

Abstract

Hypertension, or high blood pressure, is a major risk factor for cardiovascular disease (CVD) and other comorbidities, including diabetes mellitus (DM). Hypertension and DM often share an atherosclerotic origin which contributes to the progression of each condition, respectively. Given the shared vascular pathophysiology, these conditions can often be treated concurrently. This study collected data from 7176 hypertension clinical trials, finding diabetics and those with diabetes-related complications to be frequently excluded (~75% exclusion rate). Contrarily, those with risk factors for DM and glucose intolerance were included and excluded from hypertension clinical trials more proportionately (~45% and 51% exclusion rates, respectively). Type 1 diabetes was almost exclusively excluded from hypertension clinical trials. Considering the shared pathophysiology and co-treatment potential, future clinical trials should actively include diabetics in hypertension clinical trials.

Background

Hypertension, or high blood pressure, is a major cardiovascular disease (CVD) risk factor and is often associated with other major comorbidities, including diabetes mellitus (DM). Hypertension is common in diabetics but ranges in prevalence and severity depending on DM type, duration, other comorbidities, and traditional demographic variables such as age and ethnicity. Hypertension is considered a strong risk factor for atherosclerotic CVD which is also the leading cause of morbidity and mortality in diabetics. Research has supported the use of antihypertensive therapies to reduce atherosclerotic events and complications in diabetics (De Boer et al., 2017, 1273-1284).

Hypertension and DM are associated with peripheral artery resistance which is generally caused by atherosclerosis and vascular remodeling in combination with increased body fluid volume associated with insulin resistance-based hyperinsulinemia and hyperglycemia. Moreover, diabetes-induced vascular remodeling contributes to hypertension and prompts diabetic complications, including diabetic nephropathy (Ohishi, 2018, 389-393). Research has consistently associated hypertension and DM.

Methods

This study aimed to evaluate the historical co-treatment of hypertension and DM by analyzing the eligibility criteria of hypertension clinical trials. Researchers scanned "ClinicalTrials.gov" for DM-related terms found within the eligibility criteria of all hypertension clinical trials (MeSHID D000006973) from 1990 to 2022. Python 3.9.10 was used to collect and tally the frequency of diabetes-related terms within all eligible trials. Clinical trials that did not contain distinct inclusion and exclusion sections, as well as terms that mentioned in both sections of a given study, were flagged for manual curation.

After the original data collection process, the data was imported into RStudio 2022.07.2 and the data was cleaned and organized using the R (4.2.2) tidyverse 1.3.2 suite of packages. Terms unrelated to diabetes as a chronic comorbidity, such as vague terms (e.g. “disease”, “surgery”), symptoms (e.g. “pain”, “sleepiness”) or acute illness (e.g. “fever”, “pneumonia”), were discarded. Count data was transformed to binary data to reflect the presence or absence of a term in a given study. Synonymous terms (e.g. “Type 2 diabetes” and “diabetes mellitus type 2”) were merged so that the presence of any variant was only counted once per study. Flagged studies and terms were manually checked on [ClinicalTrials.gov](https://clinicaltrials.gov) to determine the correct term assignment. Figures were created using the Tidyverse ggplot2 3.4.0 R package.

Microsoft Excel was then used to further organize and analyze the collected terms to better understand the proportional inclusion and exclusion of diabetes-related terms. Data analysis was conducted on all terms collectively and subsequently dispersed into seven groups, “Diabetes”, “Diabetes Complications”, “Diabetes Risk Factors”, “Gestational Diabetes”, “Glucose Intolerance”, “Type 1 Diabetes”, and “Type 2 Diabetes” to better understand any trends within the inclusion rate of more precise diabetes-related conditions in hypertension clinical trials. The collected data is represented in Table 1 and further presented to exemplify the proportional inclusion and exclusion of each term in Figure 1. Final data analysis was conducted using Microsoft Excel to determine statistical significance.

Results and Discussion

This study identified 7176 hypertension clinical trials initiated between 1990 and 2022. After synonymous terms were merged, 16 terms were identified in the eligibility criteria of these hypertension studies a total of 2673 times. Hypertension-related terms were mentioned solely in the inclusion sections of 430 studies, and solely in the exclusion sections of 1273 studies. Thirty-one hypertension clinical trials lacked explicit inclusion sections and 166 contained the same term in both sections—these were manually inspected and assigned to the correct group. Collectively, 1876 (70.2%) terms were found within the exclusion criteria compared to 797 (29.8%) within the inclusion criteria of hypertension clinical trials. Once grouped, notable trends were identified in the Diabetes (DM), Diabetes Complications (DC), and Type 1 Diabetes (D1) groups. Diabetes-related terms were found in frequencies of 1706 in DM, 129 in DC, and 202 in D1. in the Diabetes Diagnosis (DD), Interestingly, DM and DC yielded similar proportional exclusion rates of roughly 75% compared to an exclusion of approximately 45% in the Diabetes Risk Factors group and 51% in the Glucose Intolerance group. D1 exhibited an exclusion rate of 98%.

Table 1. Inclusion and exclusion frequencies of individual search terms related to diabetes in the eligibility criteria of hypertension clinical trials from 1990 - 2022.

Search term	Inclusion frequency	Exclusion frequency	Term grouping
Diabetes	429	1277	Diabetes
Diabetes complications	0	3	Diabetes complications
Diabetic foot	2	0	
Diabetic nephropathy	8	14	
Diabetic retinopathy	22	80	
Metabolic syndrome	19	7	Diabetes risk factors
Obese	106	129	
Overweight	25	3	
Prediabetes	19	3	
Sedentary lifestyle	5	0	
Gestational diabetes	3	7	Gestational diabetes
Glucose intolerance	13	12	Glucose intolerance
Insulin resistance	7	4	
Insulin sensitivity	2	7	Type 1 Diabetes
Type 1 Diabetes	4	198	
Type 2 Diabetes	133	132	Type 2 Diabetes
TOTAL:	797 (29.8%)	1876 (70.2%)	2673 term mentions

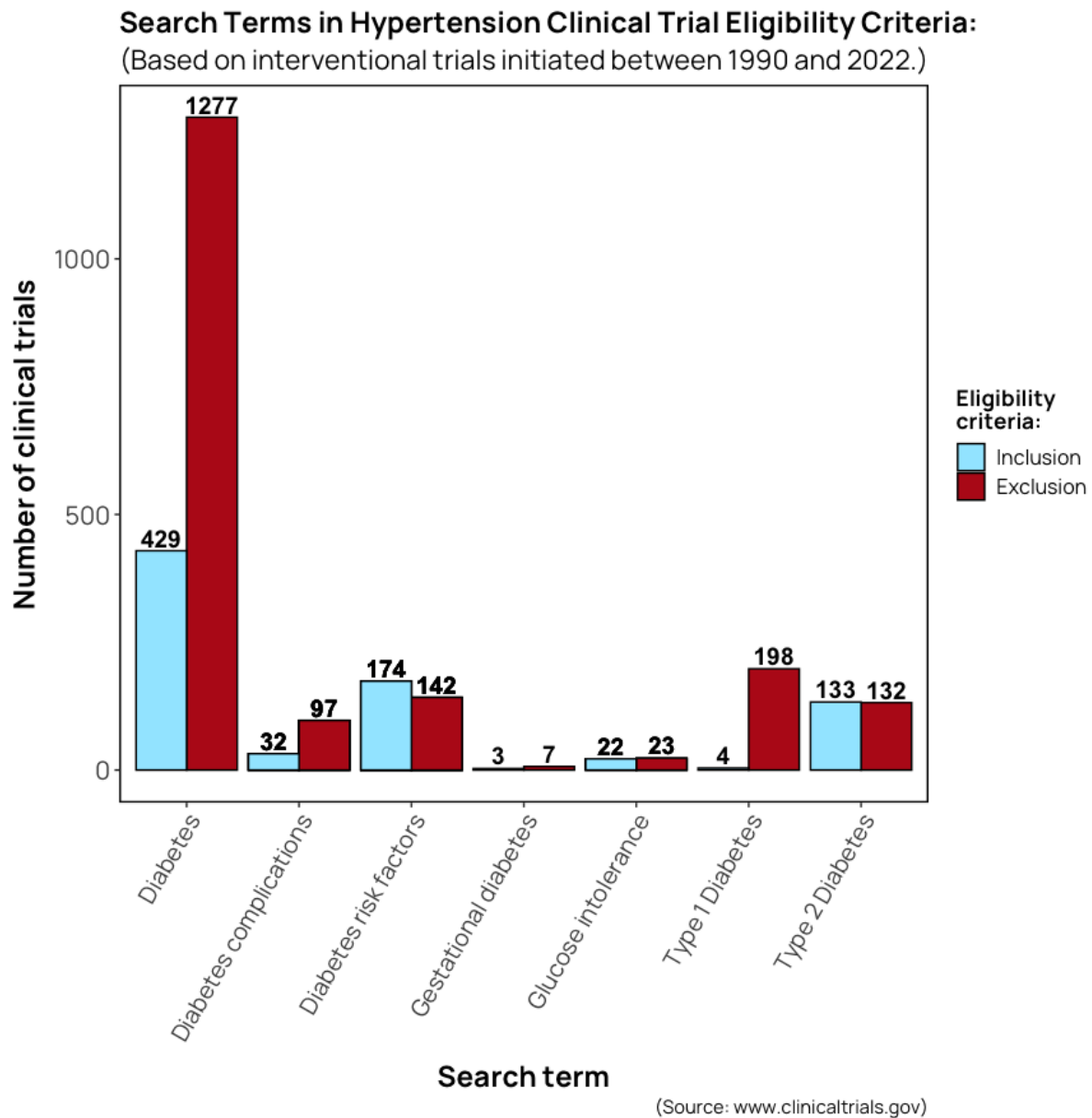


Figure 1. Inclusion and exclusion frequencies of groups of search terms related to diabetes in the eligibility criteria of hypertension clinical trials from 1990 - 2022. Individual search terms are listed in Table 1.

The collected data exhibits a disproportionate inclusion and exclusion of diabetics within hypertension clinical trials. Contrarily, those with diabetes risk factors and glucose intolerance are more proportionally included in such trials despite an obvious correspondence with DM. Additionally, Type 1 diabetes was almost exclusively excluded from hypertension clinical trials. Research has established clear benefits of antihypertensive therapies on concomitant hypertension and DM, yet clinical trials have historically limited the inclusion of diabetics despite

an apparent willingness to include those with diabetes risk factors and glucose intolerance. Future clinical trials should emphasize a greater inclusion of more advanced DM prognoses to continue improving treatment outcomes and minimizing disease progression during hypertension and DM cotreatment.

References

De Boer, Ian H., Sripal Bangalore, Athanase Benetos, Andrew M. Davis, Erin D. Michos, Paul Muntner, Peter Rossing, Sophia Zoungas, and George Bakris. "Diabetes and hypertension: a position statement by the American Diabetes Association." *Diabetes care* 40, no. 9 (2017): 1273-1284.

Ohishi, Mitsuru. "Hypertension with diabetes mellitus: physiology and pathology." *Hypertension research* 41, no. 6 (2018): 389-393.