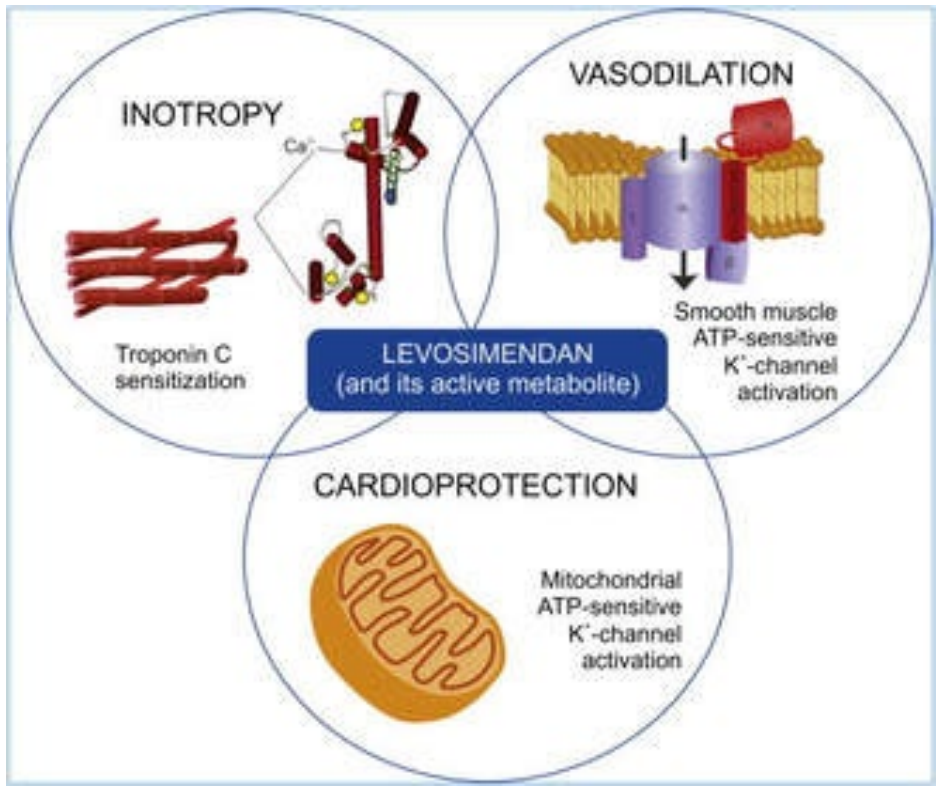
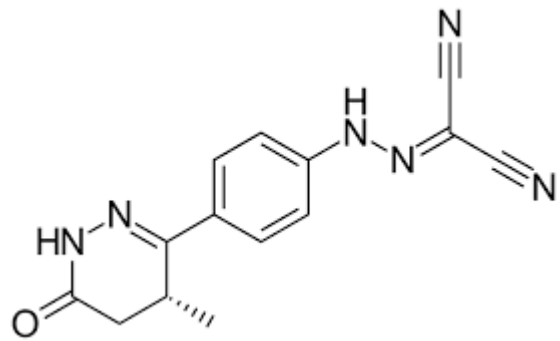
# Levosimendan profylakticky nebo až se to pokazí?

Milan Ročeň

IKEM

SIMDAX®
levosimendan



Česká společnost anesteziologie, resuscitace a intenzivní medicíny
DOPORUČENÉ POSTUPY DIAGNOSTIKY A TERAPIE
PERIOPERAČNÍ SRDEČNÍ SELHÁNÍ
Připravila pracovní skupina: Vladimír Černý, Karel Cvachovec, Aleš Březina, Ota Hlinomaz
Schváleno výborem ČSARIM dne 26.2.2008

PERIOPERAČNÍ SRDEČNÍ SELHÁNÍ

3.3. Doporučovaná farmaka
· Analgetika
- morfin v úvodní dávce 2-5 mg i.v.
- fentanyl v úvodní dávce 50-100 ucg i.v.
· Diuretika
- furosemid bolus v úvodní dávce 10-40 mg i.v. (u nemocných s předchozí diuretickou
terapií lze úvodní vbolusovou dávku zvýšit) nebo v kontinuální infuzi 5-40 mg/hod.
· Vasodilatancia
- isosorbid dinitrát titračně v dávce 1-10 mg/hod i.v.
- nitroglycerin titračně v dávce 20-200 ucg/kg/min.
· Inotropika
- Levosimendan, dobutamin a milrinon jsou nejčastěji doporučovaná inotropika
- Levosimendan
o EBM klasifikace IIa/evidence B*
o Doporučené dávkování: 0,1-0,2 ucg/kg/min po dobu 24 hod bez bolusové úvodní dávky
o hodnota SBP před zahájením levosimendanu by měla být nejméně 100 mm Hg
- Dobutamin
o EBM klasifikace IIa/evidence C*
o Doporučené dávkování: 5-20 ucg/kg/min
- Milrinon
o EBM klasifikace IIb/evidence C*
o Doporučené dávkování: 0,375-0,75 ucg/kg/min

European Journal of Cardio-Thoracic Surgery 57 (2020) 210–251
doi:10.1093/ejcts/ezz267 Advance Access publication 2 October 2019

# 2019 EACTS/EACTA/EBCP guidelines on cardiopulmonary bypass in adult cardiac surgery

Authors/Task Force Members: Alexander Wahba[a,b,*,†] (Chairperson) (Norway), Milan Milojevic[c,d,*,†] (Serbia, Netherlands), Christa Boer [e] (Netherlands), Filip M.J.J. De Somer [f] (Belgium), Tomas Gudbjartsson[g] (Iceland), Jenny van den Goor [h] (Netherlands), Timothy J. Jones [i] (UK), Vladimir Lomivorotov[j] (Russia), Frank Merkle [k] (Germany), Marco Ranucci [l] (Italy), Gudrun Kunst[m,*,†] (Chairperson) (UK) and Luc Puis [n,*,†] (Chairperson) (Belgium)

## Recommendations for use of positive inotropes

| Recommendations | Class[a] | Level[b] | Ref[c] |
|---|---|---|---|
| Positive inotropic and/or vasopressor agents are recommended as a first-line treatment to reduce mortality rates in patients with haemodynamic instability. | I | A | [342] |
| The use of phosphodiesterase inhibitors should be considered to increase weaning success. | IIa | B | [344, 345] |
| The prophylactic infusion of levosimendan to reduce adverse events and mortality is not recommended. | III | A | [347, 348] |
| Levosimendan as a therapeutic strategy in selected difficult-to-wean patients having CPB may be considered. | IIb | C | |
| In patients requiring haemodynamic support after cardiac surgery, adding levosimendan to other positive inotropes or vasopressors is not recommended. | III | B | [349] |

[a]Class of recommendation.
[b]Level of evidence.
[c]References.
CPB: cardiopulmonary bypass.

# Levosimendan

- Indikovat?
- Komu?
- Kdy?
- Jak podat?

# Effect of levosimendan on clinical outcomes in adult patients undergoing cardiac surgery: a meta-analysis of randomized controlled trials



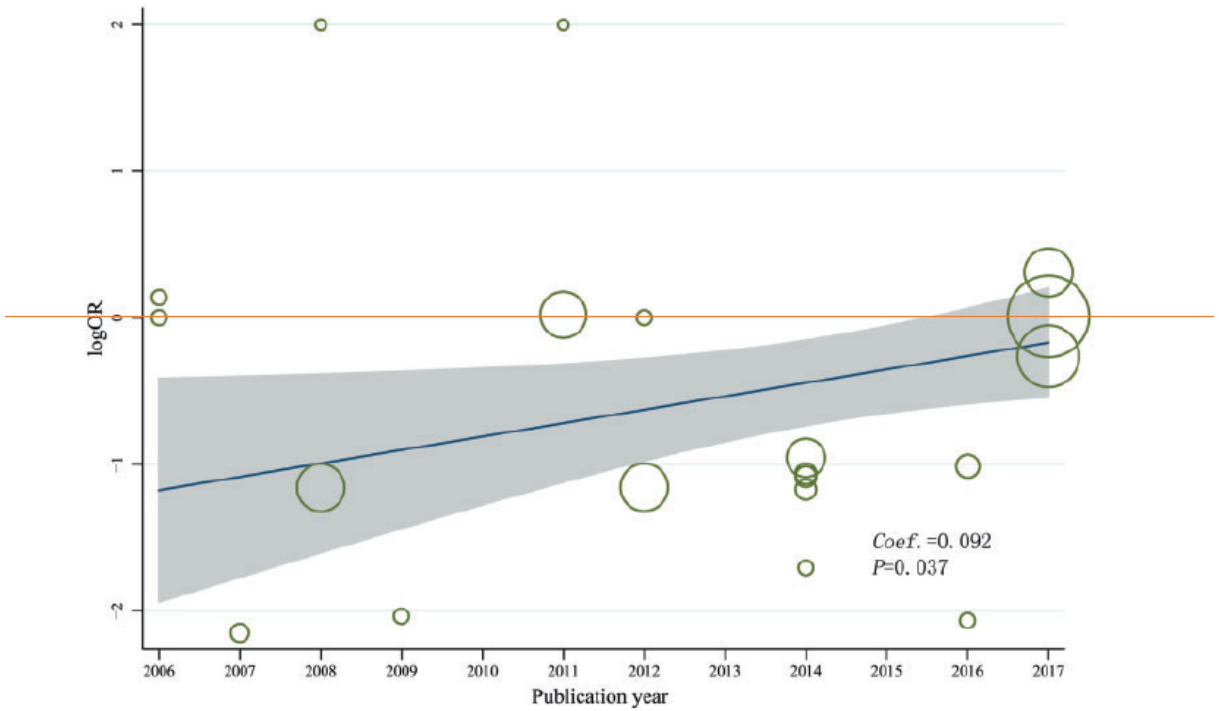



**Figure 3:** Meta-regression indicated that publication year influenced the association between levosimendan and mortality. An increase of 1 year in the *Y*-axis is associated with an increase of logOR value by 0.092. OR: odds ratio.

Interactive CardioVascular and Thoracic Surgery 26 (2018) 1016–1026
doi:10.1093/icvts/ivy017 Advance Access publication 3 February 2018

The NEW ENGLAND JOURNAL of MEDICINE

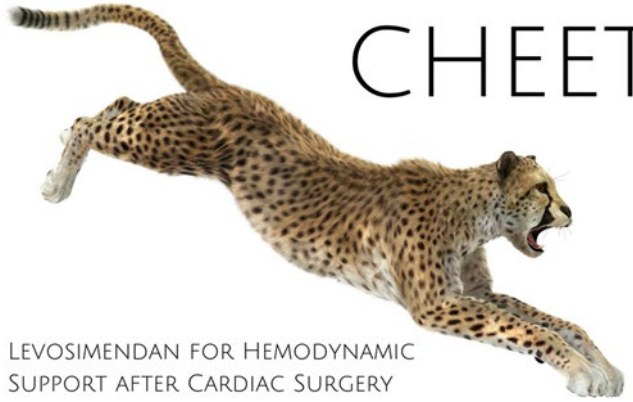
ORIGINAL ARTICLE

# Levosimendan for Hemodynamic Support after Cardiac Surgery

G. Landoni, V.V. Lomivorotov, G. Alvaro, R. Lobreglio, A. Pisano, F. Guarracino, M.G. Calabrò, E.V. Grigoryev, V.V. Likhvantsev, M.F. Salgado-Filho, A. Bianchi, V.V. Pasyuga, M. Baiocchi, F. Pappalardo, F. Monaco, V.A. Boboshko, M.N. Abubakirov, B. Amantea, R. Lembo, L. Brazzi, L. Verniero, P. Bertini, A.M. Scandroglio, T. Bove, A. Belletti, M.G. Michienzi, D.L. Shukevich, T.S. Zabelina, R. Bellomo, and A. Zangrillo, for the CHEETAH Study Group*

**CONCLUSIONS**

In patients who required perioperative hemodynamic support after cardiac surgery, low-dose levosimendan in addition to standard care did not result in lower 30-day mortality than placebo. (Funded by the Italian Ministry of Health; CHEETAH ClinicalTrials.gov number, NCT00994825.)



CHEETAH

LEVOSIMENDAN FOR HEMODYNAMIC SUPPORT AFTER CARDIAC SURGERY

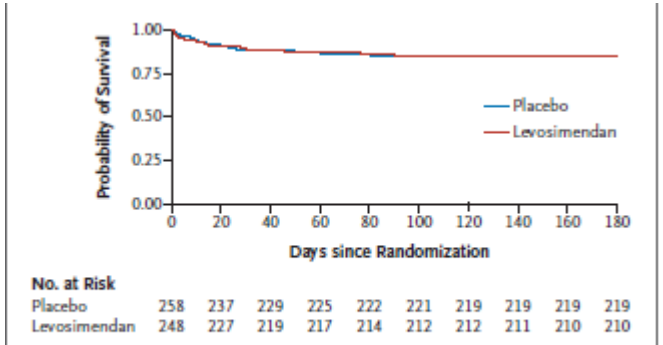



Figure 2. Kaplan–Meier Survival Estimates of All-Cause Mortality.

N Engl J Med 2017;376:2021-31.
DOI: 10.1056/NEJMoa1616325

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

# Levosimendan in Patients with Left Ventricular Dysfunction Undergoing Cardiac Surgery

R.H. Mehta, J.D. Leimberger, S. van Diepen, J. Meza, A. Wang, R. Jankowich, R.W. Harrison, D. Hay, S. Fremes, A. Duncan, E.G. Soltesz, J. Luber, S. Park, M. Argenziano, E. Murphy, R. Marcel, D. Kalavrouziotis, D. Nagpal, J. Bozinovski, W. Toller, M. Heringlake, S.G. Goodman, J.H. Levy, R.A. Harrington, K.J. Anstrom, and J.H. Alexander, for the LEVO-CTS Investigators*

**CONCLUSIONS**

Prophylactic levosimendan did not result in a rate of the short-term composite end point of death, renal-replacement therapy, perioperative myocardial infarction, or use of a mechanical cardiac assist device that was lower than the rate with placebo among patients with a reduced left ventricular ejection fraction who were undergoing cardiac surgery with the use of cardiopulmonary bypass. (Funded by Tenax Therapeutics; LEVO-CTS ClinicalTrials.gov number, NCT02025621.)

N Engl J Med 2017;376:2032-42.
DOI: 10.1056/NEJMoa1616218


**Table 4. End Points.***

| End Point | Levosimendan (N=428) | Placebo (N=421) | Odds Ratio (95% CI)† | P Value |
|---|---|---|---|---|
| Primary end points — no. (%) | | | | |
| Four-component end point‡ | 105 (24.5) | 103 (24.5) | 1.00 (0.66–1.54) | 0.98 |
| Two-component end point§ | 56 (13.1) | 48 (11.4) | 1.18 (0.76–1.82) | 0.45 |
| Components of primary end points — no. (%) | | | | |
| Death at 30 days | 15 (3.5) | 19 (4.5) | 0.77 (0.38–1.53) | 0.45 |
| Renal-replacement therapy at 30 days | 9 (2.1) | 16 (3.8) | 0.54 (0.24–1.24) | 0.15 |
| Myocardial infarction at 5 days | 67 (15.7) | 63 (15.0) | 1.06 (0.73–1.53) | 0.78 |
| Use of mechanical cardiac assist device at 5 days | 47 (11.0) | 38 (9.0) | 1.24 (0.79–1.95) | 0.34 |
| Secondary end points¶ | | | | |
| Duration of stay in ICU — days‖ | | | | |
| Median | 2.8 | 2.9 | — | 0.25 |
| Interquartile range | 1.6–4.8 | 1.8–4.9 | | |
| Low cardiac output syndrome — no. (%)‖ | 78 (18.2) | 108 (25.7) | 0.62 (0.44–0.88) | 0.007 |
| Use of inotrope at or beyond 24 hr after infusion initiation — no. (%)‖ | 235 (54.9) | 264 (62.7) | 0.71 (0.53–0.94) | 0.02 |
| Other efficacy end points — no. (%) | | | | |
| Rehospitalization at 30 days‖ | 54 (12.6) | 48 (11.4) | 1.14 (0.75–1.7) | 0.55 |
| Myocardial infarction at 6–30 days | 1 (0.2) | 0 | — | — |
| Safety end points — no. (%) | | | | |
| Death at 90 days | 20 (4.7) | 30 (7.1) | 0.64 (0.37–1.13) | 0.12 |
| Any adverse event | 238 (55.6) | 232 (55.1) | — | 0.86 |
| Adverse event considered by site investigator to be related to trial regimen | 9 (2.1) | 13 (3.1) | — | 0.34 |
| Any serious adverse event | 77 (18.0) | 70 (16.6) | — | 0.62 |
| Serious adverse event necessitating permanent discontinuation of trial regimen | 6 (1.4) | 3 (0.7) | — | 0.42 |
| Common prespecified postoperative events — no. (%)** | | | | |
| Hypotension | 155 (36.2) | 138 (32.8) | — | 0.29 |
| Atrial fibrillation | 163 (38.1) | 139 (33.0) | — | 0.12 |
| Ventricular tachycardia or fibrillation | 46 (10.7) | 41 (9.7) | — | 0.63 |
| Resuscitated cardiac arrest | 8 (1.9) | 7 (1.7) | — | 0.82 |
| Stroke | 15 (3.5) | 10 (2.4) | — | 0.33 |
| Deep venous thrombosis | 3 (0.7) | 3 (0.7) | — | 0.98 |
| Pulmonary embolism | 0 | 3 (0.7) | — | 0.08 |
| Mechanical ventilation for >24 hr | 35 (8.2) | 37 (8.8) | — | 0.75 |
| Pneumonia | 9 (2.1) | 14 (3.3) | — | 0.27 |
| Congestive heart failure | 46 (10.7) | 57 (13.5) | — | 0.21 |
| Wound infection | 13 (3.0) | 12 (2.9) | — | 0.87 |

# LEVO-CTS trial

Considering that the post hoc analysis of the LEVO-CTS trial showed reduced LCOS and lower 90-day mortality, levosimendan could improve outcomes when targeted toward patients of advanced age >65, female sex, EF 25% and anticipated to have multiple cardiac interventions and prolonged CPB time.

In this prespecified subgroup analysis of the LEVO-CTS trial, levosimendan reduced the risk of LCOS, inotrope use beyond 24 hours, and mortality in patients with reduced LVEF undergoing isolated CABG surgery. In contrast, no benefits were observed with levosimendan in patients undergoing isolated valve or combined CABG and valve surgery.

Our findings suggest that the efficacy of preoperative prophylactic levosimendan in cardiac surgery may be heterogeneous, with the greatest benefit in patients with ischemic cardiomyopathy undergoing isolated CABG surgery.

# An update on levosimendan in acute cardiac care: applications and recommendations for optimal efficacy and safety

Matthias Heringlake, Julian Alvarez, Dominique Bettex, Stefaan Bouchez, Sonja Fruhwald, Massimo Girardis, Elena Grossini, Fabio Guarracino, Antoine Herpain, Wolfgang Toller, Luigi Tritapepe & Piero Pollesello

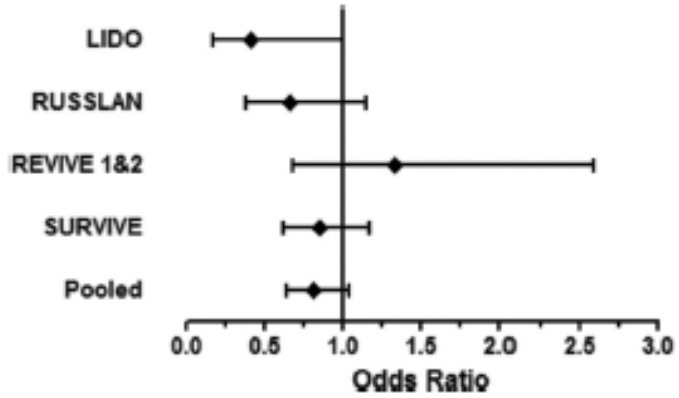



Figure 2. Meta-analysis of the effect of levosimendan on 31-day survival in the four phase III regulatory trials submitted to the authorities for the introduction of levosimendan as a treatment for acutely decompensated heart failure: LIDO (203 patients) [47]; RUSSLAN (504 patients) [48]; REVIVE 1 and 2 (700 patients) [107]; and SURVIVE (1327 patients) [117]. Pooled statistics were calculated using the Cochran–Mantel–Haenszel test, controlling for study. Total events in the pooled levosimendan arms were 167/1519 (11.0%) and total events in the pooled comparator arms were 145/1215 (11.9%). Odds ratio 0.81; 95% confidence interval 0.64–1.04.

**Expert opinion:** Levosimendan can be a valuable resource in the treatment of acute cardiac dysfunction, especially in the presence of beta-blockers or ischemic cardiomyopathy. When attention is given to avoiding or correcting hypovolemia and hypokalemia, an early use of the drug in the treatment algorithm is preferred.

EXPERT REVIEW OF CARDIOVASCULAR THERAPY
2021, VOL. 19, NO. 4, 325–335
https://doi.org/10.1080/14779072.2021.1905520

# Early Levosimendan Administration Improved Weaning Success Rate in Extracorporeal Membrane Oxygenation in Patients With Cardiogenic Shock

*Yu-Wen Chen[1], Wei-Chieh Lee[2,3]*, Po-Jui Wu[4], Hsiu-Yu Fang[4], Yen-Nan Fang[4], Huang-Chung Chen[4], Meng-Shen Tong[5], Pei-Hsun Sung[4], Chieh-Ho Lee[4] and Wen-Jung Chung[4]*

**Conclusion:** Early levosimendan administration may contribute to increasing the success rate of VA-ECMO weaning and may help to decrease CV and all-cause mortality.

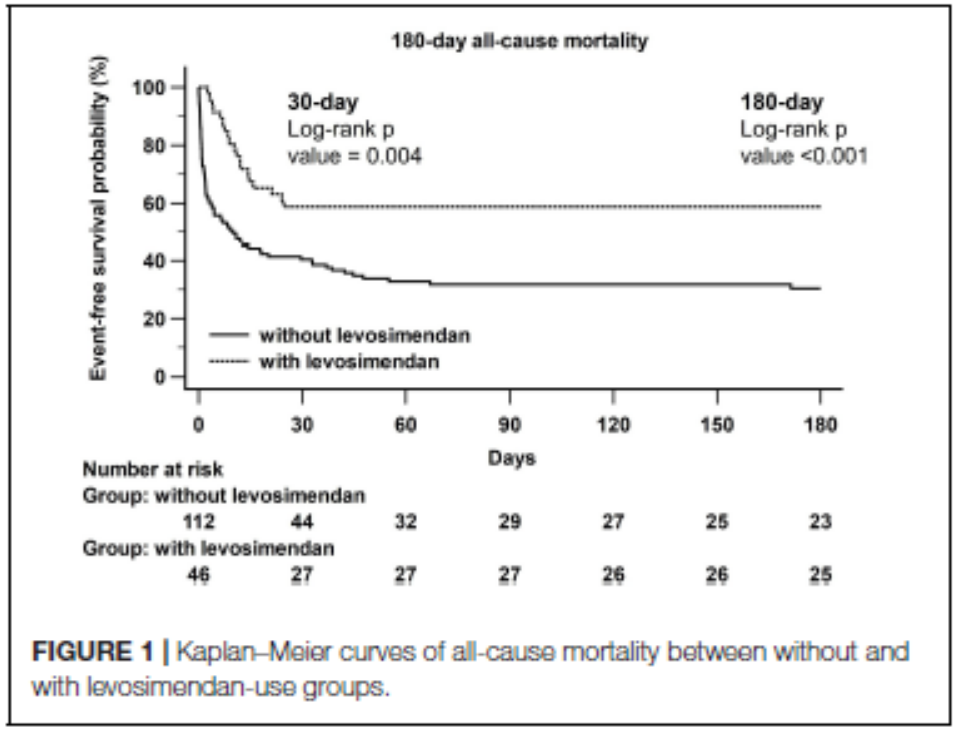
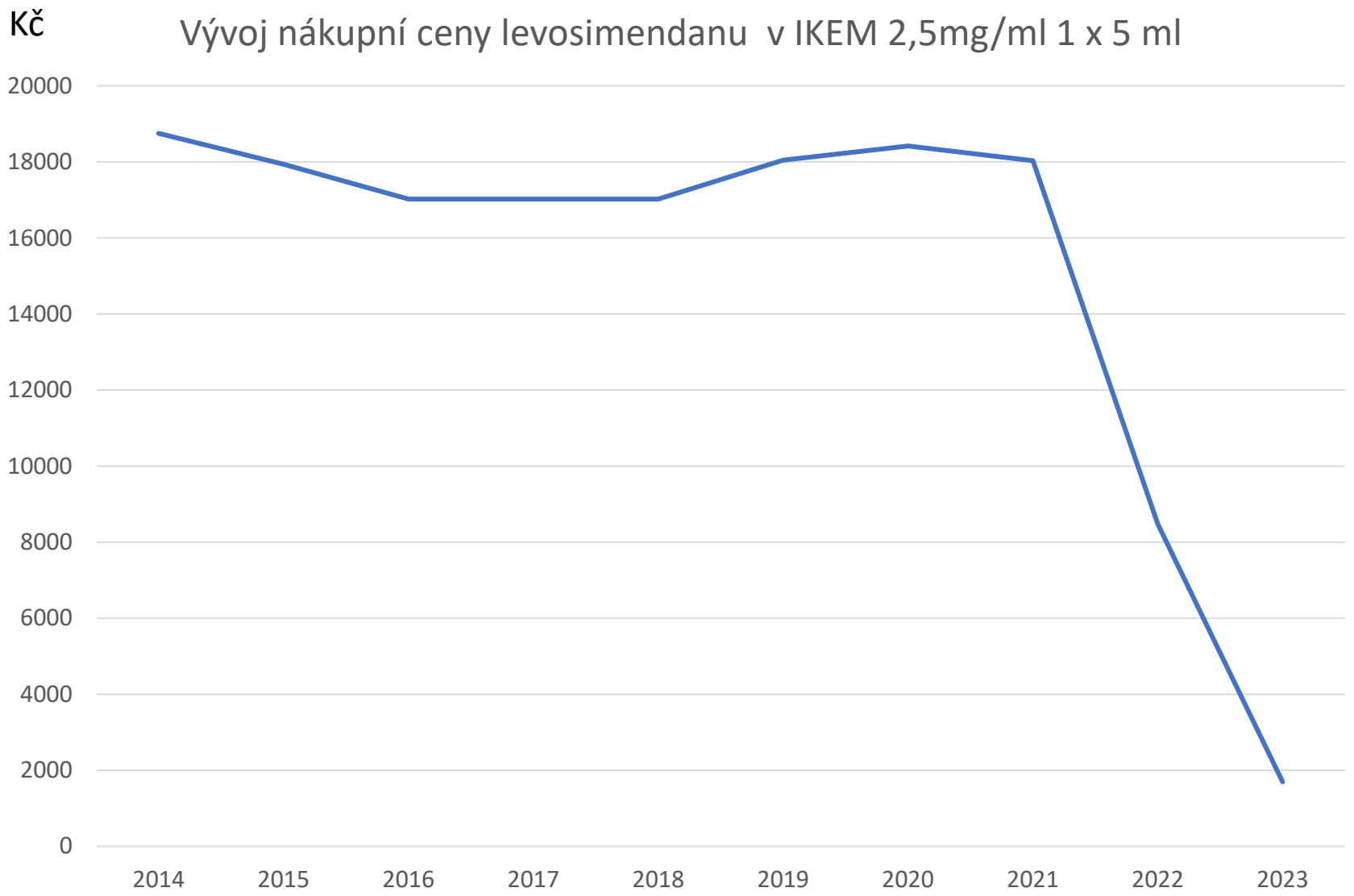



**FIGURE 1 |** Kaplan–Meier curves of all-cause mortality between without and with levosimendan-use groups.


Kč
Vývoj nákupní ceny levosimendanu v IKEM 2,5mg/ml 1 x 5 ml
20000
18000
16000
14000
12000
10000
8000
6000
4000
2000
0
2014
2015
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