

## Defibrillation Testing During Icd Implantation – Should we or Should We Not?

Justin Hayase<sup>1</sup>, Noel G. Boyle<sup>1</sup>

<sup>1</sup>*UCLA Cardiac Arrhythmia Center, UCLA Health System, David Geffen School of Medicine at UCLA, Los Angeles, CA, USA.*

### Abstract

The implantable cardioverter defibrillator (ICD) is an established therapy for improving mortality for primary and secondary prevention of sudden cardiac death. Whether to perform defibrillation threshold testing (DFT) either intraoperatively or post-operatively remains a controversial issue. The DFT is defined as the minimum energy required at which two shocks can successfully terminate ventricular fibrillation and dates from the era of surgically implanted devices with epicardial patches. Typically, a safety margin of at least 10J is employed for device programming, though some trial data suggest that a margin of 5J could be just as effective. Various methods have been utilized to perform DFT testing, and no particular method has been shown to be superior to another (Figure 1). Previously, guideline recommendations addressed the indications for ICD implantation but did not comment on DFT testing. Recent consensus statements now provide some guidance as to when it is appropriate to perform or not perform DFT testing in light of new trial data. This review will address some of the risk factors for having a higher DFT, impact of DFT testing on patient outcomes, and some of the risks and contraindications of DFT testing.

### Introduction

The implantable cardioverter defibrillator (ICD) is an established therapy for improving mortality for primary and secondary prevention of sudden cardiac death. Whether to perform defibrillation threshold testing (DFT) either intraoperatively or post-operatively remains a controversial issue.<sup>[1]-[6]</sup> The DFT is defined as the minimum energy required at which two shocks can successfully terminate ventricular fibrillation and dates from the era of surgically implanted devices with epicardial patches.<sup>[7]</sup> Typically, a safety margin of at least 10J is employed for device programming, though some trial data suggest that a margin of 5J could be just as effective.<sup>[8]</sup> Various methods have been utilized to perform DFT testing, and no particular method has been shown to be superior to another [Figure 1]. Previously, guideline recommendations addressed the indications for ICD implantation but did not comment on DFT testing.<sup>[9]</sup> Recent consensus statements now provide some guidance as to when it is appropriate to perform or not perform DFT testing in light of new trial data.<sup>[10]</sup> This review will address some of the risk factors for having a higher DFT, impact of DFT testing on patient outcomes, and some of the risks and contraindications of DFT testing.

### Risk factors for higher defibrillation threshold and troubleshooting high thresholds

Certain patients may be more likely to have a higher DFT, which comes primarily from observational study data. Higher risk patients

### Key Words:

Defibrillation testing, Implantable Cardioverter-Defibrillator, atrial fibrillation.

### Corresponding Author:

Noel G. Boyle, MD, PhD UCLA Cardiac Arrhythmia Center  
UCLA Health System David Geffen School of Medicine at UCLA 100  
UCLA Medical Plaza,  
Suite 660 Los Angeles CA 90095-7392  
Phone: 310 206 2235 Fax: 310 825 2092 E-mail: nboyle@mednet.ucla.edu

include those with non-ischemic cardiomyopathy, younger patients, lower ejection fraction, longer QRS interval, undergoing generator change or replacement, or taking amiodarone.<sup>[11]-[12]</sup> It should be noted, however, that no single variable is a strong clinical predictor of high DFT.<sup>[1]</sup> A history of ventricular arrhythmias does not seem to predict risk for high DFT based on current data.<sup>[10]</sup>

Various techniques can be employed in order to achieve an adequate safety margin. In the INTRINSIC RV study of 1530 ICD patients, there were 59 patients who did not initially meet the 10J safety margin. An adequate 10J safety margin was achieved in all patients by reversing polarity in 56% of patients or repositioning the RV lead in 32%. Adding a subcutaneous array or repeating testing at a later date were other strategies utilized in 2% of patients each.<sup>[13]</sup> Repeating testing at a later date may allow for better optimization of heart failure medical therapy and performing device revision if needed. In a series published by Vischer, et al. there were nine patients who initially did not meet the 10J safety margin. An acceptable DFT was achieved by changing polarity, modifying the SVC coil to either “on” or “off”, revising the “pocket” or repositioning the generator, adding a subcutaneous array, changing to a higher energy device, or adding a coronary sinus coil.<sup>[14]</sup> A series by Cesario, et al. also reported successful implantation of azygous vein coils in order to achieve adequate safety margins.<sup>[15]</sup> In a study by Guenther, et al., of 783 patients who underwent ICD implantation, eleven patients had failure of DFT testing. In two patients, there was sensing failure requiring lead modification. In three patients, reversing polarity was sufficient to achieve acceptable thresholds. The remaining six required either subcutaneous array or lead revision. Additionally, in this study, there was no difference in DFT efficacy based on single versus dual coil or based on different manufacturers.<sup>[3]</sup>

### Impact of DFT testing on patient outcomes

The impact of DFT testing on patient outcomes is still

**Table 1: Summary of defibrillation testing yield in published observational studies with over 500 subjects. Adapted from Russo, et al.<sup>6</sup>**

Study	Year	N	Implant criteria	No. of patients not meeting implant criteria	High DFT (% implants)
Russo et al <sup>12</sup>	2005	1139	10J safety margin	71	6.2%
Blatt et al <sup>32</sup>	2008	717	30J (max 2 inductions)	0	0% (2.2% with <10J safety margin)
Day et al <sup>13</sup>	2008	1530	10J safety margin	59	3.9%
Healey et al <sup>33</sup>	2010	1268	10J safety margin	44	3.5%
Sauer et al <sup>34</sup>	2011	853	10J safety margin (follow-up test)	38	2.4%
Keyser et al <sup>35</sup>	2013	718	<21J	28	3.9%
Lin et al <sup>11</sup>	2013	2138	10J safety margin	48	2.2%

controversial. As devices and techniques improve, the yield of DFT testing (requiring intervention or inability to achieve <10J margin) has progressively decreased. Recent observational studies suggest the yield of DFT testing is approaching 3%.<sup>3</sup> (Table 1)

Furthermore, the impact of DFT testing on outcomes has been unclear. In an observational cohort of 835 patients by Pires, et al., overall long-term survival was significantly better in the group that did not undergo DFT testing.<sup>16</sup> In another cohort of 256 patients by Michowitz, et al., there was no difference in overall survival between patients who were tested and those who were not tested.<sup>17</sup> Data from the SCD-HeFT trial suggests that any ICD shocks, whether appropriate or inappropriate, are associated with increased mortality.<sup>18</sup> However, meta-analysis data suggests that while appropriate shocks portend poorer outcomes, inappropriate shocks are not associated with increased mortality.<sup>19</sup> Whether DFT testing shocks themselves are associated with poorer outcomes is unknown.

Recently, two large clinical trials, the NORDIC and the SIMPLE trials, have attempted to address the question as to whether or not DFT testing affects patient outcomes.<sup>20, 21</sup> The NORDIC trial was a randomized, non-inferiority study of 1077 patients undergoing ICD implantation. All subjects had ICD shocks programmed to 40J regardless of DFT testing results and were followed for one year. The majority (65%) of patients had ischemic cardiomyopathy, and a minority (11%) were on Amiodarone. There was no difference in the primary end-point of first shock efficacy between the two groups.

There was a significant difference in intraoperative hypotension, which occurred more frequently in the DFT testing group than in those without DFT testing. Notably, patients undergoing right-sided implants or sub-cutaneous ICDs were excluded from the trial. The SIMPLE trial was another randomized, non-inferiority study of 2500 patients that compared DFT testing to no DFT testing, with all subjects having ICD shocks programmed to 31J. Subjects were followed for an average of one year. The primary outcome was a composite of failed appropriate shock or arrhythmic death. The no DFT testing group was found to be non-inferior to the DFT testing group with regards to the primary outcome. (Figure 2) Again, the majority of patients had established coronary artery disease (65%)

and a minority was taking Amiodarone (15%). Also, subcutaneous devices and right-sided implants were excluded.

### Areas of uncertainty and special patient populations

These recent trial data show that standard ICD programming without DFT testing is non-inferior to DFT testing at the time of device implantation. However, data are still lacking regarding DFT testing outside of the time of initial implant. There is no data to support annual DFT testing in high risk patients, though historically, this was common practice. Some argue for repeat DFT testing with certain changes in clinical condition such as when changing antiarrhythmic therapy (e.g. – initiation of amiodarone) or if concerned about a lead status; however, current guidelines do not address this, and routine follow-up testing is of low yield.<sup>10, 22</sup> Additionally, whether to perform

**Table 2: Summary of HRS/EHRA/APHS/SOLACEE expert consensus statement on optimal ICD programming and testing. Class I indicates a strong recommendation, benefit greatly exceeding risk. Class IIa is a somewhat weaker recommendation, benefit probably exceeding risk. Class III is a recommendation against treatment. Level of evidence A indicates highest level of evidence from more than 1 high-quality randomized clinical trial. Level of evidence B indicates moderate-quality evidence from either RCTs with meta-analysis (B-R) or non-randomized clinical trials with meta-analysis (B-NR). Level of evidence C indicates randomized or non-randomized observational or registry studies with limited data (C-LD).<sup>10</sup>**

Intraoperative DFT testing recommendations	Class of recommendation	Level of evidence
Defibrillation efficacy testing is recommended in patients undergoing a subcutaneous ICD implantation	I	C-LD
It is reasonable to omit defibrillation efficacy testing in patients undergoing initial left pectoral transvenous ICD implantation procedures where appropriate sensing, pacing, and impedance values are obtained with fluoroscopically well-positioned RV leads	IIa	B-R
Defibrillation efficacy testing is reasonable in patients undergoing right pectoral transvenous ICD implantation or ICD pulse generator changes	IIa	B-NR

DFT testing at the time of generator change remains unclear, though in limited data, reported DFT failures seem to occur at rates similar to initial device implantation.<sup>4, 14</sup>

Congenital heart disease patients also pose particular challenges with regard to implantation of ICDs owing to variable anatomy. Data are minimal for this patient population. In a multicenter study of 443 congenital heart disease patients by Berul, et al., the reported rate of high or inadequate DFT was similar to that reported in the general patient population at 2%.<sup>23</sup> However, this experience can be quite variable. A study by Stephenson, et al. described<sup>22</sup> congenital heart disease patients who underwent ICD implantation who could not receive a transvenous coil or epicardial patch. Four patients had a high DFT, representing 16% of the studied population.<sup>24</sup> Additionally, follow-up DFT testing in this patient group may be of higher yield, particularly as these patients grow and generally are more active than the elderly adult population.<sup>25</sup>

### Risks and contraindications of DFT testing

Although rare, there are risks associated with DFT testing. Studies suggest that life-threatening complications occur at a rate of 0.17-0.4% and the mortality rate is 0.016-0.07%. Life-threatening complications generally result from the induction of ventricular fibrillation and include events such as stroke, pulmonary embolism, or prolonged resuscitation.<sup>26, 27</sup> Kolb, et al. performed a risk-benefit

analysis by using estimates of mortality reduction of 7-8% with an ICD and DFT testing yield of 2.5%. Under these assumptions, the mortality prevention rate by DFT testing is less than 0.2%, which would imply that the number needed to undergo DFT testing in order to save one life is 500.<sup>28</sup> Depending on the estimated risk of life-threatening complications (0.17% versus 0.4%), DFT testing may provide either a favorable or unfavorable risk. While DFT testing does not come with additional cost, per se, since there appears to be equipoise in terms of risk and benefit based on current literature, DFT testing seems to be cost neutral.

Absolute contraindications to DFT testing include intracardiac

In the large trials that established the benefit of ICD implantation, DFT testing was performed routinely per research protocols.<sup>29, 30</sup> Currently, FDA approved labels for usage of ICDs include information on performing DFT testing at the time of device implantation, which is at the discretion of the implanting physician.<sup>31</sup> However, as devices have improved, the yield of such testing has declined, and we now have randomized trial data on patient outcomes with regards to DFT testing. These data would suggest that there is no clinical benefit to performing routine DFT testing, and significant adverse events, though rare, can occur. Thus, it would seem prudent to perform DFT testing in only select individuals in whom there is a high expected yield, such as in those undergoing right-sided implants, subcutaneous device implantation, or in patients with multiple risk factors for a high DFT such as younger patients with non-ischemic cardiomyopathy on amiodarone, or in patients with complex anatomy such as those with congenital heart disease.

**Conflict Of Interests**

None.

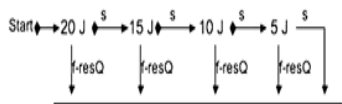
**Disclosures**

None.

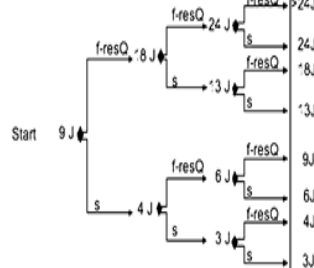
**References**

1. Swerdlow Charles D, Russo Andrea M, Degroot Paul J. The dilemma of ICD implant testing. *Pacing Clin Electrophysiol.* 2007;30 (5):675-700.
2. Viskin Sami, Rosso Raphael. The top 10 reasons to avoid defibrillation threshold testing during ICD implantation. *Heart Rhythm.* 2008;5 (3):391-3.
3. Guenther M, Rauwolf T, Brüggemann B, Gerlach M, Wässing N K, Christoph M, Braun M U, Strasser R H, Wunderlich C. Pre-hospital discharge testing after implantable cardioverter defibrillator implantation: a measure of safety or out of date? A retrospective analysis of 975 patients. *Europace.* 2012;14 (2):217-23.
4. Phan Kevin, Kabunga Peter, Kilborn Michael J, Sy Raymond W. Defibrillator Threshold Testing at Generator Replacement: Is it Time to Abandon the Practice?. *Pacing Clin Electrophysiol.* 2015;38 (7):777-81.
5. JS Healey, MBrambatti. Is defibrillation testing necessary for implantable transvenous defibrillators?: defibrillation testing should not be routinely performed at the time of implantable cardioverter defibrillator implantation. *Circulation Arrhythmia and electrophysiology.* 2014;0:347-351.
6. Russo Andrea M, Chung Mina K. Is defibrillation testing necessary for implantable transvenous defibrillators?: defibrillation testing is necessary at the time of implantable cardioverter defibrillator implantation. *Circ Arrhythm Electrophysiol.* 2014;7 (2):337-46.
7. Marchlinski F E, Flores B, Miller J M, Gottlieb C D, Hargrove W C. Relation of the intraoperative defibrillation threshold to successful postoperative defibrillation with an automatic implantable cardioverter defibrillator. *Am. J. Cardiol.* 1988;62 (7):393-8.
8. Gold Michael R, Higgins Steven, Klein Richard, Gilliam F Roosevelt, Kopelman Harry, Hessen Scott, Payne John, Strickberger S Adam, Breiter David, Hahn Stephen. Efficacy and temporal stability of reduced safety margins for ventricular defibrillation: primary results from the Low Energy Safety Study (LESS). *Circulation.* 2002;105 (17):2043-8.
9. Hylek E M, Skates S J, Sheehan M A, Singer D E. An analysis of the lowest effective intensity of prophylactic anticoagulation for patients with nonrheumatic atrial fibrillation. *N. Engl. J. Med.* 1996;335 (8):540-6.
10. Connolly Stuart J, Ezekowitz Michael D, Yusuf Salim, Eikelboom John, Oldgren Jonas, Parekh Amit, Pogue Janice, Reilly Paul A, Themeles Ellison, Varrone Jeanne, Wang Susan, Alings Marco, Xavier Denis, Zhu Jun, Diaz Rafael, Lewis Basil S, Darius Harald, Diener Hans-Christoph, Joyner Campbell D, Wallentin Lars. Dabigatran versus warfarin in patients with atrial fibrillation. *N.*

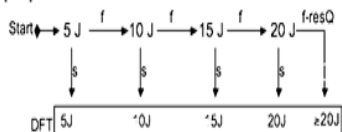
**Step Down DFT Method**



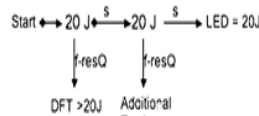
**Binary Search DFT Method**



**Step Up DFT Method**



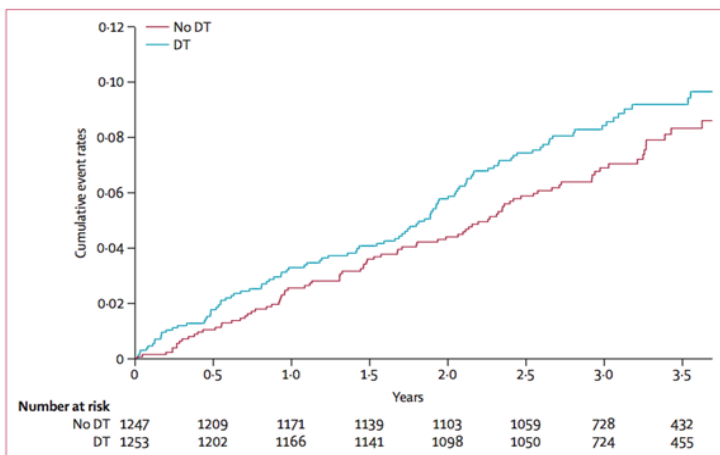
**Safety Margin Method**



**Figure 1:** Various methods to determine DFT at time of ICD implant. “s” indicates defibrillation success. “f-resQ” indicates failure followed by rescue shock. “LED” indicates lowest energy tested that defibrillates. Adapted from Swerdlow, et al.<sup>1</sup>

thrombus, atrial fibrillation without anticoagulation, severe aortic stenosis, acute coronary syndrome and hemodynamic instability requiring inotropic support. Relative contraindications include severe unrevascularized coronary artery disease, recent coronary artery stent placement, recent stroke or transient ischemic attack, and hemodynamic instability not requiring inotropic support.<sup>1, 10</sup>

**Conclusions**



**Figure 2:** Kaplan-Meier curve of time to cumulative event of either failed appropriate shock or arrhythmic death from the SIMPLE Trial.<sup>21</sup> DT = defibrillation testing. The ‘no-defibrillation testing’ group was non-inferior to the testing group.

Engl. J. Med.2009;361 (12):1139–51.

11. PatelManesh R, MahaffeyKenneth W, GargJyotsna, PanGuohua, SingerDaniel E, HackeWerner, BreithardtGünter, HalperinJonathan L, HankeyGraeme J, PicciniJonathan P, BeckerRichard C, NesselChristopher C, PaoliniJohn F, BerkowitzScott D, FoxKeith A A, CaliffRobert M.Rivaroxaban versus warfarin in nonvalvular atrial fibrillation.N. Engl. J. Med.2011;365 (10):883–91.
12. GrangerChristopher B, AlexanderJohn H, McMurrayJohn J V, LopesRenato D, HylekElaine M, HannaMichael, Al-KhalidiHussein R, AnsellJack, AtarDan, AvezumAlvaro, BahitM Cecilia, DiazRafael, EastonJ Donald, EzekowitzJustin A, FlakerGreg, GarciaDavid, GerdalMargarida, GershBernard J, GolitsynSergey, GotoShinya, HermosilloAntonio G, HohnloserStefan H, HorowitzJohn, MohanPuneet, JanskyPetr, LewisBasil S, Lopez-SendonJose Luis, PaisPrem, ParkhomenkoAlexander, VerheugtFreek W A, ZhuJun, WallentinLars.Apixaban versus warfarin in patients with atrial fibrillation.N. Engl. J. Med.2011;365 (11):981–92.
13. GiuglianoRobert P, RuffChristian T, BraunwaldEugene, MurphySabina A, WiviottStephen D, HalperinJonathan L, WaldoAlbert L, EzekowitzMichael D, WeitzJeffrey I, ŠpinarJindřich, RuzylloWitold, RudaMikhail, KoretsuneYukihiko, BetcherJoshua, ShiMinghao, GripLaura T, PatelShirali P, PatelIndravadan, HanyokJames J, MercuriMichele, AntmanElliott M.Edoxaban versus warfarin in patients with atrial fibrillation.N. Engl. J. Med.2013;369 (22):2093–104.
14. KooimanJudith, van der HulleTom, MaasHugo, WiebeSabrina, FormellaStephan, ClemensAndreas, van BurenMarjolijn, JanssenMartien, RabelinkTon J, HuismanMenno V.Pharmacokinetics and Pharmacodynamics of Dabigatran 75 mg b.i.d. in Patients With Severe Chronic Kidney Disease.J. Am. Coll. Cardiol.2016;67 (20):2442–4.
15. FoxKeith A A, PicciniJonathan P, WojdylaDaniel, BeckerRichard C, HalperinJonathan L, NesselChristopher C, PaoliniJohn F, HankeyGraeme J, MahaffeyKenneth W, PatelManesh R, SingerDaniel E, CaliffRobert M.Prevention of stroke and systemic embolism with rivaroxaban compared with warfarin in patients with non-valvular atrial fibrillation and moderate renal impairment.Eur. Heart J.2011;32 (19):2387–94.
16. CBFordyce, ASHellkamp, YLokhnygina, SMLindner, JPPicini, RCBecker, SDBerkowitz, GBreithardt, KAFox, JLHalperin, GJHankey, KWMahaffey, CCNessel, DESinger, MRPatel.On-treatment outcomes in patients with worsening renal function with rivaroxaban compared with warfarin.Insights from ROCKET AF. Circulation.2015;0:0–0.
17. ChanKevin E, GiuglianoRobert P, PatelManesh R, AbramsonStuart, JardineMeg, ZhaoSophia, PerkovicVlado, MadduxFranklin W, PicciniJonathan P.Nonvitamin K Anticoagulant Agents in Patients With Advanced Chronic Kidney Disease or on Dialysis With AF.J. Am. Coll. Cardiol.2016;67 (24):2888–99.
18. ChanKevin E, EdelmanElazer R, WengerJulia B, ThadhaniRavi I, MadduxFranklin W.Dabigatran and rivaroxaban use in atrial fibrillation patients on hemodialysis. Circulation.2015;131 (11):972–9.
19. ChangMing, YuZhigang, ShenkerAndrew, WangJessie, PursleyJanice, ByonWonkyung, BoydRebecca A, LaCretaFrank, FrostCharles E.Effect of renal impairment on the pharmacokinetics, pharmacodynamics, and safety of apixaban.J Clin Pharmacol.2016;56 (5):637–45.
20. WangXiaoli, TirucheraiGiridhar, MarburyThomas C, WangJessie, ChangMing, ZhangDonglu, SongYan, PursleyJanice, BoydRebecca A, FrostCharles. Pharmacokinetics, pharmacodynamics, and safety of apixaban in subjects with end-stage renal disease on hemodialysis.J Clin Pharmacol.2016;56 (5):628–36.
21. BohulaErin A, GiuglianoRobert P, RuffChristian T, KuderJulia F, MurphySabina A, AntmanElliott M, BraunwaldEugene.Impact of Renal Function on Outcomes With Edoxaban in the ENGAGE AF-TIMI 48 Trial.Circulation.2016;134 (1):24–36.
22. KatoEri Toda, GiuglianoRobert P, RuffChristian T, KoretsuneYukihiko, YamashitaTakeshi, KissRobert Gabor, NordioFrancesco, MurphySabina A, KimuraTetsuya, JinJames, LanzHans, MercuriMichele, BraunwaldEugene, AntmanElliott M.Efficacy and Safety of Edoxaban in Elderly Patients With Atrial Fibrillation in the ENGAGE AF-TIMI 48 Trial.J Am Heart Assoc.2016;5 (5):–.
23. NgKuan H, ShestakovskaOlga, ConnollyStuart J, EikelboomJohn W, AvezumAlvaro, DiazRafael, LanasFernando, YusufSalim, HartRobert G.Efficacy and safety of apixaban compared with aspirin in the elderly: a subgroup analysis from the AVERROES trial.Age Ageing.2016;45 (1):77–83.
24. HXu, CTRuff, RPGiugliano, SAMurphy, FNordio, IPatel, MShi, MMercuri, EMantman, EBraunwald.Concomitant use of single antiplatelet therapy with edoxaban or warfarin in patients with atrial fibrillation.Analysis from the ENGAGE AF-TIMI48 trial.2016;0:0–0.
25. ChanKevin E, GiuglianoRobert P, PatelManesh R, AbramsonStuart, JardineMeg, ZhaoSophia, PerkovicVlado, MadduxFranklin W, PicciniJonathan P.Nonvitamin K Anticoagulant Agents in Patients With Advanced Chronic Kidney Disease or on Dialysis With AF.J. Am. Coll. Cardiol.2016;67 (24):2888–99.
26. EikelboomJohn W, ConnollyStuart J, BrueckmannMartina, GrangerChristopher B, KappeteinArie P, MackMichael J, BlatchfordJon, DevennyKevin, FriedmanJeffrey, GuiverKelly, HarperRuth, KhderYasser, LobmeyerMaximilian T, MaasHugo, VoigtJens-Uwe, SimoonsMaarten L, Van de WerfFrans.Dabigatran versus warfarin in patients with mechanical heart valves.N. Engl. J. Med.2013;369 (13):1206–14.
27. YadlapatiAjay, GrohChristopher, MalaisrieS Chris, GajjarMark, KruseJane, MeyersSheridan, PassmanRod.Efficacy and safety of novel oral anticoagulants in patients with bioprosthetic valves.Clin Res Cardiol.2016;105 (3):268–72.
28. JonesWilliam Schuyler, HellkampAnne S, HalperinJonathan, PicciniJonathan P, BreithardtGunter, SingerDaniel E, FoxKeith A A, HankeyGraeme J, MahaffeyKenneth W, CaliffRobert M, PatelManesh R.Efficacy and safety of rivaroxaban compared with warfarin in patients with peripheral artery disease and non-valvular atrial fibrillation: insights from ROCKET AF.Eur. Heart J.2014;35 (4):242–9.
29. LeibsonCynthia L, RansomJeanine E, OlsonWayne, ZimmermanBruce R, O'fallonW Michael, PalumboPasquale J.Peripheral arterial disease, diabetes, and mortality.Diabetes Care.2004;27 (12):2843–9.
30. BrambattiMichela, DariusHarald, OldgrenJonas, ClemensAndreas, NoackHerbert H, BrueckmannMartina, YusufSalim, WallentinLars, EzekowitzMichael D, ConnollyStuart J, HealeyJeff S.Comparison of dabigatran versus warfarin in diabetic patients with atrial fibrillation: Results from the RE-LY trial.Int. J. Cardiol.2015;196 (1):127–31.
31. ConnollyStuart J, EzekowitzMichael D, YusufSalim, ReillyPaul A, WallentinLars. Newly identified events in the RE-LY trial.N. Engl. J. Med.2010;363 (19):1875–6.
32. BrambattiMichela, DariusHarald, OldgrenJonas, ClemensAndreas, NoackHerbert H, BrueckmannMartina, YusufSalim, WallentinLars, EzekowitzMichael D, ConnollyStuart J, HealeyJeff S.Comparison of dabigatran versus warfarin in diabetic patients with atrial fibrillation: Results from the RE-LY trial.Int. J. Cardiol.2015;196 (1):127–31.
33. DouxfilsJonathan, BuckinxFanny, MullierFrançois, MinetValentine, RabendaVéronique, ReginsterJean-Yves, HainautPhilippe, BruyèreOlivier, DognéJean-Michel.Dabigatran etexilate and risk of myocardial infarction, other cardiovascular events, major bleeding, and all-cause mortality: a systematic review and meta-analysis of randomized controlled trials.J Am Heart Assoc.2014;3 (3):–.
34. LoffredoLorenzo, PerriLudovica, VioliFrancesco.Myocardial infarction and atrial fibrillation: different impact of anti-IIa vs anti-Xa new oral anticoagulants: a meta-analysis of the interventional trials.Int. J. Cardiol.2015;178 (1):8–9.
35. NoseworthyPeter A, KapaSuraj, DeshmukhAbhishek J, MadhavanMalini, Van HoutenHolly, HaasLindsey R, MulpuruSiva K, McLeodChristopher J, AsirvathamSamuel J, FriedmanPaul A, ShahNilay D, PackerDouglas L.Risk of stroke after catheter ablation versus cardioversion for atrial fibrillation: A

propensity-matched study of 24,244 patients. Heart Rhythm. 2015;12 (6):1154-61.