



ASP3282
NON-CONFIDENTIAL SUMMARY



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ASTELLAS' TARGET PRODUCT PROFILE

	Target Product Profile for ASP3282
Value proposition	<ul style="list-style-type: none"> Reduction in incidence of postoperative atrial fibrillation (POAF) after cardiothoracic surgery without affecting cardiac function
Expected label (Indication)	<ul style="list-style-type: none"> Novel prophylactic agent for POAF, administered during open chest cardiac surgery (i.e. CABG, valve surgery, and thoracic aortic surgery)
Mechanism of Action	<ul style="list-style-type: none"> NGF neutralization (antibody Fab fragment)*
Target Patient Segmentation	<ul style="list-style-type: none"> Patients receiving on-pump cardiac surgery (CABG, valvular, aortic)
Dosing	<ul style="list-style-type: none"> Single administration into four epicardial fat pads prior to finishing surgery
Comparator	<ul style="list-style-type: none"> Placebo
Efficacy (in pivotal study)	<ul style="list-style-type: none"> 50 to 70% reduction in incidence of atrial fibrillation occurring within 7 days after surgery
Safety and Tolerability	<ul style="list-style-type: none"> No negative impact on cardiac function Adverse drug reactions similar to placebo
Dosing and Administration	<ul style="list-style-type: none"> 124 mg (Based on current assumption, to be determined by future studies) Single administration by epicardial fat pad injections during surgical process

*ASP6294 is PEGylated form of ASP3282 with seven additional amino acids in the C-terminal; the cell line of ASP6294 is different from that of ASP3282

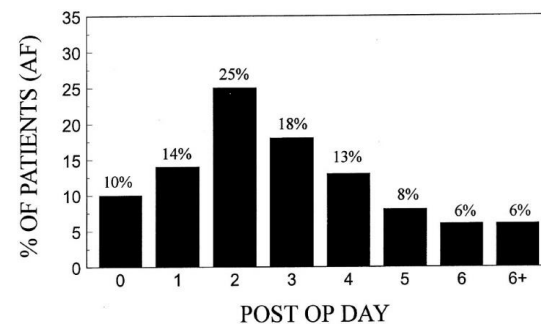


POSTOPERATIVE ATRIAL FIBRILLATION

Incidence

- The most common complication after cardiac surgery; incidence rate: approximately 30% after isolated coronary artery bypass grafting (CABG) surgery, 40% after valve replacements or repair, 50% after combined procedures ¹⁾
- Peak incidence: post operative day 2–4 ^{2), 3)}

Patients receiving on-pump cardiac surgery (CABG, valvular, aortic)



Prevention and treatment

- Pharmacological prevention (described in guidelines^{1), 3), 4)}
 - ✓ β -blockers: risk of hypotension etc.
 - ✓ amiodarone: risk of bradycardia, hypotension and arrhythmia etc.

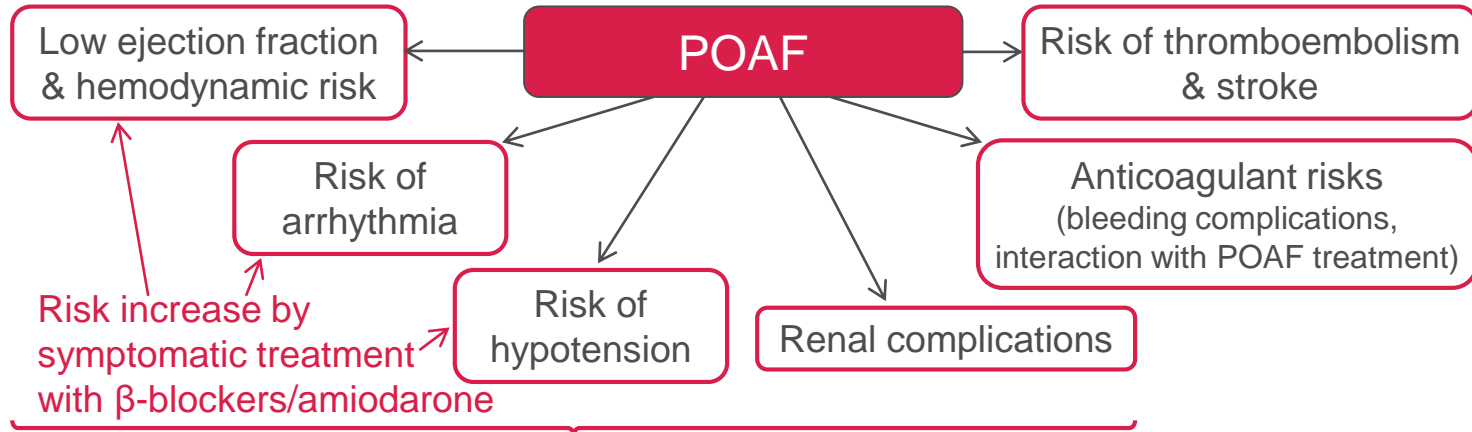
→ NOT used aggressively due to concerns about perioperative hemodynamic instability
- Symptomatic treatment: pharmacological treatment (mainly with β -blockers and amiodarone) followed by electrical conversion

1) J Am Coll Cardiol 51:793-801 (2008)
2) Circulation 94:390-7 (1996)

3) Can J Cardiol 27:91-7 (2011) (CCS Atrial Fibrillation Guidelines 2010)
4) J Thorac Cardiovasc Surg 148:e153-93 (2014) (2014 AATS guidelines)



Impact on patient outcomes



Impaired postoperative recovery: different from chronic situation

Increased mortality

Impact on hospital resource and costs ¹⁾

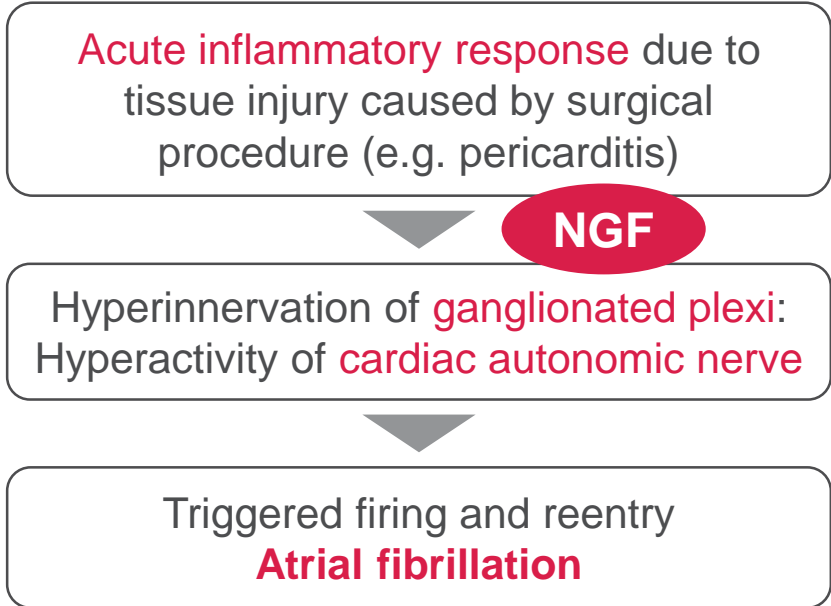
- 48 additional ICU hours and \$3,000 of increased ICU-related costs
- 3 additional hospital days and \$9,000 of increased total hospital-related costs

“Top of mind issue” for cardiac surgeons



1) Ann Thorac Surg 98:527-33 (2014)

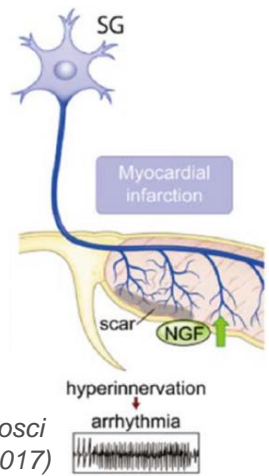
Mechanism of POAF



Anti-NGF mAb targeted to GP is an attractive upstream approach for POAF prevention.

Role of NGF

- NGF upregulation was confirmed in patients after CABG surgery. ^{1), 2)}
- Increased NGF was also observed in animals at the inflamed myocardium. ³⁾
- NGF causes plastic changes and hyperactivity of cardiac autonomic neurons which leads to the onset of arrhythmia such as atrial fibrillation. ⁴⁾⁻⁶⁾
- Infusion of NGF to stellate ganglion caused AF in a canine model. ⁷⁾



Auton Neurosci 205:1-11 (2017)
 7) *Am J Physiol Heart Circ Physiol* 289: H1851-7 (2005)

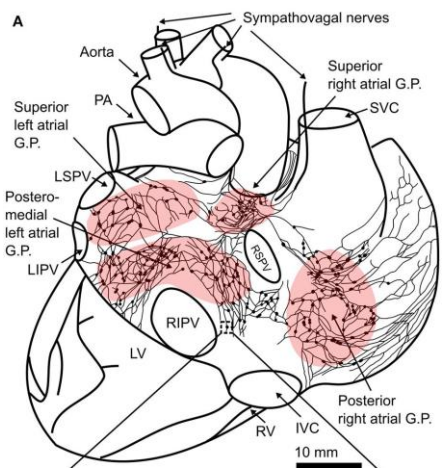
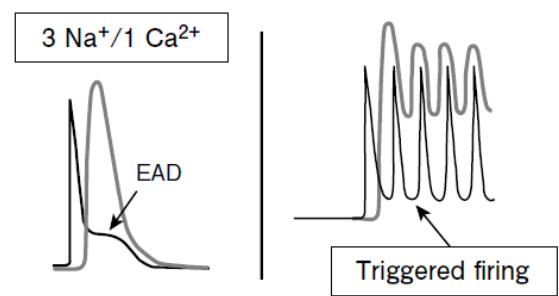
1) *Crit Care* 3(Suppl A):P12 (1999) 3) *Circ Res* 95:76-83 (2004) 5) *J Neurophysiol* 96:946-58 (2006) 7) *Am J Physiol Heart Circ Physiol* 289: H1851-7 (2005)
 2) *J Clin Exp Cardiol* 4:228 (2013) 4) *Circ Res* 86:816-21 (2000) 6) *Circ Res* 116:2005-19 (2015)

GANGLIONATED PLEXI (GP) AS A TARGET

GP: regulator of intrinsic cardiac autonomic nervous system on atrial myocardium ¹⁾

- 10% sympathetic neurons (ad.)
 - 10% parasympathetic neurons (ch.)
 - 80% interconnecting neurons (ad.+ch.)
- ad.: adrenergic, ch.: cholinergic

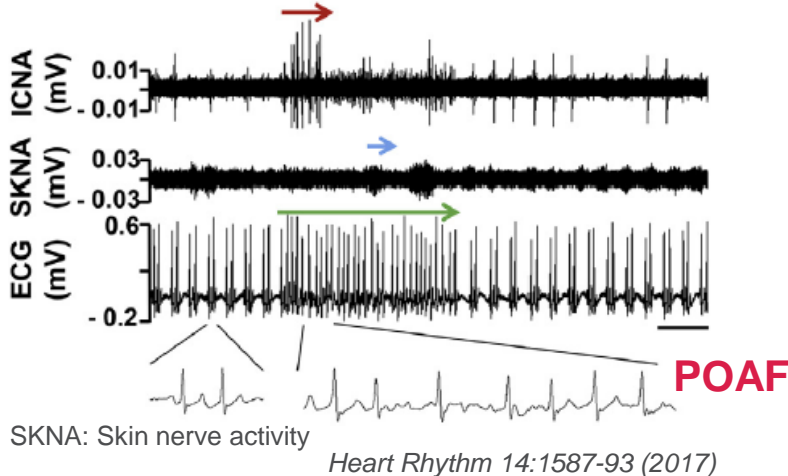
Hyperactivity of the CANS:
 Acetylcholine
 Shortens action potential
 Norepinephrine
 Increases Ca²⁺ loading



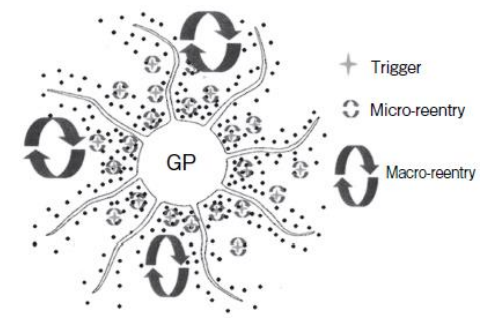
Front Physiol 9:240 (2018)

Relationship between ICNA and onset of POAF in patients after CABG surgery

ICNA: Intrinsic cardiac nerve activity



- Hyperactivity of the autonomic neurons causes excessive release of the neurotransmitters of autonomic nerves at multiple sites.
- This leads to triggered firing and reentry at multiple sites to initiate and maintain AF.



Jpn J Electrocardiology 36:49-54 (2016)



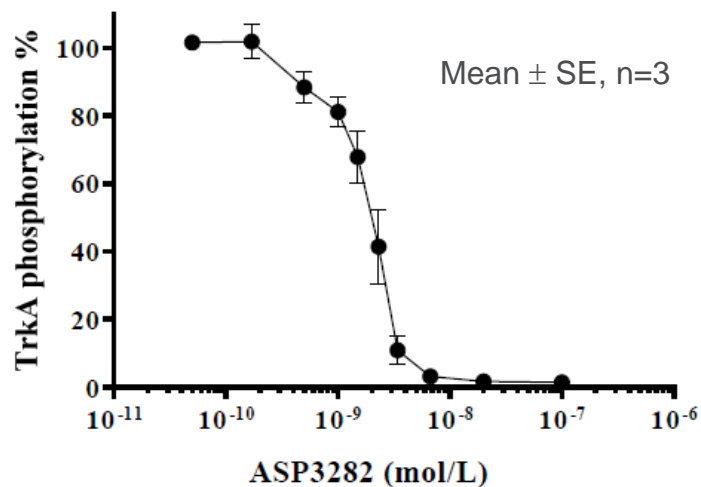
1) Jpn J Electrocardiology 31:541-8 (2011)



Binding affinity of ASP3282 for human, rat and swine NGF

Species	Geometric mean KD value, in pmol/L (95% confidence interval)
Human	13.4 (8.86 – 20.2)
Rat	25.2 (9.46 – 67.0)
Swine	5.62 (4.13 – 7.66)

Inhibition activity of ASP3282 on human NGF-induced TrkA phosphorylation

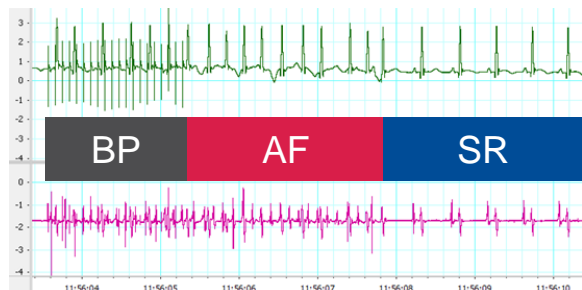
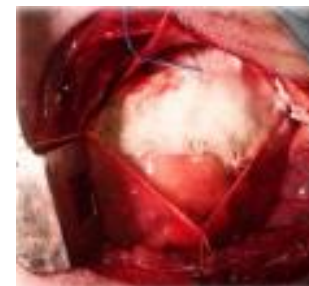


➤ ASP3282 bound to human, rat and swine NGF and inhibited TrkA receptor activation.

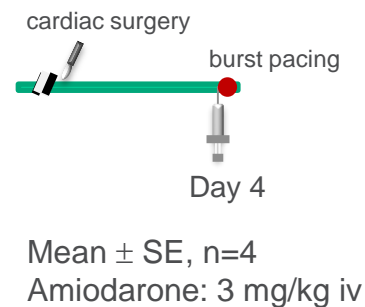
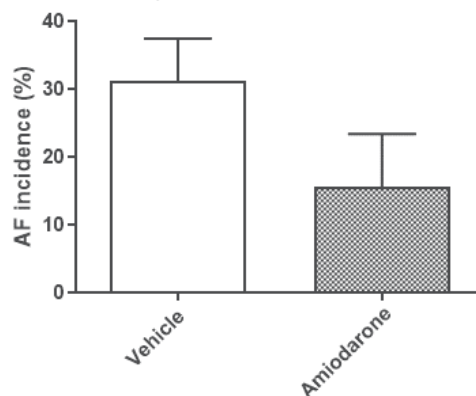


Canine sterile pericarditis model: “a model with a clinical counterpart in postoperative open heart surgical patients”¹⁾

- Surgical operation
 - ✓ thoracotomy, pericardiotomy
 - talcum powder application on atrial epicardium for 5 h
 - pericardium & chest closure
- Right atrial burst pacing & evaluation of AF induction
 - ✓ 4 sites (appendage, low lateral, high lateral, free wall), 2 times/site (= 8 times in total)



Efficacy of amiodarone

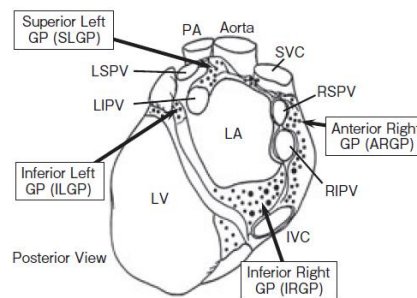


1) Europace 17:1834-9 (2015)

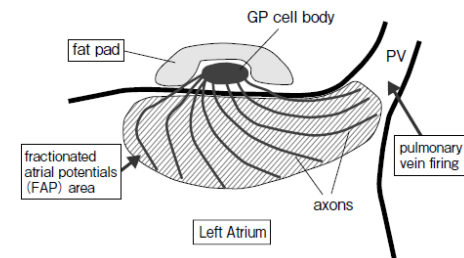
PHARMACOLOGY

Local administration during surgery

- Injections into 4 epicardial fat pads located on ganglionated plexi (GP)
- Clinical experiences reported
- Simple and easy method for surgeons

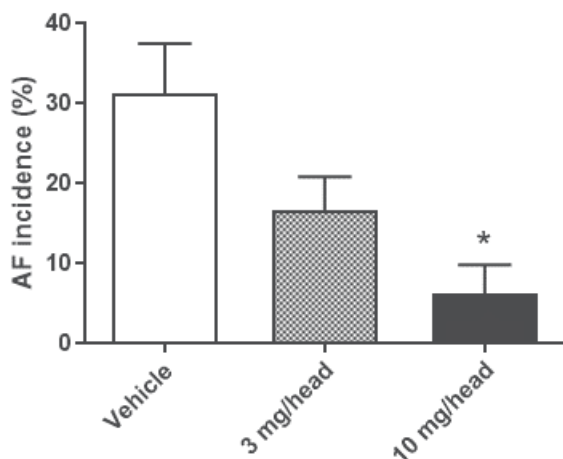


Jpn J Electrocardiology 31:541-8 (2011)

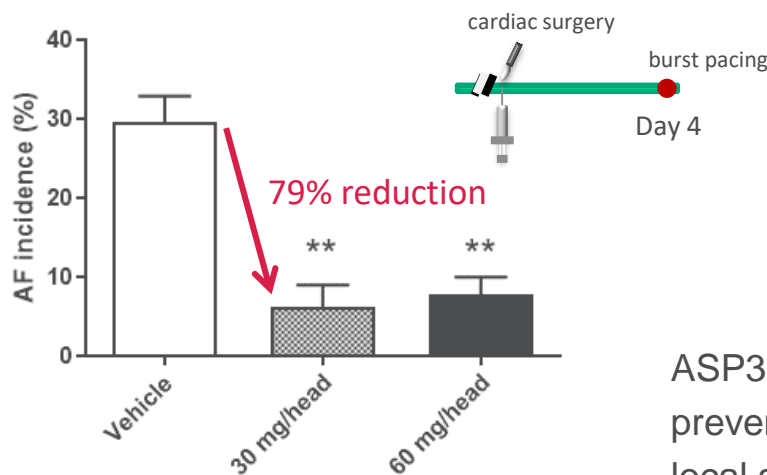


Jpn J Electrocardiology 36:49-54 (2016)

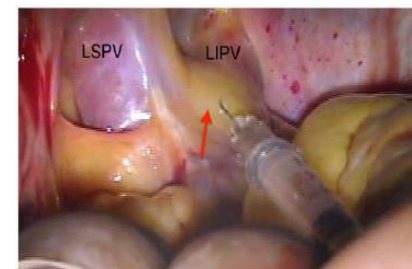
Preventive effect of ASP3282 in a dog POAF model (at Day 4)



Evaluation on Day 4
 Mean ± SE, n=4 (Vehicle & 10 mg/head) or 3 (3 mg/head)
 * $p < 0.05$ vs. Vehicle, Steel's test



Evaluation on Day 4
 Mean ± SE, n=6 (30 mg/head) or 8 (Vehicle & 60 mg/head)
 * $p < 0.05$, ** $p < 0.01$ vs. Vehicle, Steel's test



Circ Arrhythm Electrophysiol 8:1334-41 (2015)

ASP3282 significantly prevented POAF after single local administration.

Minimum effective dose in dog model: 10 mg/head, while 3 mg/head also shows some activities

ASP3282

Type of Study		Species	Route	Dose	GLP	ISN
Safety pharmacology	CNS, CV and respiratory	Cynomolgus monkey	IM/SC combo	20 mL/animal (1.5 mL/site IM x2 and 8.5 mL/site SC x2, 514 mg/animal)	Yes	3282- TX-0001
Single and repeated-dose toxicity	Single dose and 4-week					
Other	Tissue cross reactivity	Human	in vitro	2, 20 µg/mL	Yes	3282- TX-0002

IM: intramuscular, SC: subcutaneous

- No treatment-related systemic effects in the single and 4-week repeated toxicity study in cynomolgus monkeys.
- No effects on the safety pharmacology parameters in the monkey study.
- No adverse local irritation after single or repeated IM and SC dosing in the monkey study.
- Stereology examinations and neuronal immunostaining were conducted in the 4-week monkey study. No evidence of cell death or atrophic changes in dorsal root ganglia (DRG) and cranial cervical ganglia (CCG).
- No in vitro cross-reactivity to human tissues



ASP3282

Histopathology of the injection sites and electrocardiography were examined in the pharmacology study in canine sterile pericarditis model

Type of Study		Species	Route	Dose	GLP	Study No.
Pharmacology	Sterile Pericarditis Model	Beagle dogs	fat pad in heart	vehicle, 30, 60 mg/head	No	3282-PH-9008

- Histopathology: conducted at vehicle and 60 mg/head group, n=5/group
 - ✓ The incidence and severity of histopathological changes were comparable between those groups.
 - ✓ No histopathological changes were noted in the ganglion cells.
- Electrocardiography (ECG): conducted at vehicle (n=8), 30 (n=6) and 60 (n=8) mg/head group, 24hr monitoring at day 0-1
 - ✓ The incidence and severity of ECG changes were comparable between those groups.

Current situation & Unmet needs

- On average, **28% of CABG and/or heart valve replacement patients develop POAF. 93% of POAF patients receive either pharmacological or electro-cardio interventions.**
- **POAF is considered to be a “top of mind issue”** for many doctors in terms of both impact on patient outcomes (e.g. thrombosis, stroke and heart failure risk) and impact on hospital budget and efficacy (e.g. length of hospital stay).
- **Prevention was regarded as very important.** Doctors were mainly dissatisfied with currently available prophylactic therapies.

Target product profile

- **The initial reactions of all respondents to Product X (reduction of POAF by half and ICU/hospital stay and costs, single epicardial administration using a spray device) were positive.** They intend to use it for **87% of their patients** on average.
- The cost for Product X was expected to be bundled within the existing procedure DRG. **The price range (\$500-\$1,000) based on the assumed cost-saving effect by POAF prevention was considered reasonable.**

*respondents: 15 doctors (12 cardiac surgeons + 3 anesthesiologists) and 5 payers (cardiac surgery department heads)

Source: Anterio “POAF Study in the USA - Results Report” (March 2017)



COST REDUCTION FROM POAF PREVENTION

Assumptions:

incidence of POAF: 30%, additional hospital cost in POAF patients: \$9,000

→ additional hospital cost in overall (POAF & non-POAF) patients:

\$2,700/procedure on average

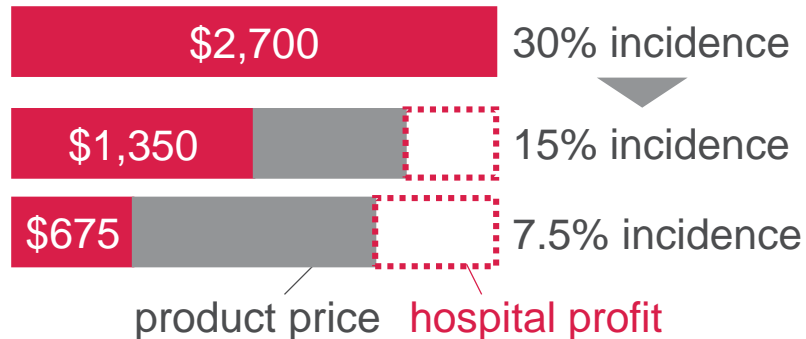
Cost reduction by prevention of AF:

POAF incidence 30% → 15%: **\$1,350/procedure**

→ 7.5%: **\$2,025/procedure**



A price less than \$1,350 or \$2,025 will bring a profit to the hospital if the POAF incidence is reduced by half or three quarters, respectively.



Patents covering ASP3282

- 1) WO2016/190263 (filed on May 20th, 2016)
- 2) WO2019/221097 (filed on May 14th, 2019)