ORIGINAL RESEARCH

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

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***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 ≥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 ≥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

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

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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

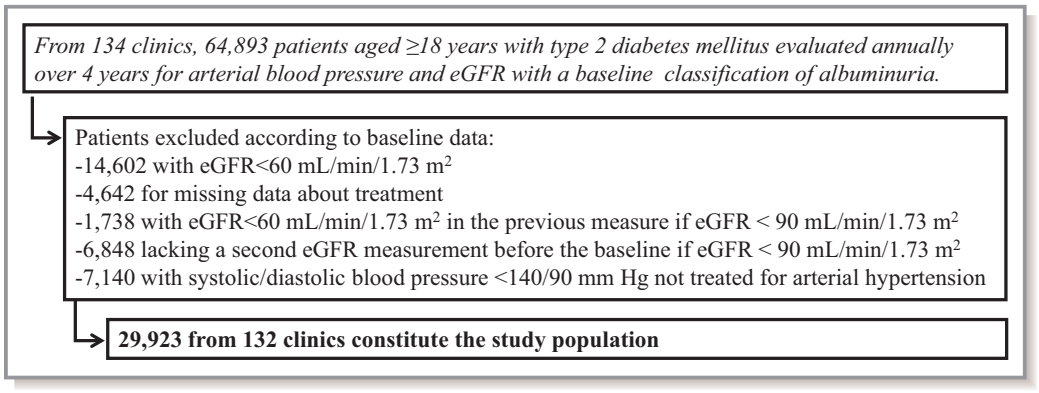

Figure 1. Flow diagram for selection of study patients. eGFR indicates estimated glomerular filtration rate.

Table 1. Baseline Characteristics of Study Patients Stratified by ATRH

	All	No aTRH	aTRH	
	n=29 923	n=24 934	n=4989	*P* Value
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.

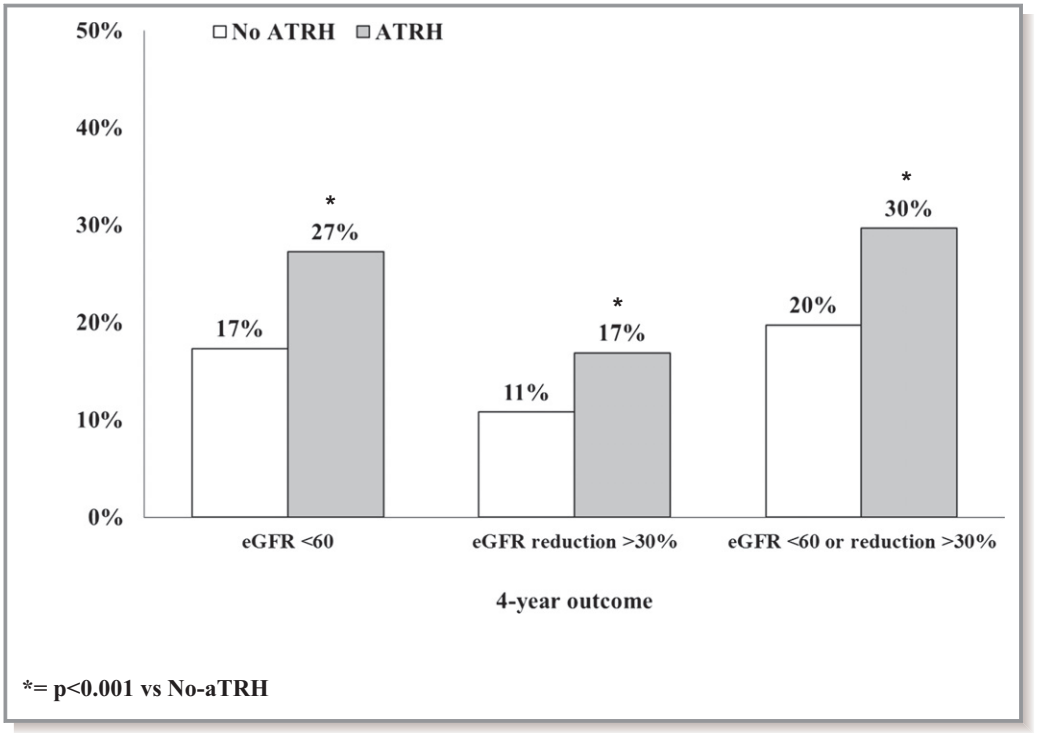

Figure 2. Cumulative incidence of renal outcomes in patients with and without aTRH and T2D. ATRH indicates apparent treatment resistant hypertension; CI, confidence interval; eGFR, estimated glomerular filtration rate; T2D, type 2 diabetes mellitus. *P<0.001 vs No-aTRH. Adjusted odds ratios for eGFR <60 mL/min per 1.73 m^2, 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 glycated 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%		
	No	Yes		No	Yes		No	Yes	
	n=24 216	n=5707	*P* Value	n=26 372	n=3551	*P* Value	n=23 501	n=6422	*P* Value
Male sex	14 071 (58.1%)	2898 (50.8%)	<0.001	15 247 (57.8%)	1722 (48.5%)	<0.001	13 743 (58.5%)	3226 (50.2%)	<0.001
Age, y	64±9	69±8	<0.001	64±9	67±9	<0.001	64±9	68±8	<0.001
Known duration of diabetes mellitus, y	10±8	12±9	<0.001	10±8	11±9	<0.001	10±8	12±9	<0.001
BMI, kg/m^2	30±5	30±5	0.132	30±5	30±5	<0.001	30±5	30±5	0.002
Serum creatinine, μmol/L	72±14	81±14	<0.001	74±15	72±15	<0.001	72±14	79±15	<0.001
eGFR, mL/min per 1.73 m^2	88±12	75±11	<0.001	86±13	85±13	<0.001	88±12	77±13	<0.001
Albuminuria	4350 (18.0%)	1524 (26.7%)	<0.001	4846 (18.4%)	1028 (28.9%)	<0.001	4173 (17.8%)	1701 (26.5%)	<0.001
Microalbuminuria	3899 (16.1%)	1222 (21.4%)	<0.001	4310 (16.3%)	811 (22.8%)	<0.001	3746 (15.9%)	1375 (21.4%)	<0.001
Macroalbuminuria	451 (1.9%)	302 (5.3%)	<0.001	536 (2.0%)	217 (6.1%)	<0.001	427 (1.8%)	326 (5.1%)	<0.001
Serum uric acid, μmol/L	311±98	335±113	<0.001	314±97	327±130	<0.001	311±98	331±110	<0.001
SUA in the top sex-specific quintile	2121 (17.5%)	757 (27.0%)	<0.001	2473 (18.7%)	405 (23.8%)	<0.001	2068 (17.5%)	810 (26.0%)	<0.001
HbA1c, %	7.2±1.3	7.3±1.3	<0.001	7.2±1.3	7.4±1.4	<0.001	7.2±1.3	7.4±1.3	<0.001
HbA1c, mmol/mol	56±14	57±14	<0.001	56±14	58±15	<0.001	55±14	57±14	<0.001
HbA1c ≥7% (≥53 mmol/mol)	12 725 (52.9%)	3262 (57.7%)	<0.001	13 920 (53.2%)	2067 (58.8%)	<0.001	12 328 (52.8%)	3659 (57.6%)	<0.001
Total cholesterol, mmol/L	4.84±0.96	4.78±0.96	<0.001	4.84±0.96	4.75±0.97	<0.001	4.84±0.96	4.78±0.97	<0.001
Triglycerides, mmol/L	1.53±0.98	1.62±0.98	<0.001	1.53±0.97	1.65±1.07	<0.001	1.53±0.98	1.63±1.00	<0.001
Triglycerides ≥150 mg/dL (≥1.69 mmol/L)	6933 (30.5%)	1847 (34.4%)	<0.001	7612 (30.7%)	1168 (34.9%)	<0.001	6687 (30.3%)	2093 (34.7%)	<0.001
HDL, mmol/L	1.32±0.37	1.32±0.39	0.290	1.32±0.37	1.31±0.39	0.396	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%)	<0.001	7502 (30.7%)	1155 (35.3%)	<0.001	6641 (30.4%)	2016 (34.1%)	<0.001
LDL, mmol/L	2.86±0.85	2.77±0.85	<0.001	2.85±0.85	2.74±0.85	<0.001	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%)	<0.001	14 724 (60.5%)	1759 (54.1%)	<0.001	13 205 (60.8%)	3278 (55.8%)	<0.001
Systolic BP, mm Hg	143±17	145±18	<0.001	143±17	145±18	<0.001	143±17	144±18	<0.001
Diastolic BP, mm Hg	81±9	80±9	<0.001	81±9	81±10	0.018	81±9	80±9	<0.001
BP ≥140/85 mm Hg	17 599 (72.7%)	4112 (72.1%)	0.221	19 113 (72.5%)	2598 (73.2%)	0.345	17 073 (72.6%)	4638 (72.2%)	0.365
Nonproliferative retinopathy	3056 (12.6%)	899 (15.8%)	<0.001	3403 (12.9%)	552 (15.5%)	<0.001	2958 (12.6%)	997 (15.5%)	<0.001
Proliferative retinopathy	861 (3.6%)	308 (5.4%)	<0.001	972 (3.7%)	197 (5.5%)	<0.001	820 (3.5%)	349 (5.4%)	<0.001

Continued

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Table 2. Continued

	eGFR <60 mL/min per 1.73 m^2			eGFR Reduction >30%			eGFR <60 or Reduction >30%		
	No	Yes		No	Yes		No	Yes	
	n=24 216	n=5707	*P* Value	n=26 372	n=3551	*P* Value	n=23 501	n=6422	*P* Value
Lipid-lowering treatment	11 610 (47.9%)	2969 (52.0%)	<0.001	12 806 (48.6%)	1773 (49.9%)	0.218	11 270 (48.0%)	3309 (51.5%)	<0.001
Treatment with statins	10 736 (44.3%)	2720 (47.7%)	<0.001	11 842 (44.9%)	1614 (45.5%)	0.769	10 436 (44.4%)	3020 (47.0%)	<0.001
Treatment with fibrates	512 (2.1%)	144 (2.5%)	0.090	564 (2.1%)	92 (2.6%)	0.117	489 (2.1%)	167 (2.6%)	0.021
Antihypertensive treatment	18 276 (75.5%)	4830 (84.6%)	<0.001	20 170 (76.5%)	2936 (82.7%)	<0.001	17 728 (75.4%)	5378 (83.7%)	<0.001
Treatment with ACE-Is/ARBs	15 408 (63.6%)	4104 (71.9%)	<0.001	17 015 (64.5%)	2497 (70.3%)	<0.001	14 936 (63.6%)	4576 (71.3%)	<0.001
Aspirin	7243 (29.9%)	2053 (36.0%)	<0.001	8132 (30.8%)	1164 (32.8%)	<0.001	7050 (30.0%)	2246 (35.0%)	<0.001
Antidiabetic therapy									
Diet	1919 (7.9%)	258 (4.5%)	<0.001	2043 (7.7%)	134 (3.8%)	<0.001	1890 (8.0%)	287 (4.5%)	<0.001
Oral antidiabetic drugs	16 581 (68.5%)	3556 (62.3%)	<0.001	17 898 (67.9%)	2239 (63.1%)	<0.001	16 105 (68.5%)	4032 (62.8%)	<0.001
Oral antidiabetic drugs and insulin	3424 (14.1%)	1135 (19.9%)	<0.001	3819 (14.5%)	740 (20.8%)	<0.001	3284 (14.0%)	1275 (19.9%)	<0.001
Insulin	2292 (9.5%)	758 (13.3%)	<0.001	2612 (9.9%)	438 (12.3%)	0.001	2222 (9.5%)	828 (12.9%)	<0.001
Apparent treatment resistant hypertension	3631 (15.0%)	1358 (23.8%)	<0.001	4143 (15.7%)	846 (23.8%)	<0.001	3507 (14.9%)	1482 (23.1%)	<0.001
BPC*	3859 (15.9%)	853 (14.9%)	0.117	4200 (15.9%)	553 (15.6%)	0.540	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.

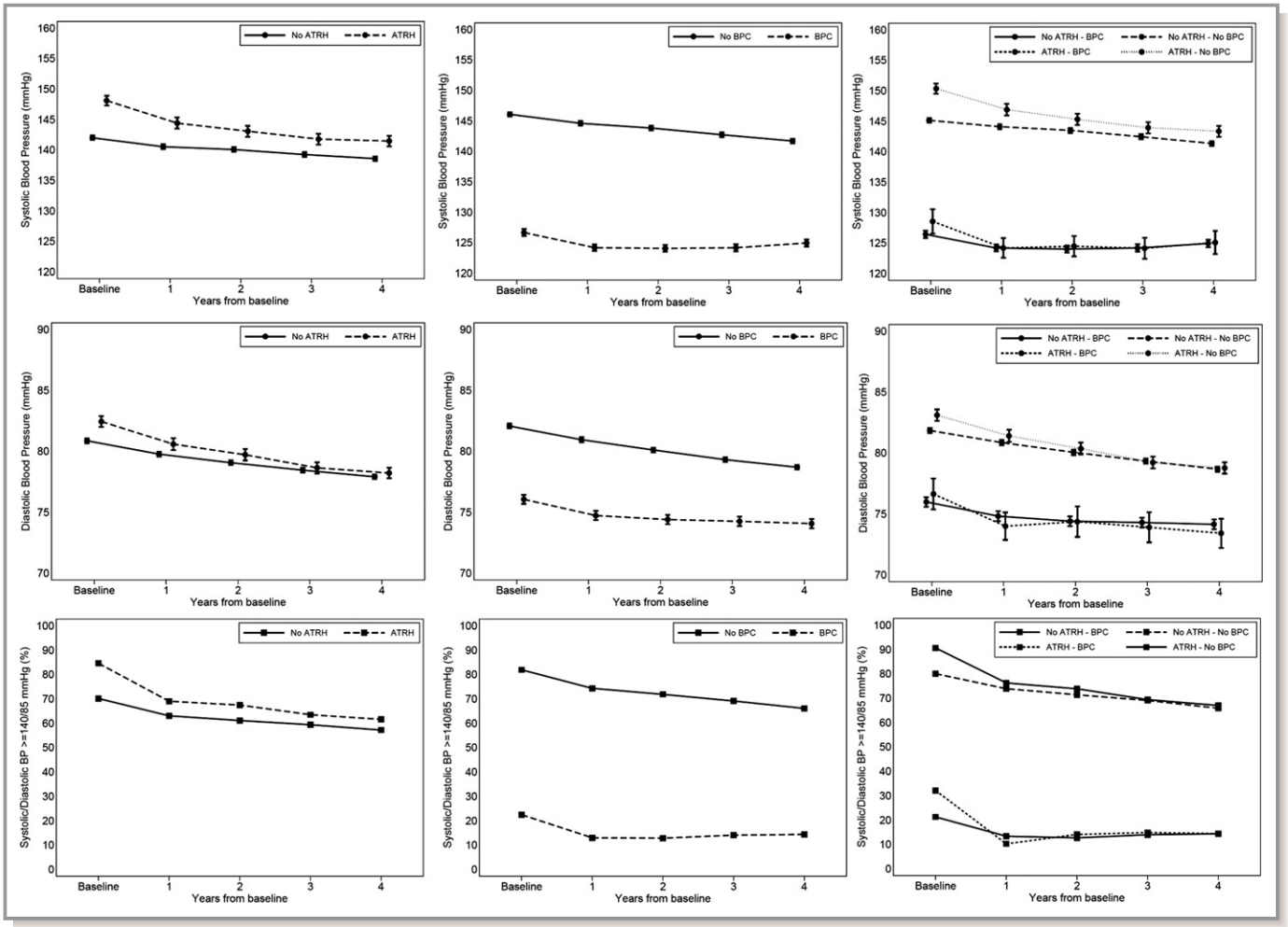

Figure 3. Blood pressure changes during follow-up. ATRH indicates apparent treatment resistant hypertension; BP, blood pressure; blood pressure control (BPC) refers to the proportion of visits with systolic and diastolic blood pressure <140/90 mm Hg.

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 m^2; (2) a reduction ≥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≥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± 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 BPC n=4198	No ATRH No BPC n=20 736	ATRH BPC n=514	ATRH No BPC n=4475	*P* Value
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	
	n=12 954	n=16 969	*P* Value
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	
	n=12 954	n=16 969	*P* Value
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±1.3% and 110±33 mg/dL, respectively. The average BP was 143±17/81±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 m^2, 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 ≥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 ≥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	
	n=4772	n=11 052	n=14 099	*P* Value
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	
	n=4772	n=11 052	n=14 099	*P* Value
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 ≥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 m^2

	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 al[12] 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 ≥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 ≥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 <40M <50F mg/dL (<1.03M <1.29F 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, ≥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 m^2

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

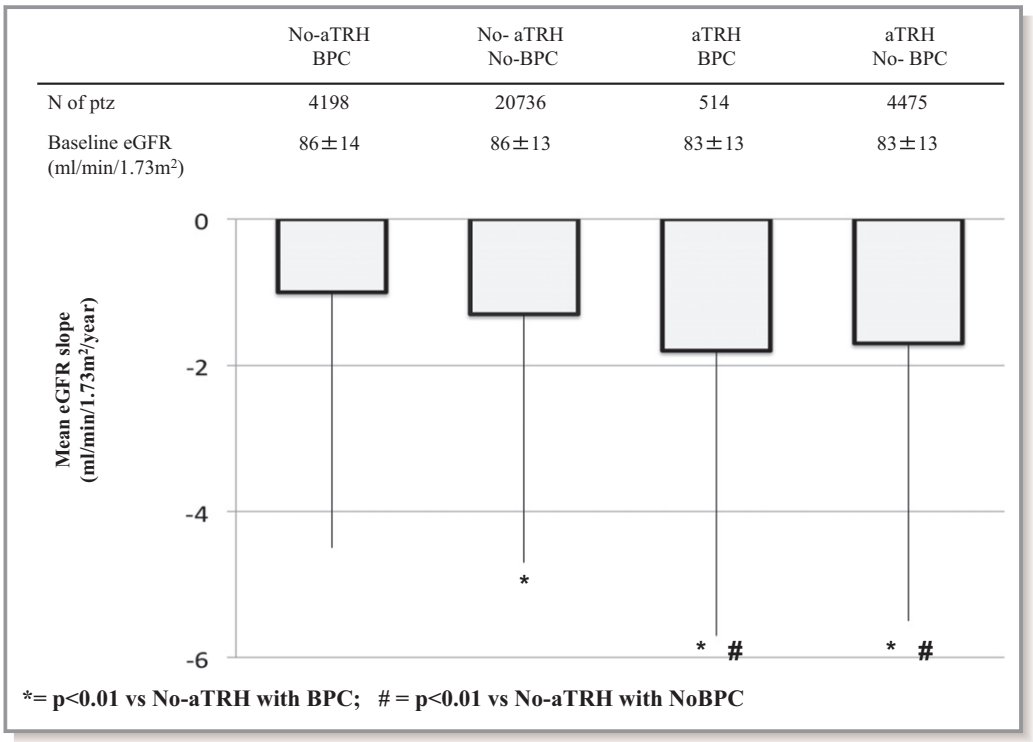

Figure 4. Mean yearly eGFR slope on the basis of the presence of aTRH and BPC. ATRH indicates apparent treatment resistant hypertension; eGFR, estimated glomerular filtration rate; BP, blood pressure control (BPC) refers to the proportion of visits with systolic and diastolic blood pressure <140/90 mm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

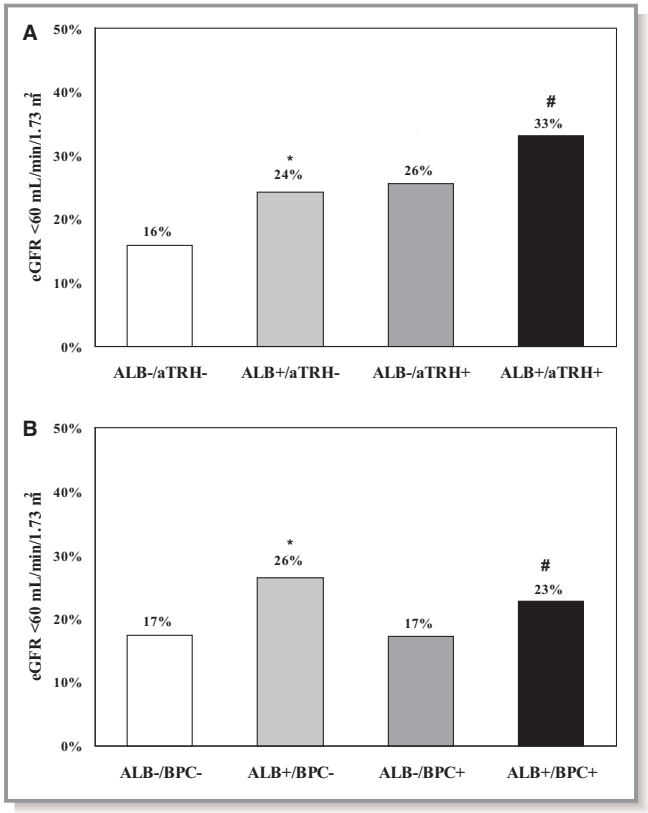

Figure 5. A, Cumulative incidence of renal end point (eGFR <60) on the basis of albuminuria status and aTRH. ALB indicates albuminuria; ATRH, apparent treatment resistant hypertension; CI, confidence interval; eGFR, estimated glomerular filtration rate. *Adjusted odds ratios for Alb+/aTRH− vs Alb−/aTRH− 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

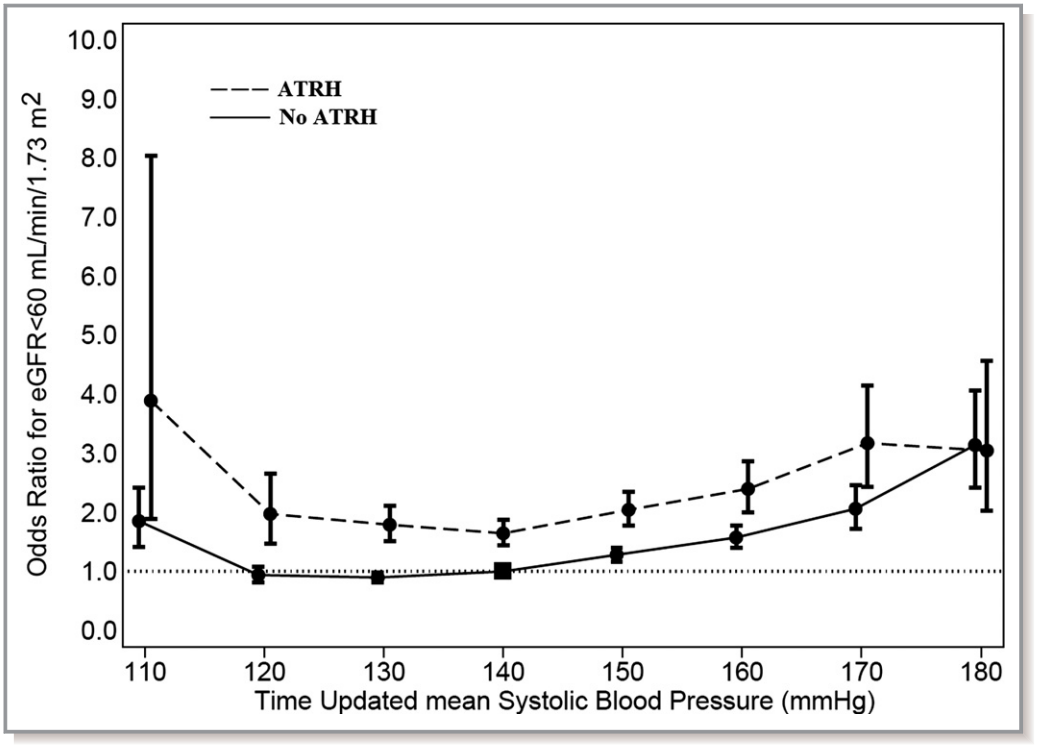

Figure 6. Odds ratios of reaching renal end point (eGFR <60 mL/min per 1.73 m^2) on the basis of time-updated mean SBP in patients with and without aTRH, taking 140 mm Hg in non aTRH as reference category. Patients were grouped into 10 mm Hg subsets (ie, those between 136 and 144 in the group labeled 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.

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Disclosures

None.

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SUPPLEMENTAL MATERIAL

Appendix

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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, Pocciati 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); Ansaldi 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, Crazzolara 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, Beldì 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); Borzì 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, Pecchielan 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); Foglini 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, Vallefuoco 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, Quieto 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, Bucciol 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, Aglialoro 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; Mameli 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 - SUSA (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, Zanone M – TORINO; Monge M, Boffano GM, Macrì 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).