

Resistant Hypertension, Time-Updated Blood Pressure Values and Renal Outcome in Type 2 Diabetes Mellitus

Francesca Viazzi, MD; Pamela Piscitelli, MD; Antonio Ceriello, MD; Paola Fioretto, MD; Carlo Giorda, MD; Pietro Guida, MSC; Giuseppina Russo, MD, PhD; Salvatore De Cosmo, MD; Roberto Pontremoli, MD, PhD; AMD-Annals Study Group*

Background—Apparent treatment resistant hypertension (aTRH) is highly prevalent in patients with type 2 diabetes mellitus (T2D) and entails worse cardiovascular prognosis. The impact of aTRH and long-term achievement of recommended blood pressure (BP) values on renal outcome remains largely unknown. We assessed the role of aTRH and BP on the development of chronic kidney disease in patients with T2D and hypertension in real-life clinical practice.

Methods and Results—Clinical records from a total of 29 923 patients with T2D and hypertension, with normal baseline estimated glomerular filtration rate and regular visits during a 4-year follow-up, were retrieved and analyzed. The association between time-updated BP control (ie, 75% of visits with BP <140/90 mm Hg) and the occurrence of estimated glomerular filtration rate <60 and/or a reduction \geq 30% from baseline was assessed. At baseline, 17% of patients had aTRH. Over the 4-year follow-up, 19% developed low estimated glomerular filtration rate and 12% an estimated glomerular filtration rate reduction \geq 30% from baseline. Patients with aTRH showed an increased risk of developing both renal outcomes (adjusted odds ratio, 1.31 and 1.43; $P<0.001$ respectively), as compared with those with non-aTRH. No association was found between BP control and renal outcomes in non-aTRH, whereas in aTRH, BP control was associated with a 30% ($P=0.036$) greater risk of developing the renal end points.

Conclusions—ATRH entails a worse renal prognosis in T2D with hypertension. BP control is not associated with a more-favorable renal outcome in aTRH. The relationship between time-updated BP and renal function seems to be J-shaped, with optimal systolic BP values between 120 and 140 mm Hg. (*J Am Heart Assoc.* 2017;6:e006745. DOI: 10.1161/JAHA.117.006745.)

Key Words: albuminuria • blood pressure • chronic kidney disease • diabetes (kidney) • glomerular filtration rate • resistant hypertension

Resistant hypertension (RH), that is, blood pressure (BP) above target levels despite optimal combination of at least 3 different drugs, including a diuretic,^{1–3} is highly prevalent in patients at high cardiovascular risk, such as those with diabetes mellitus and chronic kidney disease (CKD).^{4–6} The real prevalence of RH has been reported to vary considerably, from 10% to 40%,^{3,7} because of several confounding factors, and the term apparent treatment

resistant hypertension (aTRH) should be preferred when adherence to medications or out-of-office BP are unknown.⁸

ATRH has been associated with worse cardiovascular morbidity and mortality^{9,10} and faster progression of renal disease in CKD patients,^{6,11} underscoring the need for early identification and systematic evaluation and management of at-risk patients. In a recent, large, 5-year retrospective study among over 470 000 individuals from the Kaiser Permanente

From the Università degli Studi and IRCCS Azienda Ospedaliera Universitaria San Martino-IST, Genova, Italy (F.V., R.P.); Department of Medical Sciences, Scientific Institute “Casa Sollievo della Sofferenza”, San Giovanni Rotondo (FG), Italy (P.P., S.D.C.); Institut d’Investigacions Biomèdiques August Pii Sunyer (IDIBAPS) and Centro de Investigación Biomédica en Red de Diabetes y Enfermedades Metabólicas Asociadas (CIBERDEM), Barcelona, Spain (A.C.); Department of Cardiovascular and Metabolic Diseases, IRCCS Gruppo Multimedica, Sesto San Giovanni, Milano, Italy (A.C.); Department of Medicine, University of Padua, Italy (P.F.); Diabetes and Metabolism Unit, ASL Turin 5, Chieri (TO), Italy (C.G.); Associazione Medici Diabetologi, Rome, Italy (P.G.); Department of Clinical and Experimental Medicine, University of Messina, Italy (G.R.).

An accompanying Appendix S1 is available at <http://jaha.ahajournals.org/content/6/9/e006745/DC1/embed/inline-supplementary-material-1.pdf>

*A complete list of the AMD-Annals Study Group members are given in Appendix S1.

Correspondence to: Roberto Pontremoli, MD, PhD, Department of Internal Medicine, Università degli Studi and IRCCS Azienda Ospedaliera Universitaria San Martino-IST, Viale Benedetto XV, Genova 16132, Italy. E-mail: roberto.pontremoli@unige.it

Received June 18, 2017; accepted July 28, 2017.

© 2017 The Authors. Published on behalf of the American Heart Association, Inc., by Wiley. This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

Clinical Perspective

What Is New?

- In a large, real-life cohort study in patients with type 2 diabetes mellitus and hypertension in Italy, the presence of apparent treatment resistant hypertension entails a significantly greater risk of developing chronic kidney disease and/or a clinically relevant reduction in estimated glomerular filtration rate over a 4-year follow-up.
- The achievement and maintenance of recommended blood pressure values (ie, 75% of visits with blood pressure <140/90 mm Hg) are associated with a worse renal outcome in apparent treatment resistant hypertension patients.
- The relationship between achieved blood pressure and renal function seems to be J-shaped, at least at very low levels, with optimal systolic blood pressure values between 120 and 140 mm Hg.

What Are the Clinical Implications?

- There is a need for early identification and management of patients to prevent the development of apparent treatment resistant hypertension and associated increase in renal morbidity.
- Reduction of antihypertensive treatment should be considered in a small, but relevant, proportion of patients in order to improve renal outcome.

Southern California registry, those with RH had a greater risk for end-stage renal disease (ESRD), ischemic heart event, congestive heart failure, cerebrovascular accident, and all-cause mortality. The risk of ESRD and cerebrovascular accident were 25% and 23% greater, respectively, in RH compared with non-RH, supporting the linkage between severity of BP and both outcomes.¹²

Furthermore, and somewhat unexpectedly, in patients with aTRH, the achievement of recommended BP control does not seem to entail any cardiovascular benefit^{9,13,14} and, possibly,

is associated with a greater renal risk as compared with patients with uncontrolled aTRH.³ In a recent retrospective study on a large cohort of treated hypertensive patients in the United States, low treated BP (systolic BP [SBP] <120 and/or diastolic BP [DBP] <70 mm Hg) was associated with more cardiovascular diseases than less-stringent BP control irrespective of aTRH.¹⁵

These data raise the possibility that a J-curve effect for cardiovascular and renal disease is present, and perhaps even more evident, in the subgroup of patients with aTRH who are likely to be more adherent to treatment, but also show a worse risk profile.

Specific data on long-term renal outcome in aTRH are scanty, especially in real-life clinical conditions and with regard to de novo development of organ damage in high-risk subgroups. To get more insights on the relationship between the presence of aTRH, achievement and maintenance of recommended BP values, and renal outcome, we looked at the incidence of low estimated glomerular filtration rate (eGFR) over a 4-year follow-up in a large, real-life cohort of patients with hypertension and type 2 diabetes mellitus (T2D) in Italy.

Methods

Study Participants

As already reported,^{6–18} in Italy, diabetes mellitus care is mostly provided by a public network of approximately 700 diabetes mellitus clinics in which a team of specialists provides diagnostic confirmation, prevention, and treatment for diabetes mellitus and its complications through close patients follow-up and regular checkups.^{16–18} In the present study, we analyze a large cohort of patients with T2D followed up at 134 diabetes mellitus centers in Italy among those participating in the Italian Association of Clinical Diabetologists (Associazione Medici Diabetologi) initiative. The analysis was performed using the data set of electronic medical

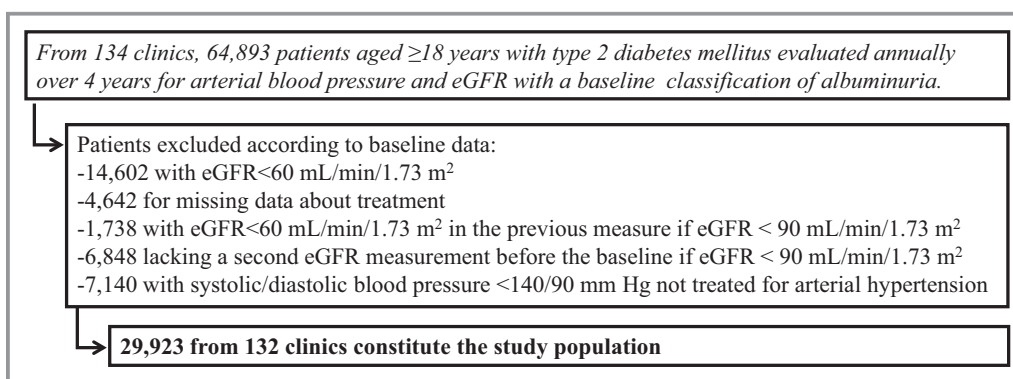


Figure 1. Flow diagram for selection of study patients. eGFR indicates estimated glomerular filtration rate.

Table 1. Baseline Characteristics of Study Patients Stratified by ATRH

| | All | No aTRH | aTRH | P Value |
|--|----------------|----------------|---------------|---------|
| | n=29 923 | n=24 934 | n=4989 | |
| Male sex | 16 969 (56.7%) | 14 432 (57.9%) | 2537 (50.9%) | <0.001 |
| Age, y | 65±9 | 64±9 | 67±8 | <0.001 |
| Known duration of diabetes mellitus, y | 11±8 | 10±8 | 11±8 | <0.001 |
| BMI, kg/m ² | 30±5 | 29±5 | 31±5 | <0.001 |
| Serum creatinine, μmol/L | 74±15 | 73±15 | 74±15 | 0.005 |
| eGFR, mL/min per 1.73 m ² | 86±13 | 86±13 | 83±13 | <0.001 |
| Albuminuria | 5874 (19.6%) | 4772 (19.1%) | 1102 (22.1%) | <0.001 |
| Microalbuminuria | 5121 (17.1%) | 4172 (16.7%) | 949 (19.0%) | <0.001 |
| Macroalbuminuria | 753 (2.5%) | 600 (2.4%) | 153 (3.1%) | 0.001 |
| Serum uric acid, μmol/L | 315±101 | 311±102 | 337±94 | <0.001 |
| SUA in the top sex-specific quintile | 2878 (19.3%) | 2112 (17.1%) | 766 (30.0%) | <0.001 |
| HbA1c, % | 7.3±1.3 | 7.2±1.3 | 7.3±1.3 | 0.049 |
| HbA1c, mmol/mol | 55.7±14.0 | 55.7±14.0 | 56.1±14.1 | 0.049 |
| HbA1c ≥7% (≥53 mmol/mol) | 15 987 (53.8%) | 13 244 (53.5%) | 2743 (55.5%) | 0.026 |
| Total cholesterol, mmol/L | 4.83±0.96 | 4.85±0.97 | 4.71±0.93 | <0.001 |
| Triglycerides, mmol/L | 1.55±0.98 | 1.54±1.00 | 1.58±0.89 | 0.002 |
| Triglycerides ≥150 mg/dL (≥1.69 mmol/L) | 8780 (31.2%) | 7181 (30.6%) | 1599 (34.2%) | <0.001 |
| HDL, mmol/L | 1.32±0.38 | 1.33±0.38 | 1.29±0.37 | <0.001 |
| HDL <40M <50F mg/dL (<1.03M <1.29F mmol/L) | 8657 (31.2%) | 7009 (30.3%) | 1648 (36.0%) | <0.001 |
| LDL, mmol/L | 2.84±0.85 | 2.86±0.85 | 2.73±0.82 | <0.001 |
| LDL ≥100 mg/dL (≥2.59 mmol/L) | 16 483 (59.7%) | 14 009 (60.8%) | 2474 (54.4%) | <0.001 |
| Systolic BP, mm Hg | 143±17 | 142±17 | 148±18 | <0.001 |
| Diastolic BP, mm Hg | 81±9 | 81±9 | 82±10 | <0.001 |
| BP ≥140/85 mm Hg | 21 711 (72.6%) | 17 491 (70.1%) | 4220 (84.6%) | <0.001 |
| Nonproliferative retinopathy | 3955 (13.2%) | 3301 (13.2%) | 654 (13.1%) | 0.906 |
| Proliferative retinopathy | 1169 (3.9%) | 934 (3.7%) | 235 (4.7%) | 0.002 |
| Lipid-lowering treatment | 14 579 (48.7%) | 11 716 (47.0%) | 2863 (57.4%) | <0.001 |
| Treatment with statins | 13 456 (45.0%) | 10 773 (43.2%) | 2683 (53.8%) | <0.001 |
| Treatment with fibrates | 656 (2.2%) | 559 (2.2%) | 97 (1.9%) | 0.123 |
| No. of antihypertensive drugs | 1.6±1.3 | 1.2±1.0 | 3.6±0.8 | ... |
| Antihypertensive treatment | 23 106 (77.2%) | 18 117 (72.7%) | 4989 (100.0%) | ... |
| Treatment with ACE-Is/ARBs | 19 512 (65.2%) | 14 767 (59.2%) | 4745 (95.1%) | ... |
| Aspirin | 9296 (31.1%) | 7354 (29.5%) | 1942 (38.9%) | <0.001 |
| Antidiabetic therapy | | | | |
| Diet | 2177 (7.3%) | 1853 (7.4%) | 324 (6.5%) | 0.018 |
| Oral antidiabetic drugs | 20 137 (67.3%) | 16 864 (67.6%) | 3273 (65.6%) | 0.008 |
| Oral antidiabetic drugs and insulin | 4559 (15.2%) | 3672 (14.7%) | 887 (17.8%) | <0.001 |
| Insulin | 3050 (10.2%) | 2545 (10.2%) | 505 (10.1%) | 0.738 |

Mean±SD or absolute frequency (percentage). Patients' baseline missing data: known duration of diabetes mellitus in 937 (3.1%), BMI in 1600 (5.3%), serum uric acid in 15 003 (50.1%), HbA1c in 231 (0.8%), total cholesterol in 2078 (6.9%), triglycerides in 1805 (6%), HDL in 2178 (7.3%), LDL in 2319 (7.7%), and smoking status in 13 650 (45.6%). ACE-Is indicates angiotensin-converting enzyme inhibitors; ARBs, angiotensin II receptor antagonists; ATRH, apparent treatment resistant hypertension; BMI, body mass index; BP, blood pressure; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; SUA, serum uric acid.

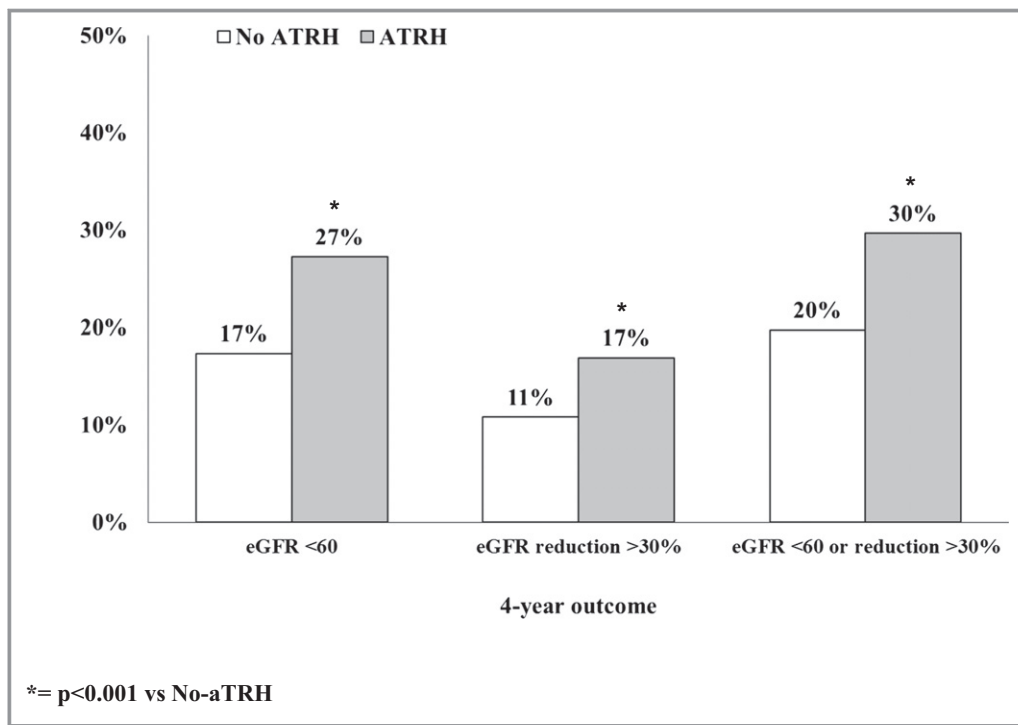


Figure 2. Cumulative incidence of renal outcomes in patients with and without aTRH and T2D. ATRH indicates apparent treatment resistant hypertension; CI, confidence interval; eGFR, estimated glomerular filtration rate; T2D, type 2 diabetes mellitus. * $P < 0.001$ vs No-aTRH. Adjusted odds ratios for eGFR <60 mL/min per 1.73 m², 1.31 (CI 1.19–1.44; $P < 0.001$), for eGFR reduction >30% from baseline, 1.43 (CI 1.28–1.58; $P < 0.001$), for eGFR <60 or reduction >30% from baseline, 1.30 (CI 1.19–1.42; $P < 0.001$).

records collected between January 1, 2004 and June 30, 2011. For the purpose of the analysis, we considered only patients at least 18 years old and with a follow-up evaluation within 6 months complete for data about BP values, eGFR, albuminuria (Alb), and information on treatment.

Of 64 893 patients identified, after exclusion of 34 970 patients without a confirmed eGFR value above 60 mL/min, or medication information, or a diagnosis of hypertension (SBP <140 mm Hg and DBP <90 mm Hg and not taking antihypertensive medications at baseline), a total of 29 923 patients from 132 clinics constitute the study population (Figure 1). The centers involved in the study were homogeneously distributed throughout the country.

Study Design

The analysis of the database is an attempt by the Italian Associazione Medici Diabetologi initiative to identify a set of indicators that can be used in the context of continuous quality improvement. Participating centers adopted the same software systems for everyday management of outpatients, whereas a specially developed software package allowed us to extract the information we intended to analyze from all the clinical databases (Associazione Medici Diabetologi Data

File). Moreover, data from all participating centers were collected and centrally analyzed anonymously. All patients gave their informed consent, and internal approval was obtained by the Associazione Medici Diabetologi Annals scientific committee.^{16–18} The current initiative includes measuring and monitoring glycosylated hemoglobin (HbA1c), BP, low-density lipoprotein cholesterol, total and high-density lipoprotein cholesterol, and triglycerides. The use of specific classes of drugs was also evaluated. Because normal ranges for HbA1c varied among centers, the percentage change with respect to the upper normal value (measured value/upper normal limit) was estimated and multiplied by 6.0 to allow comparisons among the centers. Kidney function was assessed by serum creatinine and urinary albumin excretion measurements. GFR was estimated for each patient using a standardized serum creatinine assay and the Chronic Kidney Disease Epidemiology Collaboration formula.¹⁹ Increased urinary albumin excretion was diagnosed and defined as Alb if urinary albumin concentration was more than 30 mg/L, urinary albumin excretion rate was more than 20 mg/min, or urinary albumin-to-creatinine ratio was more than 2.5 mg/mmol in men and more than 3.5 mg/mmol in women. At each participating center, all patients underwent physical examination and BP measurements according to a

Table 2. Baseline Characteristics of Study Patients on the Basis of Renal Outcome Within 4-Year

| | eGFR <60 mL/min per 1.73 m ² | | eGFR Reduction >30% | | eGFR <60 or Reduction >30% | | P Value |
|--|---|--------------|---------------------|--------------|----------------------------|--------------|---------|
| | No | Yes | No | Yes | No | Yes | |
| Male sex | 14 071 (58.1%) | 2898 (50.8%) | 15 247 (57.8%) | 1722 (48.5%) | 13 743 (58.5%) | 3226 (50.2%) | <0.001 |
| Age, y | 64±9 | 69±8 | 64±9 | 67±9 | 64±9 | 68±8 | <0.001 |
| Known duration of diabetes mellitus, y | 10±8 | 12±9 | 10±8 | 11±9 | 10±8 | 12±9 | <0.001 |
| BMI, kg/m ² | 30±5 | 30±5 | 30±5 | 30±5 | 30±5 | 30±5 | 0.002 |
| Serum creatinine, μmol/L | 72±14 | 81±14 | 74±15 | 72±15 | 72±14 | 79±15 | <0.001 |
| eGFR, mL/min per 1.73 m ² | 88±12 | 75±11 | 86±13 | 85±13 | 88±12 | 77±13 | <0.001 |
| Albuminuria | 4350 (18.0%) | 1524 (26.7%) | 4846 (18.4%) | 1028 (28.9%) | 4173 (17.8%) | 1701 (26.5%) | <0.001 |
| Microalbuminuria | 3899 (16.1%) | 1222 (21.4%) | 4310 (16.3%) | 811 (22.8%) | 3746 (15.9%) | 1375 (21.4%) | <0.001 |
| Macroalbuminuria | 451 (1.9%) | 302 (5.3%) | 536 (2.0%) | 217 (6.1%) | 427 (1.8%) | 326 (5.1%) | <0.001 |
| Serum uric acid, μmol/L | 311±98 | 335±113 | 314±97 | 327±130 | 311±98 | 331±110 | <0.001 |
| SUA in the top sex-specific quintile | 2121 (17.5%) | 757 (27.0%) | 2473 (18.7%) | 405 (23.8%) | 2068 (17.5%) | 810 (26.0%) | <0.001 |
| HbA1c, % | 7.2±1.3 | 7.3±1.3 | 7.2±1.3 | 7.4±1.4 | 7.2±1.3 | 7.4±1.3 | <0.001 |
| HbA1c, mmol/mol | 56±14 | 57±14 | 56±14 | 58±15 | 55±14 | 57±14 | <0.001 |
| HbA1c ≥7% (≥53 mmol/mol) | 12 725 (52.9%) | 3262 (57.7%) | 13 920 (53.2%) | 2067 (58.8%) | 12 328 (52.8%) | 3659 (57.6%) | <0.001 |
| Total cholesterol, mmol/L | 4.84±0.96 | 4.78±0.96 | 4.84±0.96 | 4.75±0.97 | 4.84±0.96 | 4.78±0.97 | <0.001 |
| Triglycerides, mmol/L | 1.53±0.98 | 1.62±0.98 | 1.53±0.97 | 1.65±1.07 | 1.53±0.98 | 1.63±1.00 | <0.001 |
| Triglycerides ≥150 mg/dL (≥1.69 mmol/L) | 6933 (30.5%) | 1847 (34.4%) | 7612 (30.7%) | 1168 (34.9%) | 6687 (30.3%) | 2093 (34.7%) | <0.001 |
| HDL, mmol/L | 1.32±0.37 | 1.32±0.39 | 1.32±0.37 | 1.31±0.39 | 1.32±0.37 | 1.32±0.39 | 0.198 |
| HDL <40M <50F mg/dL (<1.03M <1.29F mmol/L) | 6876 (30.6%) | 1781 (33.9%) | 7502 (30.7%) | 1155 (35.3%) | 6641 (30.4%) | 2016 (34.1%) | <0.001 |
| LDL, mmol/L | 2.86±0.85 | 2.77±0.85 | 2.85±0.85 | 2.74±0.85 | 2.86±0.85 | 2.77±0.85 | <0.001 |
| LDL ≥100 mg/dL (≥2.59 mmol/L) | 13 569 (60.7%) | 2914 (55.6%) | 14 724 (60.5%) | 1759 (54.1%) | 13 205 (60.8%) | 3278 (55.8%) | <0.001 |
| Systolic BP, mm Hg | 143±17 | 145±18 | 143±17 | 145±18 | 143±17 | 144±18 | <0.001 |
| Diastolic BP, mm Hg | 81±9 | 80±9 | 81±9 | 81±10 | 81±9 | 80±9 | <0.001 |
| BP ≥140/85 mm Hg | 17 599 (72.7%) | 4112 (72.1%) | 19 113 (72.5%) | 2598 (73.2%) | 17 073 (72.6%) | 4638 (72.2%) | 0.365 |
| Nonproliferative retinopathy | 3056 (12.6%) | 899 (15.8%) | 3403 (12.9%) | 552 (15.5%) | 2958 (12.6%) | 997 (15.5%) | <0.001 |
| Proliferative retinopathy | 861 (3.6%) | 308 (5.4%) | 972 (3.7%) | 197 (5.5%) | 820 (3.5%) | 349 (5.4%) | <0.001 |

Continued

Table 2. Continued

| | eGFR <60 mL/min per 1.73 m ² | | eGFR Reduction >30% | | eGFR <60 or Reduction >30% | | P Value |
|---|---|--------------|---------------------|--------------|----------------------------|--------------|---------|
| | No | Yes | No | Yes | No | Yes | |
| | n=24 216 | n=5707 | n=26 372 | n=3551 | n=23 501 | n=6422 | |
| Lipid-lowering treatment | 11 610 (47.9%) | 2969 (52.0%) | 12 806 (48.6%) | 1773 (49.9%) | 11 270 (48.0%) | 3309 (51.5%) | <0.001 |
| Treatment with statins | 10 736 (44.3%) | 2720 (47.7%) | 11 842 (44.9%) | 1614 (45.5%) | 10 436 (44.4%) | 3020 (47.0%) | <0.001 |
| Treatment with fibrates | 512 (2.1%) | 144 (2.5%) | 564 (2.1%) | 92 (2.6%) | 489 (2.1%) | 167 (2.6%) | 0.021 |
| Antihypertensive treatment | 18 276 (75.5%) | 4830 (84.6%) | 20 170 (76.5%) | 2936 (82.7%) | 17 728 (75.4%) | 5378 (83.7%) | <0.001 |
| Treatment with ACE-is/ARBs | 15 408 (63.6%) | 4104 (71.9%) | 17 015 (64.5%) | 2497 (70.3%) | 14 936 (63.6%) | 4576 (71.3%) | <0.001 |
| Aspirin | 7243 (29.9%) | 2053 (36.0%) | 8132 (30.8%) | 1164 (32.8%) | 7050 (30.0%) | 2246 (35.0%) | <0.001 |
| Antidiabetic therapy | | | | | | | |
| Diet | 1919 (7.9%) | 258 (4.5%) | 2043 (7.7%) | 134 (3.8%) | 1890 (8.0%) | 287 (4.5%) | <0.001 |
| Oral antidiabetic drugs | 16 581 (68.5%) | 3556 (62.3%) | 17 898 (67.9%) | 2239 (63.1%) | 16 105 (68.5%) | 4032 (62.8%) | <0.001 |
| Oral antidiabetic drugs and insulin | 3424 (14.1%) | 1135 (19.9%) | 3819 (14.5%) | 740 (20.8%) | 3284 (14.0%) | 1275 (19.9%) | <0.001 |
| Insulin | 2292 (9.5%) | 758 (13.3%) | 2612 (9.9%) | 438 (12.3%) | 2222 (9.5%) | 828 (12.9%) | <0.001 |
| Apparent treatment resistant hypertension | 3631 (15.0%) | 1358 (23.8%) | 4143 (15.7%) | 846 (23.8%) | 3507 (14.9%) | 1482 (23.1%) | <0.001 |
| BPC* | 3859 (15.9%) | 853 (14.9%) | 4200 (15.9%) | 553 (15.6%) | 3751 (16.0%) | 972 (15.1%) | 0.168 |

Mean±SD or absolute frequency (percentage). ACE-is indicates angiotensin-converting enzyme inhibitors; ARBs, angiotensin II receptor antagonists; BMI, body mass index; BP, blood pressure; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; SUA, serum uric acid.

*Blood pressure control (BPC) refers to the proportion of visits with systolic and diastolic blood pressure <140/90 mm Hg. For each renal outcome, visits after the event occurrence were excluded.

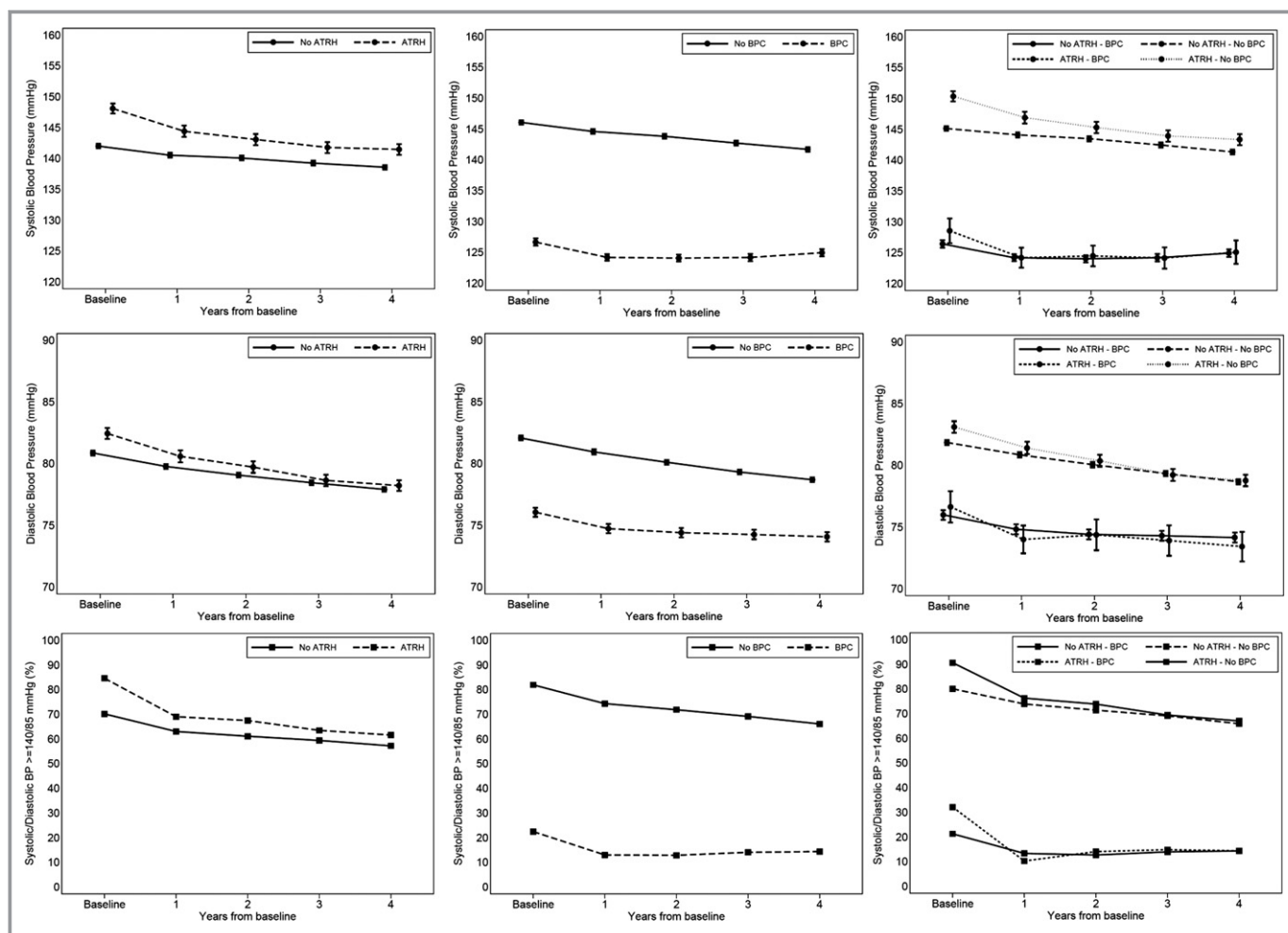


Figure 3. Blood pressure changes during follow-up. ATRH indicates apparent treatment resistant hypertension; BP, blood pressure; blood pressure control (BPC) refers to the proportion of visits with systolic and diastolic blood pressure <140/90 mm Hg.

standardized protocol. BP was measured with the patient in the sitting position after a 5-minute rest, with a mercury sphygmomanometer. SBP and DBP were read to the nearest 2 mm Hg. Disappearance of Korotkoff sounds (phase V) was the criterion for DBP. Three measurements were taken at 2-minute intervals, and the average value was used to define clinical SBP and DBP.

The main analysis was aimed at evaluating the association between aTRH, BP control (BPC), and renal outcome during the study. For each outcome, visits after the event occurrence were excluded from the BPC evaluation. The outcomes were: (1) eGFR less than 60 mL/min per 1.73 m²; (2) a reduction $\geq 30\%$ from baseline; and (3) a combination of either 1 of the above end points.

Definition of ATRH and BPC

We defined ATRH as SBP or DBP \geq the BP goal while taking ≥ 3 antihypertensive medications, including a diuretic, or taking

≥ 4 antihypertensive medications, including a diuretic, regardless of BP values at baseline visit. The BP goal of <140/90 mm Hg used for this analysis is consistent with the recommended BP goal for patients with diabetes mellitus in recent guidelines.^{20,21}

Time-updated BPC was defined as >75% of visits with SBP and DBP <140/90 mm Hg, whereas in secondary analyses time-updated mean SBP was examined as the average of all available SBP values before the occurrence of the end point, if any.

Statistical Analysis

Data are given as mean values \pm SD; categorical variables are described as frequencies and percentages. Data were analyzed by mixed models with diabetes mellitus clinics fitted as random effect considering patients as clusters of observations to take into account possible differences across centers. Continuous variables were analyzed with a

Table 3. Baseline Characteristics of Study Patients and Renal Outcomes During the 4-Year Follow-up Stratified by ATRH and BPC

| | No ATRH | No ATRH | ATRH | ATRH | P Value |
|--|--------------|----------------|--------------|---------------|---------|
| | BPC | No BPC | BPC | No BPC | |
| | n=4198 | n=20 736 | n=514 | n=4475 | |
| Male sex | 2461 (58.6%) | 11 971 (57.7%) | 280 (54.5%) | 2257 (50.4%) | <0.001 |
| Age, y | 63±9 | 65±9 | 65±9 | 67±8 | <0.001 |
| Known duration of diabetes mellitus, y | 10±8 | 11±8 | 10±9 | 11±8 | <0.001 |
| BMI, kg/m ² | 29±5 | 29±5 | 31±6 | 32±5 | <0.001 |
| Serum creatinine, μmol/L | 75±15 | 73±15 | 75±15 | 74±15 | <0.001 |
| eGFR, mL/min per 1.73 m ² | 86±14 | 86±13 | 83±13 | 83±13 | <0.001 |
| Albuminuria | 694 (16.5%) | 4078 (19.7%) | 91 (17.7%) | 1011 (22.6%) | <0.001 |
| Microalbuminuria | 616 (14.7%) | 3556 (17.1%) | 81 (15.8%) | 868 (19.4%) | <0.001 |
| Macroalbuminuria | 78 (1.9%) | 522 (2.5%) | 10 (1.9%) | 143 (3.2%) | <0.001 |
| Serum uric acid, μmol/L | 314±78 | 310±107 | 339±88 | 336±95 | <0.001 |
| Serum uric acid in the top sex-specific quintile | 491 (20.2%) | 1847 (18.6%) | 114 (36.4%) | 720 (32.1%) | <0.001 |
| HbA1c, % | 7.1±1.2 | 7.3±1.3 | 7.2±1.3 | 7.3±1.3 | <0.001 |
| HbA1c, mmol/mol | 54±13 | 56±14 | 55±14 | 56±14 | <0.001 |
| HbA1c ≥7% (≥53 mmol/mol) | 2019 (48.5%) | 11 225 (54.5%) | 256 (50.6%) | 2487 (56.1%) | <0.001 |
| Total cholesterol, mmol/L | 4.68±0.95 | 4.89±0.97 | 4.48±0.83 | 4.74±0.94 | <0.001 |
| Triglycerides, mmol/L | 1.51±0.94 | 1.55±1.01 | 1.61±0.89 | 1.58±0.89 | 0.010 |
| Triglycerides ≥150 mg/dL (≥1.69 mmol/L) | 1172 (29.5%) | 6009 (30.9%) | 173 (36.2%) | 1426 (33.9%) | <0.001 |
| HDL, mmol/L | 1.28±0.39 | 1.34±0.37 | 1.23±0.37 | 1.30±0.37 | <0.001 |
| HDL <40M <50F mg/dL (<1.03M <1.29F mmol/L) | 1373 (34.8%) | 5636 (29.3%) | 199 (42.2%) | 1449 (35.3%) | <0.001 |
| LDL, mmol/L | 2.75±0.84 | 2.88±0.85 | 2.56±0.76 | 2.75±0.83 | <0.001 |
| LDL ≥100 mg/dL (≥2.59 mmol/L) | 2155 (55.1%) | 11 854 (61.9%) | 219 (47.2%) | 2255 (55.2%) | <0.001 |
| Systolic BP, mm Hg | 126±12 | 145±16 | 129±14 | 150±17 | <0.001 |
| Diastolic BP, mm Hg | 76±8 | 82±9 | 77±9 | 83±9 | <0.001 |
| BP ≥140/85 mm Hg | 893 (21.3%) | 16 598 (80.0%) | 165 (32.1%) | 4055 (90.6%) | <0.001 |
| Nonproliferative retinopathy | 500 (11.9%) | 2801 (13.5%) | 59 (11.5%) | 595 (13.3%) | 0.008 |
| Proliferative retinopathy | 139 (3.3%) | 795 (3.8%) | 24 (4.7%) | 211 (4.7%) | 0.001 |
| Smokers | 453 (18.6%) | 1853 (16.7%) | 44 (14.9%) | 285 (11.7%) | <0.001 |
| Lipid-lowering treatment | 2427 (57.8%) | 9289 (44.8%) | 332 (64.6%) | 2531 (56.6%) | <0.001 |
| Treatment with statins | 2246 (53.5%) | 8527 (41.1%) | 304 (59.1%) | 2379 (53.2%) | <0.001 |
| Treatment with fibrates | 104 (2.5%) | 455 (2.2%) | 7 (1.4%) | 90 (2.0%) | 0.205 |
| Antihypertensive treatment | 3869 (92.2%) | 14 248 (68.7%) | 514 (100.0%) | 4475 (100.0%) | <0.001 |
| Treatment with ACE-Is/ARBs | 3069 (73.1%) | 11 698 (56.4%) | 494 (96.1%) | 4251 (95.0%) | <0.001 |
| Aspirin | 1539 (36.7%) | 5815 (28.0%) | 197 (38.3%) | 1745 (39.0%) | <0.001 |
| Antidiabetic therapy | | | | | |
| Diet | 361 (8.6%) | 1492 (7.2%) | 36 (7.0%) | 288 (6.4%) | 0.024 |
| Oral antidiabetic drugs | 2807 (66.9%) | 14 057 (67.8%) | 328 (63.8%) | 2945 (65.8%) | 0.007 |
| Oral antidiabetic drugs and insulin | 555 (13.2%) | 3117 (15.0%) | 80 (15.6%) | 807 (18.0%) | <0.001 |
| Insulin | 475 (11.3%) | 2070 (10.0%) | 70 (13.6%) | 435 (9.7%) | 0.007 |

The P values refer to the overall significance of logistic mixed regression model for categorical data or linear for continuous variables with blood pressure group as dependent variable. Mean±SD or absolute frequency (percentage). ACE-Is indicates angiotensin-converting enzyme inhibitors; ARBs, angiotensin II receptor antagonists; aTRH, apparent resistant hypertension; BMI, body mass index; BP, blood pressure; BPC, blood pressure control; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol.

Table 4. Multivariate Analysis for the Occurrence of 4-Year Renal Outcome

| | eGFR <60 mL/min per 1.73 m ² | | eGFR Reduction ≥30% | | eGFR <60 or Reduction ≥30% | |
|--|---|---------|---------------------|---------|----------------------------|---------|
| | Odds Ratio (95% CI) | P Value | Odds Ratio (95% CI) | P Value | Odds Ratio (95% CI) | P Value |
| Male sex | 0.80 (0.74–0.87) | <0.001 | 0.74 (0.68–0.80) | <0.001 | 0.76 (0.71–0.82) | <0.001 |
| Age (by 10 y) | 1.48 (1.41–1.56) | <0.001 | 1.54 (1.45–1.64) | <0.001 | 1.35 (1.29–1.42) | <0.001 |
| Duration of diabetes mellitus (by 10 y) | 1.00 (0.95–1.05) | 0.936 | 0.97 (0.92–1.02) | 0.235 | 1.00 (0.95–1.04) | 0.953 |
| BMI (by 5 kg/m ²) | 1.09 (1.05–1.14) | <0.001 | 1.08 (1.04–1.13) | <0.001 | 1.07 (1.04–1.11) | <0.001 |
| eGFR (by 10 mL/min per 1.73 m ²) | 0.40 (0.38–0.41) | <0.001 | 1.07 (1.03–1.11) | <0.001 | 0.53 (0.51–0.54) | <0.001 |
| Microalbuminuria | 1.69 (1.53–1.86) | <0.001 | 1.77 (1.59–1.96) | <0.001 | 1.70 (1.55–1.86) | <0.001 |
| Macroalbuminuria | 4.49 (3.65–5.52) | <0.001 | 4.23 (3.45–5.19) | <0.001 | 4.05 (3.34–4.92) | <0.001 |
| HbA1c ≥7% (≥53 mmol/mol) | 1.06 (0.97–1.15) | 0.172 | 1.04 (0.95–1.14) | 0.358 | 1.05 (0.97–1.13) | 0.234 |
| Triglycerides ≥150 mg/dL (≥1.69 mmol/L) | 1.17 (1.07–1.27) | <0.001 | 1.18 (1.08–1.30) | <0.001 | 1.18 (1.09–1.27) | <0.001 |
| HDL <40M <50F mg/dL (<1.03M <1.29F mmol/L) | 1.09 (1.00–1.19) | 0.039 | 1.12 (1.02–1.23) | 0.017 | 1.09 (1.01–1.18) | 0.024 |
| LDL ≥100 mg/dL (≥2.59 mmol/L) | 0.84 (0.78–0.91) | <0.001 | 0.80 (0.73–0.87) | <0.001 | 0.84 (0.79–0.9) | <0.001 |
| Nonproliferative retinopathy | 1.11 (1.00–1.24) | 0.054 | 1.12 (0.99–1.26) | 0.061 | 1.11 (1.00–1.22) | 0.051 |
| Proliferative retinopathy | 1.27 (1.06–1.53) | 0.009 | 1.20 (0.99–1.46) | 0.062 | 1.28 (1.08–1.51) | 0.004 |
| Lipid-lowering treatment | 0.93 (0.86–1.01) | 0.090 | 0.92 (0.84–1.01) | 0.071 | 0.93 (0.86–1.00) | 0.041 |
| Antihypertensive treatment | 1.42 (1.23–1.64) | <0.001 | 1.35 (1.15–1.58) | <0.001 | 1.37 (1.20–1.56) | <0.001 |
| Treatment with ACE-Is/ARBs | 0.95 (0.84–1.06) | 0.347 | 0.92 (0.81–1.05) | 0.205 | 0.96 (0.86–1.06) | 0.403 |
| Aspirin | 1.08 (0.99–1.18) | 0.086 | 1.03 (0.93–1.13) | 0.616 | 1.08 (1.00–1.17) | 0.059 |
| Antidiabetic therapy | | | | | | |
| Diet | 0.72 (0.61–0.86) | <0.001 | 0.69 (0.56–0.85) | <0.001 | 0.73 (0.62–0.85) | <0.001 |
| Oral antidiabetic drugs | 1.00 | | 1.00 | | 1.00 | |
| Oral antidiabetic drugs and insulin | 1.24 (1.11–1.38) | <0.001 | 1.24 (1.11–1.40) | <0.001 | 1.23 (1.12–1.37) | <0.001 |
| Insulin | 1.24 (1.09–1.40) | 0.001 | 1.20 (1.04–1.38) | 0.010 | 1.23 (1.09–1.38) | 0.001 |
| Group ATRH and BPC | | | | | | |
| No ATRH and BPC | 1.00 | | 1.00 | | 1.00 | |
| No ATRH and No BPC | 1.05 (0.94–1.18) | 0.393 | 1.00 (0.87–1.13) | 0.940 | 1.04 (0.93–1.16) | 0.486 |
| ATRH and BPC | 1.78 (1.37–2.32) | <0.001 | 1.87 (1.43–2.45) | <0.001 | 1.68 (1.32–2.15) | <0.001 |
| ATRH and No BPC | 1.32 (1.15–1.52) | <0.001 | 1.37 (1.18–1.59) | <0.001 | 1.30 (1.14–1.48) | <0.001 |

Blood pressure control (BPC) refers to the proportion of visits with systolic and diastolic blood pressure <140/90 mm Hg. For each renal outcome, visits after the event occurrence were excluded. Odds ratio for single renal outcome with 95% confidence interval (CI). Complete-case analysis including 24 640 patients for which all data were observed. ACE-Is indicates angiotensin-converting enzyme inhibitors; ARBs, angiotensin II receptor antagonists; ATRH, apparent treatment resistant hypertension; BMI, body mass index; BP, blood pressure; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol.

linear mixed regression model and categorical variables by using a mixed logistic regression model. Odds ratios (ORs) for each renal outcome were reported with their 95% confidence interval (95% CI). A multivariate model was fitted with a complete-case analysis performed, including patients for which all data were observed. Assuming linearity of GFR reduction over time, its slope was taken as a measure of disease progression rate. For each patient, we calculated the regression coefficient (slope) of linear regression between eGFR value and the exact time in years from the first evaluation, including all measurements from baseline to the 4-year visit. The analyses were carried out

using STATA software (version 14; StataCorp LP, College Station, TX). *P* values of <0.05 were considered statistically significant.

Results

Among the 64 893 patients evaluated annually over 4 years for arterial BP and eGFR and with a baseline classification for Alb, a confirmed past eGFR value above 60 mL/min, complete information about medications, and a diagnosis of hypertension, 29 923 patients have been selected for the present analyses (Figure 1).

Table 5. Baseline Characteristics of Study Patients Stratified by Sex

| | Women | Men | P Value |
|--|----------------|----------------|---------|
| | n=12 954 | n=16 969 | |
| Age, y | 66±9 | 64±9 | <0.001 |
| Known duration of diabetes mellitus, y | 11±9 | 10±8 | <0.001 |
| BMI, kg/m ² | 30±6 | 29±4 | <0.001 |
| Serum creatinine, μmol/L | 64±11 | 81±13 | <0.001 |
| eGFR, mL/min per 1.73 m ² | 85±13 | 86±13 | <0.001 |
| Albuminuria | 1970 (15.2%) | 3904 (23.0%) | <0.001 |
| Microalbuminuria | 1744 (13.5%) | 3377 (19.9%) | <0.001 |
| Macroalbuminuria | 226 (1.7%) | 527 (3.1%) | <0.001 |
| Serum uric acid, μmol/L | 297±111 | 329±90 | <0.001 |
| SUA in the top sex-specific quintile | 1189 (18.4%) | 1689 (20.0%) | 0.015 |
| HbA1c, % | 7.4±1.3 | 7.2±1.3 | <0.001 |
| HbA1c, mmol/mol | 57±14 | 55±14 | <0.001 |
| HbA1c ≥7% (≥53 mmol/mol) | 7362 (57.3%) | 8625 (51.2%) | <0.001 |
| Total cholesterol, mmol/L | 5.01±0.95 | 4.70±0.95 | <0.001 |
| Triglycerides, mmol/L | 1.52±0.95 | 1.57±1.00 | <0.001 |
| Triglycerides ≥150 mg/dL (≥1.69 mmol/L) | 3720 (30.5%) | 5060 (31.8%) | 0.031 |
| HDL, mmol/L | 1.42±0.39 | 1.25±0.35 | <0.001 |
| HDL <40M <50F mg/dL (<1.03M <1.29F mmol/L) | 4642 (38.7%) | 4015 (25.5%) | <0.001 |
| LDL, mmol/L | 2.93±0.86 | 2.77±0.84 | <0.001 |
| LDL ≥100 mg/dL (≥2.59 mmol/L) | 7602 (63.4%) | 8881 (56.9%) | <0.001 |
| Systolic BP, mm Hg | 144±17 | 143±17 | <0.001 |
| Diastolic BP, mm Hg | 81±9 | 81±9 | <0.001 |
| BP ≥140/85 mm Hg | 9397 (72.5%) | 12 314 (72.6%) | 0.498 |
| Nonproliferative retinopathy | 1645 (12.7%) | 2310 (13.6%) | 0.079 |
| Proliferative retinopathy | 500 (3.9%) | 669 (3.9%) | 0.565 |
| Lipid-lowering treatment | 794 (11.6%) | 1841 (19.5%) | <0.001 |
| Treatment with statins | 6395 (49.4%) | 8184 (48.2%) | 0.300 |
| Treatment with fibrates | 5979 (46.2%) | 7477 (44.1%) | 0.008 |
| No. of antihypertensive drugs | 246 (1.9%) | 410 (2.4%) | 0.008 |
| Antihypertensive treatment | 10 256 (79.2%) | 12 850 (75.7%) | <0.001 |
| Treatment with ACE-Is/ARBs | 8518 (65.8%) | 10 994 (64.8%) | 0.083 |
| Aspirin | 3543 (27.4%) | 5753 (33.9%) | <0.001 |
| Antidiabetic therapy | | | |
| Diet | 838 (6.5%) | 1339 (7.9%) | <0.001 |
| Oral antidiabetic drugs | 8477 (65.4%) | 11 660 (68.7%) | <0.001 |
| Oral antidiabetic drugs and insulin | 2285 (17.6%) | 2274 (13.4%) | <0.001 |

Continued

Table 5. Continued

| | Women | Men | P Value |
|--|--------------|--------------|---------|
| | n=12 954 | n=16 969 | |
| Insulin | 1354 (10.5%) | 1696 (10.0%) | 0.123 |
| Apparent resistant hypertension | 2452 (18.9%) | 2537 (15.0%) | <0.001 |
| BP control in at least 75% of visits for GFR <60 | 1971 (15.2%) | 2741 (16.2%) | 0.010 |
| BP control in at least 75% of visits for GFR red >30% | 1988 (15.3%) | 2765 (16.3%) | 0.010 |
| BP control in at least 75% of visits for GFR <60 or red >30% | 1982 (15.3%) | 2741 (16.2%) | 0.017 |
| 4-year outcome | | | |
| GFR <60 | 2809 (21.7%) | 2898 (17.1%) | <0.001 |
| GFR reduction >30% than baseline | 1829 (14.1%) | 1722 (10.1%) | <0.001 |
| GFR <60 or reduction >30% than baseline | 3196 (24.7%) | 3226 (19.0%) | <0.001 |

Blood pressure control (BPC) refers to the proportion of visits with systolic and diastolic blood pressure <140/90 mm Hg. For each renal outcome, visits after the event occurrence were excluded. Complete-case analysis including 29 923 patients for which all data were observed. ACE-Is indicates angiotensin-converting enzyme inhibitors; ARBs, angiotensin II receptor antagonists; BMI, body mass index; BP, blood pressure; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; SUA, serum uric acid.

Overall, the mean age was 65 ± 9 years, 57% of patients were men, and the mean duration of diabetes mellitus was 11 ± 8 years. The glycometabolic status of participants was fairly good, being the mean values of HbA1c and low-density lipoprotein cholesterol of $7.3 \pm 1.3\%$ and 110 ± 33 mg/dL, respectively. The average BP was $143 \pm 17/81 \pm 9$ mm Hg, with 73% of patients showing either SBP or DBP values above 140/85 mm Hg at the baseline visit. Seventy-seven percent of patients were receiving antihypertensive treatment (with a mean of 1.6 ± 1.3 drugs per patient), and 65% were taking an angiotensin-converting enzyme inhibitor or an angiotensin II receptor antagonist. eGFR was 86 ± 13 mL/min per 1.73 m², and 19.6% of patients had increased albuminuria (Table 1).

The prevalence of aTRH was 16.6% (n=4989). The baseline characteristics of patients with and without aTRH are also detailed in Table 1. Those with aTRH were more likely to be woman, older, with a longer duration of diabetes mellitus, and to have higher body mass index as compared with those without aTRH. On average, patients with aTRH had higher BP and HbA1c values and lower total, low-density, and high-density lipoprotein cholesterol levels than those without aTRH. Moreover, the former group had lower eGFR, higher serum uric acid levels, and were more likely to have Alb and proliferative retinopathy. As expected, patients with aTRH were more likely to be prescribed antihypertensive treatment (especially with diuretics and renin-angiotensin-aldosterone system-inhibiting agents) and lipid-lowering treatment.

Over the 4-year study follow-up, 19% (n=5707) developed low eGFR, 12% (n=3551) an eGFR reduction $\geq 30\%$ from baseline, and 21% (n=6422) a combination of either 1 of the above renal end points. Patients with aTRH showed a higher cumulative incidence for renal end point and increased risk of

developing both renal outcome (adjusted OR, 1.31; CI, 1.19–1.44; $P < 0.001$; OR, 1.43, CI, 1.28–1.58; $P < 0.001$; and OR, 1.30, CI, 1.19–1.42; $P < 0.001$, respectively), as compared with those without aTRH (Figure 2).

Baseline clinical features of patients grouped on the basis of achieved renal outcome within the study period are reported in Table 2. On average, patients who went on to develop low eGFR, an eGFR reduction $\geq 30\%$ from baseline, or either 1 of the renal end points showed a worse clinical and metabolic profile. They were older, with a longer duration of diabetes mellitus, were more likely to be woman, and to show albuminuria and proliferative retinopathy. Moreover, they had lower GFR values and higher serum uric acid, HbA1c levels, and BP values, with a greater prevalence of aTRH and similar BPC despite a greater prevalence of antihypertensive and insulin treatment.

BP changes during follow-up are shown in Figure 3.

Additional analyses explored the relationship between different hypertension categories on the basis of aTRH and time-updated BPC and renal outcomes. Individuals without BPC were more likely to be woman, were older, and with a longer duration of diabetes mellitus and higher body mass index as compared with those with persistent BPC independently of aTRH status (Table 3). On average, patients without BPC had higher BP values and HbA1c and total, low-density, and high-density lipoprotein cholesterol levels than those with good BPC. Despite similar eGFR values, patients without persistent BPC were more likely to show serum uric acid in the top sex-specific quintile, Alb, and proliferative retinopathy. As expected, patients without BPC were less likely to be prescribed antihypertensive treatment (number of drugs 1.2 ± 1.0 versus 1.6 ± 0.9 for no aTRH; $P < 0.01$; and 3.6 ± 0.8

Table 6. Baseline Characteristics of Study Patients Stratified by Age

| | <55 Years | 56 to 65 Years | >65 Years | P Value |
|--|--------------|----------------|----------------|---------|
| | n=4772 | n=11 052 | n=14 099 | |
| Male sex | 3023 (63.3%) | 6415 (58.0%) | 7531 (53.4%) | <0.001 |
| Age, y | 50±5 | 61±3 | 72±5 | ... |
| Known duration of diabetes mellitus, y | 7±6 | 9±8 | 13±9 | <0.001 |
| BMI, kg/m ² | 31±6 | 30±5 | 29±5 | <0.001 |
| Serum creatinine, μmol/L | 73±15 | 74±15 | 74±14 | <0.001 |
| eGFR, mL/min per 1.73 m ² | 97±13 | 88±12 | 80±11 | <0.001 |
| Albuminuria | 1031 (21.6%) | 2083 (18.8%) | 2760 (19.6%) | <0.001 |
| Microalbuminuria | 889 (18.6%) | 1819 (16.5%) | 2413 (17.1%) | 0.001 |
| Macroalbuminuria | 142 (3.0%) | 264 (2.4%) | 347 (2.5%) | 0.139 |
| Serum uric acid, μmol/L | 313±85 | 318±106 | 314±102 | 0.073 |
| SUA in the top sex-specific quintile | 465 (19.7%) | 1062 (19.4%) | 1351 (19.1%) | 0.809 |
| HbA1c, % | 7.4±1.5 | 7.3±1.3 | 7.2±1.2 | <0.001 |
| HbA1c, mmol/mol | 57±17 | 56±14 | 55±13 | <0.001 |
| HbA1c ≥7% (≥53 mmol/mol) | 2504 (52.8%) | 5859 (53.4%) | 7624 (54.5%) | 0.009 |
| Total cholesterol, mmol/L | 4.92±1.01 | 4.85±0.97 | 4.78±0.94 | <0.001 |
| Triglycerides, mmol/L | 1.78±1.28 | 1.60±1.05 | 1.43±0.78 | <0.001 |
| Triglycerides ≥150 mg/dL (≥1.69 mmol/L) | 1751 (39.0%) | 3548 (34.1%) | 3481 (26.3%) | <0.001 |
| HDL, mmol/L | 1.24±0.34 | 1.30±0.36 | 1.37±0.39 | <0.001 |
| HDL <40M <50F mg/dL (<1.03M <1.29F mmol/L) | 1666 (37.3%) | 3402 (33.1%) | 3589 (27.6%) | <0.001 |
| LDL, mmol/L | 2.92±0.90 | 2.85±0.85 | 2.80±0.83 | <0.001 |
| LDL ≥100 mg/dL (≥2.59 mmol/L) | 2773 (63.2%) | 6155 (60.3%) | 7555 (58.1%) | <0.001 |
| Systolic BP, mm Hg | 139±17 | 142±17 | 145±17 | <0.001 |
| Diastolic BP, mm Hg | 84±9 | 82±9 | 80±9 | <0.001 |
| BP ≥140/85 mm Hg | 3391 (71.1%) | 7949 (71.9%) | 10 371 (73.6%) | <0.001 |
| Nonproliferative retinopathy | 537 (11.3%) | 1424 (12.9%) | 1994 (14.1%) | <0.001 |
| Proliferative retinopathy | 154 (3.2%) | 428 (3.9%) | 587 (4.2%) | 0.034 |
| Lipid-lowering treatment | 722 (25.9%) | 1158 (18.8%) | 755 (10.3%) | <0.001 |
| Treatment with statins | 1973 (41.3%) | 5538 (50.1%) | 7068 (50.1%) | <0.001 |
| Treatment with fibrates | 1714 (35.9%) | 5078 (45.9%) | 6664 (47.3%) | <0.001 |
| No. of antihypertensive drugs | 172 (3.6%) | 272 (2.5%) | 212 (1.5%) | <0.001 |
| Antihypertensive treatment | 3343 (70.1%) | 8379 (75.8%) | 11 384 (80.7%) | <0.001 |
| Treatment with ACE-Is/ARBs | 2878 (60.3%) | 7154 (64.7%) | 9480 (67.2%) | <0.001 |
| Aspirin | 921 (19.3%) | 3299 (29.8%) | 5076 (36.0%) | <0.001 |
| Antidiabetic therapy | | | | |
| Diet | 403 (8.4%) | 862 (7.8%) | 912 (6.5%) | <0.001 |
| Oral antidiabetic drugs | 3219 (67.5%) | 7503 (67.9%) | 9415 (66.8%) | 0.077 |
| Oral antidiabetic drugs and insulin | 678 (14.2%) | 1734 (15.7%) | 2147 (15.2%) | 0.018 |
| Insulin | 472 (9.9%) | 953 (8.6%) | 1625 (11.5%) | <0.001 |

Continued

Table 6. Continued

| | <55 Years | 56 to 65 Years | >65 Years | P Value |
|--|-------------|----------------|--------------|---------|
| | n=4772 | n=11 052 | n=14 099 | |
| Apparent resistant hypertension | 512 (10.7%) | 1761 (15.9%) | 2716 (19.3%) | <0.001 |
| BP control in at least 75% of visits for GFR <60 | 989 (20.7%) | 1788 (16.2%) | 1935 (13.7%) | <0.001 |
| BP control in at least 75% of visits for GFR red >30% | 992 (20.8%) | 1803 (16.3%) | 1958 (13.9%) | <0.001 |
| BP control in at least 75% of visits for GFR <60 or red >30% | 988 (20.7%) | 1796 (16.3%) | 1939 (13.8%) | <0.001 |
| 4-year outcome | | | | |
| GFR <60 mL/min per 1.73 m ² | 274 (5.7%) | 1519 (13.7%) | 3914 (27.8%) | <0.001 |
| GFR reduction >30% than baseline | 362 (7.6%) | 1122 (10.2%) | 2067 (14.7%) | <0.001 |
| GFR <60 or reduction >30% than baseline | 458 (9.6%) | 1836 (16.6%) | 4128 (29.3%) | <0.001 |

Blood pressure control (BPC) refers to the proportion of visits with systolic and diastolic blood pressure <140/90 mm Hg. For each renal outcome, visits after the event occurrence were excluded. Complete-case analysis including 29 923 patients for which all data were observed. ACE-Is indicates angiotensin-converting enzyme inhibitors; ARBs, angiotensin II receptor antagonists; BMI, body mass index; BP, blood pressure; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; SUA, serum uric acid.

versus 4.0 ± 0.7 for aTRH; $P < 0.01$) and lipid-lowering treatment as compared with those with BPC.

When we performed a multivariate analysis, age, body mass index, low eGFR, presence of Alb and of proliferative retinopathy, worse lipid profile (suggestive of the insulin resistance state), and the prescription of insulin and antihypertensive treatment were significantly and independently associated with a greater risk of incident eGFR below 60 mL/min and renal function worsening, as indicated in Table 4. At variance, we found no independent relationship between known duration of diabetes mellitus, baseline HbA1c, and several treatments for cardiovascular protection, such as lipid-lowering treatment, renin-angiotensin-aldosterone system inhibition, or aspirin, and anyone of the renal end points taken into consideration in this generally well-treated study cohort (Table 4).

The relationship between aTRH, BPC, and future development of renal outcome was further investigated on the basis of sex and age. Results (Tables 5 through 10) substantially confirm main study findings and emphasize that renal risk is particularly elevated in older patients, and in those with aTRH reaching very low blood pressure values (ie, those with BPC).

Patients with aTRH showed an increased risk of developing low eGFR and eGFR reduction $\geq 30\%$ from baseline as compared with those without aTRH. Furthermore, no association was found between BPC and renal outcome in non-aTRH, whereas in aTRH, BPC was associated with a 30% ($P = 0.036$) greater risk to develop either 1 of the renal end points (Table 11).

We investigated changes in eGFR along the 4 years of follow-up on the basis of aTRH and BPC. Associations between changes in eGFR and the presence of aTRH and/or BPC were examined using adjusted mean values of eGFR slope. The yearly mean eGFR slope was significantly higher for

the aTRH patients as compared with those with no aTRH independently of BPC. Thus, whereas BPC seems to confer renal protection in patients without aTRH, those with aTRH with and without BPC showed a very similar yearly mean eGFR slope (Figure 4).

The presence of Alb was associated with worse renal prognosis both in patients without aTRH (OR, 2.00; CI, 1.80–2.23; $P < 0.001$) and in those with aTRH (OR, 1.67; CI, 1.38–2.02; $P < 0.001$; Figure 5A). Furthermore, in the absence of optimal BPC, the presence of Alb entailed greater incidence of low eGFR (Alb+/BPC– versus Alb–/BPC–; OR, 1.98; CI, 1.79–2.19; $P < 0.001$), the unfavorable prognostic role of increased Alb at baseline was unchanged when BPC was obtained (Alb+/BPC+ versus Alb–/BPC+; OR, 1.71; CI, 1.34–2.18; $P < 0.001$; Alb+/BPC+ versus ALB/BPC–; OR, 0.90; CI, 0.72–1.14; $P = 0.379$; Figure 5B).

When our data were evaluated on the basis of time-updated mean SBP, it emerged that aTRH patients showed a greater risk of developing low eGFR as compared with non-aTRH patients over the entire range of BP (Figure 6). Furthermore, whereas renal risk decreases along with BP reduction and reaches a nadir between 140 and 120 mm Hg, the achievement of lower SBP values entails a paradoxical increase in the incidence of GFR reduction, thereby confirming the existence of a J-curve relationship between SBP and renal function.

Discussion

Our study shows that, in a real-life clinical setting, in hypertensive T2D patients with normal renal function, the presence of aTRH entails a greater risk of developing CKD or a significant worsening of eGFR over a 4-year follow-up period. Furthermore, the achievement and maintenance of optimal

Table 7. Multivariate Analysis by Sex for the Occurrence of 4-Year Renal Outcome eGFR <60 mL/min per 1.73 m²

| | Women | | Men | |
|--|---------------------|---------|---------------------|---------|
| | Odds Ratio (95% CI) | P Value | Odds Ratio (95% CI) | P Value |
| Age (by 10 y) | 1.51 (1.39–1.63) | <0.001 | 1.48 (1.37–1.59) | <0.001 |
| Duration of diabetes mellitus (by 10 y) | 0.97 (0.90–1.04) | 0.375 | 1.02 (0.95–1.09) | 0.616 |
| BMI (by 5 kg/m ²) | 1.09 (1.04–1.15) | 0.001 | 1.09 (1.02–1.16) | 0.008 |
| eGFR (by 10 mL/min per 1.73 m ²) | 0.42 (0.40–0.44) | <0.001 | 0.38 (0.36–0.40) | <0.001 |
| Microalbuminuria | 1.51 (1.29–1.78) | <0.001 | 1.78 (1.57–2.03) | <0.001 |
| Macroalbuminuria | 4.00 (2.76–5.80) | <0.001 | 4.55 (3.54–5.86) | <0.001 |
| HbA1c ≥7% (≥53 mmol/mol) | 1.08 (0.96–1.22) | 0.218 | 1.05 (0.94–1.17) | 0.419 |
| Triglycerides ≥150 mg/dL (≥1.69 mmol/L) | 1.09 (0.96–1.23) | 0.192 | 1.26 (1.12–1.41) | <0.001 |
| HDL <40M <50F mg/dL (<1.03M <1.29F mmol/L) | 1.06 (0.94–1.19) | 0.350 | 1.13 (1.00–1.28) | 0.043 |
| LDL ≥100 mg/dL (≥2.59 mmol/L) | 0.80 (0.71–0.89) | <0.001 | 0.87 (0.78–0.97) | 0.009 |
| Nonproliferative retinopathy | 1.13 (0.96–1.33) | 0.131 | 1.07 (0.93–1.25) | 0.350 |
| Proliferative retinopathy | 1.33 (1.02–1.73) | 0.037 | 1.25 (0.98–1.61) | 0.074 |
| Lipid-lowering treatment | 0.92 (0.82–1.03) | 0.132 | 0.94 (0.84–1.06) | 0.315 |
| Antihypertensive treatment | 1.49 (1.21–1.83) | <0.001 | 1.36 (1.11–1.66) | 0.003 |
| Treatment with ACE-Is/ARBs | 0.93 (0.79–1.09) | 0.374 | 0.95 (0.81–1.12) | 0.565 |
| Aspirin | 1.19 (1.05–1.35) | 0.007 | 1.00 (0.88–1.12) | 0.946 |
| Antidiabetic therapy | | | | |
| Diet | 0.76 (0.59–0.97) | 0.029 | 0.69 (0.54–0.87) | 0.002 |
| Oral antidiabetic drugs | 1.00 | | 1.00 | |
| Oral antidiabetic drugs and insulin | 1.26 (1.08–1.47) | 0.003 | 1.25 (1.07–1.46) | 0.006 |
| Insulin | 1.16 (0.97–1.40) | 0.109 | 1.34 (1.13–1.59) | 0.001 |
| Group ATRH and BPC | | | | |
| No ATRH and BPC | 1.00 | | 1.00 | |
| No ATRH and No BPC | 1.01 (0.85–1.19) | 0.952 | 1.09 (0.93–1.28) | 0.294 |
| ATRH and BPC | 1.56 (1.07–2.28) | 0.022 | 2.01 (1.39–2.91) | <0.001 |
| ATRH and No BPC | 1.18 (0.96–1.44) | 0.110 | 1.47 (1.21–1.78) | <0.001 |

Blood pressure control (BPC) refers to the proportion of visits with systolic and diastolic blood pressure <140/90 mm Hg. For each renal outcome, visits after the event occurrence were excluded. Odds ratio for single renal outcome with 95% confidence interval (CI). Complete-case analysis including 10 614 women and 14 026 men for which all data were observed. ACE-Is indicates angiotensin-converting enzyme inhibitors; ARBs, angiotensin II receptor antagonists; ATRH, apparent treatment resistant hypertension; BMI, body mass index; BP, blood pressure; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol.

BPC does not seem to be associated with renal protection over time.

Although several studies conducted on high-risk hypertensive patients have previously shown that aTRH entails a greater cardiovascular and mortality risk,^{6,10,13} to date only 2 studies have investigated long-term renal outcome, namely the development of ESRD.^{12,22}

In a secondary analysis of the ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial) study, aTRH was associated with a 2-fold greater risk of ESRD, especially in the presence of diabetes mellitus even after adjustment for confounders such as baseline GFR values.²² Similarly, Sim et al¹² in a retrospective analysis of the large

Kaiser Permanente cohort of general hypertensive patients from southern California, reported a 30% greater risk of ESRD over a 5-year follow-up period in the subgroup of patients with RH.

Both these studies, however, included a relevant proportion of patients with CKD at baseline. In fact, in the Kaiser Permanente cohort, up to 30% of patients had CKD at baseline and eGFR was, on average, 60 mL/min in the aTRH subgroup. Furthermore, results from the ALLHAT study have been questioned because of the specific intervention protocol and definition of RH.

In a further, retrospective, cohort study conducted on subjects with incident hypertension in a US Registry, those

Table 8. Multivariate Analysis by Sex for the Occurrence of 4-Year Renal Outcome eGFR Reduction $\geq 30\%$

| | Women | | Men | |
|---|---------------------|---------|---------------------|---------|
| | Odds Ratio (95% CI) | P Value | Odds Ratio (95% CI) | P Value |
| Age (by 10 y) | 1.53 (1.41–1.66) | <0.001 | 1.58 (1.45–1.72) | <0.001 |
| Duration of diabetes mellitus (by 10 y) | 0.99 (0.91–1.07) | 0.741 | 0.95 (0.88–1.02) | 0.173 |
| BMI (by 5 kg/m ²) | 1.07 (1.01–1.13) | 0.017 | 1.10 (1.03–1.18) | 0.006 |
| eGFR (by 10 mL/min per 1.73 m ²) | 1.10 (1.04–1.16) | <0.001 | 1.06 (1.00–1.12) | 0.036 |
| Microalbuminuria | 1.53 (1.30–1.81) | <0.001 | 1.92 (1.68–2.21) | <0.001 |
| Macroalbuminuria | 3.99 (2.77–5.73) | <0.001 | 4.21 (3.29–5.39) | <0.001 |
| HbA1c $\geq 7\%$ (≥ 53 mmol/mol) | 1.01 (0.88–1.15) | 0.926 | 1.08 (0.95–1.23) | 0.213 |
| Triglycerides ≥ 150 mg/dL (≥ 1.69 mmol/L) | 1.15 (1.01–1.32) | 0.034 | 1.23 (1.08–1.39) | 0.002 |
| HDL < 40 M < 50 F mg/dL (< 1.03 M < 1.29 F mmol/L) | 1.09 (0.96–1.23) | 0.188 | 1.17 (1.02–1.34) | 0.023 |
| LDL ≥ 100 mg/dL (≥ 2.59 mmol/L) | 0.77 (0.68–0.87) | <0.001 | 0.82 (0.73–0.92) | 0.001 |
| Nonproliferative retinopathy | 1.11 (0.93–1.32) | 0.236 | 1.12 (0.95–1.32) | 0.185 |
| Proliferative retinopathy | 1.24 (0.94–1.64) | 0.130 | 1.19 (0.91–1.56) | 0.212 |
| Lipid-lowering treatment | 0.88 (0.78–1.00) | 0.054 | 0.97 (0.85–1.10) | 0.589 |
| Antihypertensive treatment | 1.41 (1.13–1.76) | 0.002 | 1.27 (1.01–1.59) | 0.040 |
| Treatment with ACE-Is/ARBs | 0.91 (0.76–1.08) | 0.258 | 0.94 (0.78–1.13) | 0.511 |
| Aspirin | 1.07 (0.93–1.23) | 0.324 | 0.97 (0.85–1.11) | 0.682 |
| Antidiabetic therapy | | | | |
| Diet | 0.61 (0.44–0.84) | 0.002 | 0.74 (0.56–0.97) | 0.032 |
| Oral antidiabetic drugs | 1.00 | | 1.00 | |
| Oral antidiabetic drugs and insulin | 1.23 (1.04–1.44) | 0.014 | 1.29 (1.09–1.53) | 0.003 |
| Insulin | 1.31 (1.08–1.59) | 0.006 | 1.11 (0.91–1.35) | 0.310 |
| Group ATRH and BPC | | | | |
| No ATRH and BPC | 1.00 | | 1.00 | |
| No ATRH and No BPC | 0.86 (0.72–1.04) | 0.113 | 1.15 (0.95–1.39) | 0.149 |
| ATRH and BPC | 1.66 (1.14–2.43) | 0.008 | 2.12 (1.44–3.13) | <0.001 |
| ATRH and No BPC | 1.18 (0.96–1.46) | 0.123 | 1.61 (1.29–2.00) | <0.001 |

Blood pressure control (BPC) refers to the proportion of visits with systolic and diastolic blood pressure $< 140/90$ mm Hg. For each renal outcome, visits after the event occurrence were excluded. Odds ratio for single renal outcome with 95% confidence interval (CI). Complete-case analysis including 10 614 women and 14 026 men for which all data were observed. ACE-Is indicates angiotensin-converting enzyme inhibitors; ARBs, angiotensin II receptor antagonists; ATRH, apparent treatment resistant hypertension; BMI, body mass index; BP, blood pressure; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol.

who went on to develop RH, after multivariate adjustment, were at higher risk for cardiovascular outcomes and for the development of stage 3 CKD as compared with those with non-RH over a 4-year follow-up.¹¹

Our study is the first, to our knowledge, to investigate the impact of aTRH on the early stages of kidney damage in a high-renal-risk population of patients such as those with T2D and hypertension. The choice of intermediate, but well-established, end points such as the development of stage 3 CKD and a 30% reduction in eGFR, which have been shown to predict and precede progression to ESRD,^{23,24} allowed us to accurately investigate the onset of renal function impairment over the 4 years of study follow-up.

The prevalence and clinical characteristics of patients with aTRH we observed in the present study are comparable to what has been previously reported in similar high-risk groups.²⁵ Over the follow-up period, in our generally well-treated cohort, 19% of patients developed stage 3 CKD (ie, a eGFR value below 60 mL/min) and 12% showed a significant eGFR reduction (ie, $\geq 30\%$) from baseline. In patients with aTRH, the presence of a worse cardiovascular risk profile, namely older age, body mass index, a reduction in eGFR, a worse lipid profile, or the presence of Alb or proliferative retinopathy were independent predictors of worse renal outcome. Furthermore, the presence of aTRH entailed a faster decline in renal function over time, despite the

Table 9. Multivariate Analysis by Groups of Age for the Occurrence of 4-Year Renal Outcome eGFR <60 mL/min per 1.73 m²

| | Age ≤55 Years | | Age 56 to 65 Years | | Age >65 Years | |
|--|---------------------|---------|---------------------|---------|---------------------|---------|
| | Odds Ratio (95% CI) | P Value | Odds Ratio (95% CI) | P Value | Odds Ratio (95% CI) | P Value |
| Male sex | 0.85 (0.62–1.16) | 0.296 | 0.79 (0.68–0.90) | 0.001 | 0.80 (0.73–0.89) | <0.001 |
| Age (by 10 y) | 1.01 (0.72–1.41) | 0.954 | 1.60 (1.25–2.05) | <0.001 | 1.52 (1.37–1.69) | <0.001 |
| Duration of diabetes mellitus (by 10 y) | 0.94 (0.74–1.21) | 0.635 | 0.92 (0.84–1.02) | 0.113 | 1.03 (0.97–1.09) | 0.400 |
| BMI (by 5 kg/m ²) | 1.11 (0.97–1.26) | 0.124 | 1.03 (0.96–1.10) | 0.364 | 1.13 (1.07–1.19) | <0.001 |
| eGFR (by 10 mL/min per 1.73 m ²) | 0.53 (0.47–0.59) | <0.001 | 0.43 (0.4–0.45) | <0.001 | 0.36 (0.34–0.38) | <0.001 |
| Microalbuminuria | 1.21 (0.83–1.75) | 0.324 | 1.70 (1.42–2.03) | <0.001 | 1.72 (1.51–1.96) | <0.001 |
| Macroalbuminuria | 4.72 (2.68–8.30) | <0.001 | 5.50 (3.94–7.69) | <0.001 | 3.47 (2.60–4.65) | <0.001 |
| HbA1c ≥7% (≥53 mmol/mol) | 1.05 (0.75–1.45) | 0.789 | 1.03 (0.88–1.19) | 0.736 | 1.08 (0.97–1.21) | 0.137 |
| Triglycerides ≥150 mg/dL (≥1.69 mmol/L) | 1.24 (0.91–1.70) | 0.176 | 1.24 (1.07–1.43) | 0.004 | 1.15 (1.03–1.28) | 0.014 |
| HDL <40M <50F mg/dL (<1.03M <1.29F mmol/L) | 1.07 (0.78–1.46) | 0.692 | 1.02 (0.88–1.19) | 0.776 | 1.12 (1.00–1.25) | 0.048 |
| LDL ≥100 mg/dL (≥2.59 mmol/L) | 0.74 (0.54–1.00) | 0.048 | 0.78 (0.68–0.89) | <0.001 | 0.86 (0.78–0.95) | 0.003 |
| Nonproliferative retinopathy | 1.05 (0.67–1.66) | 0.827 | 1.10 (0.90–1.35) | 0.337 | 1.13 (0.98–1.29) | 0.084 |
| Proliferative retinopathy | 1.46 (0.75–2.85) | 0.270 | 1.79 (1.32–2.44) | <0.001 | 1.02 (0.81–1.30) | 0.850 |
| Lipid-lowering treatment | 0.84 (0.62–1.16) | 0.295 | 0.99 (0.85–1.14) | 0.840 | 0.92 (0.83–1.02) | 0.096 |
| Antihypertensive treatment | 2.01 (1.19–3.39) | 0.009 | 1.50 (1.14–1.96) | 0.003 | 1.32 (1.10–1.59) | 0.003 |
| Treatment with ACE-Is/ARBs | 0.60 (0.39–0.93) | 0.022 | 0.99 (0.79–1.23) | 0.903 | 0.98 (0.85–1.12) | 0.740 |
| Aspirin | 0.97 (0.66–1.42) | 0.871 | 0.89 (0.76–1.05) | 0.168 | 1.16 (1.04–1.29) | 0.008 |
| Antidiabetic therapy | | | | | | |
| Diet | 0.79 (0.42–1.49) | 0.466 | 0.65 (0.47–0.89) | 0.007 | 0.73 (0.59–0.91) | 0.005 |
| Oral antidiabetic drugs | 1.00 | | 1.00 | | 1.00 | |
| Oral antidiabetic drugs and insulin | 1.59 (1.05–2.43) | 0.030 | 1.41 (1.16–1.71) | 0.001 | 1.15 (1.00–1.33) | 0.051 |
| Insulin | 1.71 (1.06–2.74) | 0.027 | 1.86 (1.48–2.34) | <0.001 | 1.03 (0.88–1.21) | 0.718 |
| Group ATRH and BPC | | | | | | |
| No ATRH and BPC | 1.00 | | 1.00 | | 1.00 | |
| No ATRH and No BPC | 0.82 (0.56–1.20) | 0.304 | 1.09 (0.89–1.33) | 0.407 | 1.05 (0.90–1.23) | 0.519 |
| ATRH and BPC | 1.83 (0.74–4.49) | 0.190 | 1.51 (0.96–2.39) | 0.077 | 1.96 (1.38–2.78) | <0.001 |
| ATRH and No BPC | 1.60 (0.98–2.64) | 0.063 | 1.55 (1.22–1.98) | <0.001 | 1.20 (1.00–1.43) | 0.050 |

Blood pressure control (BPC) refers to the proportion of visits with systolic and diastolic blood pressure <140/90 mm Hg. For each renal outcome, visits after the event occurrence were excluded. Odds ratio for single renal outcome with 95% confidence interval (CI). Complete-case analysis including 3942 patients aged ≤55 years, 9133 aged 56 to 65 years, and 11 565 aged >65 years for which all data were observed. ACE-Is indicates angiotensin-converting enzyme inhibitors; ARBs, angiotensin II receptor antagonists; ATRH, apparent treatment resistant hypertension; BMI, body mass index; BP, blood pressure; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol.

achievement of recommended BP values (Figure 4). As expected, the presence of Alb was associated with a greater risk of renal function loss in both aTRH and non-aTRH patients (Figure 5A).

It has been proposed that the RH population has an adverse physiology and is therefore at greater risk for morbidity and mortality. Thus, pathogenetic mechanisms as well as clinical characteristics underlying the development of cardiovascular and renal events, including BP changes and

therapeutic strategies, deserve better understanding given that this may lead to optimization of therapeutic strategies for BP reduction and comorbidities.⁷

We sought to further categorize aTRH resistant hypertension on the basis of BPC. By looking at time-updated BPC, we were able to assess the impact of BP reduction and of the persistence of good BP values over time before each renal end point was reached, if any (Table 11). Moreover, we found that the cumulative incidence of stage 3 CKD in patients with low

Table 10. Multivariate Analysis by Groups of Age for the Occurrence of 4-Year Renal Outcome eGFR Reduction $\geq 30\%$

| | Age ≤ 55 Years | | Age 56 to 65 Years | | Age >65 Years | |
|--|---------------------|---------|---------------------|---------|---------------------|---------|
| | Odds Ratio (95% CI) | P Value | Odds Ratio (95% CI) | P Value | Odds Ratio (95% CI) | P Value |
| Male sex | 0.75 (0.58–0.99) | 0.039 | 0.69 (0.59–0.80) | <0.001 | 0.75 (0.67–0.84) | <0.001 |
| Age (by 10 y) | 1.42 (1.07–1.90) | 0.016 | 1.37 (1.05–1.78) | 0.019 | 1.59 (1.41–1.81) | <0.001 |
| Duration of diabetes mellitus (by 10 y) | 0.95 (0.76–1.19) | 0.657 | 0.92 (0.83–1.02) | 0.124 | 0.99 (0.92–1.05) | 0.659 |
| BMI (by 5 kg/m ²) | 1.02 (0.91–1.14) | 0.736 | 1.04 (0.97–1.12) | 0.230 | 1.12 (1.06–1.19) | <0.001 |
| eGFR (by 10 mL/min per 1.73 m ²) | 1.26 (1.13–1.40) | <0.001 | 1.09 (1.02–1.16) | 0.007 | 1.03 (0.98–1.09) | 0.216 |
| Microalbuminuria | 1.51 (1.11–2.06) | 0.009 | 1.72 (1.43–2.07) | <0.001 | 1.80 (1.56–2.07) | <0.001 |
| Macroalbuminuria | 4.24 (2.48–7.26) | <0.001 | 4.80 (3.45–6.68) | <0.001 | 3.48 (2.59–4.67) | <0.001 |
| HbA1c $\geq 7\%$ (≥ 53 mmol/mol) | 1.11 (0.83–1.47) | 0.490 | 1.10 (0.94–1.29) | 0.250 | 1.01 (0.90–1.14) | 0.833 |
| Triglycerides ≥ 150 mg/dL (≥ 1.69 mmol/L) | 1.28 (0.97–1.68) | 0.075 | 1.26 (1.08–1.47) | 0.003 | 1.13 (1.00–1.28) | 0.058 |
| HDL $<40M$ $<50F$ mg/dL ($<1.03M$ $<1.29F$ mmol/L) | 1.21 (0.92–1.58) | 0.168 | 1.06 (0.91–1.25) | 0.442 | 1.11 (0.98–1.26) | 0.093 |
| LDL ≥ 100 mg/dL (≥ 2.59 mmol/L) | 1.03 (0.79–1.34) | 0.818 | 0.72 (0.62–0.84) | <0.001 | 0.79 (0.71–0.88) | <0.001 |
| Nonproliferative retinopathy | 1.21 (0.82–1.78) | 0.336 | 1.11 (0.90–1.37) | 0.340 | 1.11 (0.95–1.30) | 0.176 |
| Proliferative retinopathy | 1.91 (1.08–3.37) | 0.026 | 1.47 (1.07–2.03) | 0.019 | 0.97 (0.74–1.27) | 0.829 |
| Lipid-lowering treatment | 0.98 (0.74–1.29) | 0.881 | 1.00 (0.86–1.17) | 0.955 | 0.88 (0.78–0.98) | 0.026 |
| Antihypertensive treatment | 1.57 (0.99–2.48) | 0.056 | 1.29 (0.97–1.71) | 0.079 | 1.30 (1.05–1.60) | 0.015 |
| Treatment with ACE-Is/ARBs | 0.68 (0.46–1.02) | 0.062 | 0.99 (0.78–1.26) | 0.948 | 0.96 (0.81–1.12) | 0.584 |
| Aspirin | 0.95 (0.68–1.33) | 0.764 | 0.98 (0.83–1.16) | 0.812 | 1.05 (0.93–1.19) | 0.448 |
| Antidiabetic therapy | | | | | | |
| Diet | 0.79 (0.44–1.41) | 0.421 | 0.79 (0.56–1.12) | 0.188 | 0.58 (0.43–0.78) | <0.001 |
| Oral antidiabetic drugs | 1.00 | | 1.00 | | 1.00 | |
| Oral antidiabetic drugs and insulin | 1.48 (1.04–2.12) | 0.030 | 1.23 (1.00–1.51) | 0.048 | 1.22 (1.05–1.43) | 0.011 |
| Insulin | 1.16 (0.73–1.82) | 0.532 | 1.89 (1.49–2.39) | <0.001 | 0.94 (0.78–1.13) | 0.497 |
| Group ATRH and BPC | | | | | | |
| No ATRH and BPC | 1.00 | | 1.00 | | 1.00 | |
| No ATRH and No BPC | 0.86 (0.61–1.22) | 0.408 | 1.03 (0.83–1.29) | 0.794 | 1.00 (0.83–1.20) | 0.995 |
| ATRH and BPC | 1.89 (0.79–4.55) | 0.155 | 1.29 (0.78–2.16) | 0.322 | 2.31 (1.63–3.29) | <0.001 |
| ATRH and No BPC | 1.82 (1.17–2.85) | 0.008 | 1.54 (1.19–2.00) | 0.001 | 1.24 (1.01–1.52) | 0.044 |

Blood pressure control (BPC) refers to the proportion of visits with systolic and diastolic blood pressure $<140/90$ mm Hg. For each renal outcome, visits after the event occurrence were excluded. Odds ratio for single renal outcome with 95% confidence interval (CI). Complete-case analysis including 3942 patients aged ≤ 55 years, 9133 aged 56 to 65 years, and 11 565 aged >65 years for which all data were observed. ACE-Is indicates angiotensin-converting enzyme inhibitors; ARBs, angiotensin II receptor antagonists; ATRH, apparent treatment resistant hypertension; BMI, body mass index; BP, blood pressure; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol.

mean time-updated SBP (ie, <130 mm Hg) was greater than that observed in patients who achieved less-tight BP reduction independently of aTRH (Figure 6).

The subgroup of patients with tightly controlled hypertension not only had lower BP, but were also more likely to have a statin prescription and to have lower values of low-density lipoprotein cholesterol, a finding that makes low adherence to prescribed medications an unlikely explanation for worse renal outcomes.

Our results are in keeping with those reported by Egan et al,¹⁵ who also found that tight control, as compared with usual, is associated with worse cardiovascular outcomes both in patients with and without aTRH. Along the same line, more recently, in a pooled retrospective analysis of the Ontarget/Transcend database,²⁶ lowering BP to less than 130 mm Hg SBP was found to be associated with increased rates for cardiovascular events and mortality in patients at high cardiovascular risk.

Table 11. Comparative Risk for Outcomes Among Different Hypertension Categories

| eGFR <60 mL/min per 1.73 m ² | | | | |
|---|----------------------------------|----------------------------------|----------------------------------|----------------------------------|
| No ATRH and BPC | Reference | 0.95 (0.85–1.07) <i>P</i> =0.393 | 0.56 (0.43–0.73) <i>P</i> <0.001 | 0.76 (0.66–0.87) <i>P</i> <0.001 |
| No ATRH and No BPC | 1.05 (0.94–1.18) <i>P</i> =0.393 | Reference | 0.59 (0.46–0.76) <i>P</i> <0.001 | 0.80 (0.72–0.88) <i>P</i> <0.001 |
| ATRH and BPC | 1.78 (1.37–2.32) <i>P</i> <0.001 | 1.69 (1.32–2.18) <i>P</i> <0.001 | Reference | 1.35 (1.04–1.75) <i>P</i> =0.024 |
| ATRH and No BPC | 1.32 (1.15–1.52) <i>P</i> <0.001 | 1.26 (1.13–1.39) <i>P</i> <0.001 | 0.74 (0.57–0.96) <i>P</i> =0.024 | Reference |
| eGFR reduction ≥30% | | | | |
| No ATRH and BPC | Reference | 1.01 (0.88–1.14) <i>P</i> =0.940 | 0.54 (0.41–0.70) <i>P</i> <0.001 | 0.73 (0.63–0.85) <i>P</i> <0.001 |
| No ATRH and No BPC | 1.00 (0.87–1.13) <i>P</i> =0.940 | Reference | 0.53 (0.41–0.69) <i>P</i> <0.001 | 0.73 (0.65–0.81) <i>P</i> <0.001 |
| ATRH and BPC | 1.87 (1.43–2.45) <i>P</i> <0.001 | 1.88 (1.46–2.42) <i>P</i> <0.001 | Reference | 1.36 (1.05–1.77) <i>P</i> =0.020 |
| ATRH and No BPC | 1.37 (1.18–1.59) <i>P</i> <0.001 | 1.38 (1.23–1.54) <i>P</i> <0.001 | 0.73 (0.56–0.95) <i>P</i> =0.020 | Reference |
| eGFR <60 or reduction ≥30% | | | | |
| No ATRH and BPC | Reference | 0.96 (0.87–1.07) <i>P</i> =0.486 | 0.59 (0.47–0.76) <i>P</i> <0.001 | 0.77 (0.68–0.87) <i>P</i> <0.001 |
| No ATRH and No BPC | 1.04 (0.93–1.16) <i>P</i> =0.486 | Reference | 0.62 (0.49–0.78) <i>P</i> <0.001 | 0.80 (0.73–0.88) <i>P</i> <0.001 |
| ATRH and BPC | 1.68 (1.32–2.15) <i>P</i> <0.001 | 1.62 (1.28–2.05) <i>P</i> <0.001 | Reference | 1.29 (1.02–1.65) <i>P</i> =0.036 |
| ATRH and No BPC | 1.30 (1.14–1.48) <i>P</i> <0.001 | 1.25 (1.14–1.38) <i>P</i> <0.001 | 0.77 (0.61–0.98) <i>P</i> =0.036 | Reference |

Multivariate odds ratios with 95% confidence interval for each renal outcome according to models listed in Table 4. ATRH indicates apparent treatment resistant hypertension; BPC, blood pressure control refers to the proportion of visits with systolic and diastolic blood pressure <140/90 mm Hg; eGFR, estimated glomerular filtration rate.

The relationship between BPC and renal outcome in aTRH has been, so far, investigated only in the analysis by Sim et al, who observed a 25% greater risk for ESRD in individuals with uncontrolled RH as compared with controlled

RH,¹² a finding that seems to differ from those reported here.

In the Kaiser Permanente study, however, only baseline BP values were analyzed to assess the degree of BP control,

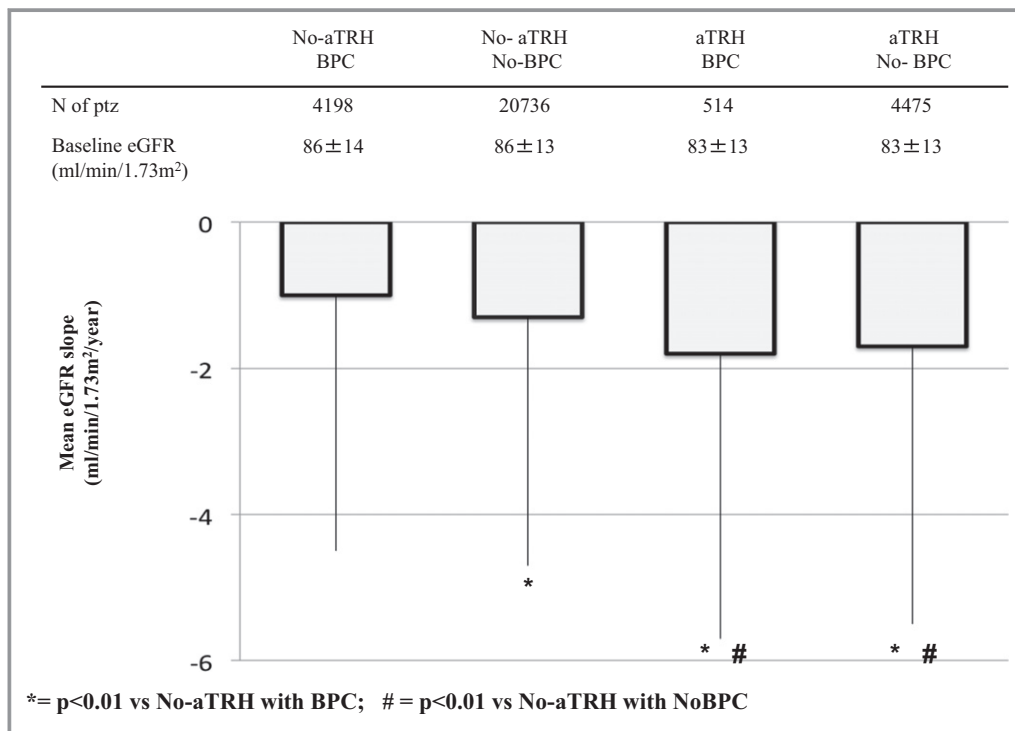


Figure 4. Mean yearly eGFR slope on the basis of the presence of aTRH and BPC. ATRH indicates apparent treatment resistant hypertension; eGFR, estimated glomerular filtration rate; BP, blood pressure control (BPC) refers to the proportion of visits with systolic and diastolic blood pressure <140/90 mm Hg. **P*<0.01 vs No-aTRH with BPC; #*P*<0.01 vs No-aTRH with NoBPC.

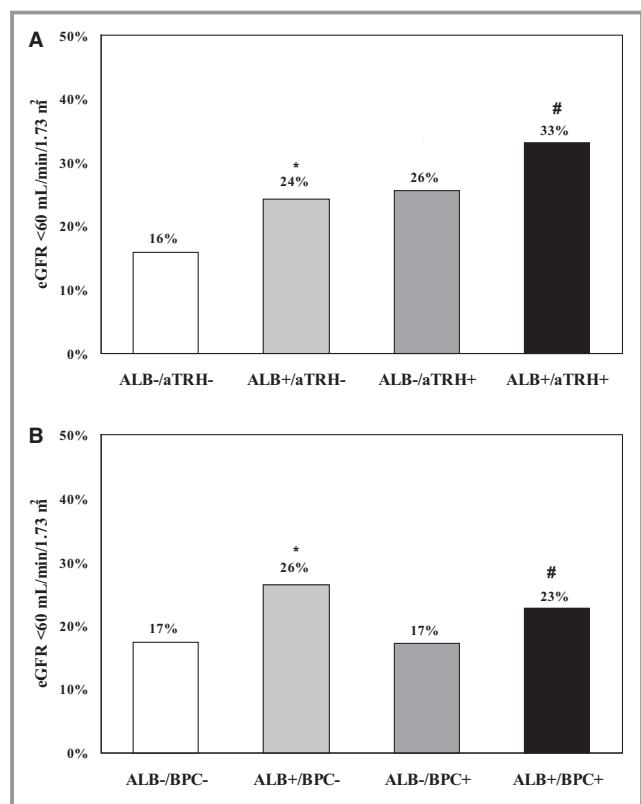


Figure 5. A, Cumulative incidence of renal end point (eGFR <60) on the basis of albuminuria status and aTRH. ALB indicates albuminuria; aTRH, apparent treatment resistant hypertension; CI, confidence interval; eGFR, estimated glomerular filtration rate. *Adjusted odds ratios for Alb+/aTRH- vs Alb-/aTRH- 2.00 (CI 1.80–2.23), $P < 0.001$ and #for Alb+/aTRH+ vs Alb-/aTRH+ 1.67 (CI 1.38–2.02), $P < 0.001$. B, Cumulative incidence of renal end point (eGFR <60) on the basis of albuminuria status and time-updated BPC. ALB indicates albuminuria; BPC, blood pressure control; eGFR, estimated glomerular filtration rate. *Adjusted odds ratios for Alb+/BPC- vs Alb-/BPC- 1.98 (CI 1.79–2.19), $P < 0.001$ and #for Alb+/BPC+ vs Alb-/BPC+ 1.71 (CI 1.34–2.18), $P < 0.001$.

therefore assuming that once individuals are categorized at baseline, they remain so thorough the observation period; in contrast, our use of a dynamic indicator of BPC allowed us a more-powerful representation of a real-world clinical scenario. In fact, a significant proportion of patients (up to 20% in our database over the study period) could have been misclassified if analyzed only at baseline, given that both treatment and degree of BPC could change over time.

In the presence of Alb, a well-known independent predictor of unfavorable cardiovascular and renal prognosis in patients with T2D and hypertension, a more-ambitious target BP than the traditional 140/90 mm Hg has been proposed by some guidelines to convey greater renal protection.^{1,6} In our study, patients with Alb and BPC (ie, <140/90) showed similar renal prognosis as compared with

those with less-tight BPC (Figure 5B). We performed further analyses to assess whether, in the presence of micro- or macro-Alb, achievement of very low BP values (ie, <130/80 mm Hg) were associated with better renal outcome. We found that patients with Alb with BP values below 130/80 in at least 75% of study visits showed a 31% incidence of stage 3 CKD as compared with 26% in those with less-tight BP, again suggesting the presence of a J-curve phenomenon, which may limit renal protection.

Thus, the presence of aTRH entails a greater renal risk in hypertensive patients with T2D as compared with non-aTRH patients. The achievement and maintenance of recommended BP values is associated with a worse renal prognosis even more so when time-updated SBP is lowered below 120 mm Hg, a condition that is associated with increased renal function loss even in non-aTRH patients.

Although the observational nature of our study does not allow us to infer causality from reported associations, the worse renal prognosis observed in patients with aTRH and BPC supports the existence of a J-curve phenomenon linking BP reduction and renal function.

Furthermore, we cannot rule out an unfavorable renal effect of renin-angiotensin-aldosterone system I in frail, high-risk patients as those with aTRH, where BP reduction was obtained using a greater load of antihypertensive drugs (Table 3), in particular renin-angiotensin-aldosterone system I. In fact, it has recently been proposed that even mild GFR reduction after initiation of treatment with angiotensin-converting enzyme inhibitors or angiotensin II receptor antagonists might entail a worse renal prognosis in the long run,²⁷ at least in a specific subgroup of patients, an issue that is currently being investigated by specifically designed ongoing studies.²⁸

Our study has some limitations as well as several strengths that should be mentioned. Among the first ones, we must acknowledge that laboratory parameters, including serum creatinine, were not measured in a single, centralized laboratory and this may have led to some variability in GFR estimation. We did not gather information on specific dosage of antihypertensive medications prescribed to each patient to confirm diagnosis of aTRH. However, BP control significantly improved, on average, over the 4-year study period, suggesting an attempt toward a therapeutic strategy of up-titration to maximum tolerated dose. Furthermore, our data may not be applicable to the population with T2D and hypertension at large because the vast majority of participants were of white origin, and ethnicity has previously been shown to bear some impact on the risk of developing renal complications.²⁹ Finally, we did not have information on extrarenal complications, such as myocardial infarction and stroke, which may affect BP or renal function changes over time. On the other hand, the large size and homogeneous clinical characteristics

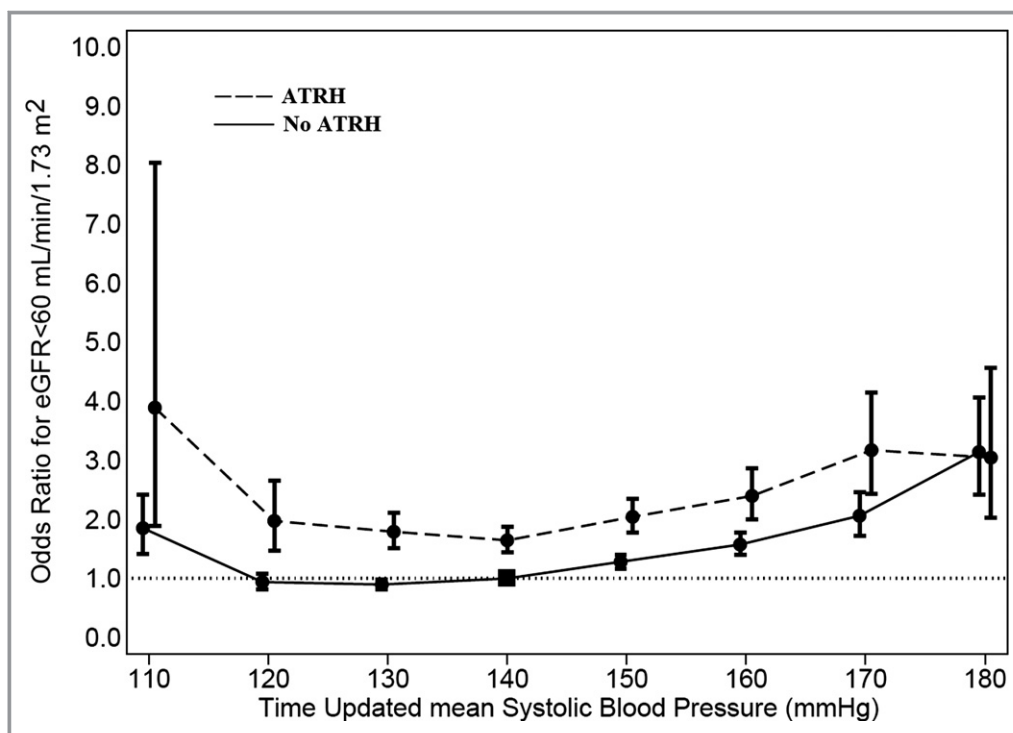


Figure 6. Odds ratios of reaching renal end point (eGFR < 60 mL/min per 1.73 m²) on the basis of time-updated mean SBP in patients with and without aTRH, taking 140 mm Hg in non aTRH as reference category. Patients were grouped into 10 mm Hg subsets (ie, those between 136 and 144 in the group labeled 140 and so on). The subset of patients with No-aTRH and 140 mm Hg SBP was taken as the reference group. ATRH indicates apparent treatment resistant hypertension; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure. Odds ratio for single renal outcome with 95% confidence interval.

of the study cohort, as well as the representative geographical distribution of the recruiting centers and the relatively long follow-up period, do contribute to make our results a reliable representation of real-life clinical condition. Moreover, at variance with several previous studies on the impact of RH on cardiovascular and renal outcomes,^{10–15} we used a very accurate definition of RH, which included the use of diuretics. Another strength of our work is the use of time-updated BP values as an indicator of achievement and maintenance of BPC over time.

Further studies are clearly needed to investigate the pathophysiological mechanism underlying the effect of BP reduction per se as well as different pharmacological strategies on renal outcome in high-risk hypertensive patients such as those with diabetes mellitus.

In conclusion, our large, real-life cohort study shows that in hypertensive patients with T2D, the presence of aTRH entails a significantly greater risk of developing CKD and/or a clinically relevant reduction in eGFR over a 4-year follow-up. Interestingly, the achievement and maintenance of optimal BP values are associated with worse renal outcome. The relationship between achieved BP and renal function seems

to be J-shaped, at least at very low levels, with optimal SBP values between 120 and 140 mm Hg.

Sources of Funding

This research was supported by the Associazione Medici Diabetologi.

Disclosures

None.

References

1. Sarafidis PA, Bakris GL. Resistant hypertension: an overview of evaluation and treatment. *J Am Coll Cardiol.* 2008;52:1749–1757.
2. 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 Committee. 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.
3. Braam B, Taler SJ, Rahman M, Fillaus JA, Greco BA, Forman JP, Reisin E, Cohen DL, Saklayen MG, Hedayati SS. Recognition and management of resistant hypertension. *Clin J Am Soc Nephrol.* 2017;12:524–535.

4. De Nicola L, Gabbai FB, Agarwal R, Chiodini P, Borrelli S, Bellizzi V, Nappi F, Conte G, Minutolo R. Prevalence and prognostic role of resistant hypertension in chronic kidney disease patients. *J Am Coll Cardiol*. 2013;61:2461–2467.
5. Wolley MJ, Stowasser M. Resistant hypertension and chronic kidney disease: a dangerous liaison. *Curr Hypertens Rep*. 2016;18:36.
6. Rossignol P, Massy ZA, Azizi M, Bakris G, Ritz E, Covic A, Goldsmith D, Heine GH, Jager KJ, Kanbay M, Mallamaci F, Ortiz A, Vanholder R, Wiecek A, Zoccali C, London GM, Stengel B, Fouque D; ERA-EDTA EURECA-m working group; Red de Investigación Renal (REDINREN) network; Cardiovascular and Renal Clinical Trialists (F-CRIN INI-CRCT) network. The double challenge of resistant hypertension and chronic kidney disease. *Lancet*. 2015;386:1588–1598.
7. Padwal RS, Rabkin S, Khan N. Assessment and management of resistant hypertension. *CMAJ*. 2014;186:E689–E697.
8. Irvin MR, Shimbo D, Mann DM, Reynolds K, Krousel-Wood M, Limdi NA, Lackland DT, Calhoun DA, Oparil S, Muntner P. Prevalence and correlates of low medication adherence in apparent treatment-resistant hypertension. *J Clin Hypertens (Greenwich)*. 2012;14:694–700.
9. Bangalore S, Fayyad R, Laskey R, Demicco DA, Deedwania P, Kostis JB, Messerli FH; Treating to New Targets Steering Committee and Investigators. Prevalence, predictors, and outcomes in treatment-resistant hypertension in patients with coronary disease. *Am J Med*. 2014;127:71–81.
10. Irvin MR, Booth JN III, Shimbo D, Lackland DT, Oparil S, Howard G, Safford MM, Muntner P, Calhoun DA. Apparent treatment-resistant hypertension and risk for stroke, coronary heart disease, and all-cause mortality. *J Am Soc Hypertens*. 2014;8:405–413.
11. 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.
12. Sim JJ, Bhandari SK, Shi J, Reynolds K, Calhoun DA, Kalantar-Zadeh K, Jacobsen SJ. Comparative risk of renal, cardiovascular, and mortality outcomes in controlled, uncontrolled resistant, and nonresistant hypertension. *Kidney Int*. 2015;88:622–632.
13. Smith SM, Gong Y, Handberg E, Messerli FH, Bakris GL, Ahmed A, Bavry AA, Pepine CJ, Cooper-Dehoff RM. Predictors and outcomes of resistant hypertension among patients with coronary artery disease and hypertension. *J Hypertens*. 2014;32:635–643.
14. Egan BM, Kai B, Wagner CS, Henderson JH, Chandler AH, Sinopoli A. Blood pressure control provides less cardiovascular protection in adults with than without apparent treatment-resistant hypertension. *J Clin Hypertens (Greenwich)*. 2016;18:817–824.
15. Egan BM, Kai B, Wagner CS, Fleming DO, Henderson JH, Chandler AH, Sinopoli A. Low blood pressure is associated with greater risk for cardiovascular events in treated adults with and without apparent treatment-resistant hypertension. *J Clin Hypertens (Greenwich)*. 2017;19:241–249.
16. Nicolucci A, Rossi MC, Arcangeli A, Cimino A, de Bigontina G, Fava D, Gentile S, Giorda C, Meloncelli I, Pellegrini F, Valentini U, Vespasiani G; AMD-Annals Study Group. Four-year impact of a continuous quality improvement effort implemented by a network of diabetes outpatient clinics: the AMD-Annals initiative. *Diabet Med*. 2010;27:1041–1048.
17. De Cosmo S, Rossi MC, Pellegrini F, Lucisano G, Bacci S, Gentile S, Ceriello A, Russo G, Nicolucci A, Giorda C, Viazzi F, Pontremoli R; AMD-Annals Study Group. Kidney dysfunction and related cardiovascular risk factors among patients with type 2 diabetes. *Nephrol Dial Transplant*. 2014;29:657–662.
18. De Cosmo S, Viazzi F, Pacilli A, Giorda C, Ceriello A, Gentile S, Russo G, Rossi MC, Nicolucci A, Guida P, Feig D, Johnson RJ, Pontremoli R; AMD-Annals Study Group. Serum uric acid and risk of CKD in type 2 diabetes. *Clin J Am Soc Nephrol*. 2015;10:1921–1929.
19. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF III, Feldman HI, Kusek JW, Eggers P, Van Lente F, Greene T, Coresh J; CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration). A new equation to estimate glomerular filtration rate. *Ann Intern Med*. 2009;150:604–612.
20. James PA, Oparil S, Carter BL, Cushman WC, Dennison-Himmelfarb C, Handler J, Lackland DT, LeFevre ML, MacKenzie TD, Oggedegbe O, Smith SC Jr, Svetkey LP, Taler SJ, Townsend RR, Wright JT Jr, Narva AS, Ortiz E. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). *JAMA*. 2014;311:507–520.
21. Weber MA, Schiffrin EL, White WB, Mann S, Lindholm LH, Kenerson JG, Flack JM, Carter BL, Materson BJ, Ram CV, Cohen DL, Cadet JC, Jean-Charles RR, Taler S, Kountz D, Townsend R, Chalmers J, Ramirez AJ, Bakris GL, Wang J, Schutte AE, Bisognano JD, Touyz RM, Sica D, Harrap SB. Clinical practice guidelines for the management of hypertension in the community a statement by the American Society of Hypertension and the International Society of Hypertension. *J Hypertens*. 2014;32:3–15.
22. Muntner P, Davis BR, Cushman WC, Bangalore S, Calhoun DA, Pressel SL, Black HR, Kostis JB, Probstfield JL, Whelton PK, Rahman M; ALLHAT Collaborative Research Group. Treatment-resistant hypertension and the incidence of cardiovascular disease and end-stage renal disease: results from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *Hypertension*. 2014;64:1012–1021.
23. Lambers Heerspink HJ, Tighiouart H, Sang Y, Ballew S, Mondal H, Matsushita K, Coresh J, Levey AS, Inker LA. GFR decline and subsequent risk of established kidney outcomes: a meta-analysis of 37 randomized controlled trials. *Am J Kidney Dis*. 2014;64:860–866.
24. Badve SV, Palmer SC, Hawley CM, Pascoe EM, Strippoli GF, Johnson DW. Glomerular filtration rate decline as a surrogate end point in kidney disease progression trials. *Nephrol Dial Transplant*. 2016;31:1425–1436.
25. Solini L, Zoppini G, Orsi E, Fondelli C, Trevisan R, Vedovato M, Cavalot F, Lamacchia O, Arosio M, Baroni MG, Penno G, Pugliese G; Renal Insufficiency And Cardiovascular Events (RIACE) Study Group. Resistant hypertension in patients with type 2 diabetes: clinical correlates and association with complications. *J Hypertens*. 2014;32:2401–2410.
26. Böhm M, Schumacher H, Teo KK, Lonn EM, Mahfoud F, Mann JF, Mancia G, Redon J, Schmieder RE, Sliwa K, Weber MA, Williams B, Yusuf S. Achieved blood pressure and cardiovascular outcomes in high-risk patients: results from ONTARGET and TRANSCEND trials. *Lancet*. 2017;389:2226–2237.
27. Schmidt M, Mansfield KE, Bhaskaran K, Nitsch D, Sørensen HT, Smeeth L, Tomlinson LA. Serum creatinine elevation after renin-angiotensin system blockade and long term cardiorenal risks: cohort study. *BMJ*. 2017;356:j791.
28. Bhandari S, Ives N, Brettell EA, Valente M, Cockwell P, Topham PS, Cleland JG, Khwaja A, El Nahas M. Multicentre randomized controlled trial of angiotensin-converting enzyme inhibitor/angiotensin receptor blocker withdrawal in advanced renal disease: the STOP-ACEi trial. *Nephrol Dial Transplant*. 2016;31:255–261.
29. Bhalla V, Zhao B, Azar KM, Wang EJ, Choi S, Wong EC, Fortmann SP, Palaniappan LP. Racial/ethnic differences in the prevalence proteinuric and nonproteinuric diabetic kidney disease. *Diabetes Care*. 2013;36:1215–1221.

SUPPLEMENTAL MATERIAL

Appendix

AMD ANNALS Study Group:

Editorial Board (in alphabetical order): Cimino Antonino¹, Fava Danila², Giorda Carlo Bruno³, Meloncelli Illidio⁴, Nicolucci Antonio⁵, Pellegrini Fabio⁵, Rossi Maria Chiara⁵, Turco Salvatore⁶, Vespasiani Giacomo⁴

Statistical analysis and Coordinating centre: Pellegrini F⁵, Graziano G⁵, Lucisano G⁵, Memmo R⁵, Pellicciotta E⁵.

Affiliations: ¹Spedali Civili, Diabetes Unit - Brescia; ²San Giovanni Addolorata Hospital, Diabetes and Metabolism Unit - Roma; ³ASL TO5, Diabets Unit - Chieri (TO); ⁴Madonna del Soccorso Hospital, Diabets Unit - San Benedetto del Tronto (AP); ⁵Department of Clinical Pharmacology and Epidemiology, Consorzio Mario Negri Sud, Santa Maria Imbaro (CH).

Regional Tutors (in alphabetical order by region): Paciotti V, Pupillo M – Abruzzo; Armentano G, Giovannini C – Calabria; Armentano V, Laudato M, Turco S – Campania; Acquati S, Ciardullo AV, Laffi G - Emilia Romagna; Felace G, Taboga C, Tortul C - Friuli Venezia Giulia; Santantonio G, Suraci C – Lazio; Ghisoni G, Raffa M – Liguria; Genovese S, Lovagnini-Scher CA, Rampini P, Rocca A, Ruggeri P – Lombardia; Tortato E, Cotti L – Marche; Cristofaro MR, Tagliaferri M – Molise; Comoglio M, Fornengo R – Piemonte; De Cosmo S, Gentile FM - Puglia; Gigante A, Mastinu F – Sardegna; Di Benedetto A, Pata P – Sicilia; Arcangeli A, Orsini P – Toscana; Acler P, De Blasi G - Trentino Alto Adige; Cicioni G, Pociati S – Umbria; Marangoni A, Nogara A – Veneto.

Participating centres (in alphabetical order by town): Lanero M, Bertero MG, Damassino R, Bergonzini C, Schumtz L, Seksich L - ACQUI TERME (AL); Pipitone A – ADRIA (RO); Boaretto M, Manfroi I, Parmesan L, Conte B, Soccol F – AGORDO (BL); Pagano A, Papini E, Rinaldi R, Petrucci L, Graziano F, Chianelli M, Silvagni S - ALBANO LAZIALE (RM); Rosco M – ALBEROBELLO (BA); Analdi E, Malvicino F, Battezzati M, Maresca P, Palenzona C – ALESSANDRIA; Boemi M, Rabini RA, Brandoni G, Lanari L, Gatti C, Testa I – ANCONA; Cherubini V – ANCONA; Doveri G, Pecorelli L, Ciccarelli A, Gallardini MB, Courthoud R, Sara Bredy S – AOSTA; Ricciardi GP – APRILIA (LT); Vitalone G, Setti D, Contrini P – ARCO (TN); Corsi A, Ghigliotti V, Oddone G, Ponzani P, Valbonesi G – ARENZANO (GE); Mazzini V – ARGENTA (FE); Di Berardino P, Colleluori P, Montani V, Trosini V – ATRI (TE); Velussi M – AURISINA (TS); Paciotti V, Alfidi P, Verdecchia B, Baliva L, Di Pietro A, Franchi G, Luce RP – AVEZZANO (AQ); Marangoni A, Pianta A, Ferrari M, Balzano S, Beltranello G - BASSANO DEL GRAPPA (VI); Dal Fabbro S, Aricò CN, Cervo L, Zanon R, Rossa S – BELLUNO; Rosco M, Di Pace MC – BISCEGLIE (BAT); Laffi G, Ciavarella A, Giangiulio S, Grimaldi M, Mustacchio A, Santacroce G - BOLOGNA S. ORSOLA MALPIGHI; Fattor B, Monauni T, Cristini M, Orion G, Crazzolaro D, Amor F, Eisath JE, Lintner S – BOLZANO; Garavelli S, Calari T, Marini P, Sandri O, Scala M, Stroppa C, Trentin A - BORGO VALSUGANA (TN); Garavelli S, Calari T, Marini P, Carlin R, Carli B, Sandonà M - BORGO VALSUGANA (TN); Garavelli S, Calari T, Marini P, Zortea C, Bonet L, Pradel L, Reato S - BORGO VALSUGANA (TN); Buschini M, Bonfiglioli D, Mones D, Beldi F – BORGOMANERO (NO); Morea A, Bondesan L, Perbellini S – BOVOLONE (VR); Cimino A, Valentini U, Agosti B, Corsini R, Girelli A, Zarra E, Rocca L - BRESCIA; De Blasi G, Bergmann M, Pradi I, Unterkircher S, Piok M, Pichler M – BRESSANONE (BZ); Trinchera A, Palamà G, Palma P – BRINDISI; Carboni L, Murtas MG, Mudadu T, Turco MP, Floris M, Delogu A, Farris L – CAGLIARI; Songini M, Piras G, Seguro R, Floris R, Corona G, Lai M, Piras E – CAGLIARI; Contini PP, Cocco S, Pilosu RM, Sannia MC, Spanu F – CAGLIARI; Busciantella Ricci N, Cartechini MG, Agostinelli G, Fiorelli C – CAMERINO(MC); Nuzzi A, Ballauri C – CANALE (CN); Giorda CB, Lesina A, Romeo F – CARMAGNOLA (TO); Ciardullo AV, Giudici G, Maciejewska EG, Deroma A, Paduano M, Rossi L, Vagnini C – CARPI (MO); Dolci M, Mori M, Baccetti F, Gregori G – CARRARA (MS); Straface E – CASALBORDINO (CH); Pozzuoli G, Laudato M, Barone M, Stasio GB – CASERTA; Tondini S, Borgoni F - CASTEL DEL PIANO (GR); Grosso J, Rossi L, Scarsellato C, Sciulli A, De Marco F - CASTEL DI SANGRO (AQ); Confortin L, Marin N, Lamonica M – CASTELFRANCO (TV); Gialdino S – CASTROVILLARI (CS); Borzi V, Gatta C, Rapisard R, Strano S, Calabrò M – CATANIA; Puccio L – CATANZARO; Zolli M, Coracina A – CAVARZERE (VE); Starnone V, Del Buono A, Terracciano AM – CELLOLE (CE); Monda MV – CENTO (FE); Castro F, Guaglianone A, Maccari V – CETRARO (CS); Corsi L, Versari G, Falivene MR, Boletto N, Corsi S – CHIAVARI (GE); Giorda CB, Marafetti L – CHIERI (TO); Vitacolonna E, Capani F, Caputo L, Di Nisio L, Simonetti F – CHIETI; Boscolo Bariga A, Nogara A, Ballarin G, De Boni S, Di Benedetto S – CHIOGGIA (VE); Chiambretti AM, Fornengo R, Di Vito L, Pascuzzo MD, Urli P – CHIVASSO (TO); Rocca A, Rumi P, Balzarini B, Galli P, Castellan M, Giannetti

A, Russotti C, De Blasi A, Perna A - CINISELLO BALSAMO (MI); Campanelli C, Ranchelli A, Biccheri D, Dadi G - CITTA' DI CASTELLO (PG); Santantonio G, Massa L, Baldi GP, Sciacca F, Costanzo E, Spada M, Paolini G - CIVITAVECCHIA (RM); Ziller P, Portolan F, Pasolini G - CLES (TN); Ghilardi G, Fiorina P - CLUSONE (BG); Grata ML - CODIGORO (FE); Capretti L, Speroni G, Fugazza L - CODOGNO (LO); Massafra C, Lovagnini Scher A - COLOGNO MONZESE (MI); Cimicchi MC, Percudani C, Risolo T, Saccò P - COLORNO (PR); Grata ML - COMACCHIO (FE); Gidoni Guarnieri GL, Piccolo D, Bravin C, De Noni E, Scarpel M, Marcon M, Giacon F - CONEGLIANO (TV); Panebianco G, Tadiotto F, Da Tos V, D'Ambrosio M - CONSELVE (PD); Pellizzola D, Zampini MA, Frezzati E, Mari E, Raminelli E - COPPARO (FE); Gaiti D, Bosi EA, Chierici G, Pilla S, Copelli M, Zanichelli P, Bertelli L, Caretta P, Vezzani V, Bodecchi S - CORREGGIO (RE); Longobucco A - COSENZA; Ruggeri P, Di Lembo S, Spotti E, Carrai E, Degli Innocenti A, Manini L, Persico R, Rossi C - CREMONA; Magro G - CUNEO; Marelli G, Vilei V, Andrioli M, Bellato L, Fedeli M, Merlini A, Pinelli G - DESIO (MI); Marin G, Contin ML, Gallo A, Parlato P, Pecchiolan W, Jacovacci J - DOLO (VE); Placentino G - DOMODOSSOLA (VB); Richini D, Molinari S, Strazzeri R - ESINE (BS); Panebianco G, Tadiotto F, Da Tos V, D'Ambrosio M - ESTE (PD); Fabbri T, Di Bartolo P - FAENZA (RA); Cotti L, Garrapa G - FANO (PU); D'Incau F, Lagomanzini P, Conte P, Todesco F - FELTRE (BL); Fogliani P, Tortato E, Pantanetti P, Bedetta C, Maricotti R - FERMO; Tomasi F, Monesi M, Graziani R, Beretta F, Penna L - FERRARA; Guberti A, Dazzi D - FIDENZA (PR); Dolci M, Mori M, Baccetti F, Gregori G - FIVIZZANO (MS); Pocciati S - FOLIGNO (PG); Forte E, Gasbarrone A, Marrocco T, Moschetta R - FONDI (LT); Tuccinardi F, De Meo F, Forte E, Coppola A, Pirolozzi P, Placitelli E, Vallefucio R - GAETA (LT); Taboga C, Catone B, Ceschia S, Urban M - GEMONA DEL FRIULI (UD); Ghisoni G, Fabbri F, Torresani M, Crovetto R - GENOVA; Corsi A, Battistini M, Fabbri F, Carosia P - GENOVA; Viviani GL, Durante A, Pais F, Lilliu V - GENOVA; Rosco M, Quietto C - GIOIA DEL COLLE (BA); D'Ugo E, Squadrone M, Amenduni T, Iovannisci MM, Della Penna L, Potente F, Delle Donne T, Massa C, Ulisse MA - GISSI (CH); De Berardinis S, Guarnieri I, Pace S, Splendiani M, Di Giuseppe R - GIULIANOVA (TE); Tortul C, Brunato B, Assaloni R, Muraro R, Loro R, Buccioli S - GORIZIA; Rosco M, Lavacca C - GRAVINA (BA); Rossi M, Sabbatini G, Quadri F, Sambuco L, Santacroce C - GROSSETO; Bosi EA, Chierici G, Pilla S, Gaiti, Copelli, Zanichelli, Bertelli, Paola Caretta D, Vezzani V, Bodecchi S - GUASTALLA (RE); Marino C, Micheletti A, Petrelli A - GUBBIO (PG); Corda A, Pisano L, Guaita G, Deias C - IGLESIAS (CI); Trevisan G, Coletti I - JESOLO (VE); Iannarelli R - L'AQUILA; Pupillo M, De Luca A, Minnucci A, Antenucci D, Di Florio C, Angelicola G, Bosco A, Fresco R, Di Marco G - LANCIANO (CH); Ugolotti D, Cadossi T, Ferrari M - LANGHIRANO (PR); Tagliaferri M, Di Caro P, Mazzocchetti M - LARINO (CB); Buzzetti R, Leto G, Gnessi C, Cipolloni L, Foffi C, Moretti C, Venditti C - LATINA; Morea A, Bondesan L, Perbellini S - LEGNAGO (VR); Meniconi R, Bertoli S, Cosimi S - LIDO DI CAMAIORE (LU); Di Cianni G, Orsini P, Turco A, Richini A, Marconi S, Sannino C, Lemmi P, Giuntoli S, Manfrè N - LIVORNO; Giannini F, di Carlo A, Casadidio I - LUCCA; Melandri P, Di Bartolo P - LUGO (RA); Maolo G, Polenta B, Piccinini N - MACERATA; Pozzuoli G, Laudato M, Barone M, Stasio GB - MADDALONI (CE); Vincenti C, Pastore N, Mega P, Magurano E, Cananiello A - MAGLIE (LE); Francescutto CA, Brussa Toi E, Gaspardo G, Angeli L, Ronchese L - MANIAGO (PN); Sciangula L, Ciucci A, Contartese A, Banfi E, Castelli E - MARIANO COMENSE (CO); Tatti P, Bloise D, Di Mauro P, Masselli L - MARINO (RM); Lo Presti A, Scarpitta AM, Gambina F - MARSALA (TP); Venezia A, Morea R, Lagonigro G, Copeta G, Iannucci V, Milano V, Trupo M - MATERA; Lochmann A, Marchetto PE, Incelli G, De Paola G, Steiger MM, Gamper MA, Breitenberger S, Holzner M, Frischmann J - MERANO (BZ); Lambiase C, Di Vece T, D'Aniello M, Fezza M, Giordano C, Leo F - MERCATO S. SEVERINO (SA); Saitta G - MESSINA; Di Benedetto A, Cucinotta D, Di Vieste G, Pintaudi B - MESSINA; Pata P, Mancuso T - MESSINA; Musacchio N, Giancaterini A, Lovagnini Scher A, Pessina L, Salis G, Schivalocchi F - MILANO; Testori G, Rampini PA, Cerutti N, Morpugo PS, Cavaletto ML, Bonino G, Morreale F - MILANO; Mariani G, Ragonesi PD, Bollati P, Colapinto P - MILANO; Bosi E, Falqui L - MILANO; Bortolato L, Cosma A, Pistolato P, Centenaro B, Ceccato A; MIRANO (VE); Campobasso G - MODUGNO (BA); Gentile FM, Zaurino F, Mazzotta G - MOLA DI BARI (BA); Comoglio M, Manti R, Giorda CB - MONCALIERI (TO); Tortul C, Da Ros R, Carlucci S, Narduzzi L, Bortolotto D, D'Acunto L, Stanic L, Brunato B, Assaloni R - MONFALCONE (GO); Volpi A, Coracina A, Cospite AM - MONTEBELLUNA (TV); Manicardi V, Michelini M, Finardi L, Borghi F, Manicardi E - MONTECCHIO EMILIA (RE); Lombardi S, Tommasi C, Iaccarino M, Cozza S, Binotto M, Marini F, Mecenero I, Massignani S, Stecco P, Urbani E, Massariol W, Parolin R - MONTECCHIO MAGGIORE (VI); Gatti A, Bonavita M, Creso E, Giannettino R, Gobbo M - NAPOLI; Turco S, Iovine C, Turco AA, Riccardi G - NAPOLI; Iazzetta N, Giannattasio C - NAPOLI; Armentano V, Egione O, Galdieri S, Velotti A, Azzolina A, Annicelli G - NAPOLI; Sorrentino T, Gaeta I, Del Buono A - NAPOLI; Zenari L, Bertolini L, Sorgato C, Grippaldi F - NEGRAR (VR); Stroppiana M, Popolizio R, Carbone N, Grasso S, Abate S, Gaggero GC - NIZZA MONFERRATO (AT); Strazzabosco M, Brun E - NOVENTA VICENTINA (VI); Carlesi GP, Garrone S - NOVI LIGURE (AL); Gigante A, Cicalò AM, Clausi C, Cau R - NUORO; Manconi A, Carboni A, Angius MF, Pinna AA, Caria S, Filigheddu GD, Tonolo G, Carta I - OLBIA (OT); Calebich S, Burlotti C - OME (BS); Saglietti G, Placentino G, Schellino A - OMEGNA (VB); Mastinu F, Madau G, Cossu M, Mulas F, Zoccheddu S - ORISTANO; Balsanelli M, Fetonti M, Rotolo A, Sambo P - OSTIA (RM); Secchi E, Angotzi MA, Loddoni S, Brundu I, Careddu F, Becciu A, Gabriella Piras G - OZIERI (SS); Novara F, Cipro F - PACECO (TP); Torchio G, Palumbo P, Bianchi A, Colucci G, La Motta G - PADERNO DUGNANO (MI); Tiengo A, Avogaro A, Bruttomesso D, Crepaldi C, Fadini G, Guarnieri G, Lavagnini MT, Maran A, Vedovato M, de Kreutzenberg V - PADOVA; Fedele D, Lapolla A, Sartore G, Bax G, Cardone C, Dalfrà MG, Masin M, Toniato R, Francesco Piarulli - PADOVA; Mattina G - PALERMO;

Fulantelli MA – PALERMO; Gioia D, Conti M – PALERMO; Ridola G – PALERMO; D'Agati F – PALERMO; Grossi G, De Berardinis F – PAOLA (CS); Zavaroni I, Dei Cas A, Franzini L, Usberti E, Antonimi M, Anelli N, Poli R, Ridolfi V, Michela M, Haddoub S, Prampolini G, Muoio A – PARMA; Cimicchi MC, Ugolotti D, Filippi D, Ferrari M, Bucci F – PARMA; Tardio SM, Calderini MC, Magotti MG, Quarantelli C, Vernazza MA, Carolfi A, Saracca R – PARMA; Picchio E, Del Sindaco P – PERUGIA; Spalluto A, Maggiulli L, Torreggiani V, Rastelletti S, Ugolini C, Pucci N, Magi S, Muratori S – PESARO; La Penna G, Consoli A – PESCARA; Galeone F, Magiar AV – PESCIA (PT); Gherardini V, Moretti L, Bientinesi M, Landi L, Bernardi A – PIOMBINO (LI); Del Prato S, Miccoli R, Bianchi C, Penno G, Venditti F – PISA; Anichini R, De Bellis A, Bruschi T, Butelli L, Gioffredi M, Gori R, Picciafuochi R, Malagoli R, Bernini A - PISTOIA; Gelisio R, Zanon M, Del Bianco A, Bamiston A, Signorato M – PORTOGRUARO (RO); Mazzini V – PORTOMAGGIORE (FE); Citro G – POTENZA; Arcangeli A, Calabrese M, Ianni L, Lorenzetti M, Marsocci A, Guizzotti S, Memoli G – PRATO; Cabasino F, Farci F, Atzori A, Sanna A, Ghiani M, Siotto I, Sedda M, Manis A, Loddo C, Loddo I, Pisano L, Seguro P, Cuomo A, Orlando L, Olanda GB - QUARTU SANT'ELENA (CA); Pucci A - QUATTROMIGLIA DI RENDE (CS); Massenzo M - QUATTROMIGLIA DI RENDE (CS); Di Bartolo P, Sardu C – RAVENNA; Giovannini C - REGGIO CALABRIA; Perrone G, Corazziere F, La Puzza I - REGGIO CALABRIA; Tripodi PF, Riggio S, Giampaolo A - REGGIO CALABRIA; Mannino D - REGGIO CALABRIA; Aleandri AR, Guidi MV, Battisti B, Faraglia MR, Lilli V – RIETI; Leotta S, Suraci C, Visalli N, Gagliardi A, Fontana L, Altomare M, Carletti S, Abbruzzese S – ROMA; Chiaramonte F, Giordano R, Rossini M, Migneco G – ROMA; Cappelloni D, Urbani A – ROMA; Piergiovanni F, Fava D, Simonetta A, Massimiani F – ROMA; Bulzomì R – ROMA; Giuliano M, Pennafina MG, Di Perna P – ROMA; D'Accinni MP, Paolucci D, D'Ubaldi A, D'Angelo MT, Masaro G, Pietrantoni M, Fratini M, La Rosa R – ROMA; Poggi M, Piccirilli F, Pisano R, Saponara C, Conforti I, Penza A - ROMA; Scalpone R, Lo Pinto S, Iacovella L, Caccamo C, Sposito S, Teodonio C - ROMA; Armentano G, Restuccia MG, Mirto G – ROSSANO (CS); Girardello R, Gennaro R, De Moliner L, Bettini E, Mattuzzi A, Speese K, Frisinghelli F – ROVERETO (TN); Genovese S, Locatelli F – Rozzano (MI); Nicoletti M, Trojan N, Centis R - S.VITO AL TAGLIAMENTO (PN); Li Volsi P, Levis E, Zanette G – SACILE (PN); Comba G, Ballatore L – SALUZZO (CN); Cattaneo A, Agliadoro A, Guido R, Patrone M, Zecchini M – SAMPIERDARENA (GE); Vespasiani G, Meloncelli I, Clementi L, Galetta M, Marconi V - SAN BENEDETTO DEL TRONTO (AP); Bordin P, Perale L - SAN DANIELE DEL FRIULI (UD); Vinci C, Sira Zanon M, Geretto L, Toffolo C, Furlan MG, Mazzanti G - SAN DONÀ DI PIAVE (VE); Vinci M, Gelisio R - SAN DONA' DI PIAVE (VE); Sica V, Armeni M, Derai R, Ennas O, Mamusa S, Pisano MA, Carreras L - SAN GAVINO MONREALE (SV); De Cosmo S, Rauseo A - SAN GIOVANNI ROTONDO (FG); Cervone S, Leggieri A, Pontonio M - SAN MARCO IN LAMIS (FG); Sturaro R, Raffa M, Quattrocchi F, Molinaro M, Trasatti M, Ferretti B – SANREMO (IM); Rosco M, Labarile G – SANTERAMO (BA); Baule GM, Gentilini A, Spanu MA, Fancellu A, Bianco P – SASSARI; Lione L, Massazza G, Bocchio G, Bosco E – SAVONA; Monachesi M, Carta G, Boschetti M, Ceresola E, Venier E – SAVONA; Calcaterra F, Cataldi F, Miola M – SCHIO(VI); Manfrini S – SENIGALLIA(AN); Lai A, Locci B, Putzu D – SENORBI (CA); Tanganelli I, Leonini M – SIENA; Egger K, Marchiotto W – SILANDRO (BZ); Vincis L, Orlandini V, Pilloni C, Farci R, Pelligra I, Renier G - SIRAI – CARBONIA; Mamei M, Pala A, Devigus E – SORGONO (NU); Felace G, Fumagalli I – SPILIMBERGO (PN); Lalli C, Leandri M, Agliani M, De Pascalis L – SPOLETO (PG); Malci F, De Ciocchis A – SUBIACO (RM); Diodati MB, Macerola B – SULMONA (AQ); Davì S, Caccavale A, Brocato L, Pognant Gros M, Borla S - SUSÀ (TO); Lattanzi E, Piersanti C, Piersanti A, Spinelli I, Tuzzoli L, Tulini V, Quaranta G, Iorio V, Tirabovi M – TERAMO; De Candia - TERLIZZI (BA); Cicioni G, Massarelli MG, Venturi S – TERNI; Travaglini A, Draghi P – TERNI; Pomante P - TOCCO DA CASAURIA (PE); Richiardi L, Clerico A – TORINO; Bruno A, Cavallo Perin P, Ghigo E, Porta M, Scuntero P, Arcari R, Bertaina S, Bo S, Broglio F, Bruno G, Degiovanni M, Fornengo P, Grassi G, Inglese V, Maccario M, Maghenzani G, Marena S, Martina V, Passera P, Ruiu G, Tagliabue M, Zalone M – TORINO; Monge M, Boffano GM, Macri K, Maio P – TORINO; Ozzello A, Pergolizzi E, Gaia D, Gennari P, Micali G, Rossetto E, Dalmazzo C, Oreglia M, Stefani T – TORINO; Dossena C, Paglia P, Bosoni S – TORTONA (AL); Acler P, Romanelli T, Inchiostro S, Dauriz M – TRENTO; Bossi CA, Meregalli G, Balini A, Berzi D, Filippini B, Crotto G – TREVIGLIO (BG); Paccagnella A, Orrasch M, Sambataro M, Citro T, Kiwanuka E, Bagolin E, Almoto B – TREVISO; Macchia A, Branca MT, Filesi M – TRICASE (LE); Candido R, Caroli E, Manca E, Petrucco A, Tommasi E, Jagodnik G, Baskar B, Daris N, Dal Col P – TRIESTE; Pellegrini MA, Tonutti L, Venturini G – UDINE; Andreani M, Turchi F, Fedrighelli F, Martinelli G – URBINO; Sposito S, Rongioletti R, Candidi M – VELLETRI (RM); Pais M, Moro E – VENEZIA; Cervellino F, Sinisi R, Zampino A – VENOSA (PZ); Saglietti G, Placentino G, Schellino A - VERBANIA PALLANZA (VB); Mingardi R, Lora L, Reitano R, Stocchiero C – VICENZA; Strazzabosco M, Brun E, Simoncini M, Mesturino CA, Zen F – VICENZA; Di Pietro S, Scoponi C, Tilaro L, Pelliccioni S, Slongo R, Vita E; VITERBO; Garofalo A, Vitale F, Campanella B – VITTORIA (RG); Mastrilli V, Del Buono A, Borrelli T, D'Avino A – VOLLA (NA); Morea A, Perbellini A, Bondesan L – ZEVIO (VR).