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Cardiovascular and Renal Outcomes Trials—Is There a Difference?

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There is a general sense that most outcomes trials in patients receiving dialysis failed to yield statistically significant benefits, in contrast to many cardiovascular (CV) trials in the general population. It is unknown whether methodologic reasons caused this discrepancy. We performed a systematic MEDLINE search for randomized trials with mortality end points of the 42 compounds most commonly used for CV indications. In total, 115 trials were selected for review. We further reviewed 9 mortality end point trials in patients receiving dialysis. The CV trials in populations not receiving dialysis enrolled from 66 to 33,357 participants with an average of 4,910; 59% of the trials showed statistically significant results. The average hazard ratio (HR) was 0.77, ranging from 0.10 to 1.65; 10 drugs had ≥5 published trials each. In the population receiving dialysis, most drugs were studied in single trials; the average number of patients was 1,500 with a range of 127 to 3,883. The average HR was 0.77 and ranged from 0.06 to 1.30. Only 22% of the trials showed statistically significant results. The limitations listed in the general population and dialysis studies were similar. In conclusion, no apparent methodologic issues were detected (other than sample size) that could justify the lower frequency of randomized trials with statistically significant results in patients receiving dialysis. The most obvious difference was the paucity of trials with each drug in the dialysis cohorts; this lowers the chances of at least 1 trial being successful. **(Am J Cardiol 2015;116:982−988)**

The previous reports in cardiovascular (CV) medicine are replete with results from randomized clinical trials (RCTs) that have assessed the effects of various pharmacologic interventions on hard clinical end points including death. In contrast, the nephrology reports contain relatively few RCTs that have examined clinical outcomes in patients with end-stage renal disease (ESRD) on dialysis. The disparity is particularly noteworthy because patients undergoing dialysis are recognized widely to have very high morbidity and mortality rates primarily from CV causes.[1] Most RCTs completed to date in the dialysis population have had mortality as an end point, whereas other CV end points have been evaluated less often. Nearly all studies in patients with ESRD have been substantially smaller than those done in the general population, and the observed effect size has been relatively smaller. Few of the RCTs reported thus far in subjects with ESRD have demonstrated differences between treatment groups that were statistically significant.[2−7] Whether such findings are attributable to the nature of the underlying disease processes that affect this very high-risk population, to certain aspects of research design and/or statistical analysis, to the duration of the interventions being evaluated, and/or to the length of follow-up or a combination of these factors, is uncertain. We reviewed and evaluated findings from a large number of CV mortality RCTs conducted in the general population and in subjects with ESRD. We sought to determine whether there were common patterns that could help explain the failure to document statistically meaningful differences between treatment groups in RCTs that enrolled subjects with ESRD and RCTs that enrolled patients from the general population.

Methods

We initially examined the list of the most frequently prescribed medications in the United States as reported in terms of total number of prescriptions by IMS from the National Prescription Audit of 2013.[8] We selected all CV medications from that list. We further expanded the list to include the most frequently used CV medications based on the Web site of the American Heart Association.[9] This expanded list was reviewed by an academic physician (PR) with expertise in clinical trials to include drugs used for the most frequently encountered CV conditions. The final list of drugs thus contained 42 CV treatments addressing outcomes in the general population (Appendix A). For comparison, two nephrologists (KK-Z, WGG) identified 9 drugs that are most frequently used in ESRD that have been tested in randomized trials (Appendix B). This approach was possible because of the limited number of ESRD-specific drugs and trials. For the treatments identified in the previously mentioned process, we searched medical databases for

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See page 986 for disclosure information.

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Table 1
List of the largest cardiovascular outcome trials conducted in the general population with the drugs selected for these analyses

Trial Name (ref number)	Arms	Primary endpoint	N subjects	Event rate per 1000 year	HR or RR	p-value
ALLHAT[13]	amlodipine vs chlorthalidone	fatal CHD or MI	33357	13.2	0.98	0.65
Physicians' Health Study[14]	aspirin vs placebo	MI	22071	3.4	0.56	<0.00001
Dutch TIA Trial[15]	atenolol vs placebo	death from vascular causes, stroke, or MI	1473	52.2	1	n.s.
ASCOT-LLA[16]	atorvastatin vs placebo	MI or fatal CHD	10305	7.7	0.64	0.0005
CIBIS-II[17]	bisoprolol vs placebo	mortality	2647	111.6	0.66	<0.0001
CAPPP[18]	captopril vs conventional Hx treatment	MI, stroke, or cardiovascular death	10985	10.9	1.05	0.52
COMET[19]	carvedilol vs metoprolol	mortality	3029	76.0	0.83	0.002
SHEP[20]	chlorthalidone vs placebo	stroke	4736	12.3	0.64	0.0003
CAPRIE[21]	clopidogrel vs aspirin	ischaemic stroke, MI, or vascular death	19185	53.4	0.913	0.043
DIG[22]	digoxin vs placebo	mortality	7788	35.8	0.66	0.001
NORDIL[23]	diltiazem vs diuretics + beta-blockers	stroke, MI, or CV death	10881	16.4	1	0.97
CONSENSUS II[24]	enalapril vs placebo	mortality	6090	247.2	1.1	0.26
EPHESUS[25]	eplerenone vs placebo	mortality	6632	116.7	0.85	0.008
Helsinki Heart Study[26]	gemfibrozil vs placebo	MI or cardiac death	4081	6.9	0.66	<0.02
VA Cooperative Study[27]	hydralazine + isosorbide dinitrate vs placebo	mortality	642	191.7	0.879545	0.093
EWPHE[28]	hydrochlorothiazide + triamterene vs placebo	mortality	840	72.6	0.91	0.41
ACTIVE I[29]	irbesartan + placebo	stroke, MI, or vascular death	9016	52.1	0.99	0.85
ALLHAT[13]	lisinopril vs chlorthalidone	fatal CHD, MI	33357	13.2	0.99	0.81
MERIT-HF[30]	metoprolol vs placebo	mortality	3991	91.0	0.66	0.0062
Coronary Drug Project[31]	niacin vs placebo	mortality	3908	30.1	0.89	0.0004
TRITON-TIMI 38[32]	prasugrel vs clopidogrel	CV death, MI, or stroke	13608	86.6	0.81	<0.001
PPP Project[33]	pravastatin vs placebo	stroke	19768	5.8	0.8	0.01
QUIET[34]	quinapril vs placebo	cardiac death or arrest, MI, o.a.	1750	176.1	1.04	0.6
HOPE[35]	ramipril vs placebo	MI, stroke, or CV death	9297	31.8	0.78	<0.001
JUPITER[36]	Rosuvastatin vs placebo	MI, stroke, revasc., angina, or CV death	17802	10.7	0.56	< 0.00001
MRC/BHF HPS[37]	simvastatin vs placebo	mortality	20536	27.6	0.87	0.0003
RAES[38]	spironolactone vs placebo	mortality	1663	201.4	0.7	<0.001
PLATO[39]	ticagrelor vs clopidogrel	vascular death, MI, or stroke	18624	100.8	0.84	<0.001
NAVIGATOR[40]	valsartan vs placebo	development of diabetes	9306	22.6	0.96	0.22
TPT[41]	warfarin vs placebo	coronary death, MI	5499	14.0	0.79	0.02

outcomes trials with mortality as a primary or co-primary end point. Specifically, we completed a MEDLINE search using the name of each compound together with the publication type "randomized controlled trial" and the MeSH term "cardiovascular diseases/mortality." We also searched product inserts and *clinicaltrials.gov* to capture trials that might have been missed in the MEDLINE search.

The PubMed/MEDLINE search on the 42 selected drugs for the general population resulted in 1,083 references based on our search design. On screening the abstracts, we selected 349 articles and abstracted 224 articles reporting on 198 trials. There were more articles than trials because some articles reported different analyses from the same trial. Because our analyses focused on long-term indications, we excluded 83 trials conducted in the perioperative period and as short-term treatment (i.e., <30 days follow-up), bringing the total number of trials in the general population to 115. Our search for outcomes studies in ESRD resulted in 9 trials.[2–7,10–12] Overall, we summarized data from 124 trials published before May 2014: 115 long-term CV trials in the general population and 9 trials in patients with ESRD (Supplementary Tables 1 and 2). We compiled tables containing information about the number, duration, the size of the trials, the rate of primary events, effect size, and precision. A p value <0.05 was considered statistically significant. The limitations of each study as described in the original reports were also noted.

Results

The 115 RCTs in the general population encompassed the use of 30 therapies (i.e., no mortality trials were found for the remaining 12 therapies from the search list). Among the 30 therapies for which we found mortality trials, 10 drugs were evaluated in 5 or more outcomes trials. The number of study participants ranged from 66 to 33,357 with

Table 2
List of the largest pharmacotherapy outcome trials in the dialysis population conducted with the drugs selected for these analyses

Trial Name (ref number)	Arms	Primary endpoint	N subjects	Event rate per 1000 year	HR or RR	p-value
EVOLVE[3]	cinacalcet vs placebo	death, MI, angina, HF, or PVE	3883	91.3	0.93	0.11
GDDS[2]	atorvastatin vs placebo	cardiac death, MI, or stroke	1255	95.0	0.92	0.37
NHS[4]	normal-hematocrit vs low-hematocrit	death or MI	1233	254.4	1.3	ns
FOSRENOL trial[5]	lanthanum carbonate vs standard therapy	mortality	1354	108.7	0.86	0.18
AURORA[6]	rosuvastatin vs placebo	CV death, MI, stroke	2776	90.5	0.96	0.59
DCOR[7]	sevelamer vs calcium-based phosphate binders	mortality	2101	177.3	1.02	0.8
DOHAS[12]	spironolactone vs control	CV or cerebrovascular death or hospitalization	309	30.2	0.404	0.017

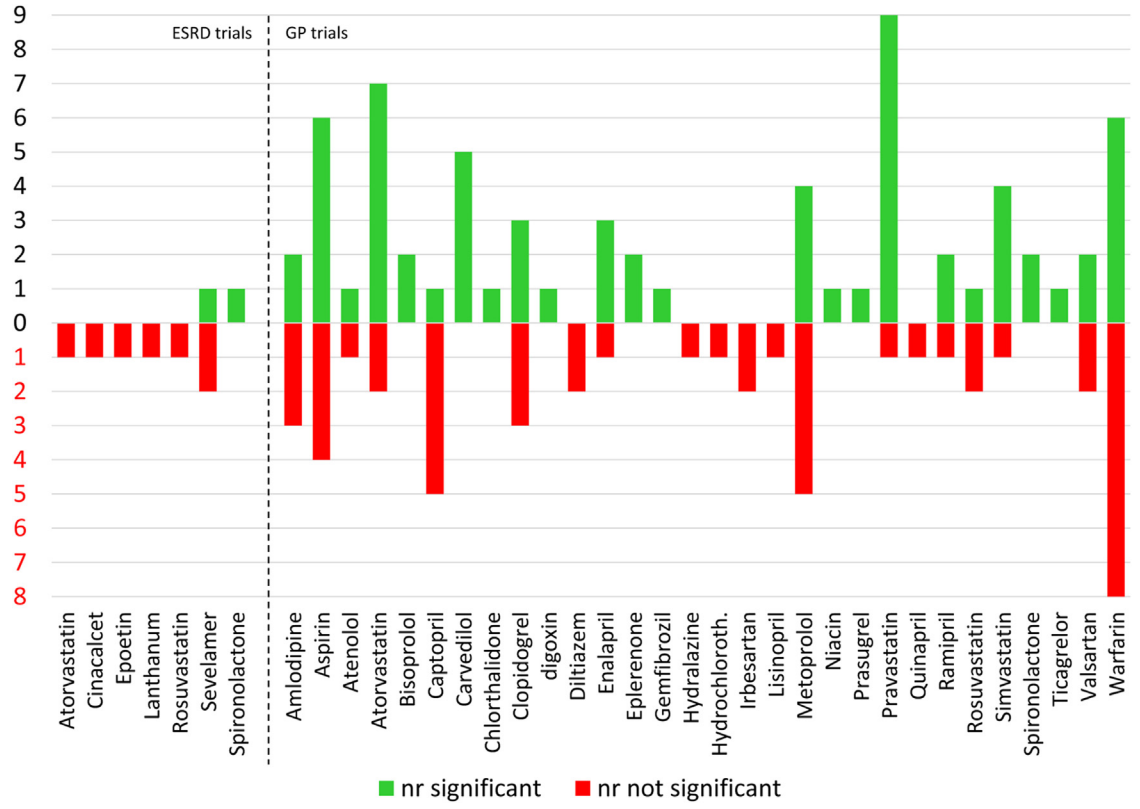

Figure 1. Number of clinical trials and results by statistical significance (we included only therapies for which at least 1 trial with mortality as an end point was available). GP = general population.

an average of 4,910. A statistically significant result was observed in 59%, with an average hazard ratio (HR) of 0.77, ranging from 0.10 to 1.65. Table 1 provides the duration and size of the largest trials we reviewed for each compound in the general population.

In patients with ESRD, a total of 9 outcomes trials were identified. Only 4 of 9 ESRD-specific therapies had outcomes RCTs with mortality as a part of the primary end point. The phosphate-binding agent sevelamer was the only therapeutic compound studied in more than 1 RCT, and 3 RCTs were done with this drug. For all other therapeutic interventions, the outcome data were derived from a single RCT. Overall, studies in subjects with ESRD were smaller than those done in the general population, ranging in size from 127 to 3,883 subjects with an average enrollment of 1,500. The average HR of 0.77 was similar to that observed in studies from the general population and ranged from 0.06 to 1.30. The summary of the largest trial for each compound in ESRD is presented in Table 2.

Figure 1 shows the number of trials done with each therapeutic agent and the number of statistically significant and nonsignificant results. There were more trials per compound in the general population than in ESRD, and many of them did not reach statistical significance: 41% of the CV trials and 78% of the ESRD trials, respectively, were not statistically significant.

There were no pattern differences in the number of events per trial. The number of events in ESRD trials ranged from 28 to 1,890 with an average of 593, whereas in the general population, it ranged from 8 to 2,835 with an

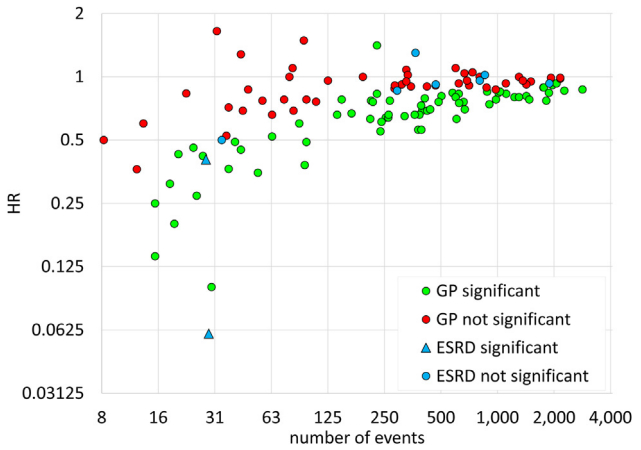

Figure 2. Trials effect size in relation to number of events and statistical significance. GP = general population.

Table 3
Summary of the reported trial limitations

	ESRD trials		Non-ESRD trials	
	Non-significant results	Significant results	Non-significant results	Significant results
Power low by design	0	1	9	6
Enrollment low	0	0	4	0
Event rate low	2	1	8	5
Discontinuation / withdrawal high	1	0	4	1
Imbalance in baseline characteristics	1	0	1	1
Stopped early	0	0	3	2
Other	2	0	15	10
All trials	7	2	47	68

Other limitations included reasons that do not directly correlate with the likelihood of a significant trial result, such as: no placebo/open-label or PROBE design; balance of subgroups with positive and negative effect; definition of condition not clear; concomitant drug use; dose inadequate; limited follow-up time; insufficient access to data sources.

average of 530 events. Figure 2 shows the effect size reported in the general population and ESRD trials in relation to the statistical significance and the number of clinical events in each trial. Effect sizes in ESRD trials were smaller, although many non-ESRD trials also reported small effect sizes. Small effect sizes were significant in larger trials. There was a relation between number of events and effect size in the trials reviewed, which is likely a reflection of power calculations at the trial design stage. The sample size of the trial per se did not influence the outcome of a trial in either the general population or the ESRD population.

Limitations of the all trials, when reported, most frequently referred to lack of power (Table 3). A total of 15 trials reported a low power by design, 22 reported low enrollment or a low event rate, and 6 reported problems with high discontinuation rate or withdrawal.

Discussion

We reviewed RCTs that tested the most frequently used CV agents in the general population in North America and compared them with the most relevant outcome trials in the ESRD population. We reviewed exclusively trials that reported mortality or a composite end point inclusive of all-cause mortality and other hard CV end points. Trials in the general population varied in size from small (66 subjects) to very large (30,000 to 40,000 patients), and there were numerous trials per each compound (in several cases, there were >5 trials per drug). Among the 115 trials reviewed, 59% were statistically significant and 41% were not. The effect size varied and correlated with the study size, which is the probable result of pretrial power calculations. In comparison, the ESRD trials were fewer (only 9 trials, generally 1 per compound with the exception of 1 drug), small to moderate in size (from ~300 to 3,000 patients), and the interventions showed no benefit. Only 2 mortality outcome ESRD trials yielded statistically significant results. Obviously, the probability of a statistically significant trial result does not reside in its size alone because several of the significant trials in the general population were small. Hence, the most likely reason for the apparent frequent failure of ESRD trials is that a single trial cannot firmly establish the efficacy of a pharmacologic agent, and most trials in ESRD were single. Patient selection criteria (inclusion or exclusion of diabetic patients, and so forth), race/ethnic background, and study settings (single vs double blind, academic vs community setting, and so forth) may influence the outcome of a trial with a specific drug but not necessarily another trial with the same compound conducted in a different population and different settings. This notion is supported by that over 40% of the trials conducted in the general population were statistically nonsignificant. The size of the patient pools is very different between the general population and ESRD, and it may be impractical to enroll equally large cohorts from the ESRD and the general pool.

The complexity of the disease state may be another important consideration. ESRD and dialysis are states of heightened systemic inflammation, and patients typically suffer from chronic conditions known to predispose to CV disease. The overall severity of these patients' condition is further compounded by the development of uremia-specific complications such as mineral and bone disorders, leading to bone fragility, vascular calcification, and loss of vascular elasticity.[42] Jager et al[43] suggested that patients with ESRD suffer from multiple co-morbidities that exponentially increase their risk of death. Hence, a single drug intervention would probably be less effective in such a disease state. Outcome trials of nonpharmacologic therapies in ESRD have not been successful either,[44–46] further illustrating the point that demonstrating convincing effects on clinical outcomes in ESRD has been challenging for all sorts of medical interventions. It should further be considered that studies conducted in prevalent dialysis populations are most likely affected by a survival bias as the death rate is proportionally higher in the earlier stages of kidney disease or right after initiating dialysis than 3 years into receiving renal replacement therapy.[43]

In view of these objective limitations, there may be a need to interpret ESRD trial results with a more flexible approach than the one used for trials conducted in large segments of the general population. It is probable that strict adherence to a mathematical criterion to define significance may prevent the researchers from highlighting useful clinical information.[47] Although the primary outcome of mortality or another hard outcome may have been missed statistically, additional post hoc or secondary analyses, particularly on the prespecified end points, could provide very helpful information for example, related to heterogeneity of the effect by clinically meaningful subpopulations, responder analyses, or on-treatment analyses.[3,48] In contrast with the standard ITT analysis, prespecified on-treatment analyses are important in light of adherence to treatment and treatment crossover especially when the drug being investigated is already available on the market.

Typical randomized clinical trials include a set of defined exclusion and inclusion criteria to select the most appropriate population to answer a prespecified question. Very often, however, the selected trial population is not generalizable to the larger population affected by the disease of interest. Furthermore, a statistically significant result of a trial does not immediately mean that the tested intervention is in fact successful in clinical practice. An intervention may work as demonstrated by real-world clinical experience, but trials may fail statistically for a number of reasons including lack of power, enrolled population mismatch, poor trial conduct, early drug discontinuation, and so forth, leading to a situation where a trial is rendered "nondefinitive" or a statistical failure. The trial results, definitive or not, need to be interpreted in the context of other clinical evidence including real-world clinical experience.

Disclosures

Dr. Raggi has received consulting and research support from Amgen; Dr. Boer has worked as a paid consultant for Amgen on the present and other projects; Dr. Goodman is an Amgen shareholder; Drs. Kalatar-Zadeh and Chertow have received research grants from Amgen; Dr. Belozeroff is an employee and shareholder of Amgen.

Appendix A: Cardiovascular Therapies Included in the Search

- Anticoagulants
  - Dalteparin (Fragmin)
  - Enoxaparin (Lovenox)
  - Heparin (various)
  - Warfarin (Coumadin)
- Antiplatelet agents
  - Aspirin
  - Clopidogrel
  - Prasugrel
  - Ticagrelor
- ACE inhibitors
  - Captopril (Capoten)
  - Enalapril (Vasotec)
  - Lisinopril (Prinivil)
  - Quinapril (Accupril)
  - Ramipril (Altace)
- Angiotensin II receptor blockers
  - Irbesartan (Avapro)
  - Valsartan (Diovan)
- Beta blockers
  - Atenolol (Tenormin)
  - Bisoprolol (Ziac, Zebeta)
  - Metoprolol (Lopressor, Toprol XL)
  - Carvedilol (Coreg)
- Calcium channel blockers
  - Amlodipine (Norvasc, Lotrel)
  - Diltiazem (Cardizem, Tiazac)
- Diuretics
  - Chlorthalidone (Hygroton)
  - Triamterene (Dyrenium)
  - Furosemide (Lasix)
  - Hydrochlorothiazide (Esidrix, Hydrodiuril)
  - Spironolactone (Aldactone)
- Vasodilators
  - Isosorbide dinitrate (Isordil)
  - Hydralazine (Apresoline)
- Digitalis Preparations
  - Digoxin (Lanoxin)
- Statins
  - Simvastatin
  - Pravastatin
  - Atorvastatin
  - Rosuvastatin
- Other
  - Nicotinic acid (niacin)
  - Gemfibrozil
  - Eplerenone
- Thrombolitics for acute MI
  - TNK
  - Streptokinase
  - tPA
- IIb/IIIa inhibitors for ACS
  - Abciximab
  - Eptifibatide
  - Tirofiban

Appendix B: ESRD-Specific Therapies Included in the Search

- Calcimimetics
  - Cinacalcet HCl (Sensipar)
- Phosphate binders
  - Sevelamer (Renagel, Renvela)
  - Calcium acetate (PhosLo)
  - Calcium carbonate
  - Lanthanum (Fosrenol)
- Vitamin D sterols
  - Paricalcitol (Zemplar)
  - Doxercalciferol (Hectorol)
  - Calcitriol (Calcijex)
- Erythropoiesis-stimulating therapies
  - Erythropoetin alpha (Epogen)

Supplementary Data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.amjcard.2015.06.024.

1. U.S. Renal Data System. USRDS 2013 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases [Internet]. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 2013. Available at: *http://www.usrds.org/atlas13.aspx*. Accessed on December 12, 2014.
2. Wanner C, Krane V, März W, Olschewski M, Mann JF, Ruf G, Ritz E; German Diabetes and Dialysis Study Investigators. Atorvastatin in patients with type 2 diabetes mellitus undergoing hemodialysis. *N Engl J Med* 2005;353:238−248.
3. EVOLVE Trial Investigators, Chertow GM, Block GA, Correa-Rotter R, Drüeke TB, Floege J, Goodman WG, Herzog CA, Kubo Y, London GM, Mahaffey KW, Mix TCH, Moe SM, Trotman M-L, Wheeler DC, Parfrey PS. Effect of cinacalcet on cardiovascular disease in patients undergoing dialysis. *N Engl J Med* 2012;367:2482−2494.
4. Besarab A, Bolton WK, Browne JK, Egrie JC, Nissenson AR, Okamoto DM, Schwab SJ, Goodkin DA. The effects of normal as compared with low hematocrit values in patients with cardiac disease who are receiving hemodialysis and epoetin. *N Engl J Med* 1998;339:584−590.
5. Wilson R, Zhang P, Smyth M, Pratt R. Assessment of survival in a 2-year comparative study of lanthanum carbonate versus standard therapy. *Curr Med Res Opin* 2009;25:3021−3028.
6. Fellström BC, Jardine AG, Schmieder RE, Holdaas H, Bannister K, Beutler J, Chae D-W, Chevaile A, Cobbe SM, Grönhagen-Riska C, De Lima JJ, Lins R, Mayer G, McMahon AW, Parving H-H, Remuzzi G, Samuelsson O, Sonkodi S, Sci D, Süleymanlar G, Tsakiris D, Tesar V, Todorov V, Wiecek A, Wüthrich RP, Gottlow M, Johnsson E, Zannad F; AURORA Study Group. Rosuvastatin and cardiovascular events in patients undergoing hemodialysis. *N Engl J Med* 2009;360:1395−1407.
7. St Peter WL, Liu J, Weinhandl E, Fan Q. A comparison of sevelamer and calcium-based phosphate binders on mortality, hospitalization, and morbidity in hemodialysis: a secondary analysis of the Dialysis Clinical Outcomes Revisited (DCOR) randomized trial using claims data. *Am J Kidney Dis* 2008;51:445−454.
8. IMS Health - US. National Prescription Audit 2013, *http://www.imshealth.com/deployedfiles/imshealth/Global/Content/Corporate/IMS%20Health%20Institute/Reports/Secure/IIHI_US_Use_of_Meds_for_2013.pdf*. Accessed on April 14, 2015.
9. American Heart Association, American Stroke Association. Cardiac Medications [Internet]. Available at: *http://www.heart.org/HEARTORG/Conditions/HeartAttack/PreventionTreatmentofHeartAttack/Cardiac-Medications_UCM_303937_Article.jsp*. Accessed on December 12, 2014.
10. Di Iorio B, Molony D, Bell C, Cucciniello E, Bellizzi V, Russo D, Bellasi A; INDEPENDENT Study Investigators. Sevelamer versus calcium carbonate in incident hemodialysis patients: results of an open-label 24-month randomized clinical trial. *Am J Kidney Dis* 2013;62:771−778.
11. Block GA, Raggi P, Bellasi A, Kooienga L, Spiegel DM. Mortality effect of coronary calcification and phosphate binder choice in incident hemodialysis patients. *Kidney Int* 2007;71:438−441.
12. Matsumoto Y, Mori Y, Kageyama S, Arihara K, Sugiyama T, Ohmura H, Yakushigawa T, Sugiyama H, Shimada Y, Nojima Y, Shio N. Spironolactone reduces cardiovascular and cerebrovascular morbidity and mortality in hemodialysis patients. *J Am Coll Cardiol* 2014;63:528−536.
13. ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial. 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). *JAMA* 2002;288:2981−2997.
14. Final report on the aspirin component of the ongoing Physicians' Health Study. Steering Committee of the Physicians' Health Study Research Group. *N Engl J Med* 1989;321:129−135.
15. Trial of secondary prevention with atenolol after transient ischemic attack or nondisabling ischemic stroke. The Dutch TIA Trial Study Group. *Stroke* 1993;24:543−548.
16. Sever PS, Dahlöf B, Poulter NR, Wedel H, Beevers G, Caulfield M, Collins R, Kjeldsen SE, Kristinsson A, McInnes GT, Mehlsen J, Nieminen M, O'Brien E, Ostergren J; ASCOT investigators. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial—Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. *Lancet* 2003;361:1149−1158.
17. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. *Lancet* 1999;353:9−13.
18. Hansson L, Lindholm LH, Niskanen L, Lanke J, Hedner T, Niklason A, Luomanmäki K, Dahlöf B, de Faire U, Mörlin C, Karlberg BE, Wester PO, Björck JE. Effect of angiotensin-converting-enzyme inhibition compared with conventional therapy on cardiovascular morbidity and mortality in hypertension: the Captopril Prevention Project (CAPPP) randomised trial. *Lancet* 1999;353:611−616.
19. Poole-Wilson PA, Swedberg K, Cleland JG, Di Lenarda A, Hanrath P, Komajda M, Lubsen J, Lutiger B, Metra M, Remme WJ, Torp-Pedersen C, Scherhag A, Skene A; Carvedilol Or Metoprolol European Trial Investigators. Comparison of carvedilol and metoprolol on clinical outcomes in patients with chronic heart failure in the Carvedilol Or Metoprolol European Trial (COMET): randomised controlled trial. *Lancet* 2003;362:7−13.
20. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. Final results of the Systolic Hypertension in the Elderly Program (SHEP). SHEP Cooperative Research Group. *JAMA* 1991;265:3255−3264.
21. CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). CAPRIE Steering Committee. *Lancet* 1996;348:1329−1339.
22. Digitalis Investigation Group, Ahmed A, Waagstein F, Pitt B, White M, Zannad F, Young JB, Rahimtoola SH. Effectiveness of digoxin in reducing one-year mortality in chronic heart failure in the Digitalis Investigation Group trial. *Am J Cardiol* 2009;103:82−87.
23. Hansson L, Hedner T, Lund-Johansen P, Kjeldsen SE, Lindholm LH, Syvertsen JO, Lanke J, de Faire U, Dahlöf B, Karlberg BE. Randomised trial of effects of calcium antagonists compared with diuretics and beta-blockers on cardiovascular morbidity and mortality in hypertension: the Nordic Diltiazem (NORDIL) study. *Lancet* 2000;356:359−365.
24. Swedberg K, Held P, Kjekshus J, Rasmussen K, Rydén L, Wedel H. Effects of the early administration of enalapril on mortality in patients with acute myocardial infarction. Results of the Cooperative New Scandinavian Enalapril Survival Study II (CONSENSUS II). *N Engl J Med* 1992;327:678−684.
25. Pitt B, Remme W, Zannad F, Neaton J, Martinez F, Roniker B, Bittman R, Hurley S, Kleiman J, Gatlin M; Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study Investigators. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med* 2003;348:1309−1321.
26. Frick MH, Elo O, Haapa K, Heinonen OP, Heinsalmi P, Helo P, Huttunen JK, Kaitaniemi P, Koskinen P, Manninen V. Helsinki Heart Study: primary-prevention trial with gemfibrozil in middle-aged men with dyslipidemia. Safety of treatment, changes in risk factors, and incidence of coronary heart disease. *N Engl J Med* 1987;317:1237−1245.
27. Cohn JN, Archibald DG, Ziesche S, Franciosa JA, Harston WE, Tristani FE, Dunkman WB, Jacobs W, Francis GS, Flohr KH. Effect of vasodilator therapy on mortality in chronic congestive heart failure. Results of a Veterans Administration Cooperative Study. *N Engl J Med* 1986;314:1547−1552.
28. Amery A, Birkenhäger W, Brixko P, Bulpitt C, Clement D, Deruyttere M, De Schaepdryver A, Dollery C, Fagard R, Forette F. Mortality and morbidity results from the European Working Party on High Blood Pressure in the Elderly trial. *Lancet* 1985;1:1349−1354.
29. ACTIVE I Investigators, Yusuf S, Healey JS, Pogue J, Chrolavicius S, Flather M, Hart RG, Hohnloser SH, Joyner CD, Pfeffer MA, Connolly SJ. Irbesartan in patients with atrial fibrillation. *N Engl J Med* 2011;364:928−938.
30. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). *Lancet* 1999;353:2001−2007.
31. Canner PL, Berge KG, Wenger NK, Stamler J, Friedman L, Prineas RJ, Friedewald W. Fifteen year mortality in Coronary Drug Project patients: long-term benefit with niacin. *J Am Coll Cardiol* 1986;8:1245−1255.

32. Wiviott SD, Braunwald E, McCabe CH, Montalescot G, Ruzyllo W, Gottlieb S, Neumann F-J, Ardissino D, De Servi S, Murphy SA, Riesmeyer J, Weerakkody G, Gibson CM, Antman EM; TRITON-TIMI 38 Investigators. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2007;357:2001−2015.
33. Byington RP, Davis BR, Plehn JF, White HD, Baker J, Cobbe SM, Shepherd J. Reduction of stroke events with pravastatin: the Prospective Pravastatin Pooling (PPP) Project. *Circulation* 2001;103:387−392.
34. Pitt B, O'Neill B, Feldman R, Ferrari R, Schwartz L, Mudra H, Bass T, Pepine C, Texter M, Haber H, Uprichard A, Cashin-Hemphill L, Lees RS; QUIET Study Group. The QUinapril Ischemic Event Trial (QUIET): evaluation of chronic ACE inhibitor therapy in patients with ischemic heart disease and preserved left ventricular function. *Am J Cardiol* 2001;87:1058−1063.
35. Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. *N Engl J Med* 2000;342:145−153.
36. Ridker PM, Danielson E, Fonseca FA, Genest J, Gotto AM, Kastelein JJP, Koenig W, Libby P, Lorenzatti AJ, MacFadyen JG, Nordestgaard BG, Shepherd J, Willerson JT, Glynn RJ; JUPITER Study Group. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N Engl J Med* 2008;359:2195−2207.
37. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet* 2002;360:7−22.
38. Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, Palensky J, Wittes J. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. *N Engl J Med* 1999;341:709−717.
39. Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, Horrow J, Husted S, James S, Katus H, Mahaffey KW, Scirica BM, Skene A, Steg PG, Storey RF, Harrington RA, PLATO Investigators, Freij A, Thorsén M. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2009;361:1045−1057.
40. NAVIGATOR Study Group, McMurray JJ, Holman RR, Haffner SM, Bethel MA, Holzhauer B, Hua TA, Belenkov Y, Boolell M, Buse JB, Buckley BM, Chacra AR, Chiang F-T, Charbonnel B, Chow C-C, Davies MJ, Deedwania P, Diem P, Einhorn D, Fonseca V, Fulcher GR, Gaciong Z, Gaztambide S, Giles T, Horton E, Ilkova H, Jenssen T, Kahn SE, Krum H, Laakso M, Leiter LA, Levitt NS, Mareev V, Martinez F, Masson C, Mazzone T, Meaney E, Nesto R, Pan C, Prager R, Raptis SA, Rutten GEHM, Sandstroem H, Schaper F, Scheen A, Schmitz O, Sinay I, Soska V, Stender S, Tamás G, Tognoni G, Tuomilehto J, Villamil AS, Vozár J, Califf RM. Effect of valsartan on the incidence of diabetes and cardiovascular events. *N Engl J Med* 2010;362:1477−1490.
41. Thrombosis prevention trial: randomised trial of low-intensity oral anticoagulation with warfarin and low-dose aspirin in the primary prevention of ischaemic heart disease in men at increased risk. The Medical Research Council's General Practice Research Framework. *Lancet* 1998;351:233−241.
42. Raggi P, Giachelli C, Bellasi A. Interaction of vascular and bone disease in patients with normal renal function and patients undergoing dialysis. *Nat Clin Pract Cardiovasc Med* 2007;4:26−33.
43. Jager KJ, Stel VS, Zoccali C, Wanner C, Dekker FW. The issue of studying the effect of interventions in renal replacement therapy—to what extent may we be deceived by selection and competing risk? *Nephrol Dial Transpl* 2010;25:3836−3839.
44. Cooper BA, Branley P, Bulfone L, Collins JF, Craig JC, Fraenkel MB, Harris A, Johnson DW, Kesselhut J, Li JJ, Luxton G, Pilmore A, Tiller DJ, Harris DC, Pollock CA; IDEAL Study. A randomized, controlled trial of early versus late initiation of dialysis. *N Engl J Med* 2010;363:609−619.
45. Eknoyan G, Beck GJ, Cheung AK, Daugirdas JT, Greene T, Kusek JW, Allon M, Bailey J, Delmez JA, Depner TA, Dwyer JT, Levey AS, Levin NW, Milford E, Ornt DB, Rocco MV, Schulman G, Schwab SJ, Teehan BP, Toto R; Hemodialysis (HEMO) Study Group. Effect of dialysis dose and membrane flux in maintenance hemodialysis. *N Engl J Med* 2002;347:2010−2019.
46. Grooteman MPC, van den Dorpel MA, Bots ML, Penne EL, van der Weerd NC, Mazairac AH, den Hoedt CH, van der Tweel I, Lévesque R, Nubé MJ, ter Wee PM, Blankestijn PJ; CONTRAST Investigators. Effect of online hemodiafiltration on all-cause mortality and cardiovascular outcomes. *J Am Soc Nephrol* 2012;23:1087−1096.
47. Stang A, Poole C, Kuss O. The ongoing tyranny of statistical significance testing in biomedical research. *Eur J Epidemiol* 2010;25:225−230.
48. Cannon CP, Blazing MA, Giugliano RP, McCagg A, White JA, Theroux P, Darius H, Lewis BS, Ophuis TO, Jukema JW, De Ferrari GM, Ruzyllo W, De Lucca P, Im K, Bohula EA, Reist C, Wiviott SD, Tershakovec AM, Musliner TA, Braunwald E, Califf RM; IMPROVE-IT Investigators. Ezetimibe added to after acute coronary syndromes. *N Engl J Med* 2015;372:2387−2397.