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

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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 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 were 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.
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,
matched-pair analysis, multicenter studies, double-blind methods, 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:

\[ R_x = \alpha \left( \prod_{t=1}^{n-1} W_{X_t} D_{X_t}^{-1} W_{X_t} x + (1-\alpha) U/X_1 \right) R_{X_1} \]

where \( t \in \{1, \ldots, n-1\} \), \( n \) 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 \( |X_1| \times |X_1| \) unit matrix; \( |X_1| \) is the total number of objects of type \( X_1 \); \( \alpha \) 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.

**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 \( \leq 1977 \), \( \leq 1980 \), \( \leq 1984 \), \( \leq 1988 \), \( \leq 1993 \), \( \leq 1997 \), \( \leq 2003 \), and \( \leq 2013 \) [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 \( \leq 2013 \), 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 \( \beta \)-antagonists, adrenergic \( \alpha \)-antagonists, antihypertensive drugs, 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 \( \leq 1984 \), \( \leq 1988 \), \( \leq 1993 \), \( \leq 1997 \), \( \leq 2003 \), \( \leq 2013 \) and \( \leq 2015 \), are summarized.
Table 1. Numbers of papers, authors and journals over time.

|        | Papers | Authors | Journals |
|--------|--------|---------|----------|
| ≤1977  | 0      | 0       | 0        |
| ≤1980  | 0      | 0       | 0        |
| ≤1984  | 21     | 52      | 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-agonists, adrenergic β-agonists, 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. 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
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 | Trandolapril |
| 11            | – | – | Cyclopenthiazide* |
| McNemar’s Test | P=0.375 | P=0.125 | P=1.00 |

* Not consistent with the guideline.
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.

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 | –      | –             |
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 noncardiovascular 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 sulfonylure 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
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.

**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|

| Country or area | MeSH |
|-----------------|------|
| 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                  |                                           |
| Bashkortostan           |                                           |
| 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                  |                                           |

| Country or area          | MeSH                                      |
|-------------------------|-------------------------------------------|
| 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                 |                                           |
| 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                   |                             |
Supplementary Table 2. List of ranking results in 1984.

| Ranking order | Drug name                                                                 | Medrank result |
|---------------|---------------------------------------------------------------------------|----------------|
| 1             | Metoprolol                                                                | 0.759174311926605 |
| 2             | Clonidine                                                                 | 0.240825688073394 |
| 3             | Tocopherolquinone                                                         | 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(F-Chlorophenyl)Acetic Acid                                            | 0              |
| 14            | Chlorthalidone                                                            | 0              |
| 15            | Cyclopenthiazide                                                          | 0              |
| 16            | Nip 121                                                                   | 0              |
| 17            | Cyclohexide                                                               | 0              |
| 18            | N(1),N(11)-Diethynorspermine                                              | 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            | Moxonidine                                                                | 0              |
| 28            | 1-0-Octadecyl                                                             | 0              |
| 29            | 2-0-Acetyl Sn-Glycero-3-Phosphorylcholine                                  | 0              |
| 30            | 5-(Dimethylamino)-N-(3,4-Dimethyl-5-Isoxazolyl)-1-Naphthalenesulfonamide   | 0              |
| 31            | Atrial Natriuretic Factor Prohormone (103-126)                            | 0              |
| 32            | 2-(4-(2-Carboxyethyl)Phenethylamino)-5'-N-Ethylcarboxamidoadenosine         | 0              |
| 33            | 3-Nitropropionic Acid                                                     | 0              |
| 34            | 5-(Dimethylaminoo)-N-(3,4-Poly Dimethyl-S-Isoxazolyl)-1- | 0              |
| 35            | Lacidipine                                                                | 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-Pyrolidinyl)-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            | Angiotensin I (1-7)                                                       | 0              |
| 56            | Nitroprusside                                                             | 0              |
| 57            | 3-Nitropropionic Acid                                                     | 0              |
| 58            | 5-(Dimethylaminoo)-N-(3,4-Poly Dimethyl-S-Isoxazolyl)-1- | 0              |
| 59            | Lacidipine                                                                | 0              |
| 60            | Timolol                                                                   | 0              |
| 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            | Azapetine  | 0              |
| 77            | Telmisartan | 0             |
| 78            | Clentiazem | 0              |
| 79            | Aprenolol  | 0              |
| 80            | Fk 409     | 0              |
| 81            | Flesinoxan | 0              |
| 82            | Gynanotoxin I | 0      |
| 83            | Dihydralazine | 0         |
| 84            | Exp3174    | 0              |
| 85            | N-Cyano-N'-(2-Nitroxyethyl)-3-Pyridinecarboximidamide Methanesulfonate | 0 |
| 86            | Latanoprost | 0            |
| 87            | Linsidomine | 0            |
| 88            | Lofexidine | 0              |
| 89            | Indorenate | 0              |
| 90            | Isopropyl Unoprostone | 0        |
| 91            | L 158809   | 0              |
| 92            | Oxprenolol | 0              |
| 93            | Bimatoprost | 0            |
| 94            | Bosentan   | 0              |
| 95            | Bq 788     | 0              |
| 96            | Buprebuline | 0            |
| 97            | Berbamine  | 0              |
| 98            | Bimakalim  | 0              |
| 99            | Bimatoprost | 0            |
| 100           | Dauricine  | 0              |
| 101           | Diallyl Disulfide | 0        |
| 102           | Bezpinidine | 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           | Nifrendipine | 0        |
| 116           | Felodipine | 0              |
| 117           | Captopril  | 0              |
| 118           | Alacepril  | 0              |
| 119           | Ceronapril | 0              |
| 120           | Imipramine | 0              |
| 121           | Telmisartan | 0            |
| 122           | Nifedipine | 0              |
| 123           | Hydrochlorothiazide | 0      |
| 124           | Spirapril  | 0              |
| 125           | Temocapril | 0              |
| 126           | Zofenopril | 0              |
| 127           | Libenzapril | 0            |
| 128           | Efondipine | 0              |
| 129           | Omapatrilat | 0           |
| 130           | Guanethidin | 0            |
| 131           | Amosulalol | 0              |
| 132           | Talinolol  | 0              |
| 133           | Tobanum    | 0              |
| 134           | Medroxalol | 0              |
| 135           | Trichlormethazide | 0       |
| 136           | Mibebradil | 0              |
| 137           | Dihydroalprenol | 0      |
| 138           | Metipranol | 0              |
| 139           | Bendazepam | 0              |
| 140           | Nadolol    | 0              |
| 141           | Alprenolol | 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              |
### 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            | 0.086390806812228 |
| 4             | Acebutolol           | 0.0553206961592188 |
| 5             | Atenolol             | 0.0367689007022248 |
| 6             | Ketanserin           | 0.0368740750712854 |
| 7             | Hydrochlorothiazide  | 0.0361650151920702 |
| 8             | Carvedilol           | 0.0283249643352 |
| 9             | Furosemide           | 0.0276603480796094 |
| 10            | Furosemide           | 0.02653934156425 |
| 11            | Indapamide           | 0.0164606460241176 |
| 12            | Enalapril            | 0.012345845180882 |
| 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           | Terlipressin               | 0              |
| 21           | Treprostinil               | 0              |
| 22           | Lercanidipine              | 0              |
| 23           | Chlorthalidone             | 0              |
| 24           | Cyclopenthiazide           | 0              |
| 25           | Chlorthiazide              | 0              |
| 26           | Cyclothiazide              | 0              |
| 27           | Terlipressin               | 0              |
| 28           | Benoxapropride             | 0              |
| 29           | Scoparone                  | 0              |
| 30           | Medroxalol                 | 0              |
| 31           | Trichlormethiazide         | 0              |
| 32           | Metolazone                 | 0              |
| 33           | Medroxalol                 | 0              |
| 34           | Prostacyclin               | 0              |
| 35           | Proline                    | 0              |
| 36           | Mecamylamine               | 0              |
| 37           | Epoprostenol               | 0              |
| 38           | Fenoldopam                 | 0              |
| 39           | Hexamethonium              | 0              |
| 40           | Pentolinium Tartrate       | 0              |
| 41           | Pinacidil                  | 0              |
| 42           | Protovateratines           | 0              |
| 43           | Minoxidil                  | 0              |
| 44           | Pargyline                  | 0              |
| 45           | Pempidine                  | 0              |
| 46           | L-Proline,N2-((1S)-1-    | 0              |
|              | Carboxy-3-Phenylpropyl-N6- |                |
|              | 4-Hydroxyphenyl)iminomethyl-L-Lysyl- |            |
| 47           | Ryodipine                  | 0              |
| 48           | 3,4-Dichloro-N-Methyl-N-(2-| 0              |
|              | 1-Pyrroolidinyl)-Cyclohexyl |                |
|              | Benzeneacetamide, (Trans)-Isomer |          |
| 49           | Viprostol                  | 0              |
| 50           | Bis(P-Chlorophenyl)Acetic Acid | 0          |
| 51           | Cyclo(Methyltyrosyl-    | 0              |
|              | Isoleucyl-Prolyl-Leucyl)  |                |

**Ranking order**

| Drug name                  | Medrank result |
|----------------------------|----------------|
| 52           | Diltiazem                   | 0              |
| 53           | Cromakalim                  | 0              |
| 54           | Debrisoquin                 | 0              |
| 55           | Adrenomedullin              | 0              |
| 56           | Bethanidine                 | 0              |
| 57           | Nitroprusside               | 0              |
| 58           | 1-Hexadeyl-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-Octadecyl                 | 0              |
| 64           | Atrial Natriuretic Factor Prohormone (103-126) | 0 |
| 65           | Azepeoxide                  | 0              |
| 66           | Bendazole                   | 0              |
| 67           | 5-(Dimethylamino)-N-(3,4-Dimethyl-5-Isoxazolyl)-1-Naphthalenesulfonamide | 0 |
| 68           | Angiotensin I (1-7)         | 0              |
| 69           | Aprikalim                   | 0              |
| 70           | Nitroprusside               | 0              |
| 71           | Essential 303 ForE          | 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            | Bromonidine             | 0              |
| 99            | Berbamidine             | 0              |
| 100           | Bimakalim               | 0              |
| 101           | Bimatoprost             | 0              |
| 102           | Cudralazine             | 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           | Teplotide               | 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           | Omapatril                        | 0              |
| 128           | Spirapril                        | 0              |
| 129           | Temocapril Hydrochloride         | 0              |
| 130           | Imidapril                        | 0              |
| 131           | Libenzapril                      | 0              |
| 132           | Efondipine                       | 0              |
| 133           | Guanethidine                     | 0              |
| 134           | Amosulalol                       | 0              |
| 135           | Talinolol                        | 0              |
| 136           | Tobanum                          | 0              |
| 137           | Mibefradil                       | 0              |
| 138           | Lisinopril                       | 0              |
| 139           | Nebivolol                        | 0              |
| 140           | Dihydroalprenol                  | 0              |
| 141           | Metipranol                       | 0              |
| 142           | Nadolol                          | 0              |
| 143           | Alprenol                         | 0              |
| 144           | Bupranol                         | 0              |
| 145           | Carteolol                        | 0              |
| 146           | Monatepl                        | 0              |
| 147           | Candesartan                      | 0              |
| 148           | Eprosartan                       | 0              |
| 149           | Guanfacine                       | 0              |
| 150           | Methyldopa                       | 0              |
| 151           | Reserpine                        | 0              |
| 152           | Ixipamide                        | 0              |
| 153           | Dialyl 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           | Benoxathiam                      | 0              |
| 163           | Naftopidil                       | 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             | Diltiazem                      | 0.043577140678444 |
| 9             | Indapamide                     | 0.0365668297365585 |
| 10            | Hydrochlorothiazide            | 0.0298915439851632 |
| 11            | Isradipine                     | 0.0290720690747235 |
| 12            | Carvedilol                     | 0.0248799715762873 |
| 13            | Cilazapril                     | 0.019274528894099 |
| 14            | Betaxolol                      | 0.013292252996666 |
| 15            | Indoramin                      | 0.01290229958200223 |

| Ranking order | Drug name                      | Medrank result |
|---------------|--------------------------------|----------------|
| 16            | Furosemide                     | 0.012573816951632 |
| 17            | Clonidine                      | 0.00093596490308347 |
| 18            | Propranolol                    | 0.00088936696517029 |
| 19            | Cilazapril                     | 0.0051338423185767 |
| 20            | Acebutolol                     | 0.0031304295467089 |
| 21            | Prazosin                       | 0.0032856859083891 |
| 22            | Amosulalol                     | 0.0026177129518373 |
| 23            | Nisoldipine                    | 0.00177584332465582 |
| 24            | Delapril                       | 0.00165652147735544 |
| 25            | Manidipine                     | 0.00165652147735544 |
| 26            | Sesamin                        | 0.00165652147735544 |
| 27            | Guanfacine                     | 0.0001885579095071 |
| 28            | Rilmenidene                    | 0.0001885579095071 |
| 29            | Remikiren                      | 0.0001885579095071 |
| 30            | Betaxolol                      | 0.0001885579095071 |

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Recommend antihypertensive drugs based on “Big Data” system
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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            | Hexothiazidide                                                            | 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            | Tetracydropalmatine                                                       | 0              |
| 59            | Theodrenaline                                                             | 0              |
| 60            | Cyclo(Methyltyrosyl-Isoleucyl-Prolyl-Leucyl)                               | 0              |
| 61            | L-Proline, N2-((IS)-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-Octadecyl-2-0-Acetyl Sn-Glycero-3-Phosphorylcholine                       | 0              |
| 68            | Ferulic Acid                                                              | 0              |
| 69            | Moxipril                                                                  | 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-Ethylcarbamidoadenosine         | 0              |
| 76            | 3-Nitropropionic Acid                                                     | 0              |
| 77            | 5-(Dimethylamino)-N-(3,4-Dimethyl-5-Isoxazolyl)-1-Naphthalenesulfonamide   | 0              |
| 78            | Timolol                                                                   | 0              |
| 79            | Essential 303 Forte                                                       | 0              |
| 80            | N,N-Di-N-Propyldopamine                                                   | 0              |
| 81            | Oxprenolol                                                                | 0              |
| 82            | Penbutol                                                                  | 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-Pyridinecarboximidamide                      | 0              |
| 90            | Azepoxole                                                                 | 0              |
| Ranking order | Drug name          | Medrank result |
|---------------|--------------------|----------------|
| 91            | Nicorandil         | 0              |
| 92            | FL 409             | 0              |
| 93            | Flesinoxan         | 0              |
| 94            | Dorzolamide        | 0              |
| 95            | Dihydralazine      | 0              |
| 96            | Exp3174            | 0              |
| 97            | L 158809           | 0              |
| 98            | Lisinoprost        | 0              |
| 99            | Linsidomine        | 0              |
| 100           | Grayanotoxin I     | 0              |
| 101           | Isopropyl Unoprostone | 0             |
| 102           | Bimatoprost        | 0              |
| 103           | Bilobastine        | 0              |
| 104           | Bg 788             | 0              |
| 105           | Bendazole          | 0              |
| 106           | Berbamidine        | 0              |
| 107           | Bimakalim          | 0              |
| 108           | Budralazine        | 0              |
| 109           | Diallyl Disulfide  | 0              |
| 110           | Fosinapril         | 0              |
| 111           | Imidapril          | 0              |
| 112           | Alacepril          | 0              |
| 113           | Trimethaphane      | 0              |
| 114           | Niguldipine        | 0              |
| 115           | Guanadrel          | 0              |
| 116           | Spiropride         | 0              |
| 117           | Temocapril         | 0              |
| 118           | Captopril          | 0              |
| 119           | tramadol           | 0              |
| 120           | Efonidipine        | 0              |
| 121           | Zofenopril         | 0              |
| 122           | Nimodipine         | 0              |
| 123           | Betaserpine        | 0              |
| 124           | Teprotide          | 0              |
| 125           | Lisinopril         | 0              |
| 126           | Benetofoxim        | 0              |
| 127           | Bendroflumethiazide| 0              |
| 128           | Chloridizamide     | 0              |
| 129           | Polythiazide       | 0              |
| 130           | Cadrilazine        | 0              |
| 131           | Etoxolan           | 0              |

| Ranking order | Drug name         | Medrank result |
|---------------|-------------------|----------------|
| 132           | Bisoprolol        | 0              |
| 133           | Ceronapril        | 0              |
| 134           | Imidapril         | 0              |
| 135           | Alacepril         | 0              |
| 136           | Trimepride        | 0              |
| 137           | Niguldipine       | 0              |
| 138           | Guanadrel         | 0              |
| 139           | Talinolol         | 0              |
| 140           | Tobanum           | 0              |
| 141           | Milfepridil       | 0              |
| 142           | Medroxalol        | 0              |
| 143           | Trichlormethiazide| 0              |
| 144           | Alprenolol        | 0              |
| 145           | Metipranolol      | 0              |
| 146           | Nadolol           | 0              |
| 147           | Dihydroalprenolol | 0              |
| 148           | Buprenolol        | 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       | 0              |
| 159           | Potassium         | 0              |
| 160           | Olmesartan        | 0              |
| 161           | Valsartan         | 0              |
| 162           | Muzolimine        | 0              |
| 163           | Ticnyafena        | 0              |
| 164           | Torsemide         | 0              |
| 165           | Medroxalol        | 0              |
| 166           | Labelol           | 0              |
| 167           | Bumetanide        | 0              |
| 168           | Benoxathian       | 0              |
| 169           | Liopidil          | 0              |
| 170           | Metolazone        | 0              |
| 171           | Ethacrynic Acid   | 0              |
| 172           | Oleuropein        | 0              |
| 173           | Protoversatrine   | 0              |
| 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           | Cimetidine              | 0              |
| 181           | Todralazine             | 0              |
| 182           | Magnesium Sulfate       | 0              |
| 183           | Amlodipine              | 0              |
| 184           | Trandolapril            | 0              |
| 185           | Magnesium Sulfate       | 0              |
| 186           | Amlodipine              | 0              |
| 187           | Trandolapril            | 0              |
| 188           | Celiprolol              | 0              |
| 189           | 1-Sarcosine-8-Isoleucine| 0              |
| 190           | Rentiapril              | 0              |
| 191           | Ae0047                  | 0              |
| 192           | Hydralazine             | 0              |
| 193           | Ramipril                | 0              |
| 194           | Trandolapril            | 0              |
| 195           | Perindopril             | 0              |
| 196           | Phenolamine             | 0              |
| 197           | Piperoxan               | 0              |
| 198           | Phenoxybenzamine        | 0              |
| 199           | Urapidil                | 0              |
| 200           | Doxazosin               | 0              |
| 201           | Tolazoline              | 0              |
| 202           | Nebivolol               | 0              |
| 203           | Betaxolol               | 0              |
| 204           | Losartan                | 0              |
| 205           | 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              | 0.088591122743347 |
| 4             | Nitrendipine            | 0.0841835323060517 |
| 5             | Atenolol                | 0.0560408502792917 |
| 6             | Lisinopril              | 0.0549804336677904 |
| 7             | Ramipril                | 0.05284879304965 |
| 8             | Doxazosin               | 0.04137411452941 |
| 9             | Cilazapril              | 0.032642874154701 |
| 10            | Furosemide              | 0.026947470000088 |
| 11            | Bendroflumethiazide     | 0.023173124815525 |
| 12            | Ketanserin              | 0.0228192110770944 |
| 13            | Quinapril               | 0.019367167777005 |
| 14            | Lacidipine              | 0.017893407794078 |
| 15            | Metoprolol              | 0.0172294964377578 |
| 16            | Fosinopril              | 0.0168287698288791 |
| 17            | Indapamide              | 0.0167835795361915 |
| 18            | Nicardipine             | 0.016499828395523 |
| 19            | Isradipine              | 0.014291564064658 |
| 20            | Carvediol               | 0.0135320710998319 |
| 21            | Nebivolol               | 0.0109132668566996 |

| Ranking order | Drug name               | Medrank result |
|---------------|-------------------------|----------------|
| 22            | Hydrochlorothiazide      | 0.0108346392732554 |
| 23            | Amlopidine              | 0.0096555634827490 |
| 24            | Diltiazem               | 0.00918714660265147 |
| 25            | Chlorthalidone          | 0.00767246617196031 |
| 26            | Carperamide             | 0.0073322970648646 |
| 27            | Nisoldipine             | 0.002487755993045 |
| 28            | Trandolapril            | 0.006659284973496 |
| 29            | Benazepril              | 0.0048797395800254 |
| 30            | Propranolol             | 0.0043883603886944 |
| 31            | Indoramin               | 0.0035127168378336 |
| 32            | Cyclopenthiazide        | 0.0022016977741181 |
| 33            | Clonidine               | 0.00206780992633 |
| 34            | Prazosin                | 0.0015157758979251 |
| 35            | Nifedipartan            | 0.00106037808335 |
| 36            | Delapril                | 0.0009872160512767 |
| 37            | Manidipine              | 0.0009872160512767 |
| 38            | Amosulalot              | 0.0009872160512767 |
| 39            | Acebutolol              | 0.0009872160512767 |
| 40            | Moxonidine              | 0.000113700137274801 |
| 41            | Guanfacine              | 5.3060064061574E-05 |
| Ranking order | Drug name                                                                 | Medrank result |
|--------------|---------------------------------------------------------------------------|----------------|
| 42           | N-Cyano-N′-(2-Nitroxyethyl)-3-Pyridinecarboximidamide Methanesulfonate    | 0              |
| 43           | Oxphenolol                                                                | 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)-Diethynorspermine                                               | 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              |

| Ranking order | Drug name                                                                 | Medrank result |
|--------------|---------------------------------------------------------------------------|----------------|
| 71           | Sesamin                                                                   | 0              |
| 72           | Hydipine                                                                 | 0              |
| 73           | Tibilone                                                                  | 0              |
| 74           | Terlipressin                                                              | 0              |
| 76           | Buthiazide                                                                | 0              |
| 77           | 5-(Dimethylamino)-N-(3,4-Dimethyl-5-Isoxazolyl)-1-Naphthalenesulfonamide  | 0              |
| 79           | 3-Nitropropionic Acid                                                     | 0              |
| 80           | 1-Hexadecyl-2-Acetyl-Glycerol-3-Phosphocholine                            | 0              |
| 81           | 2-(4-(2-Carboxyethyl)Phenethylamino)-5'-N-Ethylcarboxamidoadenosine        | 0              |
| 82           | Oleuropein                                                                | 0              |
| 83           | Berbamine                                                                 | 0              |
| 84           | Azepexole                                                                 | 0              |
| 85           | Aprikalim                                                                 | 0              |
| 86           | Atrial Natriuretic Factor Prohormone (103-126)                            | 0              |
| 87           | 1-Octadecyl                                                               | 0              |
| 88           | 2-0-Acetyl Sn-Glycero-3-Phosphorylcholine                                  | 0              |
| 89           | Essential 303 Forte                                                       | 0              |
| 90           | Timolol                                                                   | 0              |
| 91           | Penbutolol                                                                | 0              |
| 92           | Pindolol                                                                  | 0              |
| 93           | Nitroprusside                                                             | 0              |
| 94           | Nipradilol                                                                | 0              |
| 95           | Moexipril                                                                 | 0              |
| 96           | Diazoxide                                                                 | 0              |
| 97           | Cilectarine                                                               | 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           | Cafedrine               | 0              |
| 117           | Bq 22-708               | 0              |
| 118           | Omapatrilet             | 0              |
| 119           | Spirapril               | 0              |
| 120           | Efonidipine             | 0              |
| 121           | Imidapril               | 0              |
| 122           | Libernazepine           | 0              |
| 123           | Temocapril Hydrochloride| 0              |
| 124           | Alprenolol              | 0              |
| 125           | Dihydroalprenolol       | 0              |
| 126           | Reserpine               | 0              |
| 127           | Monatepil               | 0              |
| 128           | Carteolol               | 0              |
| 129           | Torsemide               | 0              |
| 130           | Eprosartan              | 0              |
| 131           | Ethacrynic Acid         | 0              |
| 132           | Ethacrynic Acid         | 0              |
| 133           | Eprosartan              | 0              |
| 134           | Xipamide                | 0              |
| 135           | Bupranolol              | 0              |
| 136           | Miconazole              | 0              |
| 137           | Minoxidil               | 0              |
| 138           | Pargyline               | 0              |
| 139           | Pemacilide              | 0              |
| 140           | Veratrum Alkaloids      | 0              |
| 141           | Pemacilide              | 0              |
| 142           | Alacepril               | 0              |
| 143           | Pinacidil               | 0              |

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### Supplementary Table 6. List of ranking results in 2003.

| Ranking order | Drug name                  | Medrank result |
|---------------|---------------------------|----------------|
| 1             | Enalapril                 | 0.1500205465503|
| 2             | Captopril                 | 0.0831136513337003|
| 3             | Nitrendipine              | 0.0556465015370699|
| 4             | Irbesartan                | 0.0501322393064552|
| 5             | Lisinopril                | 0.0463526819550658|
| 6             | Candesartan               | 0.0461026713657262|
| 7             | Cilnidipine               | 0.0392926587350635|
| 8             | Atenolol                  | 0.0396698261439649|
| 9             | Ramipril                  | 0.0368999585891977|
| 10            | Losartan                  | 0.0344250843122766|
| 11            | Fosinopril                | 0.0326933384043416|
| 12            | Amlodipine                | 0.0326600377088823|
| 13            | Trandolapril              | 0.0312454974706367|
| 14            | Carvedilol                | 0.0303931808748497|
| 15            | Doxazosin                 | 0.0294592856646246|
| 16            | Nioclodipine              | 0.0292658735063506|
| 17            | Indapamide                | 0.0256378916582746|
| 18            | Cilazapril                | 0.0172709364631387|
| 19            | Isradipine                | 0.0167425234873222|
| 20            | Hydrochlorothiazide       | 0.0161599577218082|
| 21            | Quinapril                 | 0.0143129570990151|
| 22            | Losartan                  | 0.014311375769114|
| 23            | Bendroflumethiazide       | 0.0141345587430979|
| 24            | Metoprolol                | 0.0139582284191943|
| 25            | Benazepril                | 0.0133456627217982|
| 26            | Furosemide                | 0.0120792150904337|
| 27            | Nebivolol                 | 0.0089513161620604635|
| 28            | Temocapril Hydrochloride  | 0.00831937752403704|
| 29            | Chlorthalidone            | 0.00784688238365008|
| 30            | Moxonidine                | 0.0074983971155167|
| 31            | Lercanidipine             | 0.00715387268459299|
| 32            | Diltiazem                 | 0.00553725034288513|
| 33            | Nicardipidine             | 0.0052369132776083|
| 34            | Lacidipine                | 0.00434654723799898|
| 35            | Nilvadipine               | 0.0025369132776083|
| 36            | Delapril                  | 0.0024087751515065|
| 37            | Propranolol               | 0.00177971886700227|
| 38            | Alacepril                 | 0.00152663497757573|
| 39            | Moxonidine                | 0.0007478225325915|
| 40            | Indoramin                 | 0.00013083621370995|
| 41            | Prazosin                  | 0.000989686428163052|
| 42            | Cyclopenthiazide          | 0.00053524089774833|
| 43            | Clonidine                 | 0.0003911816635442|
| 44            | Spirapril                 | 0.000294522866313601|
| 45            | Acebutolide               | 0.00016948092895060|
| 46            | Amosulol                  | 0.00016883497174055|
| 47            | Guanfacine                | 0.00013083621370995|
| 48            | Benoxathian               | 0.000113083621370995|
| 49            | Lofexidine                | 0.0000989686428163052|
| 50            | Chlorothiazide            | 0.0000989686428163052|
| 51            | Medroxalol                | 0.0000989686428163052|

### Rank order

| Drug name                  | Medrank result |
|---------------------------|----------------|
| Enalapril                 | 1              |
| Captopril                 | 2              |
| Nitrendipine              | 3              |
| Irbesartan                | 4              |
| Lisinopril                | 5              |
| Candesartan               | 6              |
| Cilnidipine               | 7              |
| Atenolol                  | 8              |
| Ramipril                  | 9              |
| Losartan                  | 10             |
| Fosinopril                | 11             |
| Amlodipine                | 12             |
| Trandolapril              | 13             |
| Carvedilol                | 14             |
| Doxazosin                 | 15             |
| Nioclodipine              | 16             |
| Indapamide                | 17             |
| Cilazapril                | 18             |
| Isradipine                | 19             |
| Hydrochlorothiazide       | 20             |
| Quinapril                 | 21             |
| Losartan                  | 22             |
| Bendroflumethiazide       | 23             |
| Metoprolol                | 24             |
| Benazepril                | 25             |
| Furosemide                | 26             |
| Nebivolol                 | 27             |
| Temocapril Hydrochloride  | 28             |
| Chlorthalidone            | 29             |
| Moxonidine                | 30             |
| Lercanidipine             | 31             |
| Diltiazem                 | 32             |
| Nicardipidine             | 33             |
| Lacidipine                | 34             |
| Nilvadipine               | 35             |
| Delapril                  | 36             |
| Propranolol               | 37             |
| Alacepril                 | 38             |
| Moxonidine                | 39             |
| Cyclopenthiazide          | 40             |
| Clonidine                 | 41             |
| Spirapril                 | 42             |
| Acebutolide               | 43             |
| Amosulol                  | 44             |
| Guanfacine                | 45             |
| Benoxathian               | 46             |
| Lofexidine                | 47             |
| Chlorothiazide            | 48             |
| Medroxalol                | 49             |

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| Ranking order | Drug name                                                                 | Medrank result |
|--------------|---------------------------------------------------------------------------|----------------|
| 52           | Cyclothiazide                                                             | 0              |
| 53           | Bututhiazide                                                              | 0              |
| 54           | N(1),N(11)-Dithynamnorspermine                                            | 0              |
| 55           | N-Cyano-N’-(2-Nitroxyethyl)-3-Pyridinecarboxamide-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           | Trepoxinil                                                                | 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-(1-Pyrroldinyl)-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           | Trichlorormethiazide                                                     | 0              |
| 75           | Epoprostenol                                                              | 0              |
| 76           | Tocopherylquinone                                                        | 0              |
| 77           | Traveprost                                                                | 0              |
| 78           | Tetrahydropalmatine                                                       | 0              |
| 79           | Theodrenaline                                                             | 0              |
| 80           | Tibolone                                                                  | 0              |
| 81           | 3-Nitropropionic Acid                                                     | 0              |
| 82           | 5-(Dimethylylamino)-N-(3,4-Dimethyl-5-Isoxazolyl)-1-Naphthalenesulfonamide | 0              |
| 83           | 2-(4-(2-Carboxyethyl)Phenethylamino)-5’-N-Ethylcarboxamidoadenosine        | 0              |
| 84           | 1-0-Octadecyl                                                            | 0              |
| 85           | 2-0-Acetyl Sn-Glycero-3-Phosphorycholine                                  | 0              |
| 86           | Azepeazole                                                                | 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          | Isopropylnoradrenaline                                                   | 0              |
| 112          | Dihydralazine                                                             | 0              |
| Ranking order | Drug name      | Medrank result |
|---------------|----------------|----------------|
| 113           | Bosentan       | 0              |
| 114           | Bq 789        | 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           | Cimetidine     | 0              |
| 127           | Imidapril      | 0              |
| 128           | Bietaserpine   | 0              |
| 129           | Guanadrel      | 0              |
| 130           | Nimodipine     | 0              |
| 131           | Zofenopril     | 0              |
| 132           | Telmisartan    | 0              |
| 133           | Niguldipine    | 0              |
| 134           | Etozolin       | 0              |
| 135           | Polythiazide   | 0              |
| 136           | Cadrabazine    | 0              |
| 137           | Ae0047         | 0              |
| 138           | Valerenol      | 0              |
| 139           | Parathyroid Hormone-Related Protein (1-34) | 0 |
| 140           | Trimethaphan   | 0              |
| 141           | Bispivolol     | 0              |
| 142           | Telmisartan    | 0              |
| 143           | Chlorisondamine| 0             |
| 144           | Tolvaptan      | 0              |
| 145           | Alpenolol      | 0              |
| 146           | Talinolol      | 0              |
| 147           | Valsartan      | 0              |
| 148           | Mibefradil     | 0              |
| 149           | Metipranolol   | 0              |
| 150           | Nadolol        | 0              |
| 151           | Dihydralprenol  | 0             |
| 152           | Bupranolol     | 0              |
| 153           | Captopril      | 0              |
| 154           | Bendazole      | 0              |

| Ranking order | Drug name      | Medrank result |
|---------------|----------------|----------------|
| 155           | Reserpine      | 0              |
| 156           | Monapenepi    | 0              |
| 157           | Methylprednisol| 0              |
| 158           | Guanabenz     | 0              |
| 159           | Guanethidine  | 0              |
| 160           | Xipamide      | 0              |
| 161           | Dialyl Sulphide| 0             |
| 162           | Saprisartan   | 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           | Prooveratines | 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           | Indenalol     | 0              |
| 189           | Nicotardil    | 0              |
| 190           | Epanolol      | 0              |
| 191           | Rentifranz    | 0              |
| 192           | Perindopril   | 0              |
| 193           | Nabi(11,14-BisEthyl) Homospermine| 0 |
| 194           | Remikiren     | 0              |
## Supplementary Table 7. List of ranking results in 2013.

| Ranking order | Drug name                                           | Medrank result |
|---------------|-----------------------------------------------------|----------------|
| 174           | Acebutolol                                          | 0.105587165273498 |
| 175           | Alacepril                                           | 0.092109760574610 |
| 176           | Amlodipine                                          | 0.0775967619717653 |
| 177           | Amosulalol                                          | 0.004713530922943 |
| 178           | Angiotensin II                                     | 0.007171502650149 |
| 179           | Candesartan                                        | 0.00671395688299851 |
| 180           | Carvedilol                                          | 0.00534187451578334 |
| 181           | Captopril                                           | 0.00535779048659068 |
| 182           | Chlorthalidone                                      | 0.00311640488136763 |
| 183           | Cilazapril                                          | 0.00311640488136763 |
| 184           | Clonidine                                           | 0.0011640488136763 |
| 185           | Cyclopenthiazide                                    | 0.00011640488136763 |
| 186           | Diltiazem                                           | 0.00011640488136763 |
| 187           | Eprosartan                                          | 0.00011640488136763 |
| 188           | Enalapril                                           | 0.00011640488136763 |
| 189           | Eprosartan                                          | 0.00011640488136763 |
| 190           | Furosemide                                          | 0.00011640488136763 |
| 191           | Fosinopril                                          | 0.00011640488136763 |
| 192           | Lercanidipine                                       | 0.00011640488136763 |
| 193           | Losartan                                            | 0.00011640488136763 |
| 194           | Lopinotril                                          | 0.00011640488136763 |
| 195           | Nicardipine                                         | 0.00011640488136763 |
| 196           | Nifedipine                                          | 0.00011640488136763 |
| 197           | Nisoldipine                                         | 0.00011640488136763 |
| 198           | Prazosin                                            | 0.00011640488136763 |
| 199           | Propranolol                                          | 0.00011640488136763 |
| 200           | Ryodipine                                           | 0.00011640488136763 |

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| Ranking order | Drug name                                           | Medrank result |
|---------------|----------------------------------------------------|----------------|
| 58            | 3,4-Dichloro-N-Methyl-N-(2-(1-Pyrrolidinyl)-Cyclohexyl)-Benzenecacetamide, (Trans)-Isomer | 0              |
| 59            | Oxprenolol                                          | 0              |
| 60            | Latanoprost                                         | 0              |
| 61            | Tetracydropalmatine                                 | 0              |
| 62            | L 158809                                           | 0              |
| 63            | Bretylium Tosylate                                  | 0              |
| 64            | Linsidomine                                         | 0              |
| 65            | Lofexidine                                          | 0              |
| 66            | Bethanidine                                         | 0              |
| 67            | Adrenomedullin                                      | 0              |
| 68            | Scoparone                                           | 0              |
| 69            | Nitroprusside                                       | 0              |
| 70            | Parathyroid Hormone-Related Protein (1-34)          | 0              |
| 71            | Tocopherolquinone                                   | 0              |
| 72            | Sesamin                                             | 0              |
| 73            | Terlipressin                                        | 0              |
| 74            | Terlipressin                                        | 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-Propylidopamine                            | 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-Ethylcarboxamidoadenosine | 0 |
| 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           | Efondipine                                    | 0              |
| 135           | Omapatril                                     | 0              |
| 136           | Aeo0047                                       | 0              |
| 137           | Hydralazine                                   | 0              |
| 138           | Perindopril                                   | 0              |
| 139           | Bushiazide                                    | 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           | Tolazoline                                    | 0              |
| 147           | Alpenolol                                     | 0              |
| 148           | Tanolol                                       | 0              |
| 149           | Mibefradil                                    | 0              |
| 150           | Metipranol                                    | 0              |
| 151           | Nifedipine                                    | 0              |
| 152           | Dihydroalpenol                                | 0              |
| 153           | BuPROPANOL                                    | 0              |
| 154           | Carteol                                       | 0              |
| 155           | Guanethidine                                  | 0              |
| 156           | Methylodopa                                   | 0              |
| 157           | Bietaserpine                                  | 0              |
| 158           | Guanedrilate                                  | 0              |
| 159           | Vincamine                                     | 0              |
| 160           | Medroxalol                                    | 0              |
| 161           | Xipamide                                      | 0              |
| 162           | Reserpine                                     | 0              |
| 163           | Saprisartan Potassium                         | 0              |

| Ranking order | Drug name                                      | Medrank result |
|---------------|-----------------------------------------------|----------------|
| 166           | 1-Sarcosine-8-Isoleucine                       | 0              |
| 167           | Angiotensin II                                 | 0              |
| 168           | Veratrum Alkaloids                             | 0              |
| 169           | Magnesium Sulfate                              | 0              |
| 170           | Trimepralam                                    | 0              |
| 171           | Proteratines                                   | 0              |
| 172           | Pinacidil                                     | 0              |
| 173           | Brimonidine                                    | 0              |
| 174           | N-Cyano-N’-(2-Nitroxyethyl)-3-Pyridinecarboximidamide Methanesulfonate | 0 |
| 175           | Etozolin                                      | 0              |
| 176           | Valsoartan                                     | 0              |
| 177           | Fenoldopam                                    | 0              |
| 178           | Perindopril                                   | 0              |
| 179           | Tozanol                                       | 0              |
| 180           | Debrisoquin                                   | 0              |
| 181           | Epoprostenol                                  | 0              |
| 182           | Pargyline                                     | 0              |
| 183           | Pemipidine                                    | 0              |
| 184           | Minoxidil                                     | 0              |
| 185           | Proline                                       | 0              |
| 186           | Mecamylamine                                  | 0              |
| 187           | Tobamun                                       | 0              |
| 188           | Phenolamine                                   | 0              |
| 189           | Pargyline                                     | 0              |
| 190           | Phenoxybenzamine                               | 0              |
| 191           | Trichlormethiazide                             | 0              |
| 192           | Trimazosin                                    | 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           | Butemaniol                                    | 0              |
| 206           | Ethacrylic 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 | 0.0056049480928512 |
| 28            | Ketanserin | 0.00556322044136412 |
| 29            | Imidapril | 0.0050813103166174 |
| 30            | Nisoldipine | 0.00494770091933916 |
| 31            | Moxonidine | 0.00398026899250059 |
| 32            | Diltiazem | 0.00391245441921013 |
| 33            | Bendroflumethiazide | 0.00372864540064233 |
| 34            | Furosemide | 0.00324473065981709 |

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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(4)-Bis(Ethyl) Homoserine                    | 0              |
| 79           | N(1),N(11)-Diethynorspermine                       | 0              |
| 80           | Cyclo(Methylthioseryl-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-Ethylcarboxamido- doenosine | 0   |
| 88           | Nipradilol                                         | 0              |
| 89           | 1-O-Octadecyl                                      | 0              |
| 90           | 2-Acetamid 3-Polyphosphorilic 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          | Azepoxole                                          | 0              |
| 106          | Dihydralazine                                      | 0              |
| 107          | Exp3174                                            | 0              |
| 108          | Diallyl Disulfide                                  | 0              |
| 109          | Dorzolamide                                        | 0              |
| 110          | Nicorandil                                         | 0              |
| 111          | Grayanotoxin I                                     | 0              |
| 112          | Indorenatane                                       | 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-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           | Mibebradil                         | 0              |
| 151           | Metipranolol                       | 0              |
| 152           | Nadolol                            | 0              |
| 153           | Dihydralaprenolol                  | 0              |
| 154           | Bupranolol                         | 0              |
| 155           | Carteolol                          | 0              |

| Ranking order | Drug name                          | Medrank result |
|---------------|------------------------------------|----------------|
| 156           | Guanethidine                       | 0              |
| 157           | Methylodopa                        | 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           | Protoveratrinines                  | 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              |
Supplementary Table 9. Literature citations supporting irbesartan in 2015.

| Publication                                                                 | Rank |
|----------------------------------------------------------------------------|------|
| Cost-effectiveness of Ibersartan in type II diabetic nephropathy with hypertension. A Spanish perspective | 1    |
| Serum levels of the advanced glycation end products Neptisol-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 | 2    |
| An economic evaluation of Ibersartan in the treatment of patients with type 2 diabetes, hypertension and nephropathy: cost-effectiveness of Ibesartan in Diabetic Nephropathy Trial (IDNT) in the Belgian and French settings | 3    |
| Clinically unrecognized Q-wave myocardial infarction in patients with diabetes mellitus, systemic hypertension, and nephropathy | 4    |
| 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 Ibesartan/HCTZ Blood Pressure Reductions in Diverse Patient Populations trial | 5    |
| Organ protection in hypertensive type 2 diabetic patients. Double chance with AT1 blockers | 6    |
| Observational study of blood pressure control and microalbuminuria in type 2 diabetics onirbesartan or irbesartan/HCTZ | 7    |
| Ibesartan treatment of patients with type 2 diabetes, hypertension and renal disease: a UK health economics analysis | 8    |
| The cost-effectiveness of irbesartan in the treatment of hypertensive patients with type 2 diabetic nephropathy | 9    |
| 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 | 10   |
| 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 | 11   |
| Economics of nephroprotection in arterial hypertension and type 2 diabetes mellitus | 12   |
| 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 | 13   |
| Health economic aspects of the use of irbesartan in patients in Germany with type 2 diabetes, nephropathy and hypertension | 14   |
| Albuminuria and blood pressure, independent targets for cardioprotective therapy in patients with diabetes and nephropathy: a post hoc analysis of the combined RENAAL and IDNT trials. | 15   |
| Evidence based treatment of diabetic nephropathy | 16   |
| 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 on Irbesartan 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 |
| 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 irbesartan monotherapy 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           | Hypertensive outcomes and intensity 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 vs irbesartan-hydrochlorothiazide combination on fibrinolytic function in hypertensive patients with type 2 diabetes mellitus |
| 58           | A threat to cardiovascular risk patients. “Activated renin-angiotensin system promotes end organ damage” (interview by Waldtraud Paukstadt) |
| 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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