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Anatomy of Success: The Top 100 Cited Scientific Reports Focused On Hypertension Research

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Keywords

Essential Hypertension; Blood Pressure; Bibliometrics; Citation Analysis; Scientometrics; h-Index

Introduction

Hypertension affects approximately 78 million adults (1 in 3 adults) in the United States (US) and is a major risk factor for cardiovascular disease, stroke, and chronic kidney disease.[1] Thus, hypertension represents a formidable challenge to US healthcare. In 2010, hypertension was projected to cost the US $93.5 billion in health care services, medications, and missed days of work.[2] In 2012, the National Institutes of Health (NIH), the largest funding source for biomedical research in the world, spent $215 million to support hypertension research.[3,4]

In this study, we undertook an effort to identify the most frequently cited 100 articles that describe advances focused on hypertension research. The number of citations an article receives after its publication is a measure of its recognition and suggests the impact of its information within the scientific community. Therefore, a bibliometric analysis (i.e., citation and content analysis) of the scientific literature may be used to identify influential articles, research topics, authors, etc. in a specific scientific field. To date, although a number of journals provide statistics of their own publications, we were unable to find an across-the-board bibliometric analysis of hypertension research. Here we report the results of a bibliometric analysis that aimed to examine key characteristics of the top 100 cited articles that focused on hypertension published during the past century (T100), including citation ranking, year of publication, publishing journal, type of study, country of origin, funding source, and authorship.

Methods

We used the *Science Citation Index Expanded* (1900–2013) database provided by the ISI Web of Science (Institute for Scientific Information, http://thomsonreuters.com/web-of-science/) to determine the 100 most frequently cited articles in hypertension research. The search topic terms included were: “hypertension,” “hypertensive,” or “blood pressure.” The articles identified by these search terms were accessed and reviewed online through the NIH library, and when online information was limited, we obtained the articles in print format.

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Conflicts of interest disclosure(s)
There are no conflicts of interest.

Results presented are based on the data accessed via the Internet on August 12, 2013. Each article was evaluated to ensure its focus on hypertension research. Clinical studies of hypertension (e.g., effective treatment) were included in the analysis. However, to maintain the focus on hypertension research articles with a primary focus on a single disease other than hypertension, such as diabetes, cancer, stroke, heart failure, renal failure, metabolic syndrome, preeclampsia, etc., were eliminated. Also, articles focused on pharmacological studies of drugs, blood pressure measurement studies, epidemiological or observational studies of blood pressure variation associated with various diseases, exercise, sleep, etc. were eliminated. For comparison, we also obtained total citation counts of the T100 articles as listed in the PubMed Central (PMC) database, http://www.ncbi.nlm.nih.gov/pubmed/ (retrieved on Aug 27, 2013). The number of web citations and patents citing the T100 articles were obtained by searching the Scopus database, http://www.scopus.com/search/form.url, on Aug 14, 2013. The h-index and cited article analysis of T100 were obtained from the ISI Web of Science Citation Report, retrieved on Aug 27, 2013 and September 18, 2013, respectively.

The selected T100 were analyzed according to the following parameters: citation number, authorship, source (i.e., journal), country of origin, founding source, and type of article. Articles were grouped into six different types according to their study design and goal: (1) clinical guidelines, (2) observational study, (3) randomized clinical trial, (4) basic science, (5) research review, and (6) meta-analysis. Observational studies included cohort studies, case-control studies, and case series. Randomized clinical trials included both single-blind and double-blind studies.

Results and Discussion

We are providing a list of T100 articles in descending order according to their total citations obtained from the SCI-Expanded at the time of the analysis (1–10 in Table 1; a complete list in Online Supplementary Table S1).

The most highly cited T100 had 7248 citations, and the 100th on our T100 list received 582 citations. The #1 ranked article was the 7th JNC (Joint National Committee) guidelines on prevention, detection, evaluation, and treatment of high blood pressure published in the *Journal of the American Medical Association (JAMA)* in 2003 by Chobanian *et al.*[5] This article was cited by articles in many other research areas, including cardiovascular science (38%), general internal medicine (16%), pharmacology & pharmacy (10%), urology & nephrology (8%), and public environmental occupational health (5%). The article was also cited in 10 different languages; mainly in English written reports (94%), followed by Spanish (3%) and Russian (1%) articles, indicating the world-wide reaching impact of these guidelines.

The T100 were published between 1934 and 2008: the earliest article was written by Goldblatt *et al.*[6] almost 80 years ago in *Journal of Experimental Medicine*, and the most recent were published about 5 years ago (2008) by Beckett *et al*,[7] and Jamerson *et al*,[8] both in *the New England Journal of Medicine* (*NEJM)*.

We also analyzed the main purpose and design of the T100 (Figures 1 and 2). The leading type of T100 research report was the observational study (35 articles), followed by randomized controlled clinical trials (RCT, 24 articles), and basic science studies (21 articles). Most of the articles reporting RCT studies aimed to determine the effectiveness of anti-hypertensive drugs in hypertensive patients (Online Supplementary Table S2). In addition, T100 included 10 guidelines, 6 research reviews, and 4 meta-analysis studies. Thus, the majority of the original reports that made the T100 list were clinical (59 clinical

observational and RCT) compared to pre-clinical (21) studies. The higher prevalence of clinical studies on this list might be related to the fact that most of them appeared in high impact journals. In addition, a recently published detailed bibliometric analysis suggests that the dissemination of clinical findings is very rapid.[9] Our limited survey, based on the analysis to identify the citation source for the top three T100 clinical studies, found that most of their citations (2/3) came from other original articles (both clinical and preclinical studies) with the rest of citations (1/3) being found in subsequent reviews, editorials, or meta-analyses. This distribution suggests that conclusions of these highly cited clinical studies had stimulated much subsequent original research. We also generated an alternative list that only contains the top 100 most cited original reports in hypertension research, by skipping all articles that represented reviews, guidelines, and meta-analysis studies, amounting to a total of 20 T100 publications. This alternative list thus contains 20 additional original reports and can be seen online (Supplementary Table S3).

Our extended analysis was done using the comprehensive T100 (Online Supplementary Table S1) which contained all the different type of reports. The top two most cited reports of the T100 represent the short and the complete versions of guidelines produced by the 7th JNC (Joint National Committee) on prevention, detection, evaluation, and treatment of high blood pressure supported by NHLBI, published in 2003 by Chobanian *et al.* in *JAMA*[5] and in *Hypertension*[10], respectively. The same publications were also the most and the second most cited articles on the web in hypertension research, with 299 and 263 web-citations, respectively (Table 1), reflecting a similar high public interest in these guidelines. The previously published guidelines, i.e., the sixth and the fifth JNC reports, were also identified as the 3rd and 34th T100, respectively, demonstrating the ever increasing popularity of guidelines. Taken together these statistics suggest that the JNC guidelines had a significant impact on hypertension research as well as on public interest, health programs, and policies.

We also analyzed the time distribution of T100 publication by decade (Figure 2). Overall, most of T100 (72%) were published after 1990. The distribution of most prevalent type of reports varied by decade. Articles describing clinical observational studies represented the major type of reports (50%) published before 1990. However, after 1990, the popularity of RCT studies increased, with both observational and RCT studies sharing the spotlight, each with 21 articles (29%) among T100. A special note is deserved by the three T100 published before 1950: Goldblatt *et al., J of Exp Med*, 1934[6], Keith *et al., Am J Med Sci*, 1939[11], and Goldenberg *et al., Am J Med*, 1948[12] as true “landmark” Citation Classic papers in hypertension research. These papers continue to be frequently referenced in the current publications. Among these, the paper by Goldblatt *et al.* is the oldest T100 and the most cited basic science research paper in the field of hypertension (ranked 12th among T100). This paper describes the first animal model of hypertension using a dog experimental model and demonstrates the critical role of the kidney in developing high blood pressure. In recognition of his important contributions to hypertension research, Dr. Harry Goldblatt was named the first recipient of the High Blood Pressure Research Council Award from the American Heart Association for outstanding research in 1966.

We found that the T100 were published in a variety of journals, 24 in all (Table 2). Seventeen articles were published in *NEJM*, followed by 14 articles in *Lancet*, and 10 articles in *JAMA*. Our results also show that highly cited basic science research focused on hypertension was published more frequently in *Nature* (6 articles) or *Cell* (4 articles) compared to *Science* (1 article) (see Table 2 for additional journal statistics). These journals are in the top 25 high-ranked Impact Factor Journals in 2012 according to the Journal Citation Reports, http://thomsonreuters.com/journal-citation-reports/. In addition to these so-called “High Impact Factor Journals,” specialty journals in hypertension research such as *Hypertension* and the *Journal of Hypertension* with relatively lower Impact Factors also

published highly cited papers (i.e., the 4th and 7th T100 publishing journals), providing the launching pads for 9 and 6 articles of the T100, respectively. Other bibliometric analyses[13–17] also show that highly influential reports are often published in specialty journals. These findings support the recent community call for the development of more accurate measures to assess research outputs of individuals and institutions when comparing scientific productivity and creativity.[18–21]

We decided to analyze the h-index of T100 as a way to estimate their impact on hypertension research. The h-index, introduced by J.E. Hirsh in 2005[22] as an alternative to standard bibliometric indicators (i.e., total citation counts), has been applied for different purposes and contexts to measure research output and impact of scientists, institutions, countries, publications, or journals.[23,24] The h-index listed in the ISI Web of Science for a publication[25] is meant to provide a measure of its impact among peers by computing the citations generated by the papers citing this original publication in the Web of Science database. The h-index values may vary between databases as it is calculated using their own data as input. In spite of this and other potential limitations, [22–24] this information can be a useful surrogate measure for the impact of T100 in the field of hypertension (Table 1). Ninety seven percent of the T100 articles were found to have an h-index of 40 or better, meaning that since their original publication these articles were cited by at least 40 articles that scored 40 or more citations themselves in the Web of Science database. The remaining 3% of T100 were more recent publications (2007 and 2008), having h-index scores of 31–35, consistent with the finding that h-index increases with time.

We found a general positive correlation between the h-indexes and the number of total citations (Pearson correlation coefficient=0.61). The article with the highest h-index (n=163) was the 6th JNC report by Black *et al.* published in 1997[26] (overall citation rank=3), followed by Collins *et al.* published in 1990[27] (h-index=159; overall citation rank=5), and Chobanian *et al.* published in 2003[5] (h-index=144; overall citation rank=1). A likely reason for which citation rank number 1 article by Chobanian *et al.* did not have the highest h-index is that it was the latest to be published among this line-up. One of the strong outliers when comparing total citation numbers versus h-index was the article by Halushka *et al.*,[28] which ranked 17th according to its h-index (n=108) but only 74th in the overall T100 citation rank. Interestingly, this article received the second highest citations by patents (n=154) among T100, suggesting this basic science report has been very influential in spurring technical innovation in addition to having a big impact on hypertension research.

For comparison, we also analyzed the total citation counts obtained for the T100, previously ranked using SCI-Expanded database, using the PubMed Central (PMC) database (Table 1 and Online Supplementary Table S1). PMC is a free digital database of full-text scientific literature, developed and maintained by the US National Library of Medicine of the NIH. Launched in February 2000, PMC serves as a repository for journal literature deposited by participating publishers, as well as for author manuscripts submitted in compliance with the Public Access Policy currently mandated by NIH and similar policies of other research funding agencies. The 7th JNC report by Chobanian *et al., JAMA*, 2003[5] again scored the most PMC citations among the T100 articles (PMC citations=1309), followed by the article by Chobanian *et al., Hypertension*, 2003[10] (PMC citations=909), and the article by Uehata *et al., Nature*, 1997[29] (PMC citations=386). While the citation numbers retrieved by the two data bases were different, there was a fairly good positive correlation between the number of total citations obtained from the SCI-Expanded and PMC databases (Pearson correlation coefficient=0.85). One of the strong outliers in this correlation is the article by Ong *et al.*, 2007[30] which ranked 27th in PMC citations but 95th in the SCI-Expanded citations. Ong *et al*. described an analysis of NHANES (National Health and Nutrition Examination Surveys) data regarding hypertension prevalence, awareness, and control in US adults. The authors

reported an important observation that when comparing two time periods (i.e., 1999–2000 versus. 2003–2004) hypertension awareness increased significantly from 69% to 76%, and hypertension control rates also improved from 29% to 37%.

Many journals also publish bibliometric analysis of their own publications. We compared our findings with the statistics of the specialty journal, *Hypertension*. Their monthly updated "*Most often cited 50 articles*" list is available on the journal's web site, http://hyper.ahajournals.org/reports/most-cited, and the list is based on citations provided by the HighWire press-hosted services, an archive of online free full-text science articles supported by the Stanford University Library. We found (data accessed on September 17, 2013) that all *Hypertension*-published articles we had previously identified among T100 were also listed by the journal's top 50 articles list. Of note, the top ranking 1–4 articles listed by *Hypertension* had similar order of rank as in our T100; the most cited *Hypertension* article is that published by Chobanian *et al.*, 2003 (T100 rank=2), followed by the articles by Burt *et al.*, 1995 (T100 rank=16), Laurent *et al.*, 2001 (T100 rank= 23), and Verdecchia *et al.*, 1994 (T100 rank=38), supporting consistency of information obtained from the two different databases.

We also analyzed the T100 source, identifying a total of 37 countries of origin (Table 3). Seventy one articles originated from all authors working in the same country, while 29 articles were contributed by multi-national collaborations (i.e., more than 2 countries involved). Overall, the greatest number of contributions came from the US (64 articles), followed by the UK (20 articles) and Italy (18 articles).

Eighty eight articles acknowledged their research funding source, with more than half of these (52%) acknowledging the support by the National Institutes of Health (NIH); with the National Heart, Lung, and Blood Institute (NHLBI) being the lead funding institute within NIH (85% of all NIH supported articles), consistent with NHLBI's mission to support basic, translational, and clinical studies in hypertension research. American Heart Association, a major non-profit organization supporting cardiovascular research in the US, funded 7 articles of T100 by grants and fellowship. Also, several pharmaceutical companies (i.e., Astra, Bayer, Bristol-Myers, Merck, Novartis, and Pfizer) actively sponsored a variety of clinical studies of hypertension. Pharmaceutical companies supported most of the T100 clinical trial studies of hypertension (21 out of 24 RCTs), whereas NIH supported 5 studies (21%); 3 studies were co-sponsored by NIH and industry and funding for one study was unattributed. On the other hand, NIH supported most of the basic science T100 studies (71%, 15 out of 21 articles), while industry supported only 2 studies (10%), confirming the key role of NIH funding in generation of influential basic research reports.

We also analyzed the characteristics of the T100 authorship. The great majority (94%) of T100 were the result of team works involving three or more authors. The other 6% were split between articles authored by a single author (B. Folkow, M.P. Blaustein, and A. Helgeland); and articles by two authors (M.J. Mulvany and W. Halpern; I. Hajjar and T.A. Kotchen; T.F. Luscher and P.M. Vanhoutte). The most frequently found authors were associated with clinical studies: B. Dahlof and G. Mancia (first authors, 4 articles each), J.H. Laragh and A. Zanchetti (last authors, 6 articles each), and E.J. Roccella (corresponding author, 5 articles). As to the T100 basic science, both D.G. Harrison and R.P. Lifton were the most frequent last and corresponding authors (2 articles each).

Publications obviously impact the way the people think about and implement the findings of basic and clinical research. As a measure of the T100 impact on technological innovation, we examined also the number of patents citing each of the T100 using data from the Scopus database (Table 1 and Online Table S1). Notably, we found no correlation between the SCI-

Expanded citations and patents citations ranking (Pearson correlation coefficient=0.1). Additionally, we found the top three T100 most cited by patents to be all basic science studies: (i) Uehata *et al.*, *Nature*, 1997[29], cited by 165 patents (T100 rank=14), (ii) Halushka *et al.*, *JAMA*, 1999[28], cited by 154 patents (T100 rank=74), and (iii) Mullins *et al.*, *Nature*, 1990[31], cited by 113 patents (T100 rank=69). Our findings support the idea that fundamental, basic science studies are major contributors fueling technical innovation.

We also analyzed the ranking of T100 based on their web citations, as a measure of their ability to gain popularity with a wider audience (Table 1 and Online Table S1). We found a moderately positive correlation between the number of total citations and web-citations (Pearson correlation coefficient=0.74). One of the major outliers to note was the third most web-cited article (web citations=187; T100 rank=28), a basic science study by Huang *et al.*, *Nature*, 1995,[32] which confirmed the role of nitric oxide in blood vessel relaxation through using genetically engineered mice that lack endothelial nitric oxide synthase (eNOS).

In conclusion, we performed a bibliometric analysis of the most cited reports focused on hypertension research, revealing several characteristics associated with these influential publications, including the type of study, trends in scope, journals, structure of authorship, country of origin, and funding. Our results confirm the persistent popularity of several articles considered “landmark” Citation Classics, as well as highlight some more recent “hot” topics in both basic and clinical hypertension studies. The most influential report in hypertension research seems to be the 2003 report by the 7th JNC report on prevention, detection, evaluation, and treatment of high blood pressure, supported by NHLBI/NIH. Our analysis also reveals that technical innovation heavily draws directly from influential basic science reports, suggesting a close connection between these two ends of biomedical knowledge. The present analysis also indicates that NIH investments in hypertension research have resulted in significant technological breakthroughs, provided important rational bases for changing clinical practice, and greatly increased public health awareness.

We acknowledge that our results were influenced by our choice of questions to investigate, inclusion/exclusion selection criteria, and limitations of the databases and tools we used for analysis. First, our decision to select articles with primary focus on hypertension research likely excluded articles that had otherwise significantly influenced the thinking in the field, including some of the highly cited articles that refer to investigations of blood pressure regulation in relation with disease, exercise, or sleep. Second, we derived our T100 list using primarily the SCI-Expanded database. Although the SCI-Expanded is the most commonly used database for citation analysis, it was not primarily developed for bibliometric analysis and thus important articles and information might have been missed in our analysis[33,34] (i.e., omitted articles, misspelled or incorrect citations and names, biased citations, etc.). Third, the citation rank can vary depending on the date of retrieval of such information. This may be a significant factor, especially for publications that have small differences in the number of citations; e.g., a tight range of less than 300 citations determined the ranking for the lower half of T100. Fourth, articles published in languages other than English might have received unfair citation counts due to bias and/or poor recognition in the field. As a final point, we want to note that citation counts are not a perfect reflection of scientific impact or quality.[18–21] Quite frequently, the citation of controversial topics or even erroneous results, including “negative” citations, may increase over time. We sought to eliminate articles specifically cited because they had been since proven to be flawed. Despite these limitations, the current study provides some insights into the characteristics of the most read and cited information in the field of hypertension research over the last century.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Novelty and significance

1. *What is new:* We are unaware of previous reports describing across-the-board bibliometric analyses of hypertension research.
2. *What is relevant:* We believe that sharing the results of our analysis will help the hypertension research community gain a better understanding of the features of the most influential work in this field. Our analysis also reveals the role of NIH funding in enabling basic and clinical research as a basis for scientific and technical innovation, changes in clinical practice, and as a driving force in influencing public health policies and public awareness.
3. *Summary:* We identified the Top 100 most cited articles focused on hypertension research published in the last century (T100) using the Science Citation Index Expanded (1900–2013) database. We found T100 spanned the knowledge spectrum from basic and clinical research to guidelines, with the most cited report being the 7th JNC (Joint National Committee) guidelines on prevention, detection, evaluation, and treatment of high blood pressure published in 2003. The T100 were published in 24 different journals, originated from 37 countries, with the great majority being the work of teams, most were sponsored by government and private industry funds, further emphasizing the global interest and investment in hypertension research.

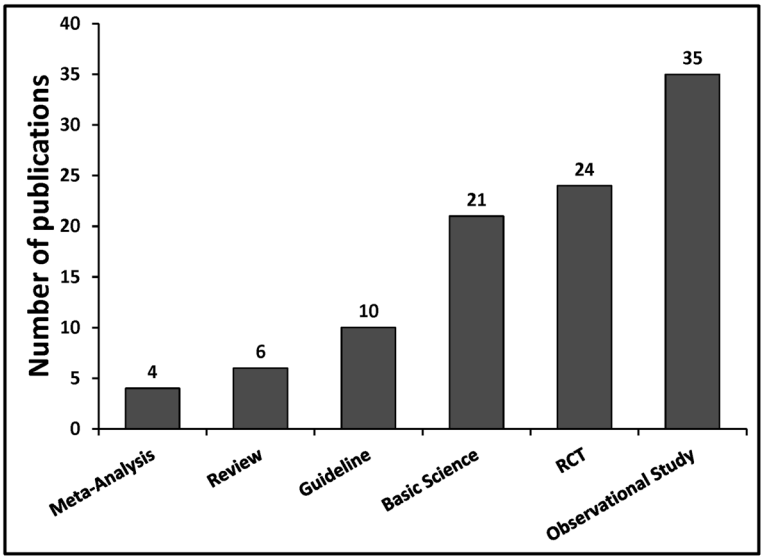

Figure 1.

The top 100 cited articles focused on hypertension research (T100) cover a variety of main goals. Our analysis showed that most T100 were observational clinical studies, followed by randomized controlled clinical trials (RCTs), and basic science. Citations were obtained from the Science Citation Index Expanded database.

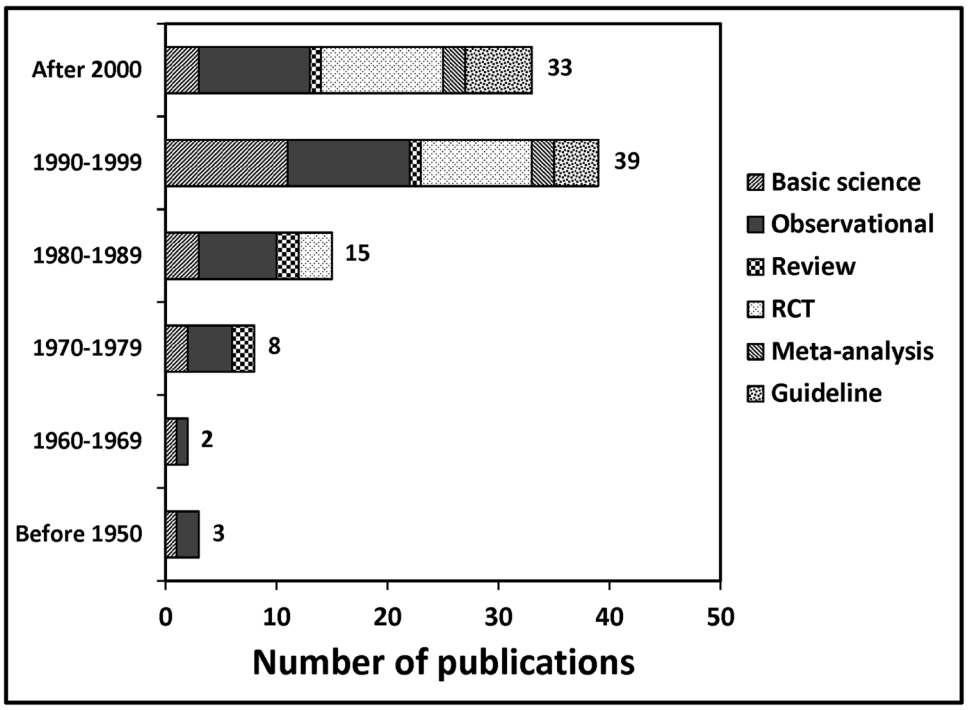

Figure 2.

Time trends in the distribution of T100 analyzed by decade. The results show that 72% of T100 were published after 1990 and T100 composition varied by decade. i.e., observational clinical studies predominated among T100 published between 1970–1989, while randomized clinical trials (RCT) increased in popularity afterward.

Table 1

Bibliometric information associated with the top ten of the Top 100 most cited articles in hypertension research (T100). See Online Supplemental Table S1 for a complete list of T100. Data were collected from the Science Citation Index Expanded, PubMed Central (PMC), and Scopus databases.

Rank	Times Cited	Author	Title	Journal	Year	*h*-index	PMC Cited	Web Cited	Patents Cited
1	7248	Chobanian et al.	The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure - The JNC 7 Report	Journal of the American Medical Association 289:2560–2572	2003	144	1309	299	13
2	4480	Chobanian et al.	Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, And Treatment of High Blood Pressure	Hypertension 42:1206–1252	2003	101	909	263	32
3	4364	Black et al.	The Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure	Archives of Internal Medicine 157:2413–2446	1997	163	271	87	6
4	3072	Hansson et al.	Effects of Intensive Blood-Pressure Lowering and Low-Dose Aspirin in Patients with Hypertension - Principal Results of the Hypertension Optimal Treatment (HOT) Randomised Trial	Lancet 351:1755–1762	1998	131	292	129	24
5	2744	Collins et al.	Blood-Pressure, Stroke, and Coronary Heart Disease. Part 2. Short-Term Reductions in Blood-Pressure: Overview of Randomized Drug Trials in their Epidemiologic Context	Lancet 335:827–838	1990	159	247	135	22
6	2673	Dahlof et al.	Cardiovascular Morbidity and Mortality in the Losartan Intervention for Endpoint Reduction in Hypertension Study (LIFE): A Randomised Trial Against Atenolol	Lancet 359:995–1003	2002	124	262	74	7
7	2628	Chalmers et al.	1999 World Health Organization International Society of Hypertension Guidelines for the Management of Hypertension	Journal of Hypertension 17:151–183	1999	108	175	122	4
8	2441	Furberg et al.	Major Outcomes in High-Risk Hypertensive Patients Randomized to Angiotensin-Converting Enzyme Inhibitor or Calcium Channel Blocker vs. Diuretic - The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)	Journal of the American Medical Association 288:2981–2997	2002	102	332	30	8
9	2261	Mancia et al.	2007 Guidelines for the Management of Arterial Hypertension - The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC)	Journal of Hypertension 25:1105–1187	2007	51	310	45	2

Rank	Times Cited	Author	Title	Journal	Year	*h*-index	PMC Cited	Web Cited	Patents Cited
10	2242	Mancia et al.	2003 European Society of Hypertension - European Society of Cardiology Guidelines for the Management of Arterial Hypertension	Journal of Hypertension 21:1011–1053	2003	85	189	76	11

Table 2

Journals in which T100 were published.

Journal	Number of Articles	Impact Factor (2012)
New England Journal of Medicine	17	51.7
Lancet	14	39.1
Journal of the American Medical Association	10	30.0
Hypertension	9	6.9
Nature	6	38.6
Circulation	6	15.2
Journal of Hypertension	6	3.8
Cell	4	32.0
Journal of Clinical Investigation	3	12.8
American Journal of Medicine	3	4.8
Annals of Internal Medicine	3	14.0
Circulation Research	3	11.9
British Medical Journal	2	17.2
Archives of Internal Medicine	2	11.5
American Journal of Hypertension	2	3.7
Journal of Experimental Medicine	2	13.2
American Journal of Physiology-Cell Physiology	1	3.7
American Journal of the Medical Sciences	1	1.3
European Heart Journal	1	14.1
Journal of the American College of Cardiology	1	14.1
Nature Genetics	1	35.2
Pediatrics	1	5.1
Physiological Reviews	1	30.2
Science	1	31.0

Table 3

Countries of origin for the top 100 most cited articles in hypertension research. T100 were originated from many different countries. Listed countries are those from which at least 5 of T100 were originated.

Country	Number of Articles
US	64
UK	20
Italy	18
Sweden	15
France	13
Germany	12
Norway	8
Netherlands	8
Finland	7
Belgium	7
Spain	6
Switzerland	5
Ireland	5
Denmark	5
Australia	5