Published in final edited form as:

Am J Cardiol. 2020 January 01; 125(1): 63–67. doi:10.1016/j.amjcard.2019.09.033.

Implications of Guideline Updates for the Management of Apparent Treatment Resistant Hypertension in the United States (A NCDR Research to Practice [R2P] Project)

Anna M. Maw, MD, MS^{a,*}, Lauren E. Thompson, MD, MSc^b, P. Michael Ho, MD, PhD^{c,d}, Kevin F. Kennedy, MS^e, Thomas M. Maddox, MD, MSc^f, Javier A. Valle, MD, MSc^{c,d}, Amneet Sandhu, MD, MSc^{c,d}, Frederick A. Masoudi, MD, MPSH^c, Franz H. Messerli, MD^g, Stacie L. Daugherty, MD, MPSH^c

^aDivision of Hospital Medicine, University of Colorado Anschutz Medical Campus, Aurora, Colorado ^bDepartment of Cardiology, Kaiser Permanente, Denver, Colorado ^cDivision of Cardiology, University of Colorado Anschutz Medical Campus, Aurora, CO ^dSection of Cardiology, VA Eastern Colorado Health Care System, Aurora Colorado ^eSaint Luke's Mid America Heart and Vascular Institute, Kansas City, Missouri ^fWashington University in St. Louis, Saint Louis, Missouri ^gDepartments of Cardiology and Clinical Research, University Hospital, Bern, Switzerland

Abstract

The 2018 resistant hypertension scientific statement offers new treatment recommendations. To determine the implications of these changes, we sought to ascertain the prevalence of apparent treatment resistant hypertension (aTRH) and the therapies used to treat it in an US national ambulatory cardiovascular registry before these recent developments. Using the PINNACLE Registry from 2013 to 2014, we identified all patients receiving treatment for hypertension and then determined the proportion with aTRH as those who met the following criteria over 2 consecutive visits: (1) 3 blood pressure medication classes including a diuretic and blood pressure >140/90, OR (2) 4 blood pressure medications. Among those with aTRH, we examined past use of therapies now recommended in guidelines including: (1) first-line therapy with an angiotensin-converting enzyme inhibitor or angiotensin-II receptor blocker, calcium channel blocker and a thiazide diuretic, (2) use of chlorthalidone, and (3) use of a mineralocorticoid receptor antagonist (MRA) for those requiring a 4th medication. Of 84,624 patients on treatment for hypertension, 11,147 (13.1%) met criteria for prevalent aTRH. Among these patients: (1) Of those on 3 antihypertensive agents (n = 1,255), 315 (25%) were on the first-line regimen now recommended in guidelines, (2) 520 (6.7%) of the 7,930 patients on thiazides were using chlorthalidone, and (3) 3061 (27%) were using a MRA; another 4,523 (40.6%) were eligible for its addition. In conclusion, our findings of low historic use of therapies now recommended in guidelines suggest opportunities to improve care among patients with aTRH.

By definition, all patients with apparent treatment resistant hypertension (aTRH) are prescribed at least 3 classes of antihypertensive medications. Until recently, guidelines for

*Corresponding author: Tel: 720 848 5113; fax: 720 848 4293. anna.maw@ucdenver.edu (A.M. Maw).

patients with aTRH did not endorse specific medication classes outside of diuretic use.^{1,2} Recent trials have provided evidence of the superiority of certain regimens.³ As a result, the 2018 resistant hypertension scientific statement⁴ endorsed several new recommendations including the use of angiotensin-converting enzyme inhibitor (ACE) or angiotensin-II receptor blocker (ARB), calcium channel blocker (CCB) and a thiazide diuretic as first-line therapy and if still uncontrolled, switching from a low-potency thiazide to chlorthalidone. If uncontrolled on ACE/ARB+CCB +chlorthalidone the guidelines now recommend adding a mineralocorticoid receptor antagonist (MRA).⁴ The extent to which these recent changes in recommendations reflect previous practice patterns among patients with aTRH is not known but may assist in identifying areas for future quality improvement interventions. Accordingly, using the National Cardiovascular Data Registry (NCDR®) PINNACLE Registry, we sought to determine the prevalence of aTRH as well as the past use of medication classes and specific medications now recommended in clinical guidelines.³ This study was carried out under the NCDR's Research to Practice (R2P) initiative.

Methods

The PINNACLE Registry is the largest observational outpatient cardiovascular registry in the US and served as the data source for this study. It was developed in 2008 by the American College of Cardiology to facilitate assessment of cardiovascular outcomes and clinician adherence to performance measures. As of January 1, 2017 there are 695 private and academic outpatient cardiology practices that contribute patient data, which represents over 32 million patient encounters. Data are collected at the point of care using a validated electronic medical record-mapping algorithm for patients with hypertension, coronary artery disease (CAD), congestive heart failure (CHF), and atrial fibrillation (A-fib).^{5,6} Data captured include demographics, diagnoses, vital signs, medications, and laboratory values. Registry data quality is maintained through standard data definitions, collection and transmission, and periodic data quality checks.⁵⁻⁷

Using the PINNACLE Registry from January 1, 2013 to December 31, 2014, we identified all patients with a diagnosis of hypertension and available BP medication data. The availability of medication data was dependent on whether complete medication lists were pulled from the practice's electronic health record during data transmission to the PINNACLE data coordinating center. Medications were identified by their NDC code and classified into the drug classes of ACE or ARB, β -blocker, CCB, thiazide diuretic, loop diuretic, MRA, alpha-blocker, and vasodilator. Patients on combination antihypertensive pills were counted as separate classes for each drug.

Among patients with hypertension on treatment, the primary outcome was the prevalence of aTRH. Secondary outcomes of interest included a description of the specific medication classes and combinations now recommended in guidelines including: (1) first-line therapy with an ACE or an ARB, CCB and a thiazide diuretic, (2) use of chlorthalidone, (3) use of a MRA, and (4) proportion eligible for a MRA among those not already taking one.

To determine the prevalent aTRH population, we applied the American Heart Association definition of resistant hypertension.⁴ First, all patients with a diagnosis of hypertension and

available medication data were identified which served as the denominator from which to calculate the prevalence of aTRH (Figure 1). Second, patients on 3 or more drug classes for hypertension were maintained in the aTRH cohort. Third, to ensure persistent use of multiple antihypertensive classes, we required patients in the aTRH study cohort to be on 3 or more drug classes over a minimum of 2 consecutive visits no more than 12 months apart. Fourth, patients were maintained in the aTRH cohort if at least one of their medications classes was a diuretic (loop or thiazide). Finally, patients were maintained in the aTRH cohort if they were (1) on 3 medication classes and their systolic BP was greater than 140 mm Hg or diastolic BP greater than 90 mm Hg, or (2) they were on 4 or more medication classes regardless of BP. Given the recent changes in the definition of hypertension, in sensitivity analysis, among patients on 3 medication classes, we repeated the last step using a systolic BP greater than 130 mm Hg or diastolic blood pressure greater than 80 mm Hg.⁸

In additional analysis, we sought to determine the subgroup of patients within the aTRH prevalent cohort who would be eligible for the addition of a MRA as a fourth agent. We based the eligibility criteria on the PATHWAY-2 trial criteria which demonstrated the superiority of an MRA as the 4th agent over other medications to obtain blood pressure control.³ To define this subgroup, the following PATHWAY-2 exclusion criteria were applied in sequence: (1) not prescribed ACE/ARB+CCB+thiazide combination, (2) systolic BP >200 mm Hg or diastolic BP >120, (3) diagnosis of chronic kidney disease (CKD), and (4) already prescribed a MRA. The remaining patients defined those patients potentially eligible for the addition of a MRA but not prescribed one (Figure 1).

Among those identified as having aTRH, we described clinical characteristics including age, gender, race, co-morbidities, and average BP. The rates of use of different medication classes and the most frequent combinations of medication classes were determined. Of particular interest was the proportion on the recent guideline recommended combination of ACEI/ARB +CCB+ thiazide⁴ and the overall use of chlorthalidone and MRAs. Given the indication for using β -blockers in conditions other than hypertension, in sensitivity analysis, we repeated the above analysis excluding patients with a diagnosis of CAD, HF or A-fib. All analyses were performed with SAS 9.4 software.

Results

A total of 148,444 patients from 83 ambulatory practices with medication data were identified in the PINNACLE Registry from January 1, 2013 to December 31, 2014. Of these, 84,626 patients had a diagnosis of hypertension, were on a blood pressure medication and served as the denominator population (Figure 1). The following sequential exclusion criteria was then applied: 1) on fewer than 3 antihypertensive classes (n=43,766), 2) on 3 or more classes over fewer than 2 consecutive visits within 12 months (n=22,402), 3) not on a diuretic (n=3,280), 4) with SBP less than 140 and DBP less than 90 mm Hg on 3 medication classes (n=4,031) (Figure 1). The 11,147 (13.1%) remaining patients represented the final prevalent aTRH cohort. In a sensitivity analysis using the new hypertension guideline thresholds of less than 130 mm Hg systolic and 80 mm Hg diastolic for the final step, overall aTRH prevalence was slightly higher at 14.3% (n=12,094).

Table 1 provides patient demographics of the prevalent aTRH cohort. The majority of patients in the prevalent aTRH cohort, 89%, were on 4 or more different classes of blood pressure medications.

Table 2 describes the medication classes most frequently prescribed in the prevalent aTRH cohort. Overall, β -blockers were the most common medication class at 89%. A total of 7930 (71%) of aTRH patients were prescribed thiazide diuretics; 530 (6.7%) of those were on chlorthalidone. In the prevalent aTRH cohort, 27% were on an MRA. In sensitivity analysis excluding those with CAD, CHF and A-fib, thiazides were the most common class used by 83%, β -blocker use remained high at 78% (Table 3). Table 4 describes the top 4 most common medication combinations for patients on 3, 4 and 5 drug classes in the prevalent aTRH cohort. Notably, among those on 3 medication classes, 25% were currently using the ACEI/ARB+CCB+thiazide combination suggested in the recent guidelines. In sensitivity analysis excluding patients with CAD, CHF and A-fib, the most common 3 drug combinations continued to include β -blockers suggesting common indications for use do not completely explain the high use of β -blockers in this cohort (Table 5).

To determine the proportion of the prevalent aTRH patients potentially eligible for a MRA, in subgroup analysis, the following were excluded based on PATHWAY-2 criteria: (1) not on ACE/ARB +CCB+Thiazide (n = 5,395, 48%), (2) systolic BP greater than 200 mm Hg or diastolic >120 (n = 24, 0.2%), (3) Diagnosis of chronic kidney disease (n = 54, 0.5%), (4) already on spironolactone (n = 1,151, 10.3%). Our final MRA eligible subgroup was 4,523 (40.6%) (Figure 1).

Discussion

In this national cohort of ambulatory cardiology patients with hypertension on treatment, more than one in 8 had aTRH. Among those with aTRH, our results suggest several notable differences between past blood pressure medication practices and new guideline recommendations. First, we found only 25% of our aTRH cohort receiving 3 antihypertensive medication classes were on the currently recommended combination of an ACEI/ARB+CCB+thiazide. This 3-drug regimen is now recommended as first-line combination therapy to reduce clinical events.⁴ Second, although 71% of our aTRH cohort were on thiazides, only 7% of those patients were prescribed chlorthalidone. Chlorthalidone provides superior BP control without higher rates of hyponatremia or hypokalemia compared with an equally potent dose of hydrochlorothiazide.^{9–11} The most recent resistant hypertension recommendations emphasize switching to a higher potency thiazide before adding a fourth agent.⁴ The low chlorthalidone use observed may in part be due to the fixed combination formulation such as those that include ACE/ARB with hydrochlorothiazide and not chlorthalidone. Third, we found that only one in 4 patients in our prevalent aTRH cohort was prescribed a MRA which is now recommended as the ideal 4th line agent.⁴ The high-quality evidence demonstrating superior BP control with a MRA as a fourth agent³ emphasizes the opportunity to improve prescription rates in the use of this class of antihypertensive. Finally, β -blockers were the most common medication class used in almost 90% of our aTRH cohort. Even after attempting to control for other indications by removing those with CHF, CAD, and A-fib, β -blockers were still used 78% of the time. Without

another indication, β -blockers are not recommended as first-line therapy for hypertension. Other studies have similarly demonstrated high rates of β -blocker as initial treatment for hypertension among cardiologists.¹² The disproportionally high rate of β -blocker use in our aTRH cohort may indicate another potential opportunity to improve hypertension care.

Our study must be interpreted in light of several limitations. First, our study cohort was drawn from those cared for in ambulatory cardiology clinics and may not be applicable to the broader population of patients with resistant HTN cared for in other settings. Second, like many studies investigating the prevalence of aTRH, we were unable to evaluate drug doses or medication adherence. Some studies have shown lower resistant hypertension prevalence estimates when medication adherence and maximally recommended dosing are considered.^{13,14} Therefore, we have used the term aTRH as true resistant hypertension cannot be determined.⁴ Third, the results presented here are only representative of patients in PINNACLE who had a diagnosis of hypertension and whose antihypertensive medications were accessible. Additionally, about 20% of our cohort of patients with HTN on 3 or more medications were missing BP measurements and were therefore excluded from our prevalent aTRH cohort. Thus, our prevalence estimates may be low. However, given 89% of aTRH cohort was prescribed 4 or more antihypertensives and BP criteria were only applied to those on 3 medications, this likely did not greatly influence our estimates. Fourth, we cannot fully evaluate indications or contraindications for specific medication classes and thus we cannot determine if our observed rates of specific medication class (e.g. high rates of β -blocker, low use of MRA) use are clinically appropriate. For instance, we do not know how many patients developed side effects on a MRA such as gynecomastia or hyperkalemia, or lower extremity edema from a CCB. Similarly, because laboratory data is variably available in the PINNACLE Registry, we were unable to apply all exclusion criteria for the use of an MRA.³ Thus, it is possible that we have overestimated eligibility for MRA therapy. However, given the large proportion of eligible patients found, our results suggest an opportunity to increase MRA use in accordance with the new recommendations for the management of aTRH. Fifth, we observed an overlap in some medication classes that may be higher than expected (17% concurrent ACE and ARB, 36% concurrent thiazide and loop diuretics) suggesting possible medication class mis-categorization. Medications were directly pulled from EHR medication lists and this overlap may be related to delays in medication reconciliation when a medication change occurred (e.g., ACE was not removed from the active medication list when a patient was switched to an ARB). However, the observed ACE/ARB overlap may also reflect the shifting body of evidence that occurred during this period in which the risk/benefit ratio of dual therapy began to change from favorable to unfavorable.¹⁵ The loop/thiazide overlap may also reflect treatment for volume overload from co-morbid heart failure¹⁶ or renal insufficiency¹⁷ in which diuresis may be more difficult to achieve. Future work should validate these findings using additional medication sources such as pharmacy fill data. Finally, our study cohort includes a population of patients cared for before the publication of the 2017 hypertension guidelines⁸ and 2018 resistant hypertension scientific statement.⁴ Our study was intended to demonstrate how past practice patterns may be influenced by these new guideline recommendations. Given the substantial time lag between the dissemination of evidence through publication and actual change in practice by

providers,¹⁸ future studies should examine whether practice patterns respond to these new recommendations.

To our knowledge, this is the first study to estimate the prevalence of aTRH in a national population of ambulatory cardiology patients. Our results suggest there are important differences between past medication classes commonly used in those with aTRH and the medication classes now recommended.⁴ This study highlights potential opportunities to improve the management of aTRH by targeting the use of guideline recommended therapies including combination ACEI/ARB+CCB+thiazide therapy, chlorthalidone, and MRA over other therapies with less evidence of benefit in aTRH such as β -blockers. Future studies should examine whether practice patterns change in response to these recent changes in recommendations.

Acknowledgments

Disclosures

Dr. Daugherty is supported by R01 HL133343 from the National Heart, Lung and Blood Institute and award 15SFDRN24470027 from the American Heart Association. The views expressed in this manuscript represent those of the authors, and do not necessarily represent the official views of the National Heart, Lung and Blood Institute or the American Heart Association.

P.M. Ho is supported by grants from NHLBI and VA HSR&D. He served on a Steering Committee for a clinical trial on medication adherence for Janssen, Inc., and is the Deputy Editor for *Circulation: Cardiovascular Quality and Outcomes*.

T. M. Maddox discloses grant funding from the NIH NCATS (1U24TR002306-01: A National Center for Digital Health Informatics Innovation), consulting for Creative Educational Concepts, Inc., employment at BJC Health-Care/Washington University School of Medicine, and honoraria payments from Brown University, Washington State Clinical Outcomes Assessment Program (COAP), Virginia Mason, University of Utah, New York Presbyterian, Westchester Medical Center, Sentara Heart Hospital, and the Henry Ford health system.

F. A. Masoudi serves as Chief Scientific Advisor of the NCDR for the American College of Cardiology.

F. H. Messerli, MD, currently has financial relationships with the following companies: Pfizer, WebMD, American College of Cardiology, Lancet, Menarini, Sandoz, Hikma, Medtronic, Novartis

References

1. Calhoun DA, Jones D, Textor S, Goff DC, Murphy TP, Toto RD, White A, Cushman WC, White W, Sica D, Ferdinand K, Giles TD, Falkner B, Carey RM, American Heart Association Professional Education C. Resistant hypertension: diagnosis, evaluation, and treatment: a scientific statement from the american heart association professional education committee of the council for high blood pressure research. *Circulation* 2008;117:e510–e526. [PubMed: 18574054]
2. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr., Jones DW, Materson BJ, Oparil S, Wright JT Jr., Roccella EJ. National Heart L. Blood Institute Joint National Committee on Prevention DE. Treatment of High Blood P. National High Blood Pressure Education Program Coordinating C. The seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure: the JNC 7 report. *JAMA* 2003;289:2560–2572. [PubMed: 12748199]
3. Williams B, MacDonald TM, Morant S, Webb DJ, Sever P, McInnes G, Ford I, Cruickshank JK, Caulfield MJ, Salsbury J, Mackenzie I, Padmanabhan S, Brown MJ, British Hypertension Society's PSG. Spironolactone versus placebo, bisoprolol, and doxazosin to determine the optimal treatment for drug-resistant hypertension (pathway-2): a randomised, double-blind, crossover trial. *Lancet* 2015;386:2059–2068. [PubMed: 26414968]

4. Carey RM, Calhoun DA, Bakris GL, Brook RD, Daugherty SL, Dennison-Himmelfarb CR, Egan BM, Flack JM, Gidding SS, Judd E, Lackland DT, Laffer CL, Newton-Cheh C, Smith SM, Taler SJ, Textor SC, Turan TN, White WB. American Heart Association Professional/Public E. Publications Committee of the Council on H. Council on C. Stroke N. Council on Clinical C. Council on G. Precision M. Council on Peripheral Vascular D. Council on Quality of C. Outcomes R. Stroke C. Resistant hypertension: detection, evaluation, and management: a scientific statement from the American Heart Association. *Hypertension* 2018;72:e53–e90. [PubMed: 30354828]
5. Masoudi FA, Ponirakis A, Yeh RW, Maddox TM, Beachy J, Casale PN, Curtis JP, De Lemos J, Fonarow G, Heidenreich P, Koutras C, Kremers M, Messenger J, Moussa I, Oetgen WJ, Roe MT, Rosenfield K, Shields TP Jr., Spertus JA, Wei J, White C, Young CH, Rumsfeld JS. Cardiovascular care facts: a report from the national cardiovascular data registry: 2011. *J Am Coll Cardiol* 2013;62:1931–1947. [PubMed: 24036027]
6. Maddox TM, Borden WB, Tang F, Virani SS, Oetgen WJ, Mullen JB, Chan PS, Casale PN, Douglas PS, Masoudi FA, Farmer SA, Rumsfeld JS. Implications of the 2013 ACC/AHA cholesterol guidelines for adults in contemporary cardiovascular practice: insights from the NCDR pinnacle registry. *J Am Coll Cardiol* 2014;64:2183–2192. [PubMed: 25447259]
7. Messenger JC, Ho KK, Young CH, Slattery LE, Draoui JC, Curtis JP, Dehmer GJ, Grover FL, Mirro MJ, Reynolds MR, Rokos IC, Spertus JA, Wang TY, Winston SA, Rumsfeld JS, Masoudi FA. Science N. Quality Oversight Committee Data Quality W. The national cardiovascular data registry (NCDR) data quality brief: the NCDR data quality program in 2012. *J Am Coll Cardiol* 2012;60:1484–1488. [PubMed: 22999725]
8. Whelton PK, Carey RM, Aronow WS, Casey DE Jr., Collins KJ, Dennison Himmelfarb C, DePalma SM, Gidding S, Jamerson KA, Jones DW, MacLaughlin EJ, Muntner P, Oviagele B, Smith SC Jr., Spencer CC, Stafford RS, Taler SJ, Thomas RJ, Williams KA Sr., Williamson JD, Wright JT Jr. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APHA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College Of Cardiology/American Heart Association task force on clinical practice guidelines. *J Am Coll Cardiol* 2018;71:e127–e248. [PubMed: 29146535]
9. Olde Engberink RH, Frenkel WJ, van den Bogaard B, Brewster LM, Vogt L, van den Born BJ. Effects of thiazide-type and thiazide-like diuretics on cardiovascular events and mortality: systematic review and meta-analysis. *Hypertension* 2015;65:1033–1040. [PubMed: 25733241]
10. Messerli FH, Makani H, Benjo A, Romero J, Alviar C, Bangalore S. Antihypertensive efficacy of hydrochlorothiazide as evaluated by ambulatory blood pressure monitoring: a meta-analysis of randomized trials. *J Am Coll Cardiol* 2011;57:590–600. [PubMed: 21272751]
11. Messerli FH, Grossman E, Goldbourt U. Are beta-blockers efficacious as first-line therapy for hypertension in the elderly? A systematic review. *JAMA* 1998;279:1903–1907. [PubMed: 9634263]
12. Egan B, Flack J, Patel M, Lombara S. Insights on beta-blockers for the treatment of hypertension: a survey of health care practitioners. *J Clin Hypertens (Greenwich)* 2018;20:1464–1472. [PubMed: 30289609]
13. Weitzman D, Chodick G, Shalev V, Grossman C, Grossman E. Prevalence and factors associated with resistant hypertension in a large health maintenance organization in israel. *Hypertension* 2014;64:501–507. [PubMed: 24958503]
14. Daugherty SL, Powers JD, Magid DJ, Tavel HM, Masoudi FA, Margolis KL, O'Connor PJ, Selby JV, Ho PM. Incidence and prognosis of resistant hypertension in hypertensive patients. *Circulation* 2012;125:1635–1642. [PubMed: 22379110]
15. de Zeeuw D The end of dual therapy with renin-angiotensin-aldosterone system blockade? *N Engl J Med* 2013;369:1960–1962. [PubMed: 24206456]
16. Jentzer JC, DeWald TA, Hernandez AF. Combination of loop diuretics with thiazide-type diuretics in heart failure. *J Am Coll Cardiol* 2010;56:1527–1534. [PubMed: 21029871]
17. Hoshino T, Ookawara S, Miyazawa H, Ito K, Ueda Y, Kaku Y, Hirai K, Mori H, Yoshida I, Tabei K. Renoprotective effects of thiazides combined with loop diuretics in patients with type 2 diabetic kidney disease. *Clin Exp Nephrol* 2015;19:247–253. [PubMed: 24821289]
18. Morris ZS, Wooding S, Grant J. The answer is 17 years, what is the question: understanding time lags in translational research. *J R Soc Med* 2011;104:510–520. [PubMed: 22179294]

Figure 1.

Flow Diagram describing patient exclusions to arrive at aTRH cohort. aTRH = apparent treatment resistant hypertension; MRA = mineralocorticoid receptor antagonist; med = medication; ACE = angiotensin converting enzyme inhibitor; ARB = angiotensin-receptor blockers; CCB= calcium channel blocker; SBP = systolic blood pressure; CKD = chronic renal disease

Table 1

aTRH patient demographics

Patient characteristic	Patients (n = 11,147)
Systolic blood pressure (mm Hg)	133 ± 21
Diastolic blood pressure (mm Hg)	74 ± 13
Age (years)	71 ± 12
White	75%
Black	22%
Men	51%
Private insurance	91%
Dyslipidemia	70%
Coronary artery disease	54%
Congestive heart failure	27%
Atrial fibrillation/flutter	34%
Chronic kidney disease	11%
Diabetes mellitus	45%
Peripheral arterial disease	7%
Chronic liver disease	4%
Stroke	7%
4+ Medications	89%

* Continuous variables expressed as mean + standard deviation; Categorical variable expressed as percentages.

Dyslipidemia - based on diagnosis billing code.

Table 2

Most frequent medication classes in aTRH patients

Medication class	Patients (n = 11,147)
Beta-blocker	9933 (89.11%)
Calcium channel blocker	8347 (74.88%)
Thiazide diuretic	7930 (71.14%)
Angiotensin converting enzyme inhibitor	7669 (68.80%)
Loop diuretic	7209 (64.67%)
Angiotensin-receptor blockers	5330 (47.82%)
Mineralocorticoid receptor antagonists	3061 (27.46%)
Alpha-blocker	2184 (19.59%)
Vasodilators	1548 (13.89%)

Table 3

Most common medication classes in aTRH patients without CAD, CHF or A-fib

Medication class	Patients (n = 3,034)
Thiazide	2526 (83.26%)
Beta-blocker	2374 (78.25%)
Calcium channel blocker	2306 (76.01%)
Angiotensin converting enzyme inhibitor	1879 (61.93%)
Angiotensin-receptor blockers	1527 (50.33%)
Loop diuretic	1274 (41.99%)
Alpha Blocker	736 (24.26%)
Mineralocorticoid receptor antagonists	499 (16.45%)
Vasodilators	373 (12.29%)

Table 4Top 4 most frequent medication class combinations in aTRH patients^{*}

Prescribed medication combinations	Patients (n = 11,147)
3 Drugs	1,255
ACE/ARB +BB +Thiazide	430 (34.26%)
ACEIARB +CCB+Thiazide	315 (25.09%)
ACE/ARB+BB+Loop	200 (15.94%)
BB+CCB+ Thiazide	57 (4.54%)
4 Drugs	5,067
ACE/ARB+BB+CCB+Thiazide	1,788 (35.29%)
ACE/ARB+BB+CCB+Loop	1,069 (21.09%)
ACE/ARB+BB+Thiazide+Loop	528 (10.42%)
ACE/ARB+BB+MRA+Loop	501 (9.89%)
5 Drugs	2,928
ACE/ARB+BB+CCB+Thiazide+Loop	1,020 (34.84%)
ACE/ARB+BB+CCB+MRA+Loop	341 (11.65%)
ACE/ARB+BB+MRA+Thiazide+Loop	304 (10.38%)
ACE/ARB+BB+CCB+AB+Thiazide	301 (10.28%)

^{*} This is not an exhaustive list of drug combinations found in the aTRH cohort. Only the top 4 combinations in regimes with 3 to 5 antihypertensive medications are listed here.

AB = alpha-blocker; ACE = angiotensin converting enzyme inhibitor; ARB = angiotensin-receptor blockers; BB = beta-blocker; CCB = calcium channel blocker; MRA = mineralocorticoid receptor antagonists

Table 5

Top 4 most common medication combinations in aTRH patients without CAD, CHF or A-fib

Prescribed medication combinations	Patients (n = 3,034)
3 Drugs	650
ACE/ARB +BB +Thiazide	230 (35.4%)
ACE/ARB +CCB+Thiazide	228 (35.1%)
ACE/ARB+BB+Loop	50 (7.7%)
BB+CCB+ Thiazide	32 (4.92%)
4 Drugs	1,402
ACE/ARB+BB+CCB+Thiazide	642 (45.8%)
ACE/ARB+BB+CCB+Loop	152 (10.8%)
ACE/ARB+BB+Thiazide+Loop	114 (8.1%)
ACE/ARB+BB+MRA+Loop	42 (3.0%)
5 Drugs	640
ACE/ARB+BB+CCB+Thiazide+Loop	172 (27.2%)
ACE/ARB+BB+CCB+Thiazide+AB	137 (21.4%)
ACE/ARB+BB+MRA+Loop	33 (5.2%)
ACE/ARB+BB+MRA+Loop+Thiazide	26 (4.1%)

* This is not an exhaustive list of drug combinations found in the aTRH cohort without CAD, CHF, or A-fib. Only the top 4 combinations in regimes with 3 to 5 antihypertensive medications are listed here.

ACEI = angiotensin converting enzyme inhibitor; ARB = angiotensin-receptor blockers; BB = beta-blocker; CCB = calcium channel blocker; MRA = mineralocorticoid receptor antagonists; AB = alpha-blocker.