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The attention on gender in studies on the treatment of hypertension: was it enough?

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Summary. Hypertension is an important cardiovascular risk factor, and its treatment is undoubtedly effective in reducing the incidence of cardiovascular and renal events in both sexes, as also reaffirmed by the most recent ESC-ESH guidelines. Our knowledge of the hypertension therapy derives from the evidence generated by a large number of controlled clinical studies carried out over the last decades; however, the authors of these studies did not always evaluate the results obtained separately for males and females. After examining the major controlled clinical studies in the field of hypertension therapy, mentioned in the guidelines, our study found that the analysis of the results had taken account of sex in 21 out of 33 cases only. The most recent meta-analyses – which in some cases concern hundreds of thousands of subjects – were then evaluated, noticing that only in a small minority of cases did the analysis of the results take sex into consideration as a variable; significant problems, such as the treatment of hypertension in the elderly or the pressure levels to be reached with treatment, have never been evaluated from a gender perspective. The study does not demonstrate the existence of gender differences, because this was not its objective, but from an extensive analysis of the literature it concludes that the existence of possible gender differences in the context of high blood pressure therapy is not being sufficiently investigated yet.

Key words. Hypertension, gender medicine, guidelines, controlled clinical trials, meta-analysis.

Attenzione al genere negli studi sul trattamento dell'ipertensione: è sufficiente?

Riassunto. L'ipertensione è un importante fattore di rischio cardiovascolare e il suo trattamento è senza dubbio efficace per ridurre l'incidenza di eventi cardiovascolari e renali in ambedue i sessi, come riaffermato anche dalle più recenti linee guida ESC-ESH. Le nostre conoscenze sulla terapia dell'ipertensione derivano dalle evidenze generate da un ampio numero di studi clinici controllati effettuati negli ultimi decenni; tuttavia gli autori di questi studi non sempre hanno valutato i risultati ottenuti separatamente per maschi e femmine. Questo studio ha preso in esame i più importanti studi clinici controllati nell'ambito della terapia dell'ipertensione, citati nelle linee guida, riscontrando che l'analisi dei risultati aveva tenuto conto del sesso solo in 21 casi su 33. Sono state poi valutate le più recenti metanalisi, che in qualche caso riguardano centinaia di migliaia di soggetti, rilevando come solo in una esigua minoranza di casi l'analisi dei risultati abbia preso in considerazione il sesso come una variabile; problematiche significative come la terapia dell'ipertensione nell'anziano o i livelli pressori da raggiungere con il trattamento non sono mai state valutate in un'ottica di genere. Lo studio non dimostra l'esistenza di differenze di genere perché questo non era il suo obiettivo, ma da una ampia analisi della letteratura conclude che l'esistenza di possibili differenze di genere nell'ambito della terapia dell'ipertensione arteriosa non è stata ancora sufficientemente indagata.

Parole chiave. Ipertensione, medicina di genere, linee guida, studi clinici controllati, metanalisi.

Introduction

High blood pressure is both an important risk factor for cardiovascular disease and, considering its high prevalence, the leading cause of morbidity and mortality worldwide.[1,2] Its prevalence increases with age and, while in youth it is greater in the male sex, in the elderly the difference is canceled, or even reversed.[3] Although our knowledge has increased in the last 50 years, and many effective and well tolerated drugs have become available, control of high blood pressure remains partial, and therefore many of the benefits that could derive from optimal blood pressure control are lost.[4] Indeed, the effectiveness of the reduction of blood pressure values is widely documented,[5] as also reaffirmed by the most recent guidelines, jointly issued by the European Society for Hypertension (ESH) and the European Society of Cardiology (ESC),[6] which in paragraph 7.1 state: "Meta-analyses of RCTs including several hundred thousand patients have shown that a 10 mmHg reduction in SBP or a 5mmHg reduction in DBP is associated with significant reductions in all major CV events by 20%, all-cause mortality by 10-15%, stroke by 35%, coronary events by 20%, and heart failure by 40%. These relative risk reductions are consistent, irrespective of baseline BP within the hypertensive range, the level of CV risk, comorbidities (eg., diabetes and CKD), age, sex, and ethnicity." Therefore, the guidelines for the treatment of arterial hypertension that constitute the reference text for those involved in the management of patients with arterial hypertension

make no gender distinction. While considering this statement widely acceptable, the purpose of this work was to verify whether the evidences on which the guidelines are based are comparable for both sexes, and whether enough attention has been paid to any possible gender difference in the results of the clinical trials.

Materials and methods

Published records of all randomized clinical trials with at least 1,000 patients, cited by the 2018 ESH-ESC guidelines and regarding hypertension treatment (both non-pharmacological and pharmacological), were collected and screened, with the aim of looking for the total number of patients enrolled and the proportion of females; the statistical analysis and the results were assessed, in order to find out whether sex was considered for subgroup analyses and whether separate results for males and females were reported. When this data was not available in the main publication of the study results, Pub-Med was checked for secondary publications over the following years pertaining to subgroup analyses. Pub-Med was also checked to collect the most important meta-analysis on hypertension treatment, published after the meta-analysis of Turnbull, that was dedicated to gender differences.[7] For these meta-analyses, we looked for the number of females included, and checked whether the results were reported separately for males and females.

Results

The 33 controlled clinical trials with >1,000 subjects mentioned by the 2018 ESH-ESC guidelines are reported in chronological order in Table 1. Overall, they included 305,249 patients; females were 135,478 (44,38%). Only eleven studies reported the results according to gender in the main paper, but other 7 did it in a subsequent publication devoted to planned subgroup analysis; 3 other trials stated in the main paper to have performed a subgroup analysis for gender, without finding any significant differences among the groups. Studies that did not perform a separate analysis of the results included 77,939 patients (25,5% of the total), and females were well represented (49.2%).

The most relevant meta-analyses are reported in Table 2.

Discussion

Until a few decades ago, medical research and the resulting evidence did not take gender differences into account; only in the last decades, with the development of gender medicine, physicians became aware of the fact that the personalization of treatments required a special attention to the gender differences that had already been found in numerous other areas. Before even considering any gender differences, it is important to evaluate whether the evidence available to date was collected with studies where males and females were equally represented, and whether the results were assessed separately. High blood pressure is the most common cardiovascular risk factor and its control hasn't been fully achieved yet. Studies show the existence of gender differences (regarding awareness, the percentage of patients treated and well-controlled, and the type of drugs most frequently prescribed) that can only be partially justified. The guidelines state without hesitation that the treatment of hypertension is effective in reducing cardiovascular events, regardless of gender. This study sought to evaluate gender equality among the evidence available in the literature in support of this claim. Given the huge amount of controlled clinical studies relating to the treatment of hypertension in the literature, we chose to refer to those mentioned in the ESH-ESC guidelines of 2018, in the belief that they represent the state of the art; consequently the 33 studies thus identified can be considered as the most representative of the available evidence. There are wide differences in the proportion of females included in the various studies (from 23.4 to 66.8%): the average is 44.38%, a value which – had the prevalence in the population been respected – would have been slightly over 50%. However, if this can somehow be accepted, much more serious is the fact that – even taking into account the secondary publications and the declaration of having performed a subgroup analysis (even in the absence of the results) – only 21 out of 33 studies considered the two sexes separately. Therefore the results in 1/4 of all the patients studied were not analyzed separately for sexes, even though males and females were equally represented. However, it must be recognized that subgroup analysis may not always be feasible and, above all, the inevitable reduction in the events observed within each subgroup can lead to statistically insignificant and/or spurious results. This problem can be overcome, at least partially, with meta-analyses which, combining the data of numerous homogeneous studies, can reach populations large enough to allow a statistically correct evaluation even for subgroups. In 1997, Gueyffier, on behalf of the INDANA group,[48] performed the first meta-analysis of data with the aim of comparing the effects of antihypertensive treatment in males and females; they gathered the individual data of 7 trials conducted between 1972 and 1990 in 20,802 females and 19,975 males. Their conclusions were that, in terms of relative risk reduction, there were no differences between females and males but, since absolute risk reduction was dependent on untreated risk, for some end-points the

Table 1. Most relevant controlled clinical trials regarding hypertension treatment

Study (year)	Total no. of patients	Males no.	Females no.	Females (%)	Separate results	Subgroup analysis by sex
SHEP (1991)[8]	4,736	2,046	2,690	56.8	Yes	
STOP (1991)[9]	1,627	608	1,019	62.6	Yes	
SYST-EUR (1997)[10]	4,695	1,557	3,138	66.8	No	No
UKPDS 38 (1998)[11]	1,148	637	511	44.5	No	No
HOT (1998)[12]	18,790	9,960	8,830	47.0	No	Yes*[13]
CAPP (1999)[14]	10,985	5,874	5,111	46.5	No	No
STOP-2 (1999)[15]	6,614	2,196	4,418	66.8	No	No
INSIGHT (2000)[16]	6,321	2,929	3,392	53.7	No	No
NORDIL (2000)[17]	10,881	5,290	5,591	51.4	No	Yes*[18]
SYST-CHINA (2000)[19]	2,394	1,541	853	35.6	Yes	
PROGRESS (2001)[20]	6,105	4,253	1,852	30.3	No	Yes*[21]
ALLHAT (2002)[22]	33,357	17,719	15,638	46.9	Yes	
ELSA (2002)[23]	2,334	1,279	1,055	45.2	No	Yes
LIFE (2002)[24]	9,193	4,230	4,963	54.0	No	Yes*[25]
INVEST (2003)[26]	22,576	10,806	11,770	52.1	Yes	
SCOPE (2003)[27]	4,964	1,780	3,184	64.1	No	Yes*[28]
VALUE (2004)[29]	15,245	8,777	6,468	42.4	No	Yes*[30]
ASCOT-BPLA (2005)[31]	19,257	14,742	4,515	23.4	Yes	
CONVINCE (2005)[32]	16,602	7,375	9,227	55.6	No	No
FEVER (2005)[33]	9,711	5,920	3,791	39.0	No	No
CAFÉ (2006)[34]	2,199	1,802	397	18.0	No	Yes
ADVANCE (2007)[35]	11,140	6,405	4,735	42.5	Yes	
ONTARGET (2008)[36]	25,620	18,789	6,831	26.7	Yes	
ACCOMPLISH (2008)[37]	11,506	6,963	4,542	39.5	Yes	
HYVET (2008)[38]	3845	1,519	2,326	60.5	No	Yes
ACCORD (2010)[39]	4,733	2,475	2,258	47.7	No	Yes*[40]
COPE (2011)[41]	3,293	1,669	1,624	49.3	No	
SCAST (2011)[42]	2,029	1,176	853	42.0	No	No
ALTITUDE (2012)[43]	8,561	5,826	2,735	31.9	No	No
INTERACT 2 (2013)[44]	2,839	1,780	1,059	37.3	No	No
PREDIMED (2013)[45]	7,447	3,165	4,282	57.5	Yes	
COLM (2015)[46]	5,141	2,653	2,488	48.4	No	No
SPRINT (2015)[47]	9,361	6,029	3,332	35.6	Yes	

*Separate results were reported in a subsequent paper.

Table 2. Most relevant meta-analyses

Author (year)	Purpose	Total no. of patients	Females no. (%)	Gender subgroup analysis
Gueyffier (1997)[48]	Efficacy of treatment in males and females	407,77	20,802 (51.0)	Yes
Turnbull (2008)[7]	Sex differences in drug efficacy	190,617	87,349 (45.8)	Yes
Law (2009)[49]	Efficacy of drug treatment	464,164	?	No
Fagard (2009)[50]	LVH regression	6,001	?	No
Briasoulis (2014)[51]	Efficacy of treatment in patients >65 yrs	114,854	?	No
Thomopoulos (2014)[52-54]	Efficacy Efficacy at different BP levels Efficacy at different CV risk	245,885 127,929 245,870	? ? ?	No No No
Thomopoulos (2015)[55, 56]	Different drugs effects Head to head comparisons	195,267 247,006	? ?	No No
Xie (2016)[57]	Less vs more and renal disease	44,989	?	No
Brunstrom (2016)[58]	Efficacy of antihypertensive treatment in diabetics	73,738	?	No
Ettehad (2016)[59]	BP targets	613,815	?	No
Thomopoulos (2016)[60-63]	Prevention of heart failure More intense vs less intense treatment Outcome reductions vs discontinuation due to AE Discontinuation due to AE with different drugs	146,810 52,235 255,970 147,788	? ? ? ?	No No No No
Bangalore (2017)[64]	Blood pressure targets	55,163	?	No
Giorgini (2017)[65]	Sex differences in outcomes with treatment	100,995	42,886 (42.5)	Yes
Weiss (2017)[66]	Efficacy of treatment in patients >60 yrs	81,395	?	No
Thomopoulos (2017)[67-69]	Differences in diabetics Outcome reductions with lower BP targets Effects of treatment in patients with high-normal BP	253,125 260,210 47,991	? ? ?	No No No
Brunstrom (2018)[70]	Efficacy of treatment	306,273	122,203 (39.9)	Yes (declared)
Karmali (2018)[71]	Efficacy of treatment/CV risk	47,872	21,912 (46.0)	No
Thomopoulos (2018)[72,73]	Efficacy of treatment in older vs younger patients Efficacy of different drugs in older and younger patients	210,558 349,726	? ?	No No
Murad (2019)[74]	Efficacy of treatment >65 yrs	42,134	?	No

BP: blood pressure; CV: cardiovascular; AE: adverse event.

benefit of the treatment in females was not statistically significant. Another important meta-analysis was published by Turnbull et al. in 2008;[7] the aims of these general analyses were to quantify the effects of blood pressure-lowering treatment in each sex, and to determine if there were important differences in the proportional benefits of the treatment between males and females. They included 31 randomized trials with 103,268 males and 87,349 females, and concluded that all the blood pressure lowering regimens studied generally provided a similar protection against major cardiovascular events in males and females, and that the differences in cardiovascular risks between the sexes are unlikely to reflect any differences in the response to blood pressure-lowering treatments.

However, Turnbull's meta-analysis[7] focused on evaluating the effectiveness of individual classes of drugs in the two sexes, while in the following years the interest of research has focused on the effectiveness of combination drugs, on the levels of pressure to be treated and to be achieved, on the differential aspects of therapy, particularly in subgroups and especially the elderly. Unfortunately, most of the subsequent meta-analysis did not investigate separately males and females.

Only Giorgini's meta-analysis[65] investigated the existence of gender differences in the efficacy of antihypertensive therapy in the 10 studies out of the 64 identified (only 15%) that reported the results separately for males and females, and found an increased residual risk of cardiovascular events in males (RR = 1.25), mainly due to the higher cardiovascular risk at baseline. In his meta-analysis,[70] which included 74 controlled clinical studies, for a total of 306,273 subjects, Brunstrom doesn't show the results for males and females separately, but states to have considered sex among the covariates, and that this did not entail significant differences in the results achieved, which confirmed the efficacy of the treatment when systolic blood pressure (BP) is >140 mmHg, while for lower values a reduction in events was demonstrable only in a subgroup with previous coronary artery disease.

All the other meta-analyses do not take into consideration the results for males and females separately (they do not even report the total number of males/females enrolled in the studies considered!), and therefore for significant questions – such as the effectiveness of the treatment also in the elderly or the goal of systolic BP to be achieved with therapy – we cannot know if there could be any gender differences.

With regard to the latter, the SPRINT study[47] played a decisive role in lowering the target BP to be achieved; here, it is not appropriate to analyze the controversial aspects of the study and its possible downsides, but it is worth pointing out that, due to the small number and the early interruption of the study, in the females' subgroup a statistically significant difference was not reached, and therefore – based on this study – the efficacy of a lower reduction in BP is not demonstrated in females. It would therefore have been helpful if the meta-analyses that dealt with this problem had considered the two sexes separately.

Even the long series of meta-analyses conducted with great scientific rigor by Thomopuolos, Mancia and Zanchetti, published in 14 papers between 2014 and 2018[52-56,60-63,67-69,72,73] and addressing different aspects of hypertension treatment, do not consider gender as a possible variable. In 2016 Muiesan et al.[75] – after describing the differences between the two sexes in the epidemiology of hypertension, in the use of the different classes of drugs and in the proportion of patients aware, treated and with BP controlled – concluded that, based on the solid evidence of large clinical trials, the efficacy of different drugs for the prevention of cardiovascular events is similar in males and females, and that there are no gender-specific suggestions. Our study was not intended to find possible gender differences, but to evaluate whether this possibility had been sufficiently investigated in the controlled clinical studies on which our knowledge and current treatment guidelines are based.

The extensive review of the literature we carried out shows that this has not always been done, and therefore useful information on gender differences may have been left out: this could prevent an effective personalization of the antihypertensive therapy.

Key messages

- Hypertension is an important risk factor for cardiovascular diseases.
- As stated in the ESC-ESH guidelines, the treatment of hypertension is associated with a significant reduction in all major cardiovascular events, irrespective of sex.
- It is not clear whether sufficient attention has been paid to gender differences in the studies that contributed to our knowledge of the hypertension treatment.
- This study shows that both sexes were almost equally represented in controlled clinical trials, but that the results were considered separately only in 21/33 of cases, and that very seldom the meta-analyses that combine the results of a large number of studies to gain enough power for subgroup analysis paid attention to gender.
- The extensive review of the literature we performed shows that not enough attention has been given to gender, and therefore useful information on gender differences may have been left out: this could prevent an effective personalization of the antihypertensive therapy.

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