Prospective Monitoring of Angiotensin Receptor Blocker Neprilysin Inhibitor in Older Adults with Heart Failure and Frailty

February 11, 2021

NCT04743063

STUDY PROTOCOL

Prospective Monitoring of Angiotensin Receptor Blocker Neprilysin Inhibitor in Older Adults with Heart Failure and Frailty

Preparation or Update Date:

01/14/2021

Protocol Revision Summary

Date	Summary of Changes
01/14/2021	Protocol preparation for study registration

BACKGROUND

1. Angiotensin receptor blocker neprilysin inhibitor (ARNI) sacubitril/valsartan (Entresto (1))
    a. Approved in July 7, 2015
    b. Indication: HF with reduced ejection fraction

2. PARADIGM-HF trial; ARNI vs enalapril (2)
    a. N=8442, follow-up 2.3 years
    b. Composite of cardiovascular death and HF hospitalization: 21.8% vs 26.5%
    c. Safety endpoints: hypotension (14.0% vs 9.2%), renal failure (3.3% vs 4.5%), hyperkalemia (16.1% vs 17.3%), angioedema (0.4% vs 0.2%)

3. 2017 ACC/AHA/HFSA guidelines for management of heart failure (3)
    a. The clinical strategy of inhibition of the renin-angiotensin system with ACE inhibitors (Level of Evidence: A), OR ARBs (Level of Evidence: A), OR ARNI (Level of Evidence: B-R) in conjunction with evidence-based beta blockers, and aldosterone antagonists in selected patients, is recommended for patients with chronic HFrEF to reduce morbidity and mortality.
    b. The use of ACE inhibitors is beneficial for patients with prior or current symptoms of chronic HFrEF to reduce morbidity and mortality (Level of Evidence: A). Although the use of an ARNI in lieu of an ACE inhibitor for HFrEF has been found to be superior, for those patients for whom ARNI is not appropriate, continued use of an ACE inhibitor for all classes of HFrEF remains strongly advised.
    c. The use of ARBs to reduce morbidity and mortality is recommended in patients with prior or current symptoms of chronic HFrEF who are intolerant to ACE inhibitors because of cough or angioedema (Level of Evidence: A). Head-to-head comparisons of an ARB versus ARNI for HF do not exist. For those patients for whom an ACE inhibitor or ARNI is inappropriate, use of an ARB remains advised.
    d. In patients with chronic symptomatic HFrEF NYHA class II or III who tolerate an ACE inhibitor or ARB, replacement by an ARNI is recommended to further reduce morbidity and mortality (Level of Evidence: B).

e. ARNI should not be administered concomitantly with ACE inhibitors or within 36 hours of the last dose of an ACE inhibitor (Level of Evidence: B). Oral neprilysin inhibitors, used in combination with ACE inhibitors can lead to angioedema and concomitant use is contraindicated and should be avoided.
f. ARNI should not be administered to patients with a history of angioedema (Level of Evidence: C).

4. 2021 ACC/AHA/HFSA focused update (4)
    a. For patients with newly diagnosed Stage C HFrEF, a beta-blocker and an ACEI/ARB/ARNI should be started in any order. Each agent should be up-titrated to maximally tolerated or target dose. Initiation of a beta-blocker is better tolerated when patients are dry and an ACEI/ARB/ARNI when patients are wet.

STUDY OVERVIEW AND DESIGN

1. Study aims: To emulate a prospective surveillance of the effectiveness and safety of ARNI vs a comparator (ARB) in older adults with HFrEF and different frailty status.

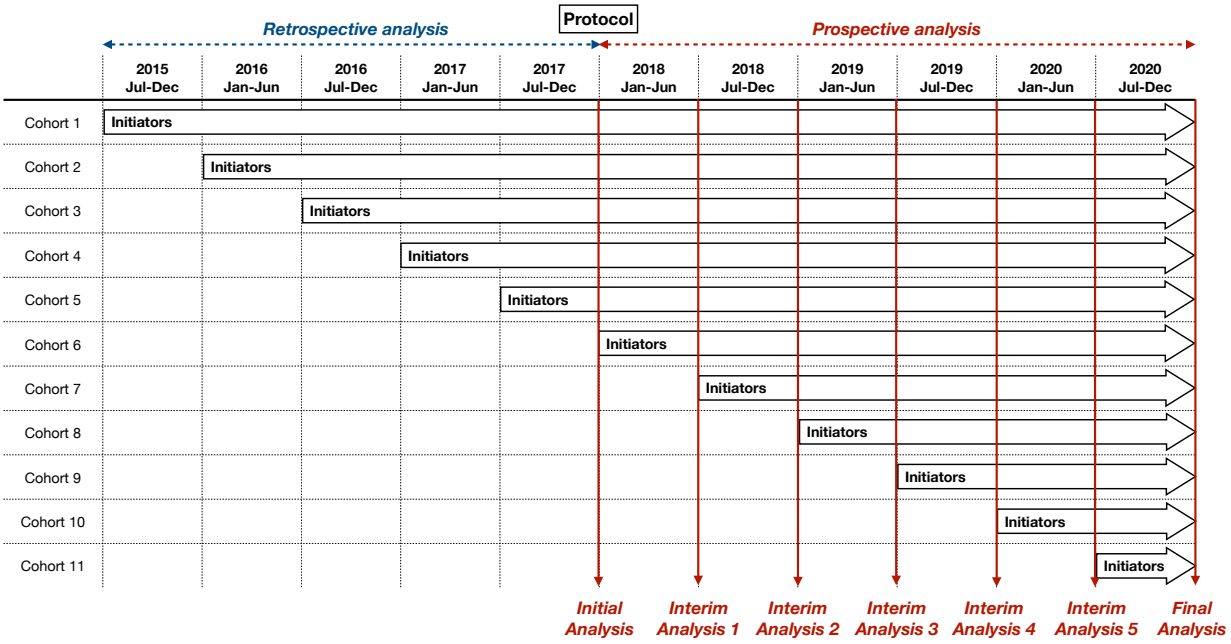
2. Data source(s): Data from 2014 up to 2020 will be used.

    a. Medicare Database
    b. Optum Database
    c. MarketScan Research Database

3. Sequential cohort monitoring design (see Figure 1): The monitoring analysis will include 1) retrospective analysis of available data (2015-2017) at the time of first analysis (January 2021) and 2) prospective analysis of new data (2018-2020) as they become available to the researchers. Within each database, we will emulate biannual updating of data by creating a propensity score (PS)-matched cohort of new users every 6-month interval, beginning on the first marketing of ARNI (July 7, 2015-December 31, 2015, and 6-month intervals afterwards). Each sequential cohort will be followed for development of the outcomes of

interest. Outcome analysis will be performed at a pre-specified 6-month interval (prospective analysis). The surveillance will be performed by frailty status (frail vs non-frail) at the time of drug initiation. The results from each database will be pooled using fixed-effects meta-analysis (assuming low heterogeneity across the databases).

Figure 1. Schematic of sequential monitoring design



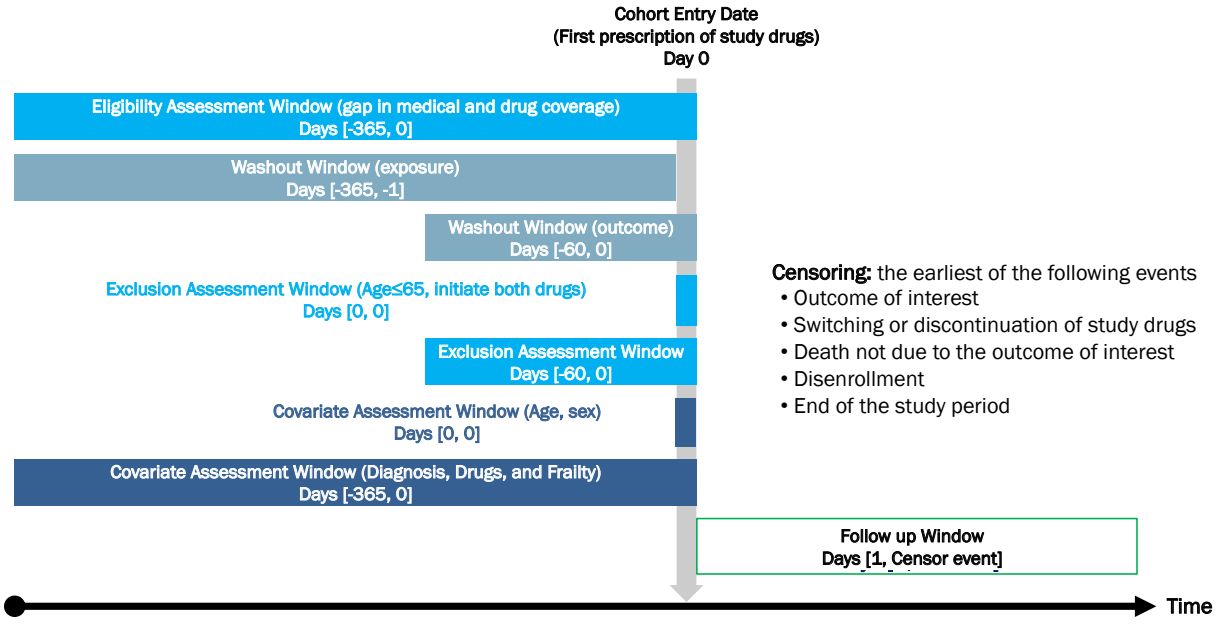
STUDY POPULATION

1. Study population (see Figure 2) is created for each calendar interval.

2. Initiation of ARNI or comparator (ARB)
    a. ARB: any of azilsartan, candesartan, eprosartan, Irbesartan, losartan, Olmesartan, telmisartan, valsartan
    b. Index date (day 0): prescription fill from July 7, 2015

3. Assessment of eligibility (eligibility assessment window: [-365, 0] days) – See Appendix for list of codes.
    a. Continuous enrollment for medical and drug insurance (Part A, B, and D)
    b. Diagnosis of HF (outpatient diagnosis x2 or inpatient x1)
    c. Reduced EF (<45%) algorithm (5)
    d. No prior use of ARNI or comparator (exposure wash-out window: [-365, -1] days)
    e. No recent HF hospitalization, defined as HF diagnosis (Appendix) in the primary position in the inpatient dataset (outcome wash-out window: [-60, 0] days)
    f. No recent nursing facility stay, defined as any of the following claims in [-60, 0] days
        i. Place of service: 31 (skilled nursing facility), 32 (nursing facility), 33 (custodial care facility)
        ii. CPT codes: 99301, 99302, 99303, 99311, 99312, 99313, 99315, 99316, 99379, 99380, G0066
    g. Excluded if age <65 years or exposure to both drugs on day 0
    h. Contraindication to either drug (exclusion assessment window: [-60, 0] days, unless specified otherwise)
        i. Hypotension
        ii. Chronic kidney disease stage IV or V or dialysis
        iii. Acute kidney injury
        iv. Hyperkalemia
        v. Angioedema: [-beginning of data, 0] days
    i. If a patient meets the above-mentioned eligibility criteria more than once, only the first record will be included.

Figure 2. Study design outline for comparative effectiveness and safety analysis



MEASUREMENTS

1. Exposure to ARNI or comparator
    a. ARNI: sacubitril/valsartan (Entresto)
    b. ARB (comparator): any of azilsartan, candesartan, eprosartan, Irbesartan, losartan, Olmesartan, telmisartan, valsartan
    c. Note: prior ACEI use (commonly used for hypertension and HFrEF) is allowed. This choice will resemble a clinic situation that involves switching from ACEI to ARB or to ARNI.
    d. Exposure risk window and gap between treatments allowed: 7 days (primary analysis) or 14 days (sensitivity analysis)

2. Outcomes
    a. Effectiveness endpoint:
        i. Primary: a composite of all-cause death or HF hospitalization
            - Note cardiovascular death was not used because National Death Index data were only available up to 2016. Instead, all-cause death was used.
            - HF hospitalization is defined as HF diagnosis primary position in the inpatient dataset
        ii. Secondary: individual components separately
    b. Safety endpoint:
        i. Primary: a composite of SAE, defined as any hospitalization or ED visit due to diagnosis codes in the primary position:
            - hypotension
            - acute kidney injury/acute kidney failure
            - hyperkalemia
            - angioedema
        ii. Secondary: individual components

3. Covariates
    a. Sociodemographic information: age, sex, race, dual eligibility
    b. Diseases: Chronic Conditions Data Warehouse (CCW) chronic conditions (see Table 2), provided in the Medicare Beneficiary Summary File (first date of satisfying the claims-based algorithm for individual conditions is available; considered present if this date is earlier than the index date)
    c. Prescription drugs: ATC3 classes with prevalence threshold >1% in a representative Medicare sample
    d. Gagne combined comorbidity score (6)
    e. Claims-based frailty index (7): Frailty status will be defined as non-frail if <0.20 or frail if ≥0.20

Table 2. CCW Chronic Conditions (8)

Acquired Hypothyroidism	Chronic Kidney Disease
Acute Myocardial Infarction	Chronic Obstructive Pulmonary Disease
Alzheimer's Disease, Related Disorders, or Senile Dementia	Depression
Anemia	Diabetes
Asthma	Glaucoma
Atrial Fibrillation	Hip / Pelvic Fracture
Benign Prostatic Hyperplasia	Hyperlipidemia
Cancer (any of the following): Cancer, Colorectal Cancer, Endometrial Cancer, Breast Cancer, Lung Cancer, Prostate	Hypertension
	Ischemic Heart Disease
	Osteoporosis
	Rheumatoid Arthritis / Osteoarthritis
	Stroke / Transient Ischemic Attack
Cataract	

STATISTICAL ANALYSIS

Estimation of treatment effectiveness and safety within each database

1. PS-matched cohorts: Within each surveillance cohort by frailty status (frail vs non-frail), we will use logistic regression that estimates the probability of receiving the drug of interest as a function of sociodemographic characteristics, diseases, prescription drugs, comorbidity index, and frailty index. Note that PS model will be fit separately by frailty status. We will perform a 1:1 ratio nearest-neighbor PS matching, with a caliper of 0.2 of the standard deviation of the logit PS (9). We will evaluate balance in covariates using standard mean difference (<0.1 is considered adequate balance) within each surveillance cohort.

2. Primary analysis for effectiveness and safety: For time-to-event analysis of the effectiveness and safety endpoints, we will use Cox proportional hazards regression to estimate the hazard ratios (HR) and 95% confidence intervals (CI) by frailty status (frail vs non-frail). The follow-up will begin on day 1 and end on the day of development of the effectiveness or safety endpoints or the earliest of the following censoring events: switching or discontinuation of the study drug, death not due to the outcome of interest, disenrollment, and end of data period (see Figure 2). Proportional hazards assumptions will be checked using Schoenfeld residuals.

3. Subgroup analyses for primary effectiveness and safety endpoints will be conducted by frailty status (frail vs non-frail):
    a. age (65-74 years vs ≥75 years)
    b. sex
    c. race (black or non-black)
    d. dual eligibility for Medicaid
    e. major multimorbidity burden/pattern (informed by latent class analysis)
    f. dementia (CCW definition)
    g. HF hospitalization status (≥2 or <2 in the past year)

4. Secondary analyses will be conducted by frailty status (frail vs non-frail):
    a. secondary endpoints (individual components of primary effectiveness and safety composite endpoints)

5. Sensitivity analysis for primary effectiveness and safety endpoints will be conducted by frailty status (frail vs non-frail):
    a. "intention-to-treat" analysis with a maximum follow-up time of 1 and 2 years from the index date
    b. exposure risk window or grace period of 14 days

6. Adjustment for multiple testing in detecting signal: We will use the maximum sequential probability ratio testing (maxSPRT) procedure to keep the overall type-1 error rate of 0.05. (10)

Estimation of the pooled treatment effectiveness and safety

7. The treatment effect estimates from 3 databases will be combined using meta-analysis techniques. We will examine the heterogeneity of treatment effect using Cochrane Q statistics and I-square statistics. If there is no statistically significant evidence of treatment effect heterogeneity, we will use inverse probability fixed-effects model to pool the database-specific estimates. If there is significant treatment effect heterogeneity, we will use random-effects model.

8. Reporting of prospective monitoring results: When a statistically significant signal is detected from the pooled analysis for the primary endpoints of effectiveness or safety from pre-specified interim analysis or at the end of the data period (12/31/2020), the findings will be reported

REFERENCES

1. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/207620s013lbl.pdf. U.S. Food and Drug Administration; 2021.
2. McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. N Engl J Med. 2014;371(11):993-1004.
3. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Jr., Colvin MM, et al. 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. Circulation. 2017;136(6):e137-e61.
4. Maddox TM, Januzzi JL, Allen LA, Breathett K, Butler J, Davis LL, et al. 2021 Update to the 2017 ACC Expert Consensus Decision Pathway for Optimization of Heart Failure Treatment: Answers to 10 Pivotal Issues About Heart Failure With Reduced Ejection Fraction. Journal of the American College of Cardiology.0(0).
5. Desai RJ, Lin KJ, Patorno E, Barberio J, Lee M, Levin R, et al. Development and Preliminary Validation of a Medicare Claims-Based Model to Predict Left Ventricular Ejection Fraction Class in Patients With Heart Failure. Circ Cardiovasc Qual Outcomes. 2018;11(12):e004700.
6. Combined Comorbidity Score for Claims Data [Internet]. Available from: https://www.drugepi.org/dope/software
7. Claims-Based Frailty Index [Internet]. 2020 [cited December 1, 2020]. Available from: https://dataverse.harvard.edu/dataverse/cfi/.
8. Chronic Conditions Data Warehouse [Internet]. 2020. Available from: https://www2.ccwdata.org/web/guest/condition-categories/
9. Austin PC. Optimal caliper widths for propensity-score matching when estimating differences in means and differences in proportions in observational studies. Pharm Stat. 2011;10(2):150-61.

10. Brown JS, Kulldorff M, Chan KA, Davis RL, Graham D, Pettus PT, et al. Early detection of adverse drug events within population-based health networks: application of sequential testing methods. Pharmacoepidemiology and Drug Safety. 2007;16(12):1275-84.

Appendix

Acute kidney injury Dx			
ICD10	**ICD9**	**ICD10 Description**	**ICD9 Description**
I120	40391	Hypertensive chronic kidney disease with stage 5 chronic kidney disease or end stage renal disease	Hypertensive chronic kidney disease, unspecified, with chronic kidney disease stage V or end stage renal disease
N170	5845	Acute kidney failure with tubular necrosis	Acute kidney failure with lesion of tubular necrosis
N171	5846	Acute kidney failure with acute cortical necrosis	Acute kidney failure with lesion of renal cortical necrosis
N172	5847	Acute kidney failure with medullary necrosis	Acute kidney failure with lesion of renal medullary [papillary] necrosis
N178	5848	Other acute kidney failure	Acute kidney failure with other specified pathological lesion in kidney
N179	5849	Acute kidney failure, unspecified	Acute kidney failure, unspecified
N19	586	Unspecified kidney failure	Renal failure, unspecified
Z4931	V560	Encounter for adequacy testing for hemodialysis	Encounter for extracorporeal dialysis
Angioedema Dx			
ICD10	**ICD9**	**ICD10 Description**	**ICD9 Description**
T783XXA	9951	Angioneurotic edema, initial encounter	Angioneurotic edema, not elsewhere classified
T783XXD	V5889	Angioneurotic edema, subsequent encounter	Other specified aftercare
T783XXS	9099	Angioneurotic edema, sequela	Late effect of other and unspecified external causes
Chronic kidney disease stage IV or V or dialysis Dx			
ICD10	**ICD9**	**ICD10 Description**	**ICD9 Description**
E1021	25043	Type 1 diabetes mellitus with diabetic nephropathy	Diabetes with renal manifestations, type I [juvenile type], uncontrolled
E1022	25041	Type 1 diabetes mellitus with diabetic chronic kidney disease	Diabetes with renal manifestations, type I [juvenile type], not stated as uncontrolled
E1029	25041	Type 1 diabetes mellitus with other diabetic kidney complication	Diabetes with renal manifestations, type I [juvenile type], not stated as uncontrolled
E1065	25043	Type 1 diabetes mellitus with hyperglycemia	Diabetes with renal manifestations, type I [juvenile type], uncontrolled
E1121	25042	Type 2 diabetes mellitus with diabetic nephropathy	Diabetes with renal manifestations, type II or unspecified type, uncontrolled
E1122	25040	Type 2 diabetes mellitus with diabetic chronic kidney disease	Diabetes with renal manifestations, type II or unspecified type, not stated as uncontrolled
E1129	25040	Type 2 diabetes mellitus with other diabetic kidney complication	Diabetes with renal manifestations, type II or unspecified type, not stated as uncontrolled
E1165	25042	Type 2 diabetes mellitus with hyperglycemia	Diabetes with renal manifestations, type II or unspecified type, uncontrolled
E1321	25040	Other specified diabetes mellitus with diabetic nephropathy	Diabetes with renal manifestations, type II or unspecified type, not stated as uncontrolled
E1322	25040	Other specified diabetes mellitus with diabetic chronic kidney disease	Diabetes with renal manifestations, type II or unspecified type, not stated as uncontrolled
E1329	25040	Other specified diabetes mellitus with other diabetic kidney complication	Diabetes with renal manifestations, type II or unspecified type, not stated as uncontrolled
I120	40391	Hypertensive chronic kidney disease with stage 5 chronic kidney disease or end stage renal disease	Hypertensive chronic kidney disease, unspecified, with chronic kidney disease stage V or end stage renal disease
I129	40390	Hypertensive chronic kidney disease with stage 1 through stage 4 chronic kidney disease, or unspecified chronic kidney disease	Hypertensive chronic kidney disease, unspecified, with chronic kidney disease stage I through stage IV, or unspecified
I130	40491	Hypertensive heart and chronic kidney disease with heart failure and stage 1 through stage 4 chronic kidney disease, or unspecified chronic kidney disease	Hypertensive heart and chronic kidney disease, unspecified, with heart failure and with chronic kidney disease stage I through stage IV, or unspecified
I1310	40490	Hypertensive heart and chronic kidney disease without heart failure, with stage 1 through stage 4 chronic kidney disease, or unspecified chronic kidney disease	Hypertensive heart and chronic kidney disease, unspecified, without heart failure and with chronic kidney disease stage I through stage IV, or unspecified
I1311	40492	Hypertensive heart and chronic kidney disease without heart failure, with stage 5 chronic kidney disease, or end stage renal disease	Hypertensive heart and chronic kidney disease, unspecified, without heart failure and with chronic kidney disease stage V or end stage renal disease
I132	40493	Hypertensive heart and chronic kidney disease with heart failure and with stage 5 chronic kidney disease, or end stage renal disease	Hypertensive heart and chronic kidney disease, unspecified, with heart failure and chronic kidney disease stage V or end stage renal disease
N181	5851	Chronic kidney disease, stage 1	Chronic kidney disease, Stage I
N182	5852	Chronic kidney disease, stage 2 (mild)	Chronic kidney disease, Stage II (mild)
N183	5853	Chronic kidney disease, stage 3 (moderate)	Chronic kidney disease, Stage III (moderate)
N184	5854	Chronic kidney disease, stage 4 (severe)	Chronic kidney disease, Stage IV (severe)
N189	5859	Chronic kidney disease, unspecified	Chronic kidney disease, unspecified
N250	5880	Renal osteodystrophy	Renal osteodystrophy
N251	5881	Nephrogenic diabetes insipidus	Nephrogenic diabetes insipidus
N2581	58881	Secondary hyperparathyroidism of renal origin	Secondary hyperparathyroidism (of renal origin)
N2589	58889	Other disorders resulting from impaired renal tubular function	Other specified disorders resulting from impaired renal function
N259	5889	Disorder resulting from impaired renal tubular function, unspecified	Unspecified disorder resulting from impaired renal function
End-Stage Renal Disease (ESRD) Dx			
ICD10	**ICD9**	**ICD10 Description**	**ICD9 Description**
I953	45821	Hypotension of hemodialysis	Hypotension of hemodialysis
N185	5855	Chronic kidney disease, stage 5	Chronic kidney disease, Stage V

Appendix

N186	5856	End stage renal disease	End stage renal disease
T82818A	99673	Embolism due to vascular prosthetic devices, implants and grafts, initial encounter	Other complications due to renal dialysis device, implant, and graft
T82828A	99673	Fibrosis due to vascular prosthetic devices, implants and grafts, initial encounter	Other complications due to renal dialysis device, implant, and graft
T82838A	99673	Hemorrhage due to vascular prosthetic devices, implants and grafts, initial encounter	Other complications due to renal dialysis device, implant, and graft
T82848A	99673	Pain due to vascular prosthetic devices, implants and grafts, initial encounter	Other complications due to renal dialysis device, implant, and graft
T82858A	99673	Stenosis of other vascular prosthetic devices, implants and grafts, initial encounter	Other complications due to renal dialysis device, implant, and graft
T82868A	99673	Thrombosis due to vascular prosthetic devices, implants and grafts, initial encounter	Other complications due to renal dialysis device, implant, and graft
T82898A	99673	Other specified complication of vascular prosthetic devices, implants and grafts, initial encounter	Other complications due to renal dialysis device, implant, and graft
T85611A	99656	Breakdown (mechanical) of intraperitoneal dialysis catheter, initial encounter	Mechanical complication due to peritoneal dialysis catheter
T85621A	99656	Displacement of intraperitoneal dialysis catheter, initial encounter	Mechanical complication due to peritoneal dialysis catheter
T85631A	99656	Leakage of intraperitoneal dialysis catheter, initial encounter	Mechanical complication due to peritoneal dialysis catheter
T85691A	99656	Other mechanical complication of intraperitoneal dialysis catheter, initial encounter	Mechanical complication due to peritoneal dialysis catheter
T8571XA	99668	Infection and inflammatory reaction due to peritoneal dialysis catheter, initial encounter	Infection and inflammatory reaction due to peritoneal dialysis catheter
T8610	99681	Unspecified complication of kidney transplant	Complications of transplanted kidney
T8611	99681	Kidney transplant rejection	Complications of transplanted kidney
T8612	99681	Kidney transplant failure	Complications of transplanted kidney
T8613	99681	Kidney transplant infection	Complications of transplanted kidney
T8619	99681	Other complication of kidney transplant	Complications of transplanted kidney
Z4822	V420	Encounter for aftercare following kidney transplant	Kidney replaced by transplant
Z4901	V561	Encounter for fitting and adjustment of extracorporeal dialysis catheter	Fitting and adjustment of extracorporeal dialysis catheter
Z4902	V562	Encounter for fitting and adjustment of peritoneal dialysis catheter	Fitting and adjustment of peritoneal dialysis catheter
Z4931	V5631	Encounter for adequacy testing for hemodialysis	Encounter for adequacy testing for hemodialysis
Z4932	V568	Encounter for adequacy testing for peritoneal dialysis	Encounter for other dialysis
Z9115	V4512	Patient's noncompliance with renal dialysis	Noncompliance with renal dialysis
Z940	V420	Kidney transplant status	Kidney replaced by transplant
Z992	V4511	Dependence on renal dialysis	Renal dialysis status

End-Stage Renal Disease (ESRD) Px			
ICD10	**ICD9**	**ICD10 Description**	**ICD9 Description**
03130JD	3993	Bypass Right Subclavian Artery to Upper Arm Vein with Synthetic Substitute, Open Approach	Insertion of vessel-to-vessel cannula
03130ZD	3927	Bypass Right Subclavian Artery to Upper Arm Vein, Open Approach	Arteriovenostomy for renal dialysis
03140JD	3993	Bypass Left Subclavian Artery to Upper Arm Vein with Synthetic Substitute, Open Approach	Insertion of vessel-to-vessel cannula
03140ZD	3927	Bypass Left Subclavian Artery to Upper Arm Vein, Open Approach	Arteriovenostomy for renal dialysis
031509V	3927	Bypass Right Axillary Artery to Superior Vena Cava with Autologous Venous Tissue, Open Approach	Arteriovenostomy for renal dialysis
03150AV	3927	Bypass Right Axillary Artery to Superior Vena Cava with Autologous Arterial Tissue, Open Approach	Arteriovenostomy for renal dialysis
03150JD	3993	Bypass Right Axillary Artery to Upper Arm Vein with Synthetic Substitute, Open Approach	Insertion of vessel-to-vessel cannula
03150JV	3927	Bypass Right Axillary Artery to Superior Vena Cava with Synthetic Substitute, Open Approach	Arteriovenostomy for renal dialysis
03150KV	3927	Bypass Right Axillary Artery to Superior Vena Cava with Nonautologous Tissue Substitute, Open Approach	Arteriovenostomy for renal dialysis
03150ZD	3927	Bypass Right Axillary Artery to Upper Arm Vein, Open Approach	Arteriovenostomy for renal dialysis
03150ZV	3927	Bypass Right Axillary Artery to Superior Vena Cava, Open Approach	Arteriovenostomy for renal dialysis

Appendix

031609V	3927	Bypass Left Axillary Artery to Superior Vena Cava with Autologous Venous Tissue, Open Approach	Arteriovenostomy for renal dialysis
03160AV	3927	Bypass Left Axillary Artery to Superior Vena Cava with Autologous Arterial Tissue, Open Approach	Arteriovenostomy for renal dialysis
03160JD	3993	Bypass Left Axillary Artery to Upper Arm Vein with Synthetic Substitute, Open Approach	Insertion of vessel-to-vessel cannula
03160JV	3927	Bypass Left Axillary Artery to Superior Vena Cava with Synthetic Substitute, Open Approach	Arteriovenostomy for renal dialysis
03160KV	3927	Bypass Left Axillary Artery to Superior Vena Cava with Nonautologous Tissue Substitute, Open Approach	Arteriovenostomy for renal dialysis
03160ZD	3927	Bypass Left Axillary Artery to Upper Arm Vein, Open Approach	Arteriovenostomy for renal dialysis
03160ZV	3927	Bypass Left Axillary Artery to Superior Vena Cava, Open Approach	Arteriovenostomy for renal dialysis
031709V	3927	Bypass Right Brachial Artery to Superior Vena Cava with Autologous Venous Tissue, Open Approach	Arteriovenostomy for renal dialysis
03170AV	3927	Bypass Right Brachial Artery to Superior Vena Cava with Autologous Arterial Tissue, Open Approach	Arteriovenostomy for renal dialysis
03170JD	3993	Bypass Right Brachial Artery to Upper Arm Vein with Synthetic Substitute, Open Approach	Insertion of vessel-to-vessel cannula
03170JV	3927	Bypass Right Brachial Artery to Superior Vena Cava with Synthetic Substitute, Open Approach	Arteriovenostomy for renal dialysis
03170KV	3927	Bypass Right Brachial Artery to Superior Vena Cava with Nonautologous Tissue Substitute, Open Approach	Arteriovenostomy for renal dialysis
03170ZD	3927	Bypass Right Brachial Artery to Upper Arm Vein, Open Approach	Arteriovenostomy for renal dialysis
03170ZV	3927	Bypass Right Brachial Artery to Superior Vena Cava, Open Approach	Arteriovenostomy for renal dialysis
031809V	3927	Bypass Left Brachial Artery to Superior Vena Cava with Autologous Venous Tissue, Open Approach	Arteriovenostomy for renal dialysis
03180AV	3927	Bypass Left Brachial Artery to Superior Vena Cava with Autologous Arterial Tissue, Open Approach	Arteriovenostomy for renal dialysis
03180JD	3993	Bypass Left Brachial Artery to Upper Arm Vein with Synthetic Substitute, Open Approach	Insertion of vessel-to-vessel cannula
03180JV	3927	Bypass Left Brachial Artery to Superior Vena Cava with Synthetic Substitute, Open Approach	Arteriovenostomy for renal dialysis
03180KV	3927	Bypass Left Brachial Artery to Superior Vena Cava with Nonautologous Tissue Substitute, Open Approach	Arteriovenostomy for renal dialysis
03180ZD	3927	Bypass Left Brachial Artery to Upper Arm Vein, Open Approach	Arteriovenostomy for renal dialysis
03180ZV	3927	Bypass Left Brachial Artery to Superior Vena Cava, Open Approach	Arteriovenostomy for renal dialysis
03190JF	3993	Bypass Right Ulnar Artery to Lower Arm Vein with Synthetic Substitute, Open Approach	Insertion of vessel-to-vessel cannula
03190ZF	3927	Bypass Right Ulnar Artery to Lower Arm Vein, Open Approach	Arteriovenostomy for renal dialysis
031A0JF	3993	Bypass Left Ulnar Artery to Lower Arm Vein with Synthetic Substitute, Open Approach	Insertion of vessel-to-vessel cannula
031A0ZF	3927	Bypass Left Ulnar Artery to Lower Arm Vein, Open Approach	Arteriovenostomy for renal dialysis
031B0JF	3994	Bypass Right Radial Artery to Lower Arm Vein with Synthetic Substitute, Open Approach	Replacement of vessel-to-vessel cannula
031B0ZF	3927	Bypass Right Radial Artery to Lower Arm Vein, Open Approach	Arteriovenostomy for renal dialysis
031C0JF	3994	Bypass Left Radial Artery to Lower Arm Vein with Synthetic Substitute, Open Approach	Replacement of vessel-to-vessel cannula
031C0ZF	3927	Bypass Left Radial Artery to Lower Arm Vein, Open Approach	Arteriovenostomy for renal dialysis
03LK0CZ	3953	Occlusion of Right Internal Carotid Artery with Extraluminal Device, Open Approach	Repair of arteriovenous fistula
03LK0ZZ	3953	Occlusion of Right Internal Carotid Artery, Open Approach	Repair of arteriovenous fistula
03LK3CZ	3953	Occlusion of Right Internal Carotid Artery with Extraluminal Device, Percutaneous Approach	Repair of arteriovenous fistula
03LK3ZZ	3953	Occlusion of Right Internal Carotid Artery, Percutaneous Approach	Repair of arteriovenous fistula

Appendix

03LK4CZ	3953	Occlusion of Right Internal Carotid Artery with Extraluminal Device, Percutaneous Endoscopic Approach	Repair of arteriovenous fistula
03LK4ZZ	3953	Occlusion of Right Internal Carotid Artery, Percutaneous Endoscopic Approach	Repair of arteriovenous fistula
03LL0CZ	3953	Occlusion of Left Internal Carotid Artery with Extraluminal Device, Open Approach	Repair of arteriovenous fistula
03LL0ZZ	3953	Occlusion of Left Internal Carotid Artery, Open Approach	Repair of arteriovenous fistula
03LL3CZ	3953	Occlusion of Left Internal Carotid Artery with Extraluminal Device, Percutaneous Approach	Repair of arteriovenous fistula
03LL3ZZ	3953	Occlusion of Left Internal Carotid Artery, Percutaneous Approach	Repair of arteriovenous fistula
03LL4CZ	3953	Occlusion of Left Internal Carotid Artery with Extraluminal Device, Percutaneous Endoscopic Approach	Repair of arteriovenous fistula
03LL4ZZ	3953	Occlusion of Left Internal Carotid Artery, Percutaneous Endoscopic Approach	Repair of arteriovenous fistula
03PY07Z	3943	Removal of Autologous Tissue Substitute from Upper Artery, Open Approach	Removal of arteriovenous shunt for renal dialysis
03PY0JZ	3994	Removal of Synthetic Substitute from Upper Artery, Open Approach	Replacement of vessel-to-vessel cannula
03PY0KZ	3943	Removal of Nonautologous Tissue Substitute from Upper Artery, Open Approach	Removal of arteriovenous shunt for renal dialysis
03PY37Z	3943	Removal of Autologous Tissue Substitute from Upper Artery, Percutaneous Approach	Removal of arteriovenous shunt for renal dialysis
03PY3JZ	3994	Removal of Synthetic Substitute from Upper Artery, Percutaneous Approach	Replacement of vessel-to-vessel cannula
03PY3KZ	3943	Removal of Nonautologous Tissue Substitute from Upper Artery, Percutaneous Approach	Removal of arteriovenous shunt for renal dialysis
03PY47Z	3943	Removal of Autologous Tissue Substitute from Upper Artery, Percutaneous Endoscopic Approach	Removal of arteriovenous shunt for renal dialysis
03PY4JZ	3994	Removal of Synthetic Substitute from Upper Artery, Percutaneous Endoscopic Approach	Replacement of vessel-to-vessel cannula
03PY4KZ	3943	Removal of Nonautologous Tissue Substitute from Upper Artery, Percutaneous Endoscopic Approach	Removal of arteriovenous shunt for renal dialysis
03VK0CZ	3953	Restriction of Right Internal Carotid Artery with Extraluminal Device, Open Approach	Repair of arteriovenous fistula
03VK3CZ	3953	Restriction of Right Internal Carotid Artery with Extraluminal Device, Percutaneous Approach	Repair of arteriovenous fistula
03VK4CZ	3953	Restriction of Right Internal Carotid Artery with Extraluminal Device, Percutaneous Endoscopic Approach	Repair of arteriovenous fistula
03VL0CZ	3953	Restriction of Left Internal Carotid Artery with Extraluminal Device, Open Approach	Repair of arteriovenous fistula
03VL3CZ	3953	Restriction of Left Internal Carotid Artery with Extraluminal Device, Percutaneous Approach	Repair of arteriovenous fistula
03VL4CZ	3953	Restriction of Left Internal Carotid Artery with Extraluminal Device, Percutaneous Endoscopic Approach	Repair of arteriovenous fistula
03WY0JZ	3994	Revision of Synthetic Substitute in Upper Artery, Open Approach	Replacement of vessel-to-vessel cannula
03WY3JZ	3994	Revision of Synthetic Substitute in Upper Artery, Percutaneous Approach	Replacement of vessel-to-vessel cannula
03WY4JZ	3994	Revision of Synthetic Substitute in Upper Artery, Percutaneous Endoscopic Approach	Replacement of vessel-to-vessel cannula
03WYXJZ	3994	Revision of Synthetic Substitute in Upper Artery, External Approach	Replacement of vessel-to-vessel cannula
05HY33Z	3895	Insertion of Infusion Device into Upper Vein, Percutaneous Approach	Venous catheterization for renal dialysis
06HY33Z	3895	Insertion of Infusion Device into Lower Vein, Percutaneous Approach	Venous catheterization for renal dialysis
0TS00ZZ	5561	Reposition Right Kidney, Open Approach	Renal autotransplantation
0TS10ZZ	5561	Reposition Left Kidney, Open Approach	Renal autotransplantation
0TY00Z0	5569	Transplantation of Right Kidney, Allogeneic, Open Approach	Other kidney transplantation
0TY00Z1	5569	Transplantation of Right Kidney, Syngeneic, Open Approach	Other kidney transplantation

Appendix

0TY00Z2	5569	Transplantation of Right Kidney, Zooplastic, Open Approach	Other kidney transplantation
0TY10Z0	5569	Transplantation of Left Kidney, Allogeneic, Open Approach	Other kidney transplantation
0TY10Z1	5569	Transplantation of Left Kidney, Syngeneic, Open Approach	Other kidney transplantation
0TY10Z2	5569	Transplantation of Left Kidney, Zooplastic, Open Approach	Other kidney transplantation
3E1M39Z	5498	Irrigation of Peritoneal Cavity using Dialysate, Percutaneous Approach	Peritoneal dialysis
5A1D70Z	3995	Performance of Urinary Filtration, Intermittent, Less than 6 Hours Per Day	Hemodialysis
5A1D80Z	3995	Performance of Urinary Filtration, Prolonged Intermittent, 6-18 hours Per Day	Hemodialysis
5A1D90Z	3995	Performance of Urinary Filtration, Continuous, Greater than 18 hours Per Day	Hemodialysis
Heart Failure Dx			
ICD10	**ICD9**	**ICD10 Description**	**ICD9 Description**
I0981	39891	Rheumatic heart failure	Rheumatic heart failure (congestive)
I110	40291	Hypertensive heart disease with heart failure	Unspecified hypertensive heart disease with heart failure
I130	40491	Hypertensive heart and chronic kidney disease with heart failure and stage 1 through stage 4 chronic kidney disease, or unspecified chronic kidney disease	Hypertensive heart and chronic kidney disease, unspecified, with heart failure and with chronic kidney disease stage I through stage IV, or unspecified
I132	40493	Hypertensive heart and chronic kidney disease with heart failure and with stage 5 chronic kidney disease, or end stage renal disease	Hypertensive heart and chronic kidney disease, unspecified, with heart failure and chronic kidney disease stage V or end stage renal disease
I501	4281	Left ventricular failure, unspecified	Left heart failure
I5020	4280	Unspecified systolic (congestive) heart failure	Congestive heart failure, unspecified
I5021	4280	Acute systolic (congestive) heart failure	Congestive heart failure, unspecified
I5022	4280	Chronic systolic (congestive) heart failure	Congestive heart failure, unspecified
I5023	4280	Acute on chronic systolic (congestive) heart failure	Congestive heart failure, unspecified
I5030	4280	Unspecified diastolic (congestive) heart failure	Congestive heart failure, unspecified
I5031	4280	Acute diastolic (congestive) heart failure	Congestive heart failure, unspecified
I5032	4280	Chronic diastolic (congestive) heart failure	Congestive heart failure, unspecified
I5033	4280	Acute on chronic diastolic (congestive) heart failure	Congestive heart failure, unspecified
I5040	4280	Unspecified combined systolic (congestive) and diastolic (congestive) heart failure	Congestive heart failure, unspecified
I5041	4280	Acute combined systolic (congestive) and diastolic (congestive) heart failure	Congestive heart failure, unspecified
I5042	4280	Chronic combined systolic (congestive) and diastolic (congestive) heart failure	Congestive heart failure, unspecified
I5043	4280	Acute on chronic combined systolic (congestive) and diastolic (congestive) heart failure	Congestive heart failure, unspecified
I50810	4289	Right heart failure, unspecified	Heart failure, unspecified
I50811	4289	Acute right heart failure	Heart failure, unspecified
I50812	4289	Chronic right heart failure	Heart failure, unspecified
I50813	4289	Acute on chronic right heart failure	Heart failure, unspecified
I50814	4280	Right heart failure due to left heart failure	Congestive heart failure, unspecified
I5082	4289	Biventricular heart failure	Heart failure, unspecified
I5083	4289	High output heart failure	Heart failure, unspecified
I5084	4289	End stage heart failure	Heart failure, unspecified
I5089	4289	Other heart failure	Heart failure, unspecified
I509	4289	Heart failure, unspecified	Heart failure, unspecified
Hypotension Dx			
ICD10	**ICD9**	**ICD10 Description**	**ICD9 Description**
I950	4581	Idiopathic hypotension	Chronic hypotension
I951	4580	Orthostatic hypotension	Orthostatic hypotension
I953	45821	Hypotension of hemodialysis	Hypotension of hemodialysis
I9589	4588	Other hypotension	Other specified hypotension
I959	4589	Hypotension, unspecified	Hypotension, unspecified
I952	45829	Hypotension due to drugs	Other iatrogenic hypotension
I9581	45829	Postprocedural hypotension	Other iatrogenic hypotension
Hyperkalemia Dx			
ICD10	**ICD9**	**ICD10 Description**	**ICD9 Description**
E875	2767	Hyperkalemia	Hyperpotassemia