



Cadrenal Therapeutics, Inc.
NASDAQ: CVKD

July 2024



Caution Concerning Forward-looking Statements

This document contains forward-looking statements. In addition, from time to time, we or our representatives may make forward-looking statements orally or in writing. We base these forward-looking statements on our expectations and projections about future events, which we derive from the information currently available to us. Such forward-looking statements relate to future events or our future performance, including: our financial performance and projections; our growth in revenue and earnings; and our business prospects and opportunities. You can identify forward-looking statements by those that are not historical in nature, particularly those that use terminology such as “may,” “should,” “expects,” “anticipates,” “contemplates,” “estimates,” “believes,” “plans,” “projected,” “predicts,” “potential,” or “hopes” or the negative of these or similar terms.

In evaluating these forward-looking statements, you should consider various factors, including: our ability to successfully develop and commercialize product candidates, our ability to raise capital when needed, and the competitive environment of our business. These and other factors may cause our actual results to differ materially from any forward-looking statement, including those risk factors disclosed in our Annual Report on Form 10-K for the year ended December 31, 2023 filed with the Securities and Exchange Commission on March 11, 2024. Forward-looking statements are only predictions. The forward-looking events discussed in this document and other statements made from time to time by us or our representatives may not occur, and actual events and results may differ materially and are subject to risks, uncertainties, and assumptions about us. We are not obligated to publicly update or revise any forward-looking statement, whether as a result of uncertainties and assumptions, the forward-looking events discussed in this document, and other statements made from time to time by us or our representatives might not occur.

Cadrenal Therapeutics Overview


Late-stage Development Company with Multiple Orphan-drug and Fast-track Designations

Developing **tecarfarin**, a novel oral and reversible vitamin K antagonist (VKA) anticoagulant to prevent heart attacks, strokes and deaths due to blood clots in patients with implanted cardiac devices or rare cardiovascular (CV) conditions who require chronic anticoagulation

Targeted at rare CV conditions where warfarin, the only available VKA, has failed to achieve sufficiently reliable anticoagulation and Direct Oral Anticoagulants, or DOACs have shown harm or no benefit



Left Ventricular Assist Devices (LVAD) for heart failure patients




FDA Orphan Drug Designation




End-stage Kidney Disease (ESKD) + Atrial Fibrillation (AFib)



FDA Orphan Drug Designation



Mechanical Heart Valve (MHV) patients with difficult-to-control TTR* or genetic resistance to warfarin



A Review of Tecarfarin

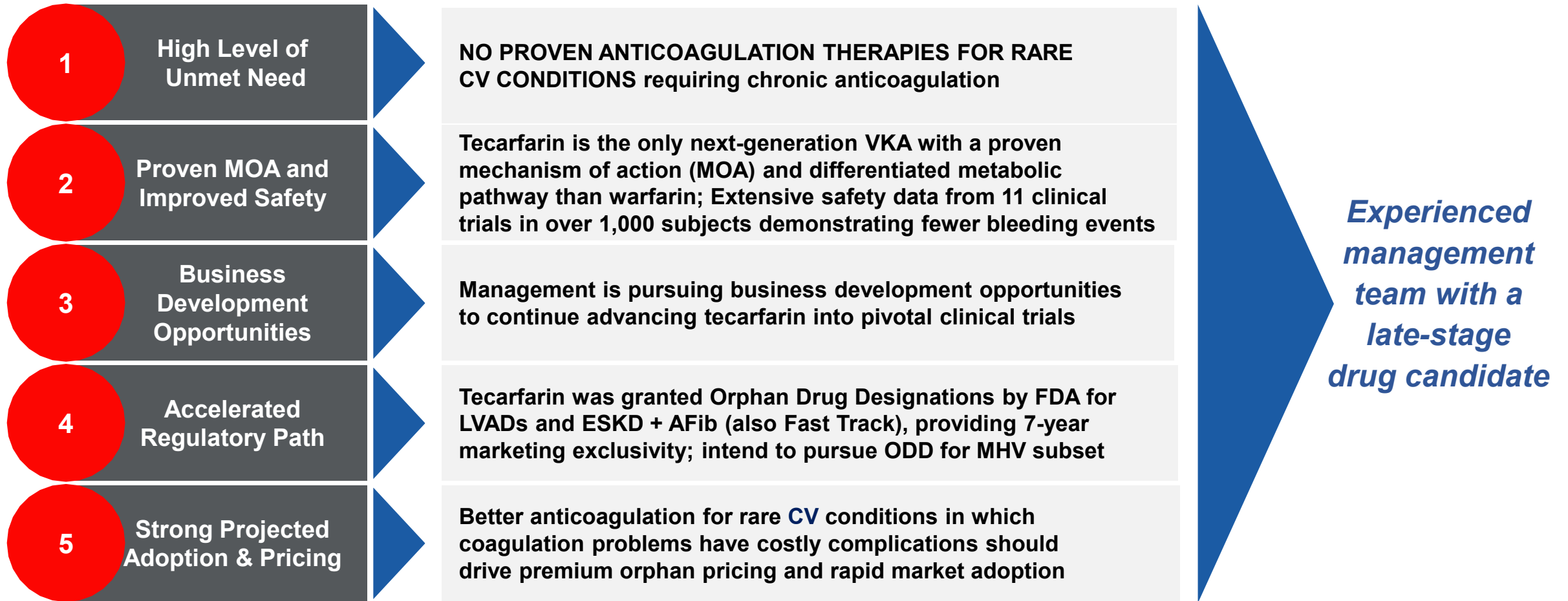
Tecarfarin is the **ONLY** next-generation VKA (blood thinner) in development for warfarin-dependent patients who have no proven therapy and cannot use the Eliquis-class drugs

TECARFARIN HIGHLIGHTS

- ➡ A novel VKA blood thinner for patients with implanted cardiac devices such as LVADs or rare CV conditions such as ESKD patients with AFib who require lifelong anticoagulation
- ➡ Other targeted patients include those with Structural Heart Diseases requiring Mechanical Heart Valves who are warfarin-resistant
- ➡ Two FDA Orphan Drug Designations with marketing exclusivity
- ➡ A New Weapon in the War Against Warfarin – “The Most Dangerous Drug in America”



Key Investment Highlights for Tecarfarin Opportunity



Leadership Team: Clinical to Commercial Expertise



Quang Pham
CEO & Founder, Chairman



Douglas Losordo, MD
Chief Medical Officer



Matthew Szot, CPA
Chief Financial Officer



Jeff Cole
Chief Operating Officer



John R. Murphy
Board Member



Steven Zelenkofske, DO
Board Member



Glynn Wilson, PhD
Board Member



Robert Lisicki
Board Member



Scientific Advisors with Deep Experience in CV and Beyond



**Mandeep, Mehra MD, MSc,
FRCP**

Medical Director of the Brigham Heart and Vascular Center,

William Harvey Distinguished Chair in Advanced Cardiovascular Medicine



Richard Whitlock, MD

Cardiac Surgeon and Professor of Surgery,
McMaster

University Medical Center Investigator,
Population Health Research Institute



Michael Lincoff, MD

Vice Chairman, Dept. of Cardiovascular Medicine,
Cleveland Clinic

Director of Clinical Research,
Lerner Research Institute



Elaine M. Hylek, MD, MPH

Professor of Medicine,
Boston University School of Medicine
Director of the Thrombosis and Anticoagulation Service at **Boston Medical Center (BMC)**



Wolfgang C. Winkelmayr, MD, MPH

Chief, Section of Nephrology,
Professor of Medicine, **Baylor University**

Director,
Selzman Institute for Kidney Health



C. Michael Gibson, MD

Professor of Medicine,
Harvard Medical School

Interventional Cardiologist,
Beth Israel Deaconess Medical Center

President & CEO,
Baim Institute for Clinical Research



Christopher Granger, MD

Professor of Medicine in the Division of Cardiology,
Duke University

Member, Duke Clinical Research Institute (DCRI)





Sean Pokorney, MD, MBA

Electrophysiologist and Assistant Professor of Medicine,
Duke University

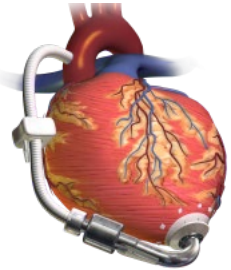
The Problem: Certain Rare CV Conditions Lack Effective Anticoagulation

Warfarin is not approved for many of the rare CV conditions for which it is prescribed, and physicians are hesitant to prescribe DOACs more broadly, given the negative evidence in clinical trials

SIGNIFICANT ISSUES WITH CURRENT THERAPIES FOR THESE PATIENTS

	Warfarin	DOACs (Pradaxa, Xarelto, Eliquis & Savaysa)
<p>LVAD</p> 	<ul style="list-style-type: none"> High frequency of hemorrhagic events despite warfarin therapy Unstable metabolism due to drug-drug interactions, genetic variability of elimination pathway Late-stage heart failure and renal dysfunction are often seen in conjunction. Chronic kidney disease (CKD) inhibits the metabolism of warfarin. 	<ul style="list-style-type: none"> Cost and time of reversal compared to VKA is not acceptable for patients at high risk of bleeding or intervention LVAD patients excluded from approval studies DOACs not in guidelines for LVAD patients
<p>ESKD+AFib</p> 	<ul style="list-style-type: none"> Higher risk of bleeding in dialysis patients with AFib compared to DOACs Multiple dose adjustments to keep patients within International Normalized Ratio (INR) range Drug interaction in patients with multiple comorbidities 	<ul style="list-style-type: none"> Limited head-to-head evidence; existing data fails to demonstrate benefit in thromboembolism and reveals stroke risk Not included in ESKD treatment guidelines Ambiguity in dosing recommendations

LVADs are a Double-digit Growth Market



LVAD Market by Application and Geography - Forecast and Analysis 2021-2025

Market growth will
ACCELERATE
at a CAGR of

12.23%



46%

of the growth will
originate from
North America

Source: [LVADS Market Size, Share, Growth, Trends Industry Analysis Forecast 2025 Technavio](#)

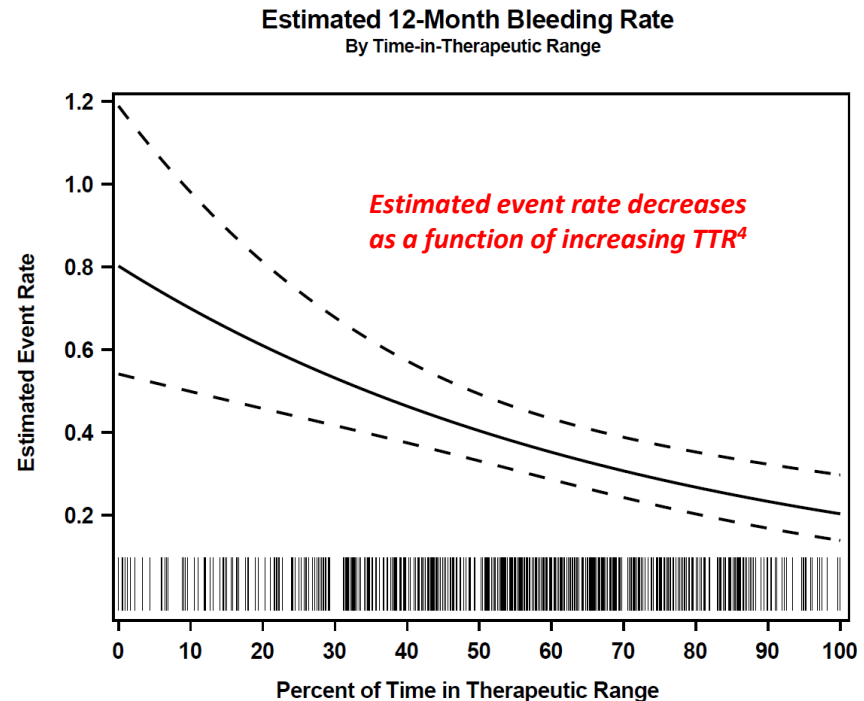


Bleeding Rate in LVAD Patients is a Major Problem

Poor quality anticoagulation, manifest as sub-target TTR, is the cause

Recent clinical evidence from the ARIES-HM3 study documents the consequences of suboptimal anticoagulation with warfarin in LVAD patients

- ❖ **Time in Therapeutic Range (TTR)^{1,2,3}**
 - Well-established marker used to evaluate anticoagulation quality (safety and efficacy)
 - Higher TTR levels correlate directly with improved clinical outcomes including rates of death, bleeding, myocardial infarction, stroke, and systemic embolism
- ❖ **TTR predictive of clinical outcomes**
- ❖ Quality of VKA management as measured by TTR correlates strongly with the occurrence of non-surgical bleeding risk in patients with the HM3 LVAD⁴
- ❖ TTR measurements correlate linearly with bleeding risk (Linear regression p-value=0.007)⁴

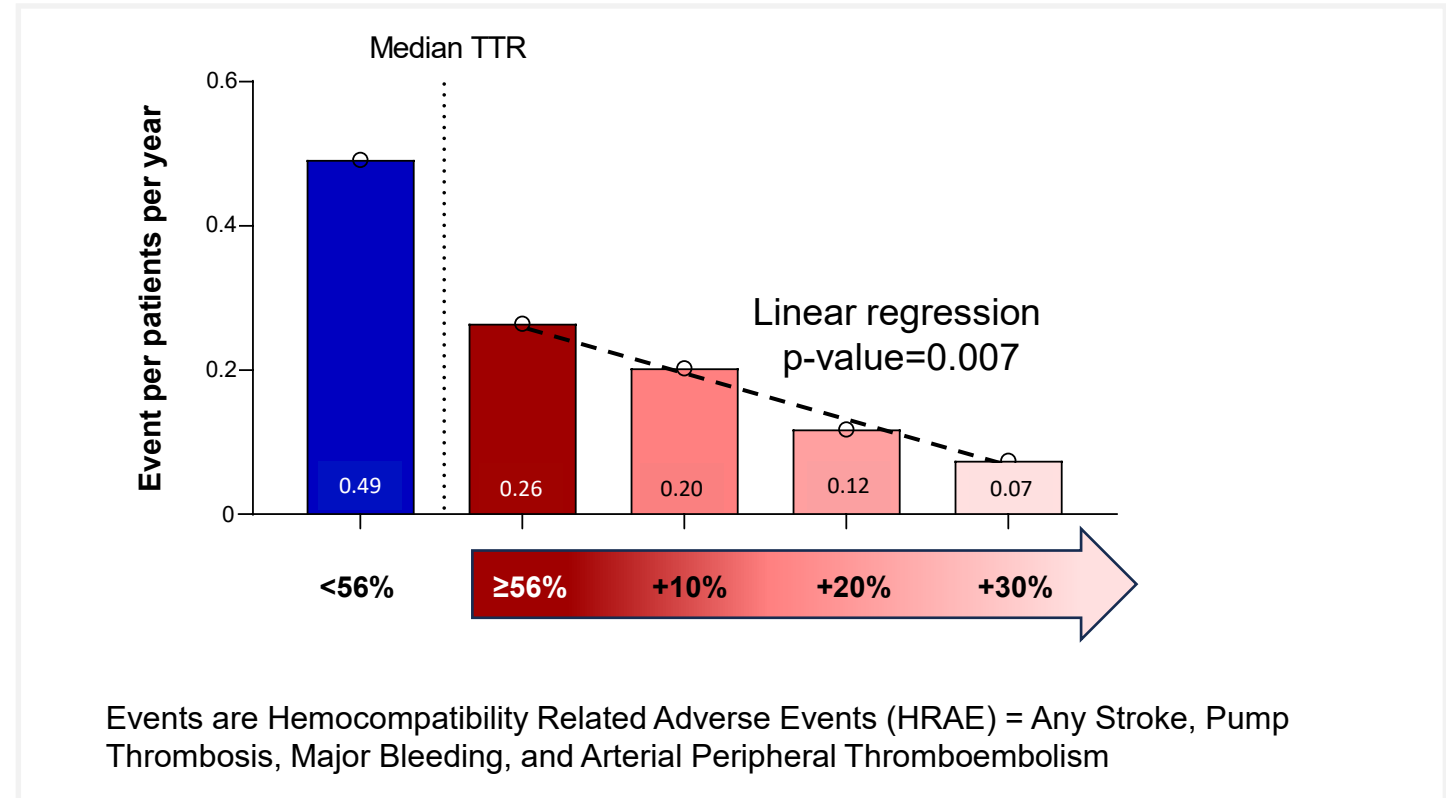


1) White et al. 2007; 2) Currie et al. 2006; 3) Jones et al. 2005

⁴Mehra et al; Impact Of Vitamin K Antagonist Therapy On Outcomes In a Randomized Controlled Trial of Aspirin Removal In Left Ventricular Assist Device Patients - A Pre-specified Analysis From the ARIES-HM3 Trial; Presented April 2024 at the ISHLT Annual Meeting

ARIES-HM3 Study (Sponsored by Abbott) Documents the Impact of Poor Anticoagulation Quality of Adverse Events in LVAD patients

- ❖ Rate of severe bleeding significantly increased when TTR falls below 56%
- ❖ Mean TTR in LVAD patients treated with warfarin is <50% (Martinez et al 2018)



The Solution: Tecarfarin Aims to Solve Warfarin's Major Problems and Fill Significant Market Void



Warfarin: Unreliable metabolism

MAJOR PROBLEM

for patients with rare CV conditions

Variable/Unreliable anticoagulation
in patients at high risk for thrombotic events

Challenging to control
despite nearly 70 years of use

Metabolism via the
cytochrome P450 pathway

potential drug-drug interactions

Significant variability in PK due to genetic
variants and competition with other drugs



SOLUTION: Tecarfarin

SPECIFICALLY DESIGNED TO
solve the warfarin metabolism problem, thereby
DECREASING RISK OF STROKE & BLEEDING

Metabolized via an alternate pathway that is
abundant and essentially insaturable

Reliable, stable PK profile. **Tecarfarin is not
impacted by kidney impairment.**



STABLE ANTICOAGULATION
with proven mechanism of action
including patients with rare CV conditions

Attractive Addressable Market Opportunities

U.S. market potential estimated more than \$2 billion for three targeted rare CV conditions



Left Ventricular Assist Devices



End-stage Kidney Disease with AFib



Mechanic Heart Valves with Difficult-to-Control TTR



Approximately

>\$2 Billion

Combined Peak Annual Market Potential*

Tecarfarin Clinical Development Pipeline

Potential 2024 catalysts for future milestones to build enterprise value

Program	Prioritized Target Indications	Regulatory Strategy/Status	Development Phase				
			Discovery	Preclinical	Phase I	Phase II	Phase III
Tecarfarin	Left Ventricular Assist Devices (LVADs)	FDA Orphan Drug Designation Granted Developing Trial Protocol	[Progress bar with red star in Phase III]				
	End Stage Kidney Disease with AFib	FDA Orphan Drug Designation Granted FDA Fast Track Designation Granted EMA Orphan Drug Application In Process	[Progress bar with red star in Phase III]				
	Mechanical Heart Valve (MHV) patients with difficult-to-control TTR or genetic resistance to warfarin	Developing FDA Orphan Drug Application	[Progress bar with red star in Phase III]				

Future milestones this year may include Ph 3 trial enrollment, anticipated data readouts and progress with strategic partnerships

Tecarfarin Demonstrates TTR Above Anticoagulation Control Target

Phase 2/3 trial shows Tecarfarin provides stable anticoagulation with >72% TTR overall and across key subgroups

Phase 2/3 Trial completed (N=607)

- Tecarfarin vs. well-controlled warfarin trial
- Randomized, double-blind trial designed to compare the quality of anticoagulation
- Average Time in Therapeutic Range (TTR) as measured by the International Normalized Ratio (INR)
- Dosing managed by a centralized dose control center



Key Tecarfarin Findings

Tecarfarin Demonstrated **TTR >72%** overall and across key subgroups

Demonstrated trends suggesting **improved TTR control** in key subgroups expected to do poorly with warfarin

Demonstrated **numerically fewer major bleeding** as warfarin and **no thrombotic events**

TTR of 70% or greater is generally accepted as the goal for stable anticoagulation with a VKA

In real world use, warfarin does not achieve this goal

Phase 2/3 Trial Shows Tecarfarin is Well-Tolerated for Stroke and Thrombus Prevention, with Fewer Hemorrhagic Events

Tecarfarin had fewer thrombotic events compared to warfarin

Randomized, double-blind clinical trial

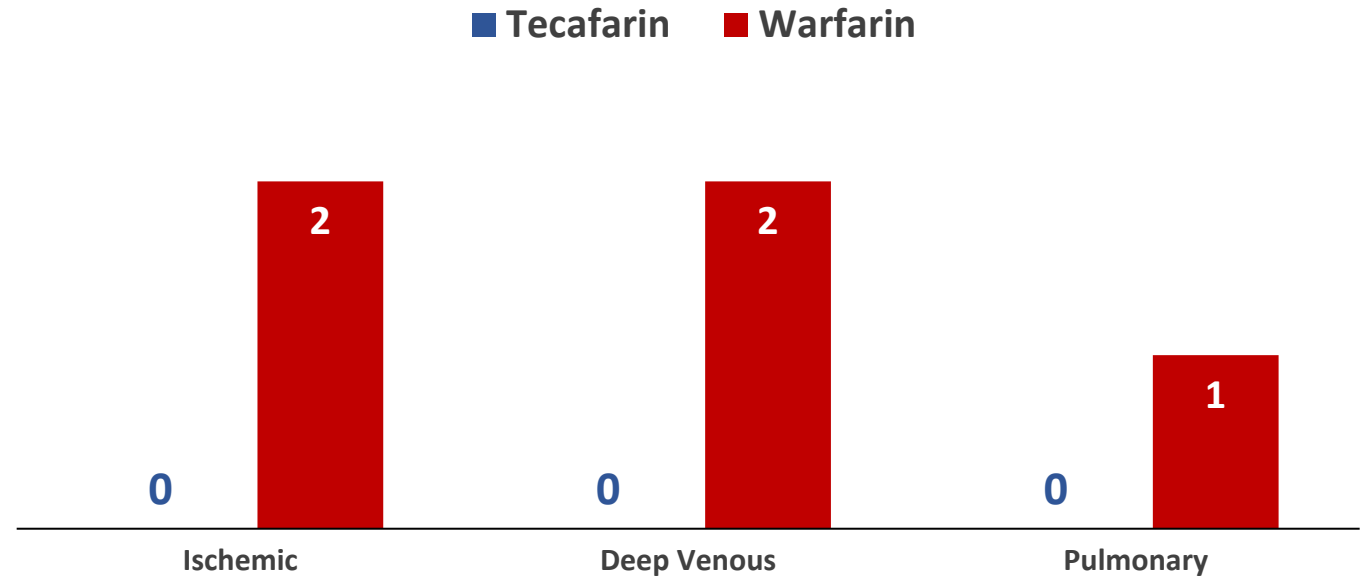


N=607

Patients with indications for chronic anticoagulation

Tecarfarin (n = 304)

Warfarin (n = 303)



Tecarfarin-treated subjects experienced numerically fewer major hemorrhages than the warfarin-treated patients and had numerically fewer thrombotic events

Tecarfarin Phase 1 PK Trial in Stage 4 CKD Patients Provides Evidence that CKD Does Not Alter Tecarfarin Exposure While Warfarin Exposure is Increased

Summary Table

% change between Stage 4 CKD patients vs healthy subjects matched for each drug using a randomized crossover design (n=23)

	Tecarfarin (% change)	(S)-Warfarin (% change)
AUC	+15%	+44%
t _{1/2}	-8%	+19%

Result Highlights

Tecarfarin



Elimination from the body was **not affected** by severe kidney dysfunction



Half-life and the amount of drug in the body were **similar** in Stage 4 CKD patients and healthy subjects

Warfarin

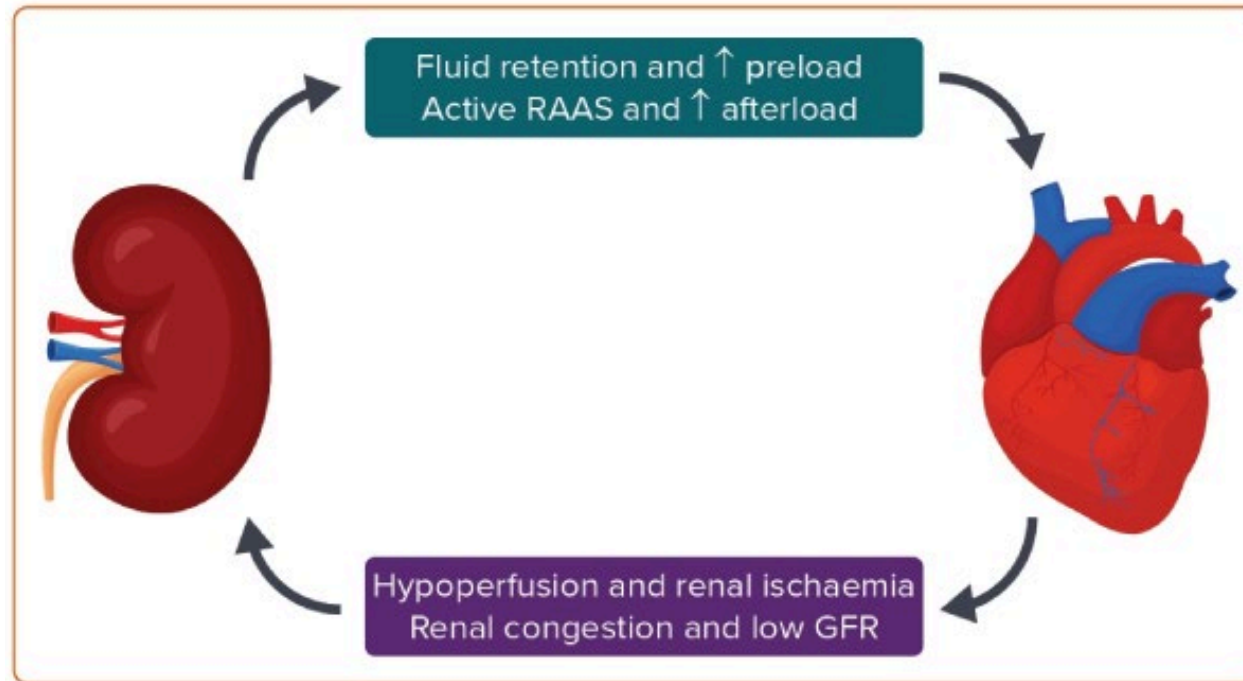
Exposure increased 44% in Stage 4 CKD patients

Plasma concentration and half-life increased in Stage 4 CKD patients

Tecarfarin may lead to dosing that is more predictable than warfarin in CKD patients who require anticoagulation therapy

Gaps in Modern Heart Failure and Chronic Kidney Disease Research

Interdependence of the Heart and Kidney in Chronic Kidney Disease (CKD) and Heart Failure (HF)



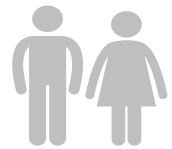
GFR = glomerular filtration rate; RAAS = renin–angiotensin–aldosterone system.

49% of HF patients also have CKD, and an estimated 17–21% of CKD patients develop de novo HF¹

Proposed Tecarfarin Pivotal Trial Design for LVAD Patients

Tecarfarin Anticoagulation and Hemocompatibility in LVAD Patients (TAH-LVAD)

A randomized, single-blind, phase 3, multicenter study to evaluate the efficacy and safety of tecarfarin compared to warfarin in patients with an approved left-ventricular assist device



Planned Enrollment
N = 440

Patients implanted with an approved LVAD and older than 18 years of age.



Tecarfarin (n = 220)

Treatment for 26 weeks

Warfarin (n = 220)

Primary Endpoint:

Win-ratio based on a hierarchical analysis

Secondary Endpoints:

Hemocompatibility related adverse events and time in therapeutic range (TTR)

Financial Summary

Cap Table

Cash (at 3/31/24)	\$6.6 million
Debt	NONE
Common Shares Outstanding	16,008,469
Warrants – Investors (avg. \$1.75)	4,285,715
Warrants - Underwriter & Placement Agt. Warrants (avg. \$2.68)	389,071
Stock Options Outstanding (avg. \$0.90)	2,195,000

Q1 2024 Financial Results

Operating Expenses (excluding non-cash items)	\$1.6 million
Cash used in operating activities	\$1.8 million

Market Capitalization








As of 7/29/24	~\$7 million
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Insider Ownership (Common Stock)

Insider Ownership as Percent of Shares Outstanding	47%
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Why Cadrenal Now?

*Tecarfarin is targeted for indications where it is NOW CLEAR FROM DATA that warfarin **FAILS** to achieve sufficiently stable anticoagulation and DOACs have clinically **NOT** shown benefit*

 	 	 	 	 
Unmet Need Certain rare cardiovascular conditions requiring chronic anticoagulation where warfarin has been unreliable, and DOACs (Eliquis-class drugs) are not FDA-approved	Proven Mechanism of Action Tecarfarin is a VKA with a well-understood mechanism of action; Phase 1 and 2/3 clinical data supports that tecarfarin is an effective and safe anticoagulant	Improved Safety Profile Tecarfarin is metabolized via a different metabolic pathway than warfarin – thus providing more stable anticoagulation than warfarin, thereby decreasing the risk of stroke and bleeding	Regulatory Pathway Tecarfarin has been granted two Orphan Drug Designations and a Fast-track designation by FDA providing potential seven-year marketing exclusivity post-approval.	Large Commercial Market & Opportunistic Strategy Marketed drugs for certain rare CV diseases command significant price premiums that value the tecarfarin addressable market at over \$2B; right team to execute commercial strategy



Contact Us



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APPENDIX

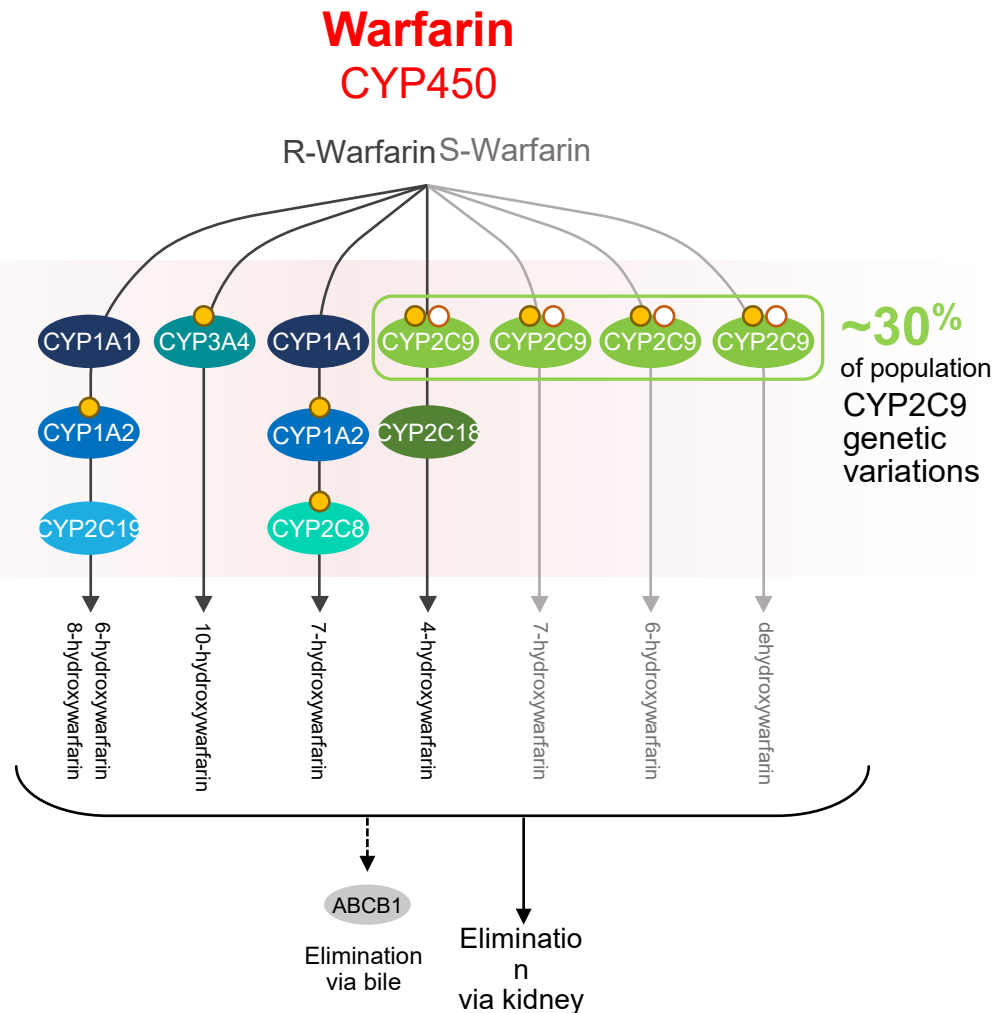


Tecarfarin's Metabolic Advantage

Tecarfarin is metabolized via an alternate pathway that is abundant and essentially insaturable, thereby avoiding the bottleneck in the CYP450 pathway where warfarin is metabolized.

- Drug interactions
- Genetic variations

7 Different CYP450 Isoenzymes involved in Warfarin Metabolism!



Tecarfarin
Human Carboxylesterase 2 (CES2)

Tecarfarin

CES2

Although genetic variation in CES2 has been identified there have been no reports of clinically significant impact

Elimination via bile

Warfarin Metabolism via CYP450 is Complicated by Known Competitors, Inhibitors and Inducers and the Established Impact of Genetic Variants

Enzymes	Substrates	Inhibitors	Inducers
CYP 3A4	amlodipine, simvastatin, warfarin , amiodarone, sildenafil, midazolam, fluoxetine, haloperidol, codeine, oxycodone, methadone, fentanyl	ciprofloxacin, ketoconazole, ritonavir, methylprednisone, imatinib, tamoxifen, cimetidine, grapefruit juice	simvastatin, efavirenz, pentobarbital, carbamazepine, phenobarbital, phenytoin, valproic acid, caffeine
CYP 1A2	alosetron, caffeine, duloxetine, melatonin, ramelteon, tacrine, tizanidine	ciprofloxacin, enoxacin, fluvoxamine, oral contraceptives, phenylpropanolamine	montelukast, phenytoin, smoking components of cigarettes
CYP 2C8	repaglinide, paclitaxel, methadone	gemfibrozil, fluvoxamine, ketoconazole, trimethoprim	rifampin
CYP 2C9	celecoxib, warfarin , phenytoin	amiodarone, fluconazole, miconazole, oxandrolone, capecitabine, etravirine, fluvastatin, metronidazole, Sulfinpyrazone, tigecycline	carbamazepine, rifampin, aprepitant, bosentan, phenobarbital, St. John's wort
CYP 2D6	lidocaine, metoprolol, haloperidol, fluoxetine, amitriptyline, metoclopramide, codeine, oxycosone, tramadol	amiodarone, chlorpromazine, citalopram, bupropion	rifampin, dexamethasone

Tecarfarin was specifically designed to avoid metabolism via the CYP450 Pathway, thus improving safety and efficacy over warfarin

Tecarfarin is Metabolized via the Human Carboxyl Esterase 2 Pathway (CES2) Provides More Effective, Safe, and More Consistent Anti-coagulation

Enzymes	Substrates	Inhibitors	Inducers
CYP 3A4	amlodipine, simvastatin, warfarin , amiodarone, sildenafil, midazolam, fluoxetine, haloperidol, codeine, oxycodone, methadone, fentanyl	ciprofloxacin, ketoconazole, ritonavir, methylprednisone, imatinib, tamoxifen, cimetidine, grapefruit juice	simvastatin, efavirenz, pentobarbital, carbamazepine, phenobarbital, phenytoin, valproic acid, caffeine
CYP 1A2	alosetron, caffeine, duloxetine, melatonin, ramelteon, tacrine, tizanidine	ciprofloxacin, enoxacin, fluvoxamine, oral contraceptives, phenylpropanolamine	montelukast, phenytoin, smoking components of cigarettes
CYP 2C8	repaglinide, paclitaxel, methadone	gemfibrozil, fluvoxamine, ketoconazole, trimethoprim	rifampin
CYP 2C9	celecoxib, warfarin , phenytoin	amiodarone, fluconazole, miconazole, oxandrolone, capecitabine, etravirine, fluvastatin, metronidazole, Sulfinpyrazone, tigecycline	carbamazepine, rifampin, aprepitant, bosentan, phenobarbital, St. John's wort
CYP 2D6	lidocaine, metoprolol, haloperidol, fluoxetine, amitriptyline, metoclopramide, codeine, oxycosone, tramadol	amiodarone, chlorpromazine, citalopram, bupropion	rifampin, dexamethasone

CES2 Substrate Drugs

Antiplatelet/Anticoagulants

- Acetylsalicylic acid
- Prasugrel
- Dabigatran etexilate

Angiotensin receptor blockers

- Candesartan cilexetil
- Olmesartan medoxomil
- Azilsartan medoxomil

Antiviral agents

- Tenofovir disoproxil
- Adefovir dipivoxil
- Valacyclovir

CNS agents

- Cocaine
- Heroin
- 6-monoacetylmorphine

Immunosuppressive agents

- Methylprednisolone sodium succinate
- Deflazacort

Oncology agents

- Irinotecan
- Capecitabine

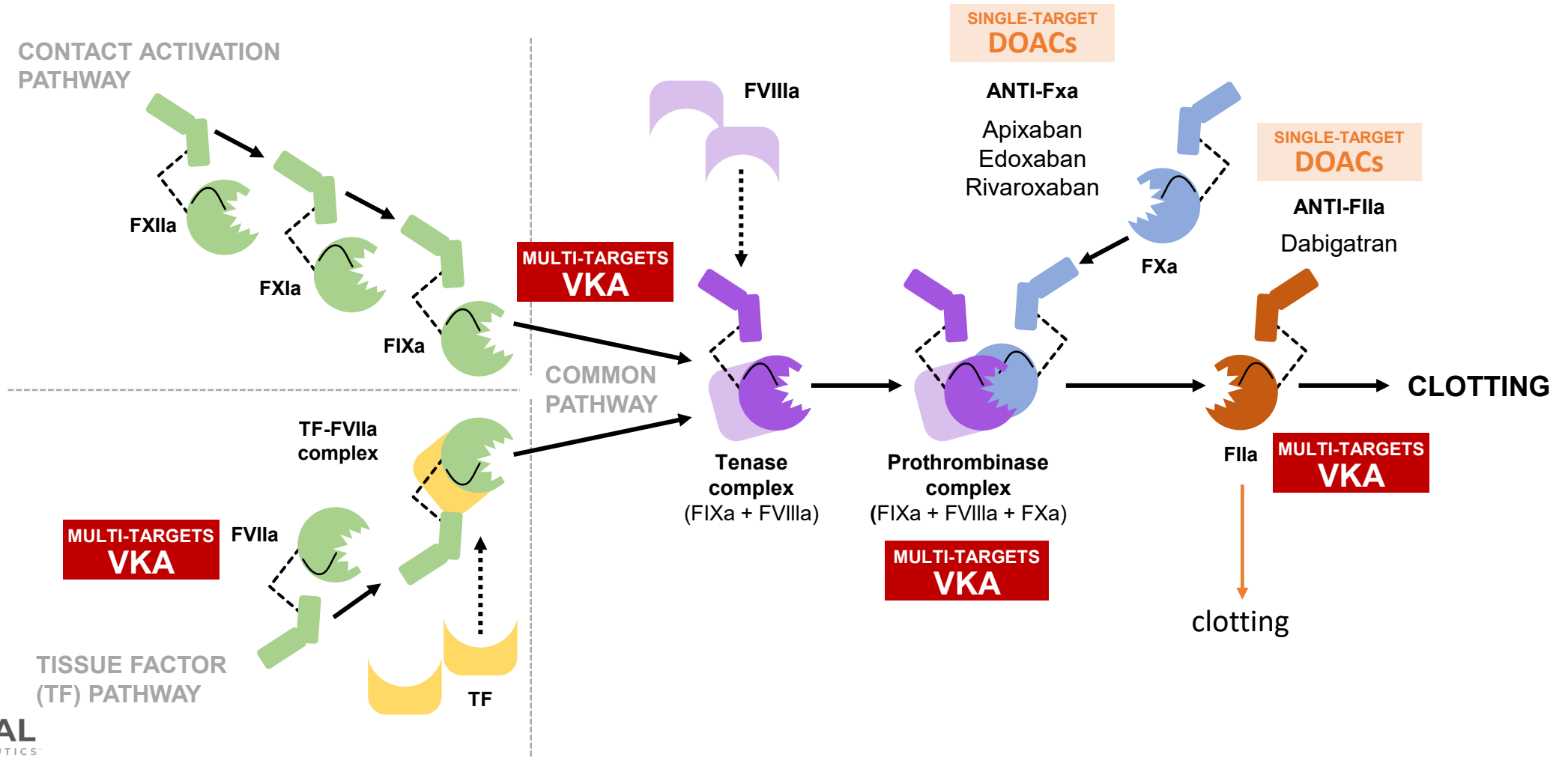
Anesthetic drug

- Procaine

Limited Substrates Identified
Genetic variation exists, but limited evidence of clinical impact

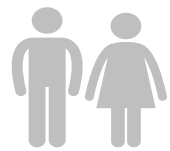
Vitamin K Antagonism Inhibits Multiple Factors (II, VII, IX, X, Proteins C & S) in the Clotting Cascade vs. Single Targets of Newer Agents

Proven mechanism of action resulting in clinically meaningful anticoagulation in certain conditions where DOACs have failed



Tecarfarin Phase 3 Trial Design for ESKD and AFib

Tecarfarin vs. Placebo in Patients with ESKD and AFib Randomized, Double-Blind, Placebo-Controlled

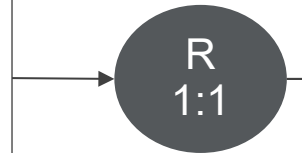


Planned Enrollment
N = 492

ESKD (eGFR < 15 mL/min/1.73 mm²)
documented chronic paroxysmal,
persistent or permanent AFib

Trial Sites:

U.S. and Canada, ROW TBD



Randomization
stratified according
to VKORC1 status

Tecarfarin (n = 246)

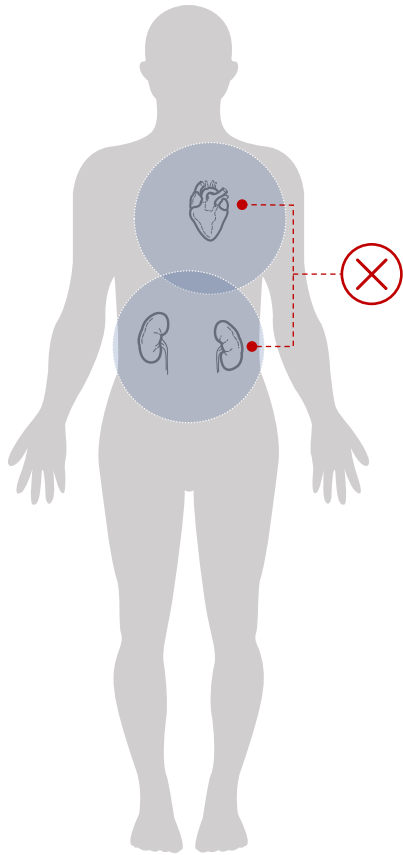
Placebo (n = 246)

12-month follow-up

for Primary Endpoint of time to
combined endpoint of ischemic
stroke or systemic embolism
(80% power to detect a 25%
treatment benefit)

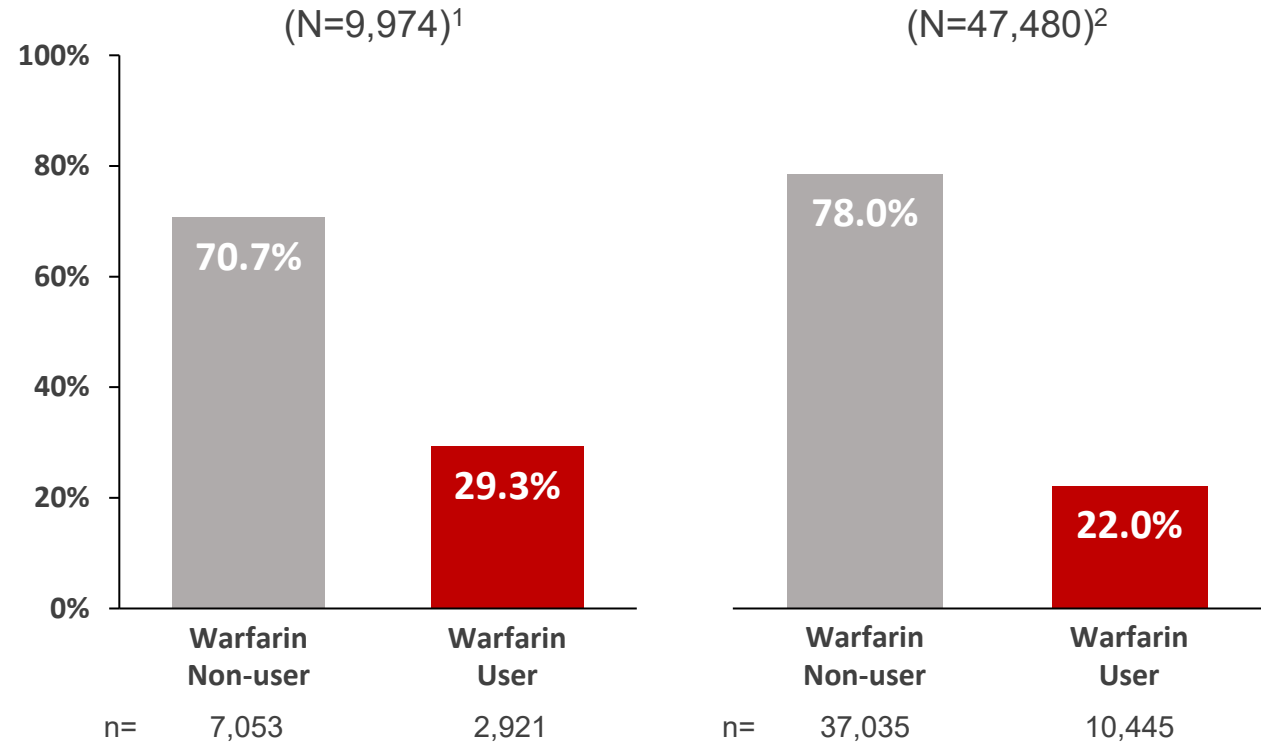
Significant Underserved Patient Populations

Despite the significantly increased risk of stroke in ESKD patients with AFib, most patients are not anticoagulated due to the lack of evidence of benefit



Most patients with ESKD + AFib are not prescribed ANY anticoagulation to reduce their risk of stroke

Use of warfarin in ESKD + AFib Patients¹



1. Yoon CY, Noh J, Jhee JH, et al. Warfarin Use in Patients With Atrial Fibrillation Undergoing Hemodialysis: A Nationwide Population-Based Study. *Stroke*. 2017;48(9):2472-2479. doi:10.1161/STROKEAHA.117.017114

2. Randhawa MS, Vishwanath R, Rai MP, et al. Association Between Use of Warfarin for Atrial Fibrillation and Outcomes Among Patients With End-Stage Renal Disease: A Systematic Review and Meta-analysis. *JAMA Netw Open*. 2020;3(4):e202175. doi:10.1001/jamanetworkopen.2020.2175

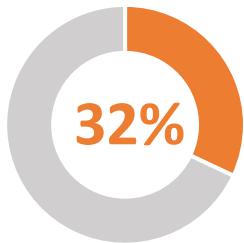
Dabigatran Versus Warfarin in Patients with Mechanical Heart Valves

EXCESS RISK AND NO BENEFIT

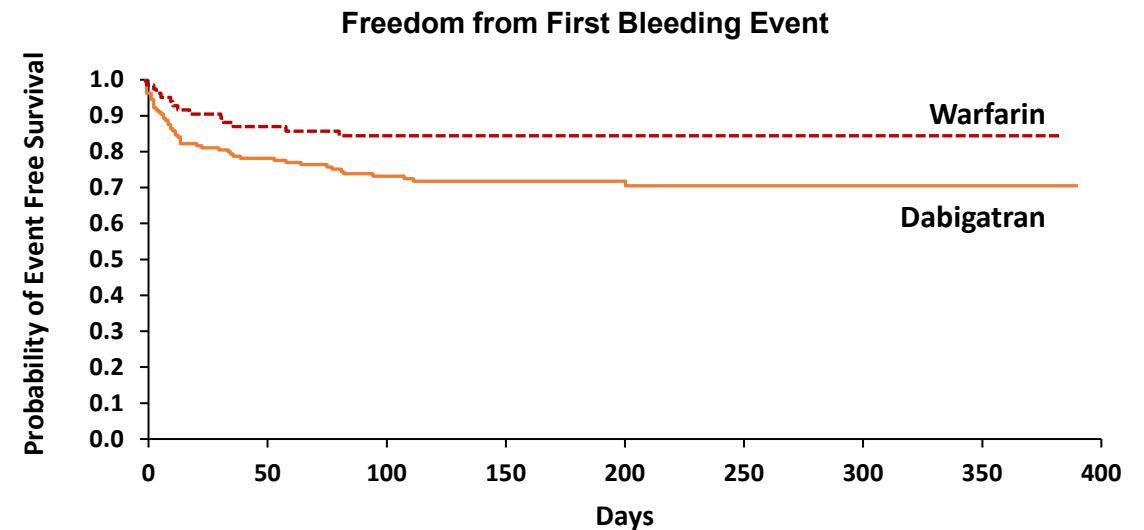
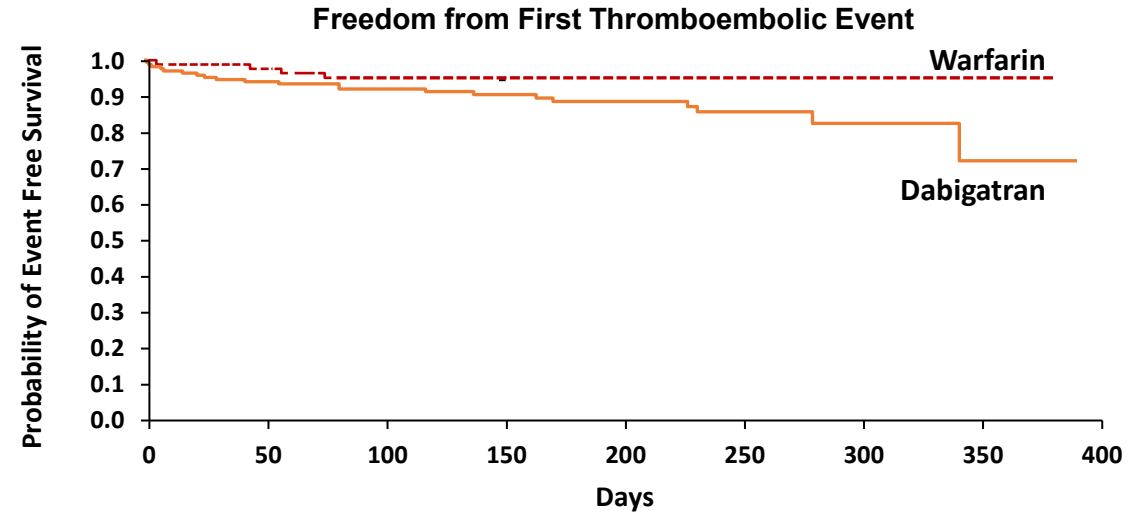


Trial terminated prematurely
due to an excess of thromboembolic and bleeding events among patients in the **dabigatran group**

	Dabigatran N=168 N (%)	Warfarin N=84 n (%)
Ischemic or unspecified stroke	9 (5.4)	0
Major bleeding	7 (4.2)	2 (2%)



32%
Dose adjustment or discontinuation of dabigatran (as-treated analysis)



TTR Decreases with CKD Severity for AFib Patients on Warfarin

AFib Patients with ESKD on Warfarin are Poorly Controlled with TTR of 42-51%, compared to the TTR goal of 70% or greater

- ❖ Time in Therapeutic Range (TTR)^{1,2,5}
 - Well-established FDA metric used to evaluate anticoagulation control (safety and efficacy)
 - Higher TTR levels correlate directly with improved clinical outcomes including rates of death, bleeding, myocardial infarction, stroke, and systemic embolism
- ❖ TTR predictive of clinical outcomes
 - Stage 4 and 5 CKD with AFib: Similar TTR cutoffs predictive of mortality and cardiovascular outcomes^{3,4}
- ❖ Overall TTR for AFib Patients with ESKD on warfarin is 42-51%⁶
- ❖ Only 21% of ESKD patients on dialysis using warfarin achieve TTR ≥60%⁶

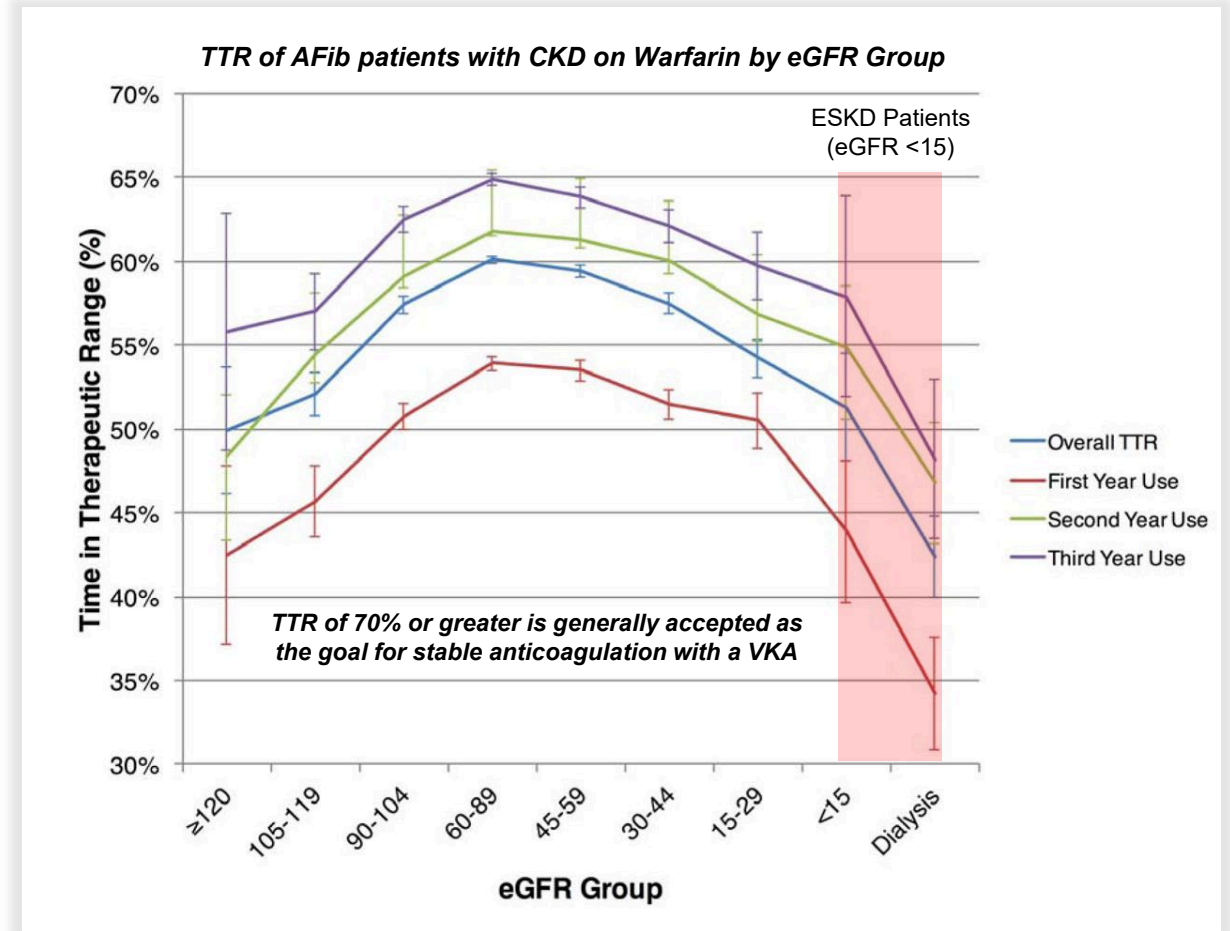


Figure 2. Warfarin Utilization and Anticoagulation Control in Patients with Atrial Fibrillation and Chronic Kidney Disease⁶