine	0
146	Tobanum	0
147	Alprenolol	0
148	Talinolol	0
149	Trichlormethiazide	0
150	Mibefradil	0
151	Metipranolol	0
152	Nadolol	0
153	Dihydroalprenolol	0
154	Bupranolol	0
155	Carteolol	0
156	Guanethidine	0
157	Methyldopa	0
158	Guanabenz	0
159	Bietaserpine	0
160	Guanadrel	0
161	Vincamine	0
162	Medroxalol	0
163	Xipamide	0
164	Reserpine	0
165	Saprisartan Potassium	0
166	1-Sarcosine-8-Isoleucine Angiotensin Ii	0
167	Veratrum Alkaloids	0
168	Magnesium Sulfate	0
169	Protoveratrines	0
170	Pentolinium Tartrate	0
171	Pinacidil	0
172	Brimonidine	0
173	Chlorothiazide	0
174	Bq 22-708	0
175	Hydroflumethiazide	0
176	Todralazine	0
177	Hexamethonium	0
178	Kallidin	0
179	Fenoldopam	0
180	Debrisoquin	0
181	Epoprostenol	0
182	Pargyline	0
183	Pempidine	0
184	Minoxidil	0
185	Proline	0
186	Mecamylamine	0
187	Phentolamine	0
188	Piperoxan	0
189	Phenoxybenzamine	0
190	Trimazosin	0
191	Urapidil	0
192	Betaxolol	0
193	Celiprolol	0
194	Indenolol	0
195	Tolazoline	0
196	Epanolol	0
197	Muzolimine	0
198	Ticrynafen	0
199	Torsemide	0
200	Ferulic Acid	0
201	Labetalol	0
202	Benoxathian	0
203	Naftopidil	0
204	Metolazone	0
205	Bumetanide	0
206	Ethacrynic Acid	0

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Supplementary Table 8. List of ranking results in 2015.

Ranking order	Drug name	Medrank result
1	Irbesartan	0.0998388913173205
2	Indapamide	0.0923823855221893
3	Amlodipine	0.092322017436277
4	Losartan	0.0768771850930778
5	Candesartan	0.0723636057059959
6	Enalapril	0.0554573730489236
7	Olmesartan	0.0522970307988893
8	Hydrochlorothiazide	0.0467660927924609
9	Carvedilol	0.0413500982753381
10	Trandolapril	0.0343787197115499
11	Ramipril	0.0338679130463818
12	Manidipine	0.0303845604995077
13	Benazepril	0.0303253450878199
14	Atenolol	0.0264710403595027
15	Lisinopril	0.0262794573151733
16	Captopril	0.0255861853730253
17	Metoprolol	0.0236812028893724
18	Nitrendipine	0.0167536359570363
19	Doxazosin	0.0137230947912968
20	Delapril	0.0130474635890242
21	Felodipine	0.0118512434125523
22	Fosinopril	0.00834273710311578
23	Nebivolol	0.00727630056990769
24	Eprosartan	0.0065745054616625
25	Quinapril	0.0065457645231684
26	Isradipine	0.0061814224364872
27	Cilazapril	0.00560494809028512
28	Ketanserin	0.00556322044136412
29	Imidapril	0.00508131031661174
30	Nisoldipine	0.00494770091933916
31	Moxonidine	0.00398026899250059
32	Diltiazem	0.00391245441921013
33	Bendroflumethiazide	0.00372864540064233
34	Furosemide	0.00324473065981709
35	Temocapril Hydrochloride	0.00251566825103383
36	Lercanidipine	0.00240300355209762
37	Chlorthalidone	0.00185196292807965
38	Nicardipine	0.00137388575811664
39	Lacidipine	0.00078530083070054
40	Nilvadipine	0.000601923836573798
41	Cyclopenthiazide	0.000592371134778591
42	Propranolol	0.000487158792736854
43	Prazosin	0.0004018082079289
44	Alacepril	0.000384019612766259
45	Amosulalol	0.000321467249738302
46	Bisoprolol	0.000309184091140952
47	Indoramin	0.000265050271889954
48	Rilmenidine	0.000242378802249636
49	Spirapril	0.000229799197968198
50	Acebutolol	0.00012872233856432
51	Clonidine	0.000115790898465303
52	Guanfacine	1.95288834404411E-06
53	Tetrahydropalmatine	0
54	Cyclothiazide	0
55	3,4-Dichloro-N-Methyl-N-(2-(1-Pyrrolidinyl)-Cyclohexyl)-Benzeneacetamide, (Trans)-Isomer	0
56	L-Proline, N2-((1S)-1-Carboxy-3-Phenylpropyl)-N6-((4-Hydroxyphenyl) Iminomethyl)-L-Lysyl-	0
57	Terlipressin	0
58	Monatepil	0
59	Ryodipine	0
60	Oxprenolol	0
61	Latanoprost	0
62	N,N-Di-N-Propyldopamine	0

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Ranking order	Drug name	Medrank result
63	L 158809	0
64	Bretylium Tosylate	0
65	Linsidomine	0
66	Lofexidine	0
67	Bethanidine	0
68	Adrenomedullin	0
69	Parathyroid Hormone-Related Protein (1-34)	0
70	Tocopherylquinone	0
71	Travoprost	0
72	Oleuropein	0
73	Tibolone	0
74	Scoparone	0
75	Remikiren	0
76	Sesamin	0
77	Bis(P-Chlorophenyl) Acetic Acid	0
78	N(1),N(14)-Bis(Ethyl) Homospermine	0
79	N(1),N(11)-Diethylnorspermine	0
80	Cyclo(Methyltyrosyl-Isoleucyl-Prolyl-Leucyl)	0
81	Treprostinil	0
82	Nip 121	0
83	Viprostol	0
84	Theodrenaline	0
85	Isopropyl Unoprostone	0
86	1-Hexadecyl-2-Acetyl-Glycero-3-Phosphocholine	0
87	2-(4-(2-Carboxyethyl) Phenethylamino)-5'-N-Ethylcarboxamidoadenosine	0
88	Nipradilol	0
89	1-0-Octadecyl 2-0-Acetyl Sn-Glycero-3-Phosphorylcholine	0
90	3-Nitropropionic Acid	0

Ranking order	Drug name	Medrank result
91	Aprikalim	0
92	Atrial Natriuretic Factor Prohormone (103-126)	0
93	5-(Dimethylamino)-N-(3,4-Dimethyl-5-Isoxazolyl)-1-Naphthalene-sulfonamide	0
94	Angiotensin I (1-7)	0
95	Nitroprusside	0
96	Timolol	0
97	Essential 303 Forte	0
98	Penbutolol	0
99	Pindolol	0
100	Telmisartan	0
101	Cicletanine	0
102	Moexipril	0
103	Clentiazem	0
104	Diazoxide	0
105	Azepexole	0
106	Dihydralazine	0
107	Exp3174	0
108	Diallyl Disulfide	0
109	Dorzolamide	0
110	Nicorandil	0
111	Grayanotoxin I	0
112	Indorenate	0
113	Fk 409	0
114	Flesinoxan	0
115	Dauricine	0
116	Bimakalim	0
117	Bimatoprost	0
118	Bendazole	0
119	Berbamine	0
120	Bosentan	0
121	Candoxatril	0
122	Budralazine	0

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Ranking order	Drug name	Medrank result
123	Bq 788	0
124	Cafedrine	0
125	Cromakalim	0
126	Ceronapril	0
127	Libenzapril	0
128	Niguldipine	0
129	Chlorisondamine	0
130	Trimethaphan	0
131	Teprotide	0
132	Nimodipine	0
133	Zofenopril	0
134	Efonidipine	0
135	Omapatrilat	0
136	Ae0047	0
137	Hydralazine	0
138	Perindopril	0
139	Buthiazide	0
140	Rentiapril	0
141	Polythiazide	0
142	N-Cyano-N'-(2-Nitroxyethyl)-3-Pyridinecarboxi-midamide Methanesulfonate	0
143	Etozolin	0
144	Valsartan	0
145	Cadralazine	0
146	Tobanum	0
147	Alprenolol	0
148	Talinolol	0
149	Trichlormethiazide	0
150	Mibefradil	0
151	Metipranolol	0
152	Nadolol	0
153	Dihydroalprenolol	0
154	Bupranolol	0
155	Carteolol	0

Ranking order	Drug name	Medrank result
156	Guanethidine	0
157	Methyldopa	0
158	Guanabenz	0
159	Bietaserpine	0
160	Guanadrel	0
161	Vincamine	0
162	Medroxalol	0
163	Xipamide	0
164	Reserpine	0
165	Saprisartan Potassium	0
166	1-Sarcosine-8-Isoleucine Angiotensin Ii	0
167	Veratrum Alkaloids	0
168	Magnesium Sulfate	0
169	Protoveratrines	0
170	Pentolinium Tartrate	0
171	Pinacidil	0
172	Brimonidine	0
173	Chlorothiazide	0
174	Bq 22-708	0
175	Hydroflumethiazide	0
176	Todralazine	0
177	Hexamethonium	0
178	Kallidin	0
179	Fenoldopam	0
180	Debrisoquin	0
181	Epoprostenol	0
182	Pargyline	0
183	Pempidine	0
184	Minoxidil	0
185	Proline	0
186	Mecamylamine	0
187	Phentolamine	0
188	Piperoxan	0
189	Phenoxybenzamine	0

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Ranking order	Drug name	Medrank result
190	Trimazosin	0
191	Urapidil	0
192	Betaxolol	0
193	Celiprolol	0
194	Indenolol	0
195	Tolazoline	0
196	Epanolol	0
197	Muzolimine	0
198	Ticrynafen	0

Ranking order	Drug name	Medrank result
199	Torsemide	0
200	Ferulic Acid	0
201	Labetalol	0
202	Benoxathian	0
203	Naftopidil	0
204	Metolazone	0
205	Bumetanide	0
206	Ethacrynic Acid	0

Supplementary Table 9. Literature citations supporting irbesartan in 2015.

Ranking order	Publication
1	Cost-effectiveness of Ibersartan in type II diabetic nephropathy with hypertension. A Spanish perspective
2	Serum levels of the advanced glycation end products Nepsilon-carboxymethyllysine and pentosidine are not influenced by treatment with the angiotensin receptor II type 1 blocker irbesartan in patients with type 2 diabetic nephropathy and hypertension
3	An economic evaluation of irbesartan in the treatment of patients with type 2 diabetes, hypertension and nephropathy: cost-effectiveness of Irbesartan in Diabetic Nephropathy Trial (IDNT) in the Belgian and French settings
4	Clinically unrecognized Q-wave myocardial infarction in patients with diabetes mellitus, systemic hypertension, and nephropathy
5	Antihypertensive efficacy and tolerability of irbesartan/hydrochlorothiazide in hypertensive patients stratified by body mass index and type 2 diabetes mellitus status: a post hoc subgroup analysis of the Irbesartan/HCTZ Blood Pressure Reductions in Diverse Patient Populations trial
6	Organ protection in hypertensive type 2 diabetic patients. Double chance with AT1 blockers
7	Observational study of blood pressure control and microalbuminuria in type 2 diabetics onirbesartan or irbesartan/HCTZ
8	Irbesartan treatment of patients with type 2 diabetes, hypertension and renal disease: a UK health economics analysis
9	The cost-effectiveness of irbesartan in the treatment of hypertensive patients with type 2 diabetic nephropathy
10	Health economic implications of irbesartan plus conventional antihypertensive medications versus conventional blood pressure control alone in patients with type 2 diabetes, hypertension, and renal disease in Switzerland
11	Cost-effectiveness of irbesartan 300 mg given early versus late in patients with hypertension and a history of type 2 diabetes and renal disease: a Canadian perspective
12	Economics of nephroprotection in arterial hypertension and type 2 diabetes mellitus
13	The efficacy and safety of low- and high-dose fixed combinations of irbesartan/hydrochlorothiazide in patients with uncontrolled systolic blood pressure on monotherapy: the INCLUSIVE trial
14	Health economic aspects of the use of irbesartan in patients in Germany with type 2 diabetes, nephropathy and hypertension
15	Albuminuria and blood pressure, independent targets for cardioprotectivetherapy in patients with diabetes and nephropathy: a post hoc analysis of the combined RENAAL and IDNT trials.
16	Evidence based treatment of diabetic nephropathy

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Ranking order	Publication
17	Angiotensin I receptor antagonist losartan. Part II. Effects in arterial hypertension and diabetic nephropathy
18	Effect of three months' treatment with irbesartan on blood and pulse pressure of hypertensive type 2 diabetic patients: open, observational study in 31,793 patients
19	Comprehensive overview: efficacy, tolerability, and cost-effectiveness of irbesartan.
20	Irbesartan reduces the albumin excretion rate in microalbuminuric type 2 diabetic patients independently of hypertension: a randomized double-blind placebo-controlled crossover study
21	Effects of dual blockade of the renin angiotensin system in hypertensive type 2 diabetic patients with nephropathy
22	Proteinuria reduction and progression to renal failure in patients with type 2 diabetes mellitus and overt nephropathy
23	Observational study of blood pressure control and microalbuminuria in type 2 diabetics onIrbesartan or Irbesartan/HCTZ
24	Irbesartan: a review of its use in hypertension and in the management of diabetic nephropathy
25	Metabolic and antihypertensive effects of moxonidine and moxonidine plus irbesartan in patients with type 2 diabetes mellitus and mild hypertension: a sequential, randomized, double-blind clinical trial
26	Dangerous deficits in management of hypertensive diabetic patients. A kidney check is far from standard procedure
27	Arterial hypertension in obese patients. Rationale for a prospective medical care study in the family doctor's practice
28	Irbesartan is projected to be cost and life saving in a Spanish setting for treatment of patients with type 2 diabetes, hypertension, and microalbuminuria
29	Current treatment of diabetic nephropathy in patients with type II diabetes mellitus. Most recent progress
30	Irbesartan has no short-term effect on insulin resistance in hypertensive patients with additional cardiometabolic risk factors (i-RESPOND)
31	A clinical trial in type 2 diabetic nephropathy
32	Health economic consequences of the use of irbesartan in patients with type 2 diabetes, hypertension and nephropathy in Switzerland
33	Angiotensin II receptor blockers and nephropathy trials
34	Predictors of blood pressure response to angiotensin receptor blocker/diuretic combination therapy: a secondary analysis of the irbesartan/hydrochlorothiazide blood pressure reductions in diverse patient populations (INCLUSIVE) study
35	Treatment of hypertension in patients with type 2 diabetes. Sartan also protects the kidneys
36	Irbesartan in clinical practice
37	The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes
38	Irbesartan treatment does not influence plasma levels of the advanced glycation end products N(epsilon)(1-carboxymethyl)lysine and N(epsilon)(1-carboxyethyl)lysine in patients with type 2 diabetes and microalbuminuria. A randomized controlled trial
39	Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes
40	A French cost-consequence analysis of the renoprotective benefits of irbesartan in patients with type 2 diabetes and hypertension
41	Health economic consequences of the use of irbesartan in patients in Germany with type 2 diabetes, nephropathy and hypertension
42	Health economic implications of irbesartan treatment versus standard blood pressure control in patients with type 2 diabetes, hypertension and renal disease: a Hungarian analysis
43	IRMA-pRAcs: irbesartan in the treatment of microalbuminuria and proteinuria in patients with type 2 diabetes and hypertension-prospective observational study involving 38,016 patients in the general practice setting

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Ranking order	Publication
44	Effect of Irbesartan treatment on plasma and urinary markers of protein damage in patients with type 2 diabetes and microalbuminuria
45	Summaries for patients. Effects of blood pressure drugs in patients with diabetes and kidney disease
46	Angiotensin receptor blockers-finally the evidence is coming in: IDNT and RENAAL
47	Efficacy and safety of irbesartan/HCTZ in severe hypertension according to cardiometabolic factors
48	Cardiovascular outcomes in the Irbesartan Diabetic Nephropathy Trial of patients with type 2 diabetes and overt nephropathy
49	Telmisartan – killing two birds with one stone
50	A comparison of the efficacy and safety of irbesartan/hydrochlorothiazide combination therapy with irbesartanmonotherapy in the treatment of moderate or severe hypertension in diabetic and obese hypertensive patients: a post-hoc analysis review
51	The effect of angiotensin-converting enzyme inhibitors on the progression of chronic renal failure
52	Irbesartan: a review of its use in hypertension and diabetic nephropathy
53	Effects of doxazosin and irbesartan on blood pressure and metabolic control in patients with type 2 diabetes and hypertension
54	Blockade of the renin-angiotensin-aldosterone system: a key therapeutic strategy to reduce renal and cardiovascular events in patients with diabetes
55	The efficacy and safety of initial use of irbesartan/hydrochlorothiazide fixed-dose combination in hypertensive patients with and without high cardiovascular risk
56	The effect of irbesartan in reducing cardiovascular risk in hypertensive type 2 diabetic patients: an observational study in 16,600 patients in primary care
57	Effect of delapril-manidipine combination vsirbesartan-hydrochlorothiazide combination on fibrinolytic function in hypertensive patients with type II diabetes mellitus
58	A threat to cardiovascular risk patients. "Activated renin-angiotensin system promotes end organ damage" (interview by WaldtraudPaukstadt)
59	Cost-effectiveness of early irbesartan treatment versus control (standard antihypertensive medications excluding ACE inhibitors, other angiotensin-2 receptor antagonists, and dihydropyridine calcium channel blockers) or late irbesartan treatment in patients with type 2 diabetes, hypertension, and renal disease
60	Cost-effectiveness of aliskiren in type 2 diabetes, hypertension, and albuminuria.
61	Renal effects of aliskiren compared with and in combination with irbesartan in patients with type 2 diabetes, hypertension, and albuminuria
62	Editorial overview: The 'sartans': is it premature to consider PPARgamma receptor agonism a bonus?
63	Treatment of diabetic nephropathy with angiotensin II receptor antagonist.
64	Clinical and health economic implications of early treatment with irbesartan of patients with type 2 diabetes mellitus, hypertension and nephropathy
65	Antihypertensive efficacy of Irbesartan/HCTZ in men and women with the metabolic syndrome and type 2 diabetes
66	Preventing nephropathy in patients with type 2 diabetes

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