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Are Observational Studies More Informative Than Randomized Controlled Trials in Hypertension?

Pro Side of the Argument

Giovanni de Simone, Raffaele Izzo, Paolo Verdecchia

Cardiovascular (CV) disease is the major cause of death and disability in United States, as well as in Europe^{1,2}. It contributes substantially to the escalating costs of health care. Over the past 10 years, the control of CV risk factors has improved especially at the older age strata,³ but most of this success does not seem to be related to a reduced impact of hypertension.^{4,5}

As recently pointed out,^{6,7} the reduction of hypertension-associated CV morbidity and mortality is almost exclusively a consequence of the results of randomized controlled trials (RCTs), especially those comparing active medications versus placebo.⁸ Unfortunately, despite this success, arterial hypertension remains the leading CV risk factor, to which 13% of global death is attributable.⁹ Uncontrolled blood pressure (BP) is one of the most frequent problems encountered in the prevention of CV diseases.¹⁰

Hypertension control has improved over time, but it is evident that this improvement is still insufficient.¹¹ Half of the patients do not achieve normalization of BP values, a rate that is especially high in elderly subjects,¹² an evidence based on analyses of effectiveness of antihypertensive therapy and of population-based cohorts.^{3,13}

Although most RCTs on antihypertensive medications present positive results, only a minority of them report the proportion of optimal BP control achieved with the treatment (Table 1). Overall, with a few exceptions,^{23,27,33} efficacy of antihypertensive therapy also does not seem optimal in the studies declaring proportion of achieved target BP.

RCTs largely offset a number of biases encountered in the real-world physician's decision making, are unavoidable in analyses of even large clinical databases,³⁴ and orient decision and guidelines or recommendations.^{35,36} However, sometimes the RCTs' results are not unequivocal, raising the need to implement meta-analyses.³⁷

Limitation of Meta-Analyses

As expected, meta-analyses substantially confirm the general pattern emerging from the original study's object of analysis, limiting, but not eliminating, contradictions,^{38,39} because of a number of critical issues,⁴⁰ including biases introduced in the process of locating, selecting, and combining studies.^{41,42}

Publication bias can seriously affect the attempts to estimate the effect under investigation. Studies with significant, positive results are generally more likely to be published and easier to be found than those with nonsignificant or negative results, raising the risk of serious bias toward positive results.⁴³ Although various methods for detecting and correcting for publication bias are useful,⁴⁴ most of them have limitations and full prevention of systematic bias is still to be achieved.^{45,46}

Selection of studies is another source of bias, especially important when examining mortality and morbidity or other specific outcomes, because the mathematical procedure used to weigh for cell size excludes studies with no reported outcome, clearly biasing results.

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Table 1. List of 19 Major Trials on Antihypertensive Therapy With Average Initial and Final Blood Pressure Values (When Reported)

Trial	BP Goal	Arm	Initial SBP, mm Hg	Initial DBP, mm Hg	Optimal BP Control, %	Last SBP, mm Hg	Last DBP, mm Hg
HAPPYS ¹⁴	<95 DBP	β-Blockers	166	107	79	140	88
		Diuretics	166	107	75	140	89
IPPPSH ¹⁵	≤140/90	β-Blockers	171/175 mol/L-F	108/108 mol/L-F	32	144	89
		Others	170/175	108/107	21	147	90
CAPP ¹⁶	?	ACE-i	162	100	?	?	?
		Others	160	99	?	?	?
STOP2 ¹⁷	?	ACE-i	194	98	?	159	81
		CCB	194	98	?	159	80
		Others	194	98	?	158	81
ANBP2 ¹⁸	?	ACE-i	167	91	?	141	79
		Diuretics	168	91	?	142	79
ALLHAT ¹⁹	<140/90	Chlorthalidone	146	84	68	134	75
		Amlodipine	146	84	66	135	75
		Lisinopril	146	84	61	136	75
ALLHAT ²⁰	<140/90	Chlorthalidone	145	83	64	135	76
		Doxazosin	145	83	58	137	76
NORDIL ²¹	?	Diltiazem	173	106	?	155	89
		Diuretics+β-blocker	173	106	?	152	89
INSIGHT ²²	≤140/90	Nifedipine	173	99	58	132	82
		Co-amlozide			57	132	82
INVEST ²³	<140/90	CCB	150	86	72	?	?
		β-Blockers	150	86	71	?	?
SCOPE ²⁴	?	ARB	169	82	?	146.5	76.3
		Others	169	82.5	?	149.1	77.7
LIFE ²⁵	≤140/90	Losartan group	174	98	48	144.1	81.3
		Atenolol group	175	98	45	145.4	80.9
VALUE ²⁶	<140/90	ARB	154.5	87.4	56	139.3	79.2
		CCB	155	88	62	137.5	77.7
ACCOMPLISH ²⁷	<140/90	Benazepril/Amlodipine	145	80	75	131.6	73.3
		Benazepril/HCTZ	145	80	72	132.5	74.4
ADVANCE ²⁸	?	Perindopril+Indapamide	145	81	?	?	?
		Placebo	145	81	?	?	?
HYVET ²⁹	?	Active treatment	173	91	?	145	78
		Placebo	173	91	?	159	83
ONTARGET ³⁰	?	Telmisartan	142	82	?	136	78
		Ramipril	142	82	?	135	77
		Telmisartan+Ramipril	142	82	?	134	76
PRoFESS ³¹	?	Very low-normal	130	79	?	113	70
		Low-normal	137	82	?	125	76
		High-normal	143	84	?	135	80
TRANSCEND ³²	?	Telmisartan	141	82	?	?	?
		Placebo	141	82	?	?	?

End points were reduction of BP in 8 trials and CV morbidity and mortality in 19 trials. Less than 50% report target BP and corresponding proportion of optimally controlled hypertensive patients at the end of trial.

ACE-i indicates angiotensin-converting enzyme inhibitors; ARB, angiotensin II-receptor blockers; BP, blood pressure; CCB, Ca⁺⁺ channel blockers; Co-amlozide, amiloride+hydrochlorothiazide; CV, cardiovascular; DBP, diastolic blood pressure; HCTZ, hydrochlorothiazide; Others, other antihypertensive drugs; and SBP, systolic blood pressure.

ACCOMPLISH indicates Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension; ADVANCE, Action in Diabetes and Vascular disease: preterAx and diamicroN-MR Controlled Evaluation; ALLHAT, The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; ANBP2, Second Australian National Blood Pressure Study Group; CAPP, Captopril Prevention Project; HAPPY, The Heart Attack Primary Prevention in Hypertension Trial Research Group; HYVET, Hypertension in the Very Elderly Trial; INSIGHT, International Nifedipine GITS study: Intervention as a Goal in Hypertension Treatment; INVEST, The International Verapamil-Trandolapril Study; IPPPSH, International Prospective Primary Prevention Study in Hypertension; LIFE, Losartan Intervention For Endpoint reduction in hypertension study; NORDIL, Nordic Diltiazem study; ONTARGET, The Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial; PRoFESS, Prevention Regimen for Effectively Avoiding Second Strokes trial; SCOPE, Study on Cognition and Prognosis in the Elderly; STOP2, Swedish Trial in Old Patients with Hypertension-2 study; TRANSCEND, Telmisartan Randomised Assessment Study in ACE intolerant subjects with cardiovascular Disease; and VALUE, Valsartan Antihypertensive Long-term Use Evaluation.

Also heterogeneity of results selected for meta-analysis can be only partially offset by statistical procedures.^{47,48} Heterogeneity is a potential problem also in observational studies produced from data repositories or registries, but in this case it is likely to reflect the true-life variability of the population that is studied. Several meta-analyses on the best antihypertensive therapy to reduce left ventricular mass or regress left ventricular hypertrophy (LVH) initially confirmed what was shown by the RCTs designed to compare angiotensin-converting enzyme inhibitors or angiotensin II-receptor blockers (ARBs) with other classes of antihypertensive medications,⁴⁹ that is, the superiority of those medications over the others, but prospective population-based studies or pragmatic trials,^{50–52} as well as more extensive and recent meta-analyses,⁵³ have challenged that conclusion.

Imbalance Between RCT Setting and Outpatient Clinic

The most important bias for RCTs and meta-analyses, especially for conditions largely prevalent, such as arterial hypertension, remains the intrinsic imbalance between recruited patients and inhomogeneous populations referred to outpatients clinics in clinical practice.

To test the efficacy of a given medication, RCTs set a specific environment, which is often based on the need to generate a positive result for regulatory purposes.³⁷ This environment is somewhat artificial because of definite characteristics: quality control, adherence to therapy, stringent inclusion and exclusion criteria, and safety issues.

Quality Control and Adherence to Therapy

The quality control in RCTs is largely regulated by contract research organizations, which are independent of the clinic recruiting patients. Errors in procedures and delays in the follow-up are readily recorded and corrected. In the setting of an RCT, patients generally perceive more attention from doctors.⁵⁴ Overall, the adherence to therapy is considered to be more rigorous in an RCT than in daily clinical practice.⁵⁵

Factors related to quality of care can influence adherence and persistence of antihypertensive therapy in real life, including access to health care and socioeconomic status (especially in a country without a public health system). In addition, physician reluctance to adjust therapy and lack of adherence to guidelines, because of poor update, disagreement based on personal clinical practice, or skepticism,⁵⁶ increases the chance of differences between RCT environment and clinical practice.

Selection of Study Population

One unequalled characteristic of RCTs, which cannot be found in observational studies, is the ability to merge a large number of variables to obtain very homogeneous series of observations and isolate the effect of treatment from potential confounders. Merging samples for comparison reduces internal variability and, as a consequence, sample size, and is superior to many statistical elaborations that can be used in observational and epidemiological studies, allowing researchers to weigh for confounders. These characteristics are the basis of the strong internal validity of RCTs. Not

necessarily, however, internal validity of an RCT tracks also external validity. To maximize internal validity and highlight the efficacy of therapy, in RCTs, the selection of the study population needs to be as homogeneous as possible. Every researcher involved in RCTs knows the difficulty of selecting patients with given characteristics to meet the requirements of the RCT's protocols. This is, for instance, the case of clinical trials focused on regression of LVH, in which only patients with clear-cut LVH are recruited.⁵³ The selection is of critical importance to try to weigh for major confounders, otherwise the size of the population samples would be too big to make a study financially affordable.

In most circumstances, therefore, the necessity to be stringent excludes a large proportion of patients, but does not avoid, afterward, the extension of indications also to those patients who were excluded because of lack of required characteristics. In many circumstances, the majority of hypertensive patients seen in routine clinical practice would not be eligible for RCTs on efficacy of a given treatment. Staessen et al,⁵⁷ after careful examination of 6 major RCTs collecting >70 000 patients, highlighted a number of limitations and concluded that from a clinical viewpoint, results from RCTs should not be extrapolated to patients with characteristics dissimilar from those who were randomly assigned.

Often the selection excludes categories of patients who are most likely to require aggressive therapy. For instance, as recently highlighted,⁵⁸ patients with stage 3 or 4 chronic kidney disease are almost invariably excluded from RCTs on angiotensin-converting enzyme inhibitors or mineralocorticoid receptor inhibitors. These exclusions generate potential problems when extending the indications beyond the limitations imposed by RCTs,^{59,60} a phenomenon known as treatment-risk paradox. The tightness of a population selection is, therefore, inversely correlated with the external validity of an RCT.⁶¹

As outlined above, a potential alternative to traditional RCTs may be offered by the so-called practical or pragmatic trials.^{33,62,63} These trials are intended to compare 2 or more drugs or interventions that are important in clinical practice and try to simulate a real-life situation as much as possible. These trials are, therefore, mostly aimed to improve external validity of results. Distinctive features of these trials include (a) broad eligibility criteria; (b) recruitment of patients in a variety of settings; (c) unblinded treatment; and (d) reasonably long follow-up.⁶³ Therefore, pragmatic trials tend to sacrifice internal validity to achieve generalizability.³³ Unfortunately, pragmatic trials in hypertension are unlikely to be again implemented, because of a number of reasons. Without the drive of new medications, pharmaceutical companies generally refuse to support large and expensive trials based on antihypertensive drugs that are already or going to be off patent.⁶⁴

Limitations of Analysis of Results of RCTs

Most translation of results from RCTs into clinical practice is based on intention-to-treat analysis, as recommended by the American Statistical Associations.⁶⁵ Intention-to-treat analysis is irrespective of whether patients actually received the treatment, dropped out, or did not follow the intended protocol

for any reason. The intention-to-treat analysis may not reflect the overall efficacy of a complex multidrug therapeutic strategy. In many cases (60%–75%), the analysis can also be influenced by missing observations and the way the missing data are treated.⁶⁶

Despite the fact that most RCTs on antihypertensive therapy are intended to test the efficacy of a given medication, the attempt to achieve the therapeutic goal is done almost invariably through various combinations of the initially studied medications with other drugs given afterward. In this context, the intention-to-treat analysis would not express the efficacy of the drug to which the patient has been initially randomized, but the efficacy of the variable combination and interaction of the initial with subsequent drugs. Also, the type and doses of the add-on medications are strictly programmed by protocol. In the real world, we can make different choices in relation to the conditions of patients and their comorbidities, their compliance, the availability of commercial combinations, the clinical setting, sometimes the need to favor cheaper medications, and, especially, the possible better interaction between 2 classes of medications. These differences from the real world may further reduce the RCT external validity.

The Real World

In clinical practice in the outpatient clinics, environments, problems, and management are very different from those found in the RCT artificial environment. The typology of patients is not selected, but recommendations and guidelines derived from RCTs and meta-analyses, translated into guidelines, are commonly applied without consideration of the specific characteristics of the population sample that produced the evidence of efficacy. Often the typologies of patient populations vary, depending on the clinical context. Isolated systolic hypertension, especially in elderly subjects, and also essential hypertension in the young are conditions that do not fit with results of most of the recent clinical trials. Rather, the physicians' behavior could be conditioned by a number of ancillary messages on the potential low efficacy of β -blockers and diuretics (most often hydrochlorothiazide, almost never chlorthalidone, despite the current evidence)⁶⁷ in controlling target organ damage, to underuse them in systolic hypertension in elderly.⁶⁸ In the Campania Salute Network,⁶⁹ an open electronic registry generated from a network of 23 community hospitals and 60 general practitioners in the Campania District, the underuse of diuretics was one of the independent correlates of insufficient BP control.⁷⁰ Table 2 shows the complexity of hypertensive participants of the Campania Salute Network, making evident the variety of clinical presentations of an open outpatient clinic, as compared with the selections operated in RCTs. In the Campania Salute Network, at presentation in the outpatient clinic, 6% of hypertensive patients had prevalent coronary heart disease; 60% had chronic kidney disease of whom 10% were with stage 3 or greater; 33% exhibited carotid atherosclerosis; and 32% had LVH. In addition to these comorbidities, 27% of hypertensive patients were obese and 32% had metabolic syndrome. Comparing these features with the selection criteria required by the major trials, only a minority of these patients could have been enrolled.

Table 2. Characteristics of Hypertensive Patients of the Campania Salute Network at the Time of the First Visit in the Outpatient Clinic, During the Last Decade

N	10698
Age, y	53.21 $\pm$ 13.4
Sex (M/W), %	57/43
Diabetes mellitus, %	7.1
Obesity (BMI $\geq$ 30), %	27.0
Obesity (BMI $\geq$ 25), %	73.3
Impaired fasting glucose, %	4.5
Hypercholesterolemia, %	27.4
Hypertriglyceridemia, %	4.2
Hypercholesterolemia+hypertriglyceridemia, %	12.6
Metabolic syndrome, %	31.6
GFR $>$ 90, %	31.7
60<GFR<90, %	58.0
30<GFR<60 or more, %	10.3
With LVH, %	31.8
With carotid atherosclerosis, %	32.7
With coronary heart disease, %	5.8

This unselected population presents with slightly greater prevalence of CV risk factors than reported in the Campania District (<http://www.istat.it/it/salute-e-sanità>), but with high prevalence of mild chronic kidney disease and target organ damage.

BMI indicates body mass index; CV, cardiovascular; GFR, glomerular filtration rate; LVH, left ventricular hypertrophy; M, man; and W, woman.

Epidemiological studies also indicate that the association of arterial hypertension with other CV risk factors or metabolic syndrome makes effective control of BP much more difficult even if aggressive therapy is used,^{70–72} paralleling the less effective reduction of LVH, as shown in the Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) study.⁷³ In the American Indian cohort of the Strong Heart Study, left ventricular mass index tended to increase in treated hypertensive participants, over 4 years of follow-up.⁷⁴ Similar preliminary results are also obtained among the treated hypertensive participants of the white cohort of the Campania Salute Network (personal communication). This is relevant also for risk profiling. In a subset of patients without LVH at entry included in the ONgoing Telmisartan Alone and in combination with Ramipril Global End point Trial (ONTARGET), the primary study outcome (composite of CV death, myocardial infarction, stroke, and congestive heart failure) occurred more frequently in association with new-onset LVH at follow-up than in its absence.⁷⁵

Conclusions

There are practical implications that can be summarized from the abovementioned considerations. First, RCTs are of utmost critical importance to improve the care of patients and generate evidence-based guidelines. However, because of their inherent limitations, the external validity of RCTs needs to be verified in large and unselected populations. Second, the possibility to externally validate the results of RCTs may be provided by accurate observational studies.

This goal can be achieved using a number of data collections,⁷⁶ including: (1) cross-sectional and longitudinal databases, mostly providing retrospective data; (2) patient and population surveys, useful for epidemiological information, but usually limited in the amount of information; (3) registries, probably the best opportunities to compare results from RCTs with real-life achievements and gain new information directly from real-world settings.

Compared with simple database repositories, registries give the advantage of minimizing selection bias, by collecting a large amount of data from representative proportions of the affected population in a given area, providing both retrospective and prospective data. Registries may be used to assess incidence of major CV events, as well as incidence and prevalence of markers of preclinical CV disease. Given these characteristics, registries may validate effectiveness of medications that have demonstrated good efficacy in RCTs and provide longer-term knowledge about safety and costs of antihypertensive strategies. Eventually, use of registries is less expensive than realizing pragmatic clinical trials, but requires careful control of bias, adequate outpatient clinic organization, standardization of data collections, and optimal data and statistical management.

Disclosures

None.

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Response to Are Observational Studies More Informative Than Randomized Controlled Trials in Hypertension? Pro Side of the Argument

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Concepts without percepts are empty; percepts without concepts are blind.¹

We appreciate the balance of Dr de Simone et al in their defense of the role of real-world datasets as a potential source of clinically relevant information, especially in those settings which are not easily covered by randomized controlled trials (RCTs). Although the benefits of such an approach are mostly yet to be determined, its theoretical advantages are undeniable. We agree that the rigorous and somewhat artificial inclusion and exclusion criteria of most randomized trials rule out a large proportion of patients seen in routine clinical practice. We also concede that application of the results of a given trial to a broader and more heterogeneous population may not always be justified.

However, we disagree with our esteemed opponents in 2 key points. First, Dr de Simone eloquently tries to persuade us that the external validity of RCTs needs to be verified in large and unselected populations. A dependable, unappealable decision of a higher court may not always be needed for well-designed trials and is often impossible to achieve from studies with a nonexperimental design such as those based on real-world databases. Second, despite their attractiveness as cheaper and more flexible tools to assess the efficacy of different treatment strategies, registries and retrospective analyses of existing databases are intrinsically more exposed to bias than trials. In our original position piece we report ≥5 major examples of misconceptions derived from observational studies, which were more or less widely accepted by the scientific and medical communities until disproven by specifically designed RCTs. We also show that selected recommendations from authoritative and widely respected clinical guidelines based on the results of observational studies have sometimes been misleading. We wonder what the clinical management of hypertension would be today without the sometimes amazing yet unquestionable results of adequately powered yet costly and non-natural RCTs. However, there is no single case of a main finding of a major RCT in the field of hypertension management and cardiovascular prevention which has been subsequently proven wrong by observational studies or by other trials.

If we may paraphrase the philosopher Immanuel Kant, we would say that RCTs without observational studies may sometimes have a limited external applicability, but observational studies without properly conducted RCTs are blind and can more easily lead to false conclusions: “only through their unison can knowledge arise.”²

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