EDISON

Acarix

Initiation and IPO

Cash raised to fuel European marketing

Acarix has developed the CE-marked CADScor System to 'hear' and detect partially blocked coronary arteries. CADScor is designed to be used by doctors to help assess patients' risk of coronary artery disease (CAD). This could enable about half of the patients to be ruled out from further, expensive testing. Acarix aims to sell CADScor from 2017 in Germany and Scandinavia. Full EU reimbursement may start in 2019. US marketing will probably require a US clinical study with sales from 2021 possible. The IPO at SEK17.60/share completed at a value of SEK405m in December 2016, raising SEK140m gross, SEK125m net. The indicative value is SEK31.62/share based on an indicative value of SEK728m.

Year end	Revenue (SEKm)	PBT* (SEKm)	EPS* (SEK)	DPS (SEK)	P/E (x)	Yield (%)
12/15	-	(15.4)	(0.1)	0.0	N/A	N/A
12/16e	-	(38.7)	(2.4)	0.0	N/A	N/A
12/17e	3.0	(49.4)	(2.0)	0.0	N/A	N/A
12/18e	3.8	(49.5)	(2.0)	0.0	N/A	N/A

Note: *PBT and EPS are normalised, excluding amortisation of acquired intangibles, exceptional items and share-based payments. The 2016 IPO increased shares in issue from 15.1m to 23.0m. The capital structure was reorganised in H2 2016.

Noisy business – listening for atherosclerosis

The Acarix test uses a highly sensitive microphone linked to a minimalist self-contained processing module that records the patient's heart sounds. Sophisticated algorithms then identify the patients who probably require no further clinical testing. Other patients are referred, as before, for further testing. CADScor in the latest Version 3 software identifies 85% of patients with CAD (sensitivity) and 50% of patients with no or low risk CAD (specificity). The US alone has over 3.8 million tests for coronary artery disease per year ordered by primary care physicians. Ladapo et al. (2014) claim that 35% of these tests are not needed and harmful. US healthcare providers could save over $500m a year if most low-risk patients could be quickly and accurately tested, reassured and sent home.

Affordable product for primary care

CADScor will sell for over €3,000. A disposable, single-use patch will be priced at least at €30 per unit. Initial customers are likely to be patients with private insurance in Germany plus some Scandinavian sales to specialists. Full sales require government reimbursement, which will take two to three years. In the US, Edison expects a *de novo* 510(k) application; if approved, sales may start in 2021.

Valuation: Indicative value of SEK728m

Management plans direct sales in Germany and Scandinavia from 2017, with distributors requiring 30-40% margins elsewhere. German reimbursement is assumed from 2019, with US launch and reimbursement from 2021. In Edison's view, Acarix could achieve profitability from 2022. The IPO on 19 December 2016 raised SEK125m net by issuing 7.96m shares at SEK17.60 each. This will fund marketing and clinical investments over 2017 and 2018. Using a discounted cash flow model, a 12.5% discount rate and a terminal valuation based on a 1% growth rate, we calculate an indicative value of about SEK728m (based on a US$/SEK rate of 9.8) vs the IPO value of SEK405m. This equates to SEK31.62/share.

Healthcare

21 December 2016

IPO Price	**SEK17.60**
Market cap	**SEK405m**

Cash (SEKm) at 31 October 2016 (Management disclosure)	19
Shares in issue (19 December 2016)	23m
Free float	29.7%
Code	ACARIX
Primary exchange	Nasdaq First North Premier
Secondary exchange	N/A

Business description

Acarix, a Swedish company with Danish origins, has developed the CE-marked CADScor to enable about half of the patients to be ruled out from further, expensive testing. Full EU sales may start from 2019. US sales might start from 2021.

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Acarix is a research client of Edison Investment Research Limited

Investment summary: Reassuring the worried well

Acarix is developing a doctor's office acoustic test device and software algorithm: CADScor. CADScor is designed to be used by doctors to help assess patients' risk of coronary artery disease (CAD). This could enable about half of the patients to be ruled out from further, expensive testing Using CADScor, about half of these people might be sent home, saving money. Acarix AB is a Swedish company (Malmö). It was founded in Denmark as Acarix A/S and has an operational office just North of Copenhagen. CADScor is a registered trademark of Acarix.

The business case rests on achieving a good penetration rate of primary care providers with the CADScor device sold for over €3,000 (Europe) and $5,000 (US). A disposable, single-use sticky patch priced at over €30 (Europe) or US$75 (US) is required to run the test. A substantial installed base of devices, if achieved over time, could generate significant sales revenues at high margin with low marketing cost. The US market alone is estimated by independent researchers to be at least 3.8 million tests per year. As a simple to use, primary care device CADScor offers a quick and relatively cheap alternative to more complex and much more expensive testing. Acarix plans to sell the test from 2017 in Germany and Scandinavia, although full government reimbursement is not likely before 2019. Distributors will be appointed for other European countries. In the US, further trials may be required and Edison expects that a *de novo* 510(k) or PMA application will be needed for FDA approval. Our model assumes US sales from 2021.

Financials: Cash to fund market development and US trials

Edison forecasts a rise in 2016 cash outflow to SEK22m up from SEK8.6m in 2015. This is then expected to rise to SEK 72m per year from 2017 after forecast sales. In Edison's view, Acarix is unlikely to be profitable before 2022. Limited direct sales into the German market are expected in 2017 with some sales progression in 2018. Acarix entered 2016 with cash of SEK2.1m. Acarix received a €2m private investment in October from Puhua Jingxin Guzhou Health Management Partnership (Puhua Jingxin). The Puhua Jingxin fund aligns strategic resources from Puhua Healthcare and Zhejiang Jingxin Pharmaceuticals to form a specialist healthcare fund; post-IPO it now owns 11.53%. Acarix completed its IPO in December 2016 at SEK17.60/share raising SEK140m gross, SEK125m net issuing 7.96m new shares.

Sensitivities: Acceptance and cash

The three major sensitivities relate to the diagnostic performance, acceptance within clinical guidelines and reimbursement. The sensitivity is good at 85% with specificity of 50%. For European sales, Acarix has a CE mark but CADScor needs to be included in various European guidelines. The US route to approval is not yet clear and CADScor also needs to be added into US guidelines. Reimbursement will require real-world clinical studies to show that use of CADScor leads to better patient care and cost savings. In the US, there are lucrative medical fees for more complex tests so a disincentive to use CADScor. However, there are concerns about over-testing and healthcare systems are increasingly cost focused, which could help uptake. Sales and timings for new diagnostic products are unpredictable and sales could be significantly different to these estimates.

Valuation: Post-IPO indicative value of SEK728m

Acarix has gained the funds it needs from the IPO to execute its market and clinical strategy to develop the CADScor business. Using a discounted cash flow model, a 12.5% discount rate and a terminal valuation based on a 1% growth rate, we calculate an indicative post-funding value of SEK728m at an exchange rate of US$/SEK of 9.8, equating to SEK31.62/share. Acarix may invest in other products and may develop further indications for its acoustic technologies.

Company description

Acarix is developing the CADScor acoustic device and sophisticated signal processing algorithms. The company is based on pioneering research from 2004 on phono echocardiography performed at Aalborg University, Denmark The technology was taken up by Coloplast and then transferred into a spinout company, Acarix A/S in 2009. Venture capital was raised in 2010 from Seed, Sunstone and Seventure Partners. Medical collaborations were established with a group of Danish hospitals. These collaborations form the basis of the current clinical trial program. The CADScor system gained a CE mark classification in 2015. A new CEO was appointed in August 2016. Acarix A/S became part of the Swedish company, Acarix AB (Malmö) in H216. Acarix has eight employees. Historic company information and accounts can be found online in the Virk.dk database. From foundation to October 2016, Acarix raised SEK121m (DKK92m) in venture capital and from Puhua Jingxin. Acarix A/S received DKK12.1m (SEK15.9m) from Danish government funding. The IPO completed on 19 December 2016 raising SEK125m net.

The device: CADScor

Every year, many patients at low and intermediate risk of CAD visit their doctor complaining of non-specific chest pains. These patients may not have angina (chest pain caused by poor blood supply to the heart). Currently, doctors have no easy physical test to separate the worried well from those at high risk of CAD who need further investigation and will be referred for hospital tests. Currently, doctors assess the probability of CAD using questionnaires based on age, gender, clinical risk factors (diabetes, smoking) and immediate symptoms. These tend to overestimate CAD risk.

CADScor, Exhibit 1, carries out an independent, patient-specific measurement and analysis of the noise made by the blood flowing in a patient's coronary arteries. The flow at very low noise frequencies is twice as loud due to turbulence if the arteries are partially blocked. Note that the sophisticated algorithm assesses multiple acoustic parameters.

Exhibit 1: The CADScor acoustic device on the base station

Source: Acarix

Simple patient data is entered into the CADScor device before the test. Otherwise, there are no external inputs. Calculation of the test result, the CAD-score, is done by the device and displayed on screen; no external software is used. A CAD-score of 20 or less identifies a patient as probably not requiring further investigation for CAD. CADScore test data from trials is discussed below.

Device design and use

CADScor consists of a sensitive microphone attuned to low-frequency sound, a sound recording and analysis unit fixed to the microphone, an external power cable and a base station. The detachable recording and analysis unit is about the size of a small smart phone. It stores data from up to 150 patients. The base station recharges the analysis unit and has a calibration system to test the microphone every night. CADScor can be wall mounted. Software updates need to be installed manually using an integral card reader. No Wi-Fi or Bluetooth connectivity is enabled currently.

To use CADScor, a disposable, single-use, double-sided adhesive patch is placed into a small assembly tool. The CADScor device is removed from the docking station and inserted into the tool so that the adhesive patch sticks to the base and is correctly aligned. The analysis unit is then stuck to the patient so the microphone is over the space between the fourth and fifth ribs. The patch has an integral clip to hold the microphone and an RFID chip to prevent re-use. It is a critical component as it ensures the close contact needed to detect low-frequency heart sounds.

Ideally, the patient will be lying on their back and relaxed with their heart rate under 80bpm. CADScor records sound for four periods each lasting eight seconds. There are rest periods in between of 20 seconds. In recording phases, patients must hold their breath.

The analysis unit then processes the data. This could take a further one to two minutes. Acarix estimates that the total time required to complete the test is about 10 minutes. Tests will probably be run by a nurse. On completion, the CAD-score is shown on screen and manually entered into the patient's medical record.

Coronary heart disease: The hidden killer

The coronary arteries are narrow arteries (4.7mm diameter or less) and supply blood to the heart muscle. Particularly important are the left coronary arteries supplying the left ventricle (the heart chamber that pumps blood around the body). Partial blockage of the arteries is caused by atherosclerosis: the formation of fatty deposits along the artery wall. These can become calcified.

The usual threshold for determining that CAD is at a dangerous level as when the main left coronary artery is blocked by 50% or more and when minor coronary arteries are blocked by 70% or more. As the coronary arteries become partially blocked, areas of the heart will receive less blood, causing pain on exercise (angina) as the heart muscles demand more oxygen to cope with the body's demand for blood due to exercise or stress. This may be clear angina or it may be initially be a generalised chest pain. Most chest pain is musculoskeletal or caused by digestive problems and is not angina.

If an atherosclerotic plaque in a coronary artery ruptures, it triggers blood clot formation that may block the artery causing a heart attack (acute myocardial infarct (AMI)). According to the US Centres for Disease Control and Prevention, "coronary heart disease is the most common type of heart disease, killing over 370,000 people annually" in the US. Every year about 525,000 Americans experience a first heart attack.

According to the American Heart Association 2016 update "about 85.6 million American adults (>1 in 3) have one or more types of heart disease". Over half of these, 45 million, are aged over 60 and so in the higher-risk groups and mostly covered by Medicare (United States government healthcare insurance for people aged over 65). It is thought that 15.5 million (between 4% and 5% of the US population) have CAD with about 8.5 million having angina (the number is falling, the 2010 AHA estimate for angina was about 10 million). The number of deaths from coronary heart disease has been decreasing, Exhibit 2.

Exhibit 2: Age standardised deaths from heart disease in the United States

Source: adapted from the American Heart Association report: Heart Disease and Stroke Statistics—2016 Update. Based upon age standardised US population of US in 2000 and converted to cases using updated population figures.

In Germany, an overall population study by Gößwald et al. (2013) gives a lifetime risk of angina and coronary heart disease of 8%, which would be about 6.4 million people; the higher relative prevalence level is explained by the much older age structure of the German population. Incidentally, the Max Planck Institute for the Biology of Ageing gives a figure of 1.5 million coronary heart disease cases in Germany (unsourced).

A 2014 UK survey estimated that 3% of the population had angina, the manifestation of CAD. That would be about 1.9m cases. The age profile is weighted to those over 75.

Testing for coronary artery disease

There are many specialist terms and procedures in cardiology. Exhibit 3 provides an overview. None of these tests are highly accurate because it is very difficult to rule out heart disease. This is because the coronary arteries can be blocked to different extents in different places and smaller occlusions are difficult to detect in the narrow and convoluted coronary arteries.

A systematic review of non-invasive testing for coronary artery disease was published in 2016 by the Agency for Healthcare Research and Quality, part of the US Department of Health and Human Services. This concluded: “no clear differences between testing strategies… with regard to clinical management outcomes on which to base recommendations”. The study also noted “that the frequency of all-cause mortality and myocardial infarction [heart attack] was low across all studies”.

Exhibit 3: Common procedures in cardiology – definitions and use

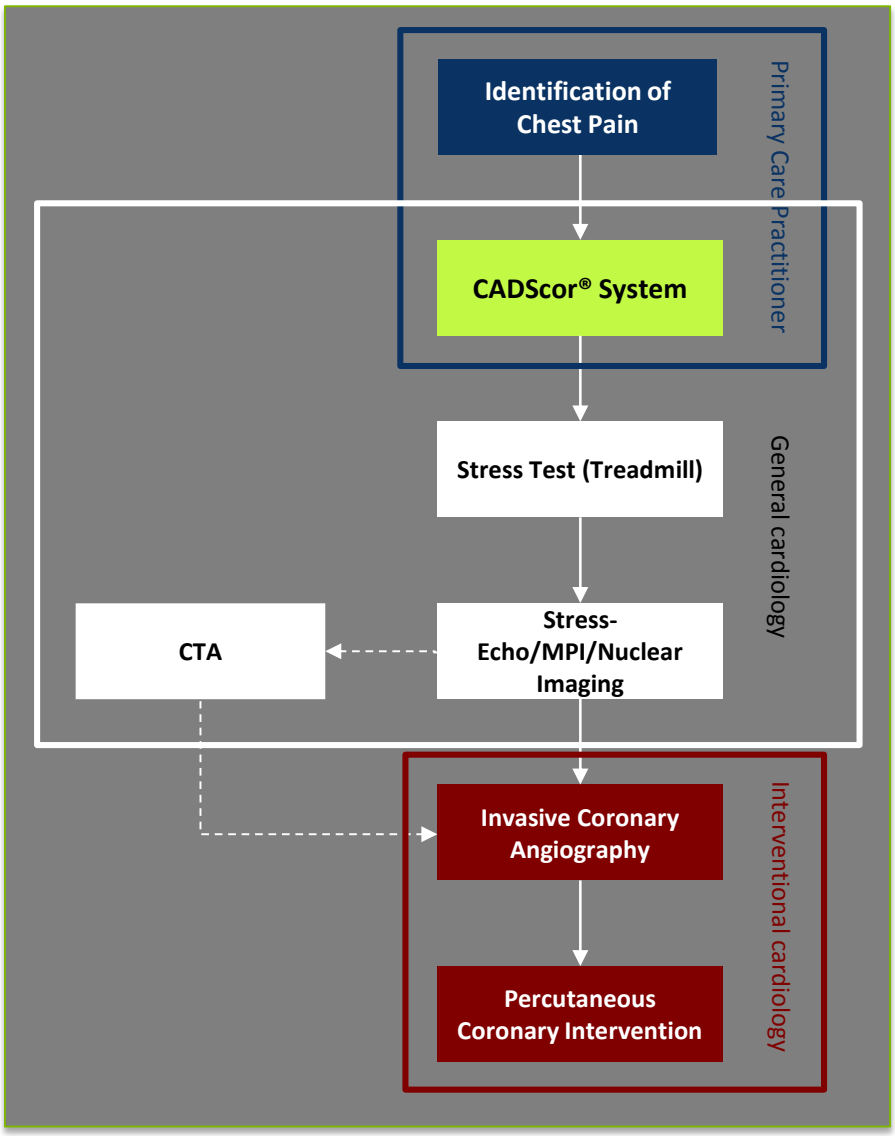
Term	Definition	Comment
Pre-test probability (PTP)	Chest pain can be caused by many different factors. To make an initial assessment, a primary care physician calculates the pre-test probability (PTP) of CAD using a questionnaire based scoring system. If a patient has obvious signs of CAD, for example, angina, the PTP level is high and the patient will be referred for sophisticated hospital tests. This also applies to patients with major clinical risk factors like diabetes, hypertension and a history of smoking.	Two common scores for patients with chest symptoms are either the updated Diamond-Forrester (DF) score), or the Duke Clinical Score (DCS). Diamond Forrester was updated and recalibrated in 2012 and is combined with other clinical risk factors like Diabetes under 2013 European Society of Cardiology Guidelines. (see below). DCS is popular in the US. For patients with no chest symptoms, other scores like Framingham (see Exhibit 6) are used to assess general cardiovascular risk over the next five or 10 years.
Functional stress test (see Exhibit 5)	There are various tests in this category but all them involve assessing the patient's heart function before and after exercise.	As these are the next stage from CAD-score, and the current alternatives to it, they are discussed in more detail below.
Coronary artery calcium score (CACS)	Score of 100, low; up to 400 some risk; over 4000 is high risk. If a high level of calcium is present in a coronary artery it will be due to calcified plaque, see Shah and Coutler (2012). CACS does not predict the extent of obstruction and non-calcified plaque can also be present. The CACS test requires a 10-minute CT scan. The test does have a very high negative predictive value of about 98%.	CACS is still regarded as investigational in the US and it is not covered by Medicare. Insurance cover is sparse for the test (Blue Cross North Carolina policy, Athena). The reimbursement code (CPT 75571) in the US is classed as a minor procedure with a 2010 price of $44.11, and so not economic: It is not recommended by the ESC. It is recommended as a negative screen in the UK health service guidelines.
Coronary angiography (CTA)	This procedure needs a computerised tomography x-ray scanner (CT scanner). A radiopaque dye is injected into the patient's arteries and the scanner is used to image the flow of blood through the coronary arteries. As discussed above, these arteries are very small and as the heart is beating the scanner needs to have both high spatial resolution and a fast time resolution to be able to produce an accurate scan. CTA can overestimate the level of stenosis if there is a high level of calcification (CACS score >400).	This procedure is non-invasive as only a radiopaque dye is required. Some patients do have negative reactions to the dyes so there is a risk. The procedure uses x-rays so is also a radiation dose using about a third of the annual natural level. The advantage of the procedure is that no invasive catheterisation is required. Most of the population data used for calculating the risk of CAD comes from patient groups who have all undergone CTA.
Invasive coronary angiography (ICA)	The only way to determine coronary artery disease status absolutely is through an invasive coronary angiogram (ICA) where a catheter is inserted through the groin and into the coronary artery and a radiopaque dye is injected near the blockage and visualised on x-ray. This clearly shows any narrowing of the artery.	An ICA will be done for diagnostic reasons in a patient, but they will be either very high risk or have shown more than 50% occlusion on coronary angiography. If a blockage is confirmed, it is usually followed immediately with angioplasty. Invasive coronary angiograms and angioplasty are invasive procedures and in the US typically cost at least $3,000 per procedure.
Percutaneous transluminal coronary angioplasty (PTCA)	Angioplasty is the most common treatment for CAD. If a blockage is found a balloon catheter is inserted over the existing guide wire and pushed through the blockage. The balloon is then inflated to crush the atherosclerotic plaque and so open up the artery. A stent (a metal framework) is normally inserted (92% of cases) to support the arterial wall.	This is a natural follow-on procedure to ICA. However, a surprising number of invasive coronary angiograms fail to find a blockage.

Source: Edison Investment Research

The positioning of CADScor in general practice

Exhibit 4 shows the proposed positioning of the Acarix test within the set of established procedures. Pre-test probability calculations, might, in Acarix's view, be superseded by the Acarix test in primary care settings, Exhibit 4 blue box. Acarix estimates that between 40% and 50% of patients will be excluded from further testing on the basis of its CADScor.

Exhibit 4: Acarix perspective on the use of the CADScor system



Source: Acarix

Pre-test probability

Pre-test probability assessment is recommended by guidelines in the US and Europe to assess a patient before any other clinical tests are run. The original Diamond-Forrester (1979) (DF) score (Exhibit 5) is simple to do using gender, age and simple chest pain symptoms. Men are at much more risk so score highly relative to women. Post-menopause, women do catch up in risk but start from a low baseline. The Duke Clinical Score (DCS), Pryor et al. (1993), used more parameters than DF: gender, age, cholesterol and chest pain symptoms including ECG data to determine angina type. The original DF and DCS scores were compared by Wasfy et al. (2012) against CA-

CTA as a standard. They found that the original DF overestimated risk, with DCS more accurate. Many other authors also noted the overestimate of risk by DF.

The DF score has now been recalibrated and renamed as CAD Consortium 1 (CAD1), Genders et al. (2012). An online calculator gives the basic, recalibrated DF score and allows it to be further modified with clinical risk factors like smoking, diabetes and hypertension. A useful interview on this can be found at Chest Pain and Predicting CAD: Time to Change the Guidelines? CAD1 was recommended by the European Society of Cardiology in 2013. The American Heart Association and American College of Cardiology recommend either the DCS or DF scores.

Exhibit 5: CAD1 scoring system (recalibrated Diamond Forrester)

Aspect	Commentary
Basis	The DF score was published in 1979 (Diamond, 1979) as an exercise in Bayesian probability to determine the risk that a patient presenting with chest pains has coronary artery disease. It is derived from age, sex and type of chest pain, which was classified as typical, atypical or non-angina. The original score overestimated risk. The CAD consortium used a database of 5,500 patients from 18 different hospitals across Europe and the US to recalibrate the system. This now adds in key clinical risk factors.
Accuracy	The weighting system has been recalibrated and named CAD Consortium 1 (CAD1). This version is recommended by the ESC. The latest version is CAD2, see Almeida et al. (2016).
Basic operation of the score	The basic parameters are age and sex: a 70-year-old vigorous male with no symptoms or clinical risk factors will have a 24% risk on the basic Diamond-Forrester score. If there are no clinical risk factors, this reduces to 13%. If atypical angina is seen, the basic risk rises to 38%, but the clinically adjusted risk is 23%. If all typical angina symptoms are seen, the basic CAD risk is 70%, but the clinically adjusted risk is 53%.
Clinical risk parameters	These are diabetes (this is a major risk factor), hypertension (140/90 mmHg), high cholesterol, and smoking history. The coronary artery calcium score can be entered if available and would further modify the risk profile.
Clinical risk factors	The scoring changes depending on clinical risk variables of smoking, diabetes (a major factor), cholesterol level (>6.5 mmol/l or 250mg/dl) and previous cardiovascular history.

Source: Edison Investment Research, calculations based on CAD Consortium Calculator

Patients without chest pain symptoms might have a generalised five- or 10-year risk of future cardiovascular events, like an AMI, assessed as part of a general health check, see Exhibit 6.

Exhibit 6: Cardiovascular risk prediction in individuals with no chest pain

Score name	Comments
Framingham	Framingham is based on the longstanding NIH run US longitudinal (started 1948) study. It predicts the 10-year and risk of developing a cardiovascular disease (choice of: coronary heart disease, stroke, peripheral artery disease or heart failure). The sex-specific scores incorporate age, total and high-density lipoprotein, cholesterol, systolic blood pressure, treatment for hypertension, smoking, and diabetic status. A risk of an event in the next 10 years below 10% is considered low, 10%-20% intermediate, and >20% high. It likes statins.
HeartScore	The ESC has developed an online risk calculator based on 205,178 patients and adapted to different populations. It is available as an online tool. This assesses age, gender, smoking, hypertension and cholesterol level. Charts allow a quick lookup of general cardiovascular (CV) risk.
PROCAM	PROCAM gives the 10-year risk of a coronary event. It is based on a 10-year trial. The calibrated risk score uses age, LDL cholesterol, smoking, high density lipoprotein (HDL cholesterol, systolic blood pressure, family history of premature myocardial infarction, diabetes mellitus and triglycerides. A chance of an event in the next 10 years of below 10% is considered low, 10-20% as intermediate risk, and >20% as high risk.
SCORE	SCORE predicts the five-year risk of fatal cardiovascular disease. The model has inputs of gender, age, systolic blood pressure, total cholesterol and smoking plus any CV clinical history. A risk of cardiovascular death within five years of 0-4% is considered low, 5-9% intermediate, and ≥10% high

Source: Edison Investment Research based on linked sites and Versteylen et at (2011)

Relationship between PTP scoring and the CAD score

The European Society of Cardiology's 2013 PTP levels for the risk of having obstructive CAD are set out on page 2962 of the ESC 2013 guidelines, Exhibit 7.

Exhibit 7: ESC CAD risk levels

Level	Action	ESC CAD PTP risk
Low	No further testing	<15%
Intermediate	Possibly refer for further testing	15<85%
High	Refer for invasive coronary angiogram, possibly leading to therapeutic intervention with angioplasty if required to open any partially blocked coronary arteries	85-100%

Source: European Society of Cardiology 2013 guidelines

As yet, it is not clear how the Acarix CADScor test fits into these guidelines given that the CAD-score is a new test parameter with limited published clinical data. Edison has not seen data relating the CADScore to PTP. The clinical data (see below) relates the CAD Score to CAD detected using CTA or invasive angiography.

In Edison's view, it is likely that doctors will use the current PTP scoring systems to eliminate low-risk patients: a risk of 15% or less. PTP scoring is validated in studies, clinically accepted, available online, very fast and costs nothing. If the patient has an intermediate score, that is between 15% and 85% risk, the doctor may, in our view, use CADScor (about 10 minutes plus the test cost) to better categorise the patient. Patents with PTP over 85% will be referred as in Exhibit 7.

Currently, if patients are felt to be an intermediate CAD risk, they may be referred for a functional test Exhibit 8. For reference, CADScor has a sensitivity of 85% and a specificity of 50% according to the latest clinical trial (see below).

Exhibit 8: Functional imaging tests used after PTP and before CTA

Test	2013 cost	Sensitivity	Specificity	Comments
ECG treadmill stress test	$114	45-50%	85-90%	The patient is wired up to an electrocardiogram system to monitor the electrical functioning of the heart. They then exercise using a treadmill or bicycle and changes in the heart rhythm are noted. One issue is that patients often cannot exercise sufficiently to get good readings and therefore appear negative. Acarix notes that as the test is not very sensitive (does not find many patients with CAD), doctors do not rely on it and often refer patients anyway.
Stress echocardiogram	$284	80-85%	80-88%	The heart is imaged using ultrasound to see if there are changes in blood supply under stress. It suffers from the same drawback as the treadmill stress test but has the advantage that the heart is directly imaged.
Myocardial perfusion imaging using SPECT	$644	73-92%	63-87%	This is a nuclear imaging technique. A radioactive agent is injected into the blood. If areas of the heart become ischaemic during exercise or in response to drugs, they receive less blood flow and will receive less radioactivity showing up as "cool" areas. Imaging can be 2D or 3D depending on equipment sophistication. There are two techniques used: single-photon emission computed tomography (SPECT) or positron emission tomography (PET).
Drug-based testing	Many individuals who not able to achieve the level of exercise needed can be given vasodilator drugs or the inotropic drug dobutamine (a heart stimulant). Because this avoids the need to exercise hard, the tests are slightly better at finding negative cases; that is, they have a higher specificity.			

Source: Edison Investment Research based on Arbab-Zadeh (2012) and Ladapo et al. (2014) Sensitivities and specificities are from ESC 2013 guidelines (table 12, page 2,962)

Market size and structure

Although there are very good statistics on AMI rates and invasive catheterisation rates for diagnosis and treatment, the market being targeted by Acarix is larger and much more diffuse. It basically comprises some proportion of patients who report chest pain to a primary care physician.

As a starting point, the number of Medicare-funded invasive angiograms in the United States was fairly level up to 2009 (Riley et al, 2009) at around 1 million per year. Private insured cases probably take this to 1.3m (AHA 2016 update). Following the initial primary care consultation, there were a further 350,000 Medicare-funded angioplasty procedures and a further 200,000 coronary artery bypass graft procedures (invasive surgery used when angioplasty is not possible). So half the patients tested invasively did not need therapeutic intervention. This again indicates the need for better screening systems in primary care.

Patel et al. (2010) found that after elective coronary angiography, only 37.6% of patients actually had obstructive CAD and 39.2% of the patients had no CAD. This study covered 398,978 patients across 663 hospitals. The authors concluded that: "Better strategies for risk stratification are needed... to increase the diagnostic yield of cardiac catheterization in routine clinical practice".

Ladapo et al. (2014) found that 45 in every 10,000 primary care or hospital outpatient visits resulted in a cardiac stress test: that is 3.8m referrals (out of 863m primary care visits of all types).[1] These referrals were of patients who had no prior diagnosis of CAD, the target market for CADScor.

Of these 3.8m referrals, about 1.1 million patients had chest pain and 2.7m had other symptoms. They could also be split into 1.3m low risk and 2.5m high risk on the basis of clinical symptoms.[2] Ladapo concluded that: "At least 34.6% [of the cardiac tests ordered] were probably inappropriate, with associated annual costs… of $501m". Referrals were for either an ECG treadmill stress test, a stress echocardiogram or stress myocardial perfusion imaging. The most "popular" functional test was stress imaging with 87% use. This is also the most expensive (over $600) but gives direct heart perfusion images. If positive, patients may be referred for CTA or ICA

An analysis of UK healthcare records by Ruigómez et al. (2006) found that 1.5% of primary care visits in 1996 were due to unspecified chest pain and that 11% of these individuals were diagnosed with CAD within a year. In a control group, only 1% were. The relative risk was 14.9 times greater after statistical adjustments. This primary care data shows both that chest pain symptoms are common and can be due to CAD and that CAD (diagnosed with a year) is rare.

In the UK in 2013, there were 340 million primary care consultations at an average of six per year per patient (source: British Medical Association). If 1.5% of the patients had nonspecific chest pain (850,000 cases) about 92,000 might have CAD after CTA.

Extrapolating to the bigger EU states plus other rich European countries (population about 400 million) implies about 5m chest pain consultations per year with about 500,000 CAD cases diagnosed. However, these are very rough figures.

Current clinical guidelines

To become a mainstream test, CADScor and the CAD-score will have to be incorporated into the various national guidelines for the diagnosis of angina and coronary heart disease, Exhibit 9. These are surprisingly varied indicating that conclusive clinical studies are lacking in many areas. It can also take a number of years to be accepted and to be included in the next guideline iteration.

Exhibit 9: National guidelines

Country/areas	Title	Key recommendations
England and Wales	Chest pain of recent onset: assessment and diagnosis, CG95	The UK National Institute for Health and Care Excellence (NICE) conducts rigorous health assessments and economic analysis for the UK national health service in England and Wales. NICE issued guidance in 2010 and revised in 2014 where there is no direct evidence of CAD or angina (the target population for the Acarix test): Low risk (up to 29% probability of CAD) – coronary artery calcium scoring (CACS); medium risk (30–60%) - functional imaging as the first-line diagnostic investigation; high risk (61-90%) – invasive coronary angiography as the first-line diagnostic investigation if appropriate.
Europe	European Society of Cardiology "guidelines"	These appear to favour coronary artery CT angiography (CTA), which is stated to have has a high negative predictive value of 97-99% with sensitivity of 95-99% and specificity of 64-83%. The guidelines do not recommend Coronary Artery Calcium score use as it has a poor prognostic value. The ECS notes that treadmill testing where a patient exercises wearing a 12-lead ECG monitor can be useful but the test has a sensitivity of 45-50% and a specificity of 85-90%. Hence, it can exclude but is weak at identifying at risk patients.
US	Stable Ischaemic Heart Disease	The American Heart Association and American College of Cardiology in their joint guidance suggest exercise testing and functional imaging to determine if any ischaemia is present. CTA is used if functional imaging is unclear. CACS is not in the current guidelines.

Source: Edison Investment Research, plus sources as hyperlinked

[1] These data were collected in the US National Ambulatory Medical Care Survey (NAMCS) and National Hospital Ambulatory Medical Care Survey (NHAMCS) from 1993–2010. This survey provides a systematic evidence base for the number of consultations by healthy individuals for cardiovascular disease.

[2] Low risk defined as not a smoker, having no chest pain and no diagnosis for hypertension, dyslipidemia, diabetes or obesity. Note that CAD was not diagnosed by CTA so this is not a medically defined group.

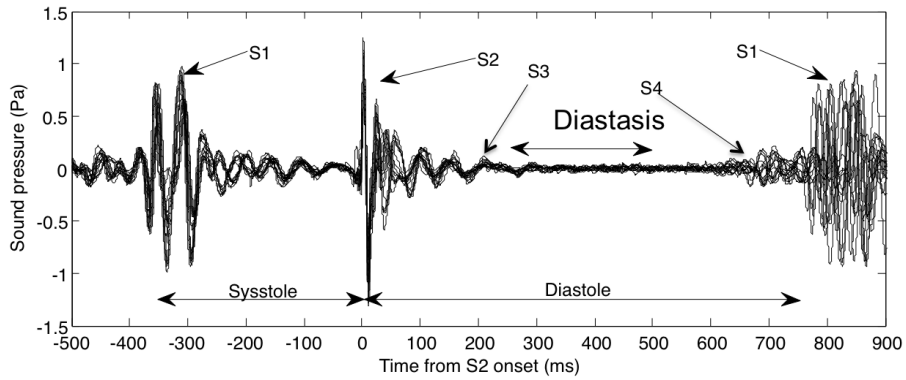
Acarix's acoustic algorithms: The key advantage

There has been interest for many decades in developing acoustic methods to determine coronary artery disease. The problem has always been that the sound of blood flow in the small coronary arteries is very faint compared to the other sounds made by the heart and body. Consequently, the algorithm used to select the noise features and analyse them is a key proprietary advantage. Acarix has patented a number of innovations in this area, see below. It is easier to get software patents approved in the United States than it is in Europe. Enforcement can also be difficult.

As the algorithm is a software construct, it has been adapted and calibrated as more data has been acquired. The current version is 3.0. Version 2.0 was used for the CE mark in the AC003 trial. There is no requirement to reapply for a CE mark unless there is a substantive change. However, at some point in clinical development, the software needs to be fixed for regulatory purposes, with future iterations validated against that reference point. The FDA also requires medical software to be written and tested appropriately. This section looks at the acoustic algorithm used, which is the key proprietary advantage, and then looks at the trial data available to date.

Exhibit 10 shows a sound profile of a heartbeat. In the systolic phase, the left ventricle contracts to force blood around the body. This creates various sounds including the opening and shutting of heart valves. The diastolic phase is when oxygenated blood from the lungs flows from the left atrium into the left ventricle. This is a largely passive so fairly quiet. This period, between S3 and S4 in Exhibit 10 (labelled diastasis), is when CADScor samples the noise of the coronary arteries.

Exhibit 10: Sound profile of a heartbeat



Source: Acarix

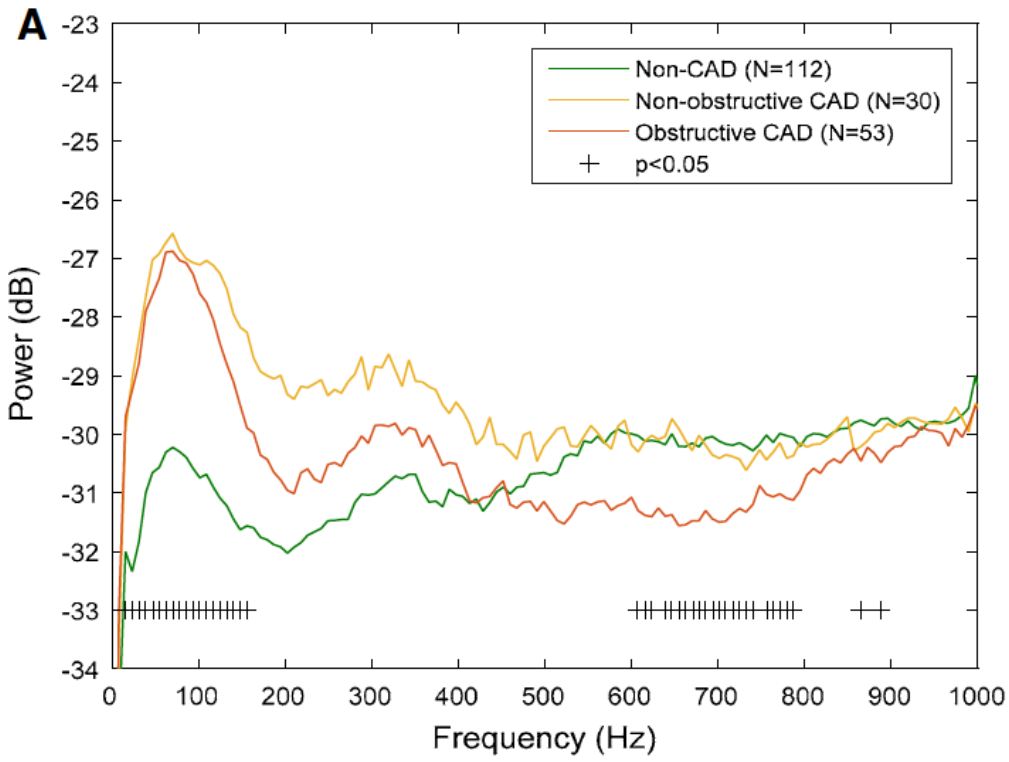
Exhibit 11 shows the acoustic spectrum at three levels of coronary artery disease.

There are significant differences in sound power between non-CAD patients and those with non-obstructive and obstructive disease. Decibels are logarithmic so the peak difference of over 4 dB (at 100 Hz) means that the coronary arteries of patients with CAD are twice as noisy as the arteries of non-CAD patients. This seems to be due to turbulent blood flow over partial occlusions.

The current algorithm looks at eight characteristics of the acoustic spectrum up to 1,000 Hz and mainly uses the lowest frequency region of up to 200 Hz (management information). To obtain this acoustic information requires a calibrated microphone of the appropriate sensitivity and a low background noise.

The acoustic processing uses a patented combination of mathematical techniques. These include the frequency power ratio, principal component analysis, auto mutual information and the amplitude of the fourth heart sound.

Exhibit 11: Acoustic spectrum of patients with different levels of coronary artery disease



Source: Acarix, published in Winther et al. 2016. Note: Crosses indicate significant differences between non-CAD and the other dataset. Note that these are dB, a logarithmic scale relative to a baseline value. These sounds are quieter than the baseline so have negative values.

Patents and intellectual property

The patents listed at the European Patent Office (EPO) are in Exhibit 12. Hyperlinks are provided.

In this area of acoustic signal processing, there are often several ways to approach a problem and equipment can be designed differently. The key patent may be US 8,911,383 B2, a granted patent on "An adhesive patch for monitoring acoustic signals" with a US patent extension of 411 days. This is also granted in Europe.[3] The Acarix patch is the key to profitability and generic competition on the high-margin patches would limit the return on investment. The patches have an RFID chip, offering direct protection against generics.

Exhibit 12: Acarix patent portfolio

Patent name	Date	Status	Comment
Method for segmenting a cardiovascular signal	2006	Granted in US only	Covers acoustic signal processing
Multi parametric classification of cardiovascular	2007	Granted in Europe, US and Japan	This patent covers the classification of cardiac sounds into diastolic and systolic
Segmenting a cardiac acoustic signal	2010	Granted in US only	Covers the signal processing steps used in CADScor
An adhesive patch for monitoring acoustic signa	Dec 2008	Granted in Europe, US and Japan	Covers the patch, so protects the consumable
System for indicating risk of coronary artery dise	2011	Granted in US, in process with EPO	Covers the functional internal operation of CADScor
Monitoring system	2013	In process	Covers the CADScor device with the analysis unit and microphone
Algorithm for adaptive filtering	2016	Not yet published	A method for determining the risk for coronary artery disease

Source: Acarix, EPO database

Edison cannot comment on the strength of patents or any infringement issues if they exist.

[3] European patents are issued by individual national patent agencies but applications are centralised.

Clinical performance of CADScor

The Acarix CADScor test aims to exclude ("rule out") patients from further testing. Exhibit 13 explains the simple statistics but somewhat confusing terminology used in this section.

Exhibit 13: Diagnostic statistics, what they mean

Aspect	Meaning	Commentary
Sensitivity	Sensitivity is the number of true positives found by the test as a percentage of the number of true positive cases. For example, if a test detects eight true positives when there are 10 cases of disease, the sensitivity is 80%. There are then two false negatives, people with the disease deemed health by the test.	Many diagnostic companies focus on this value since they are attempting to find individuals with a particular disease. In general, the higher the sensitivity of the test the lower will be the specificity (see below).
Specificity	Specificity is percentage of true negatives found by the test as a percentage of the number of true negative cases. To be meaningful, this value needs to be very high. For example, if there are 990 negative patients (healthy) and specificity is 90%, the test will find 891 true negatives (heathy and tested as healthy). It will also indicate that 99 healthy patients have the disease, these are false positives.	If a test is weak at discriminating between heathy and diseased individuals, many healthy patients are deemed to have the disease. As the majority of patients in an initial screening test are healthy, this leads to a large number of further investigations, risk and cost for both the healthcare provider and the patient.
Accuracy	Accuracy as a value is useful when comparing various tests and when developing a test, but it is of little use in clinical practice. It is defined as the area under the curve when sensitivity is plotted against 1-specificity.	A value of 0.5 (or 50%) means a test has no predictive value. A value of 1 (or 100%) means the test is totally accurate; none are. All tests will be calibrated onto particular sensitivity and specificity values.
Positive predictive value (PPV)	This is the percentage of positive test results reported that are correct: If the sensitivity was 80% in 10 disease cases, then 8 true positives would be found. If the specificity was 90% of 990 heathy cases, then there would be 99 false positive results. Adding these to the eight true positives gives 107 positive test results so the PPV is 8/107 or 7.5%: that is, fewer than one in 13 positive results are correct so a positive result is not very meaningful although better than the 1 in 100 disease prevalence.	PPV depends only on the population tested so if many people have the disease, then the PPV will be higher. In most tests, PPV is naturally low as true positives are rare so getting a high PPV level is hard to achieve and needs a very high specificity.
Negative predictive value (NPV)	This is the percentage of negative test results that are correct: the chance that a negative result means that a patient does not have the disease. For example, if 10 in 1,000 have the disease, 990 are healthy. In the example, 891 people test as true negatives and two with the disease test as false negatives. This makes 893 negative test results. This would give an NPV of 99.8% (891/893): Note that, 99% of patients are healthy.	The NPV, like the PPV applies only to the population tested so when a condition is rare, most tests are negative and NPV will be high.

Source: Edison Investment Research. Note these are example numbers assuming 1,000 patients tested and not CADScor data.

So far, all the trials conducted by Acarix, Exhibit 14, have been run in Denmark. The best reported study is AC003. The large Dan-NICAD has been completed with preliminary data, but not yet formally published. Edison has seen only limited data.

Exhibit 14: Acarix clinical trials

Trial name	Patients		Algorithm version	Commentary
	Recruited	Analysed		
AC 003	255	228	2.0	This study has been published by Winther et al (2016) and was the basis for clinical approval under the CE mark system.
Dan-NICAD	1,676	1,437	3.0	This study is not yet published although the study design is available (Nissen et al., 2016). It is registered as NCT02264717. Initial results from the study are discussed below.
Negative control cohort	754	606	3.0	This is an age-matched negative control cohort: a group of patients with no coronary artery disease used to train the algorithm further.

Source: Edison Investment Research based upon Acarix information

Clinical registration study: AC003

This study was used for registration of the CE mark for the CADScor system. There were 228 patients who could be analysed fully, of whom 63 had CAD, 41 had partial occlusion of less than 50% (intermediate risk) and 124 had no CAD. All of these either went through either coronary CT angiography or invasive coronary angiography to determine their level of coronary artery disease. The study was published as Winther 2016.[4] The study found that the Version 2 CAD-score

[4] Winther S, Schmidt SE, Holm NR, et al. Diagnosing coronary artery disease by sound analysis from coronary stenosis induced turbulent blood flow: diagnostic performance in patients with stable angina pectoris. *The International Journal of Cardiovascular Imaging*. 2016;32:235-245. doi:10.1007/s10554-015-0753-4.

diagnostic accuracy was 72%, lower than (but not statistically different to) the adjusted Diamond Forrester score at 79%. Statistical analysis showed that combining the Version 2 CAD-score and the Diamond Forrester score gave an accuracy of 82%.

Initial Dan-NICAD data

In version 3 of the algorithm, the three Diamond Forrester parameters are entered into CADScor. This then calculates the PTP using basic CAD1 score parameters. If this is over 85%, the patient should be referred to further testing.

If the doctor decides to run a CADScor test, the acoustic measurement is adjusted using age, gender and hypertension parameters to produce the final CAD-score, Exhibit 15.

Exhibit 15: Use of clinical risk factors by CADScor V3 and in CAD1 (updated Diamond-Forrester)

Clinical risk factor	Used in CAD1	Used in Version 3 CAD-score	Comment
Age	Yes	Yes	Age is a critical factor in scoring systems. For example a healthy male with no non-specific chest pain has a CAD risk of 14% at 60 years old, 24% at 70 and 37% at 80.
Gender	Yes	Yes	Men have a much higher risk of CAD than women. For example, an 80-year-old healthy male has a 37% risk of CAD, whereas an 80-year-old healthy female has a 13% risk.
Hypertension	No	Yes	Acarix has found that this is a useful parameter in calibrating the acoustic score. Note that hypertension is a clinical risk factor used to adjust the basic CAD1 score.
Chest pain symptoms	Yes	No	Symptoms have a high effect on the basic CAD1 score. For example, a 70-year-old male with typical angina would have a score of 70% but only 24% with non-specific chest pain.

Source: Edison Investment Research based on Acarix management comments

The Dan-NICAD study is not yet published, but Acarix has made available limited preliminary data. Exhibit 16 shows the outcome, as currently known, of the study (standard version 3 algorithm).

Exhibit 16: Dan-NICAD results using algorithm V3

		Angiography result		Total CADScor result		
		+ve (CAD)	-ve (no or intermediate CAD)			
CAD-score	+ve	176	1032	1218	PPV	14.6%
	-ve	31	1032	1063	NPV	97.1%
Actual result on CTA		207	2,064	2271		
		Sensitivity	Specificity			
		85.0%	50%			

Accuracy 75% (measured separately and not shown)

Source: Edison Investment Research based upon Acarix data

The trial recruited 1,676 patients, of whom 1,437 were available for analysis. About 10% (144 assumed) of those are stated by Acarix to have had CAD identified by CTA.

In addition, the trial analysis included a historic negative control cohort of 754 patients of whom 606 were included in the dataset. These individuals were selected from the 1156 patient DanRisk study, results in Diederichsen 2012) and confirmed to have no CAD by CTA,

The 228 patients from AC003 were also included; there were 63 CAD cases. This gives 2,271 patients, of whom 207 are believed to have CAD: about 9%. Note that exact numbers have not been provided by Acarix.

The accuracy was 75%, below the combined DF CAD-score found in AC003 of 82%.

Comparison of version 2 and version 3 algorithms

Exhibit 17 compares the various algorithms tested. The V3 algorithm is based on Version 2 with clinical risk factors added. The Version 3 algorithm has decreased the sensitivity from 90% to 85%, and increased specificity from 45% to 50%, Exhibit 17.

Exhibit 17: Comparison of different algorithms

	V2	V2+DF	V3
Sensitivity	90%	81%	85%
Specificity	45%	65%	50%
PPV	38%*	47%	15%
NPV	93%	90%	97%
Accuracy	72%	82%	75%

Source: Edison Investment Research based on Acarix data and Winther 2016

Note that the NPV and PPV values are calculated using the clinical population from the trial. Different clinical populations will give different PPV and NPV values. The AC003 trial had a high proportion, 28%, of CAD patients. This automatically increased the PPV and reduced the NPV.

In Dan-NICAD, by adding in a 606 patients with no CAD into the analysis, the percentage of CAD patients dropped to about 9%. The combination of a very low specificity with a low percentage of true cases in the population studied explains the reduction in the PPV to 15%. The same effect explains the increase in the NPV to 97%.

US trials

Acarix has no stated path to FDA approval for the CADScor system. The options are in Exhibit 18. The US would be the biggest market, but there are serious regularity barriers

Exhibit 18: US regulatory pathways for diagnostics

Pathway	Comment	Commercial issues
510(k)	The simplest route, 510(k), requires that a similar device is already approved. There are many electronic stethoscopes approved, but none of them detect coronary artery disease.	Acarix could not make any novel claims if a 510(k) was used. However, this is an unlikely route to use and *de novo* 510(k) is more likely.
de novo 510(k)	This is where there is no 510(k) comparable device (as with CADScor). It can only be used if the FDA accepts that the device is safe.	If CAD score gains approval by this route, it will become the reference for other systems. This potentially facilitates the entry of competitors to the market as they can use a simple 510(k).
Pre-market approval, PMA	This route requires a full set of clinical trials and some of these will need to be run in the US. This will take several years to complete with a full review process at the end so is expensive and slow.	This creates a barrier to entry for competitors who would need more clinical data. It allows novel claims to be made, if the FDA agrees.

Source: Edison Investment Research

Edison is unable to judge which route is possible but, given the specific diagnostic claim being made, it is possible that the FDA may require a PMA application. This could delay US launch.

Test economics

Acarix has not made available any economic analysis. CADScor works economically if it stops enough healthy people from being referred on, so saving money, time and hospital resources.

To find patients that probably do not need further testing, CADScor is tuned for high, 85%, sensitivity. This detects most cases of CAD. However, CADScor also identifies 50% of patients who do not have CAD as positives (the specificity). This means that only half the patients are excluded even though a low percentage, maybe 10-15% overall, will actually have CAD – depending on the population tested. Note that many of these false positives may actually have some level of partial coronary artery blockage but this is not defined as CAD unless 50% obstruction or more is found.

Currently, US healthcare insurers tend to require that they give prior authorisation for non-acute cardiology investigations (Acarix commissioned market survey) to control costs. If healthcare providers were to require a CAD-score as an extra check after PTP scoring before they authorised more expensive testing, the device will have established a solid and sustainable position in the healthcare market.

Acarix has supplied some regional Danish healthcare statistics[5] on the number of patients referred and tested for possible CAD. The data show that of 2,954 cases in 10 centres during Q216, 80% had intermediate or no CAD, about 4% were unknown and about 16% had CAD. There was a wide variation between centres, the range of no and intermediate CAD risk was from 72% to 92%. This is a real sample of the types of cases that CADScor could be used to screen.

Applying the Dan-NICAD sensitivity and specificity and treating unknowns as not having CAD, the outcome is shown in Exhibit 19. If all these patients had been tested with CADScor, the PPV would be 24%, that is about one in four cases referred would be true CAD cases. Of the negative results, 19 out of 20 would be correct. Potentially, 1,314 people would have avoided further testing. However, 70 of those should have been tested further.

Exhibit 19: DAN-NICAD results applied to a Danish patient sample

		Angiography result		Total CADScor result		
		+ve (CAD)	-ve (no or intermediate CAD)			
CAD-score	+ve	397	1,243	1,640	PPV	24%
	-ve	70	1,244	1,314	NPV	95%
Actual result on CTA		467	2,487	2,954		
		Sensitivity	Specificity			
		85.0%	50.0%			

Accuracy 75% (measured separately and not shown)

Source: Edison Investment Research based upon Acarix Dan-NICAD data and Danish Hospital data

Acarix has not carried out any formal economic studies. Exhibit 20 is an attempt by Edison to try and quantify the potential savings to the healthcare system based on the Danish data cited above and applying US costs (as cited in Exhibit 8). It was noted earlier that 87% of cases in the US were tested using nuclear imaging. From CTA studies, it is assumed by Edison that 20% of patients have a CTA; this could be higher.

This shows possible savings of nearly $1.5m for these patients less the cost of the test itself ($440k) making $1.1m net savings or $380 per patient. Note that the CADScor cost cited of $150 includes healthcare staff time to run the test plus the cost of the sticky patches and an element for amortisation on the device cost. Acarix may get $132k after distributor margins. This of course is from one region of Denmark for one quarter of the year and assuming US pricing.

Exhibit 20: Theoretical model of US cost savings from the use of CAD-score

	Percentage use	Price US$	Patients	Overall costs US$
ECG treadmill	3%	114	39	4,446
Stress echocardiogram	10%	284	131	37,204
Myocardial perfusion imaging	87%	644	1,143	736,092
Coronary angiogram	20%	3,000	263	789,000
			1,576	1,566,742
CADScor		-150	2,954	(443,100)
Saving				1,123,642
Theoretical saving per patient				380

Source: Edison Investment Research based on Arbab-Zadeh (2012) and Ladapo et al. (2014)

Note that Exhibit 20 assumes that all the 1,314 negative CADScor patients in Exhibit 19 are "cost saved" and it is further assumed that 20% of these would have undergone a CTA test as well as a functional test making 1,576 tests. In real life, all 2,954 from Exhibit 19 underwent further testing although the data does not disclose what tests were used or the Danish costs incurred.

[5] VestDansk Hjertedatabase 1/4 until 30/6 2016.

Extrapolating this to the 3.8 million US referrals found by Ladapo gives a theoretical saving of $1.4bn per year. However, these gains, if achievable, are spread across the entire healthcare system and individual providers will see less benefit.

It should be re-emphasised that this is not a proper health economic study, but simply an indication of what such a study might look like. This does not take into account any quality life year assessments. Acarix will need to run real-life clinical trials to establish clearly how the device is used in practice and to prove the cost savings that can arise.

By comparison, if one substitutes stress ECG echocardiography into the above analysis (a first line test) using the Danish sample in Exhibit 19, then 533 patients would be referred (vs 1,640) and 2,421 would be "ruled out" (vs 1,314). This is despite a poor ECG sensitivity of 47.5%. The figures are better because the ECG stress specificity is much higher at 87.5% vs 50% on CADScor.

However, and this matters more to doctors, the ECG stress test will fail to find 245 patients with disease whereas CADScor would miss only 70. Acarix notes that doctors do not think that ECG stress testing is reliable. Nonetheless, in this example Danish population, because of the higher specificity, the ECG stress PPV is 42% vs CADScor 24% with NPV at 90% vs CADScor 95%.

Competition

The main competitor to the CADScor system is medical inertia and the current set of tests. Medical professionals are typically slow to adopt new tests even when they are reimbursed. Some cardiologists may be reluctant to move from established tests which they are often paid to carry out in the US. There is also a risk that healthcare providers see the CADScor as just an additional cost as they are unable to identify the savings in their accounts. This has limited adoption of other medical devices even when there is a robust, evidence-backed economic case.

Any direct competitor might come from electronic stethoscopes, of which there are many. An example of an innovative primary care device with a specific objective of reducing hospital admissions is the Cardiosleeve, approved by the FDA under a 510(k), as similar to other electronic stethoscopes on the market. However, it may not be possible to do CADScor type testing on such systems and Acarix holds patents protecting its signal processing.

A small US mid-west company, AUM Cardiovascular has a hand-held device and claims that "acoustic detection with the CADence system provides a completely new method for detecting obstructive coronary artery disease". A clinical trial (NCT01743040) involving 1,054 patients completed in late 2015; no results have been released yet, but publication may occur in 2017: The product is stated to be CE marked. No other data are available.

Financials: Gearing up for product launch

Acarix entered 2016 with cash of SEK2.1m. It gained an SEK9m convertible loan from shareholders in H1. Expenditure reported was SEK11.7m to 30 September. From mid-2016, development costs were capitalised; total investment to 30 September on development and equipment was SEK9.8m. Cash on 30 September was SEK1.9m. Acarix raised further funds of €2m (SEK20m) in October 2016 from Puhua Jingxin which increased cash to SEK19m (information from management). In 2016 some SEK24m of non-cash financing costs were charged due to a technical adjustment on conversion of a shareholder loan into 3.3m shares. We assume the cost of the SEK140m IPO, expected to be about SEK15m, to be offset against the IPO funds raised. We expect cash at the end of 2016 to be about SEK125m.

Our forecast anticipates a rise in cash expenditure (burn rate) to around SEK72m per year from 2017. This is research and clinical of SEK32m, marketing of SEK20m and administration of SEK23m. Of this, we expect SEK18m of development to be capitalised plus some capital expenditure of SEK1m. Amortisation of development at SEK2.6m is expected starting in the 2017 accounts. No US trials are currently forecast or disclosed by Acarix. Limited direct product sales into the German market are expected in 2017 with sales progression in 2018. These largely consist of base units with private patients, or their insurers, reimbursing the cost. Disposable revenues should rise as the number of base units in use rises. Sales should partially offset cash use, making a net cash outflow of SEK72m for 2017. Depending on sales progression, Acarix may need further funding in 2018. A nominal SEK50m interest-free loan is included as forecasts for 2018 as a result.

Sensitivities: Acceptance and cash

The two major sensitivities relate to the diagnostic performance of the product and reimbursement. The sensitivity is very good at 85%, but the current specificity is low at 50% relative to other tests like stress ECG. For European sales, Acarix has a CE mark but CADScor needs to be written into the guidelines set by the ESC and NICE. The US route to approval is not yet clear and the FDA may require further trials. The American Heart Association and American College of Cardiology then need to incorporate the test into the guidelines. The second major challenge is to get reimbursement and that will depend on economic studies. This will require real-world clinical/economic trials to show that use of CADScor leads to better patient care and cost savings. For cardiologists in the US, there are lucrative fees associated with more complex tests, so a disincentive to use CADScor. However, there are concerns in the literature about over testing and the added radiation exposure from CTA and nuclear stress testing. The US healthcare system is slowly becoming more cost focused and European systems are already very cost conscious which could help uptake. Sales of new diagnostic products are very hard to forecast and sales could be significantly higher or lower than these estimates. Timing of events is highly unpredictable. Finally, as a Sweden-listed company, the reported accounts and company valuation will be sensitive to the US dollar and euro exchange rates as these are the two major markets. Some costs are in Danish krone so the DKK/SEK rate is also a factor.

Valuation: A novel product with global reach

With no track history of a comparable product on which to base a market forecast, Edison has developed a simple model based on what appear to be realistic sales targets split between the US and Canada, Germany and Scandinavia (direct sales), rest of Europe and Rest of World. The characteristics of these markets and the assumptions used are shown in Exhibit 21.

Exhibit 21: Valuation model parameters 2017-2030

	Germany and Scandinavia	Rest of Europe	North America	Rest of world
Direct or distributor sale	Direct	Distributor	Distributor	Distributor
Launch year or period	2017	2018-19	2021	2018
Distributor discount	Direct sale	40%	40%	40%
Number of CADScor units sold per year	600	900	2000	525
CADScor unit list price used in model	€3,000	€3,000	$5,000	$5,000
Patch price/patient	30	30	75	75
Tests (= patches used) per CADScor per year	100	100	150	100
Market sales in 2030 before probability adjustment (m)	€32.71	€25.57	$110.14	$26.19
Probability adjustment used	50%	40%	30%	35%
Probability adjusted, discounted sales NPV (m)	€26.84	€14.00	$29.69	$13.51

Source: Edison Investment Research. Unit prices may be higher

Exhibit 22: National market characteristics

Market	Reimbursement	Probability and market assumptions
Germany and Scandinavia	These are the first markets targeted by Acarix with direct sales. The price is within the typical capital budget of a German primary healthcare provider. In Germany, test reimbursement is mostly from the government-run insurance schemes (there are 158 such schemes). About 10% of Germans prefer to use private insurance from a variety of providers. These private providers operate their own coding and reimbursement scheme and are often early adopters of new technologies since these innovations make their health insurance products more attractive to customers. Each insurer makes its own decision about reimbursement and this is a slow process. The government scheme will take at least two years to decide whether to reimburse and at what level.	The German market can be difficult to enter and reimbursement is not guaranteed. However, it is Acarix's major target market and private medical insurers are willing to adopt new technology before government reimbursement is guaranteed. For these reasons a low level of sales is projected over 2017 and 2018, with government reimbursement assumed from 2019. Acarix is planning to spend significantly on marketing and sales during this period: Edison forecasts about DKK28m (€3.6m), although this will obviously cover reimbursement activities in other markets as well. Long term, Edison assumes that Acarix spends 20% of its German and Scandinavian revenues on marketing. Edison has used a 50% probability of achieving the forecast sales targets.
Other European territories	Acarix will start discussions with national health assessment bodies for example the UK National Institute for Clinical Excellence (NICE). Reimbursement in the UK will be determined by the policy of local clinical commissioning groups, which fund the costs of hospital referrals for patients. They are unlikely to purchase the product before NICE has given a clear opinion of the clinical validity and economics of the CADScor system. Other European countries will, in practice, have similar systems although they differ in detail and they note any NICE findings.	Because of the higher barriers in the other European markets, Edison has used a 40% probability of achieving the forecast sales targets. Edison assumes that a list price for the product is the same as Germany but there are 40% distributor discounts. Level of discount reflects the investment required by distributors and the probably smaller individual national markets. Adoption is likely to be slow and the need for capital expenditure may slow uptake.
US and Canada	Once FDA approval has been obtained, Acarix will need to obtain reimbursement for the test. Part of this will be to gain inclusion in guidelines issued by the two medical cardiology associations in the US (American Heart Association and American College of Cardiology). Medicare covers Americans over 65 years old so the higher-risk group for coronary artery disease. Medicare sets its own reimbursement rate once a Current Procedural Terminology (CPT) code has been obtained for the test. CPT codes are issued by the American Medical Association. Medicare is not obliged to reimburse a procedure even if it has a CPT code. Private health insurers and health maintenance organisations usually refuse to cover investigational tests.	Edison assumes that Acarix can overcome these hurdles and that a price per unit of $5,000 is achievable with a 40% distributor discount. The price for the consumable patch is set at $75 before distributor discount with an average use rate of 150 per year; this is above the European level but the US tends to adopt new technology more enthusiastically. Edison assumes that Acarix will sell up 2,000 units per year in the US with 5% growth once the market is mature and 2% price rises. Sales are not expected before 2021 with the first significant sales year being 2024. Because of the higher regulatory and reimbursement hurdles to overcome in the US market, Edison has used a 30% probability of success in achieving the forecast sales level.
Canada	Canada is a major market in its own right. It has its own regulatory system: Health Canada. CADScor was approved by Health Canada in July 2016. Acarix has not disclosed any commercialisation plan.	For simplicity, Canada is recognised in the Edison model as being 7% of the US forecast. This is slightly less than the US on a pro rata population basis, but Canada is a more price-sensitive market.
Rest of world including China	The intention to set up a Joint Venture with Zhejiang Jingxin Pharmaceuticals is a very positive strategic development although no details have been disclosed. This could be a good route into the Chinese market with a strong and committed partner. If on average about 4% of the population has coronary artery disease, there should be at least 44 million cases in China. The Chinese regulatory system will probably require some local trials to be run. Edison remains cautious about forecasting significant Chinese sales until the commercial strategy becomes clearer.	The rest of world sales are modelled by assuming they are 15% of the European and North American sales combined. The probability of achieving these forecasts in rest of world is set at 35% since the regulatory barriers are lower than in the US but the commercial challenges are varied. Although prices on imported medical products are often high, getting widespread uptake can be a problem.

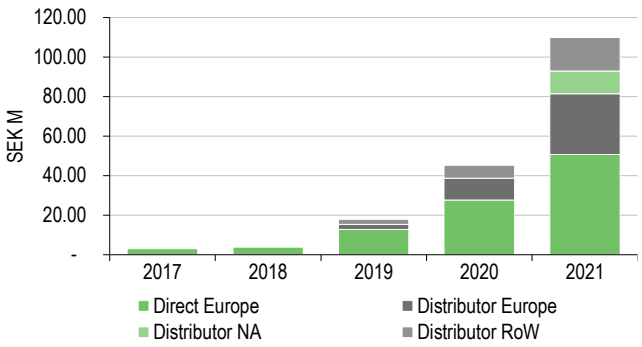
Source: Edison Investment Research

Sales forecast

The sales of units are particularly important in the first few years of any market, but as the installed base of systems grows the consumable patch use rate becomes the key growth driver factor. Exhibit 23 shows the forecast market development up to 2021 before probability adjustment. This period is dominated by European with German full reimbursement assumed from 2019.

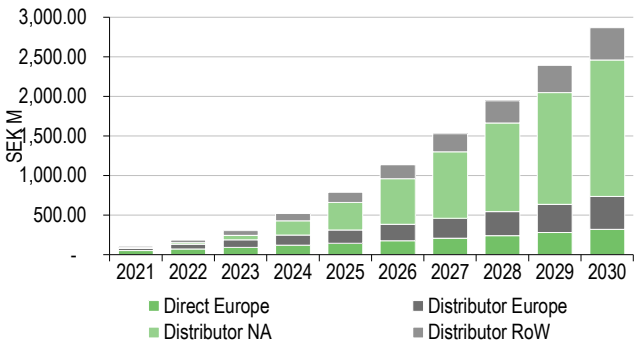
Exhibit 24 shows the non-risk-adjusted forecast from 2021 to 2030. This indicates Acarix 2030 sales of about $270m/€260m (SEK2.5bn) before risk adjustment. This is a significant market for a diagnostic product. The probability-adjusted sales forecast is $72m/€69m (SEK677m). From 2031 onwards, a long-term growth rate of 1% is assumed as the market may then have matured and competitors have entered as the patents will have expired. In the terminal year of 2030, Edison forecasts 4,500 units sold globally and disposable patch sales of 4.2 million units.

Exhibit 23: Forecast overall sales by market to 2021 before probability adjustment (SEK)



Source: Edison Investment Research forecast

Exhibit 24: Forecast overall sales by market 2021-30 before probability adjustment (SEK)



Source: Edison Investment Research forecast

Discounted cash flow valuation

There are two elements to the valuation, Exhibit 25.

Exhibit 25: Acarix valuation

		SEK	DKK	€
Discounted value of cash flows	12.50% discount rate	89.5	68.0	9.2
Terminal value 2030	1% long-term growth rate	638.6	485.7	65.3
Indicative value (Jan 2017)		728.2	553.7	74.5
Value per share	**23.0m in issue**	**SEK31.62**	**DKK24.05**	**€3.24**

Source: Edison Investment Research. Rates used SEK 1.31/DKK; SEK 9.8/$; DKK 7.43/€; DKK7.14/$

Firstly, the discounted value of cash flows between 2017 and 2030 is estimated using a 12.5% discount rate. A Swedish corporation tax rate of 22% is used. Tax losses to mid-2016 have been stated by management to be worth DKK40m (SEK578m). Because of the long period of marketing investment required to commercialise the product, this estimated value of cash flows to 2030 is relatively low at about SEK90m.

Secondly, as a diagnostic product established as the brand leader in its market, the company should have a continuing value. With lower marketing costs, due to the distributor strategy, and no further part investments, the profitability could be very high since most revenues could come from high-value consumables requiring a low level of marketing support. The terminal value in 2030 of SEK3.3bn discounted to 2017 gives a terminal value of SEK639m. Note that Acarix is expected invest in other products and will probably spend additional resources on developing further indications for its acoustic technologies. Cash flows from new products are not estimated as we do not have any information on possible projects.

At the IPO listing 19 December 2016), Acarix had 23m shares in issue. The combined indicative value is SEK728m implying a fair value of SEK31.62/share relative to an IPO price of SEK17.60/share.

Acarix now has the cash to invest in marketing and consider and plan US trials. Any future funding need from 2018 depends on a successful launch in Germany and on the company's cost base. Edison forecasts profitability from 2022 if full European reimbursement is gained and a US approval is obtained. Financial forecasts to 2018 in SEK are shown in Exhibit 26. These will be updated when audited accounts for 2016 are available.

Investors are referred to the 2016 IPO prospectus issued by Acarix for guidance on detailed aspects of the company.

Exhibit 26: Financial summary

SEK 000	2014	2015	2016e	2017e	2018e
Year end 30 June	IFRS	IFRS	IFRS	IFRS	IFRS
PROFIT & LOSS					
Revenue	-	-	-	3,023	3,847
Cost of Sales	-	-	-	(983)	(1,038)
Gross Profit	-	-	-	2,040	2,809
EBITDA	(23,831)	(15,248)	(15,325)	(49,760)	(49,491)
Operating Profit (before GW and except)	(23,989)	(15,377)	(15,483)	(49,918)	(49,648)
Intangible Amortisation	-	-	-	(2,630)	(2,630)
Exceptionals	-	-	-	-	-
Operating Profit	(23,989)	(15,377)	(15,483)	(52,548)	(52,278)
Other	-	-	-	-	-
Net Interest	74	(23)	(23,250)	526	197
Profit Before Tax (norm)	(23,915)	(15,400)	(38,733)	(49,392)	(49,451)
Profit Before Tax (FRS 3)	(23,915)	(15,400)	(38,733)	(52,022)	(52,081)
Tax	4,706	3,007	3,288	3,288	3,288
Profit After Tax (norm)	(19,209)	(12,393)	(35,446)	(46,104)	(46,164)
Profit After Tax (FRS 3)	(19,209)	(12,393)	(35,446)	(48,734)	(48,794)
	-	-	-	-	-
Average Number of Shares Outstanding (m)	14	18	23	23	23
EPS - normalised (c)	(135)	(67)	(235)	(200)	(200)
EPS - FRS 3	(135)	(67)	(235)	(212)	(212)
Dividend per share (c)	-	-	-	-	-
	-	-	-	-	-
Gross Margin (%)	-	-	-	89	96
EBITDA Margin (%)	-	-	-	(2,165)	(1,692)
Operating Margin (before GW and except.) (%)	-	-	-	(2,172)	(1,697)
	-	-	-	-	-
BALANCE SHEET	-	-	-	-	-
Fixed Assets	2,128	8,670	26,409	48,988	71,568
Intangible Assets	-	5,971	19,335	40,796	62,258
Tangible Assets	2,128	2,699	4,000	5,118	6,235
Other	-	-	3,074	3,074	3,074
Current Assets	16,156	6,912	130,114	58,734	37,296
Stocks	-	-	-	-	-
Debtors	2,665	1,771	2,630	2,893	5,260
Cash	8,705	2,121	124,196	52,554	28,748
Other	4,786	3,020	3,288	3,288	3,288
Current Liabilities	(3,161)	(3,443)	(1,315)	(1,315)	(1,315)
Creditors	(1,085)	(1,128)	(900)	(900)	(900)
Short term borrowings	(2,076)	(2,315)	900	900	900
Short term leases	-	-	-	-	-
Other	-	-	(1,315)	(1,315)	(1,315)
Long Term Liabilities	-	-	-	-	-
Long term borrowings	-	-	-	-	-
Long term leases	-	-	-	-	-
Other long term liabilities	-	-	-	-	-
Net Assets	15,123	12,139	155,208	106,408	107,548
	-	-	-	-	-
CASH FLOW	-	-	-	-	-
Operating Cash Flow	(22,247)	(13,570)	(17,417)	(50,049)	(51,884)
Net Interest	(79)	(4)	-	526	197
Tax	1,455	4,943	3,288	3,288	3,288
Capex	(810)	(6,520)	(14,274)	(25,407)	(25,407)
Acquisitions/disposals	-	-	-	-	-
Net Financing	14,504	8,840	150,334	-	50,000
Dividends	-	-	-	-	-
Other	740	(296)	3,373	-	-
Net Cash Flow	(6,437)	(6,607)	125,304	(71,642)	(23,806)
Opening net debt/(cash)	(13,066)	(8,705)	195	(125,097)	(53,454)
HP finance leases initiated	-	-	-	-	-
Other	-		-	-	(50,000)
Closing net debt/(cash)	(8,705)	195	(125,097)	(53,454)	20,352

Source: Edison Investment Research, Acarix accounts

Contact details	Revenue by geography
Acarix AB World Trade Center Skeppsgatan 19 211 11 Malmö Sweden www.acarix.com	N/A

Management team

CEO: Søren Rysholt Christiansen	Chairman: Dr. Werner Braun
Søren Christiansen joined Acarix in August 2016. He brings a strong commercial and general management background from over 16 years in the medical device industry. He brings extensive international business experience and has been stationed in Australia, New Zealand, Italy and India. Prior to joining Acarix, Søren was at Cook Medical, GN ReSound, Elos Medtech and BK Ultrasound. Søren holds a graduate diploma in international business and an executive MBA from Copenhagen Business School.	Dr. Werner Braun has international experience from leading positions in companies from Germany, Austria and Schwitzerland. Dr. Werner Braun has a Ph.D. in Physics from the Technical University of Munich, Germany.
COO and co-founder: Claus Bo Vöge Christensen	**Interim CFO: Christian Lindholm**
Claus Christensen is a co-founder of Acarix. Claus has experience working at Novozymes A/S, MIC-DTU and Coloplast A/S as director of the Medical Monitoring & Diagnostics unit. He holds a PhD in molecular biology from the University of Copenhagen (1998) and an Executive MBA from TEM at the Technical University of Denmark.	Christian Lindholm works as an interim manager and was retained by Acarix in July 2016. Christian was employed as CFO at Doro AB till October 2015. He was formerly with Trial Forms Support AB, a Contract Research Organisation. He holds qualifications from the Universities of Kristianstad and Växjö.

Principal shareholders post IPO	(%)
Sunstone LSV Fund II	20.6
SEED Capital DK II	20.6
Jingxin	11.5
Coloplast A/S	7.1
Seventure Partners	4.3
Peter Samuelsen (co-founder)	2.4
Aalborg Universitet plus associates	2.2
Claus B. V. Christensen (COO and co-founder)	0.7
W Rong	0.4
Other pre-IPO	0.1
IPO investors	29.9

Note: All shareholders pre-IPO are locked in.

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