Betablokátory v těhotenství - které, kdy a komu

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XXXIV. VÝROČNÍ SJEZD ČESKÉ KARDIOLOGICKÉ SPOLEČNOSTI

KVO v těhotenství

- KVO v těhotenství jsou hlavní příčinou mateřské morbidity a mortality, komplikují 4-11 % těhotenství v zemích s vysokými příjmy (high-income countries)
  - stoupá počet těhotných žen se získanými, vrozenými nebo dědičnými KVO
  - příčiny: vyšší věk žen v prvním těhotenství
    narůstající počet žen s VVS v reprodukčním věku
    rostoucí prevalence komorbidit

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ESC GUIDELINES

2025 ESC Guidelines for the management of cardiovascular disease and pregnancy

Developed by the task force on the management of cardiovascular disease and pregnancy of the European Society of Cardiology (ESC)

Endorsed by the European Society of Gynecology (ESG)

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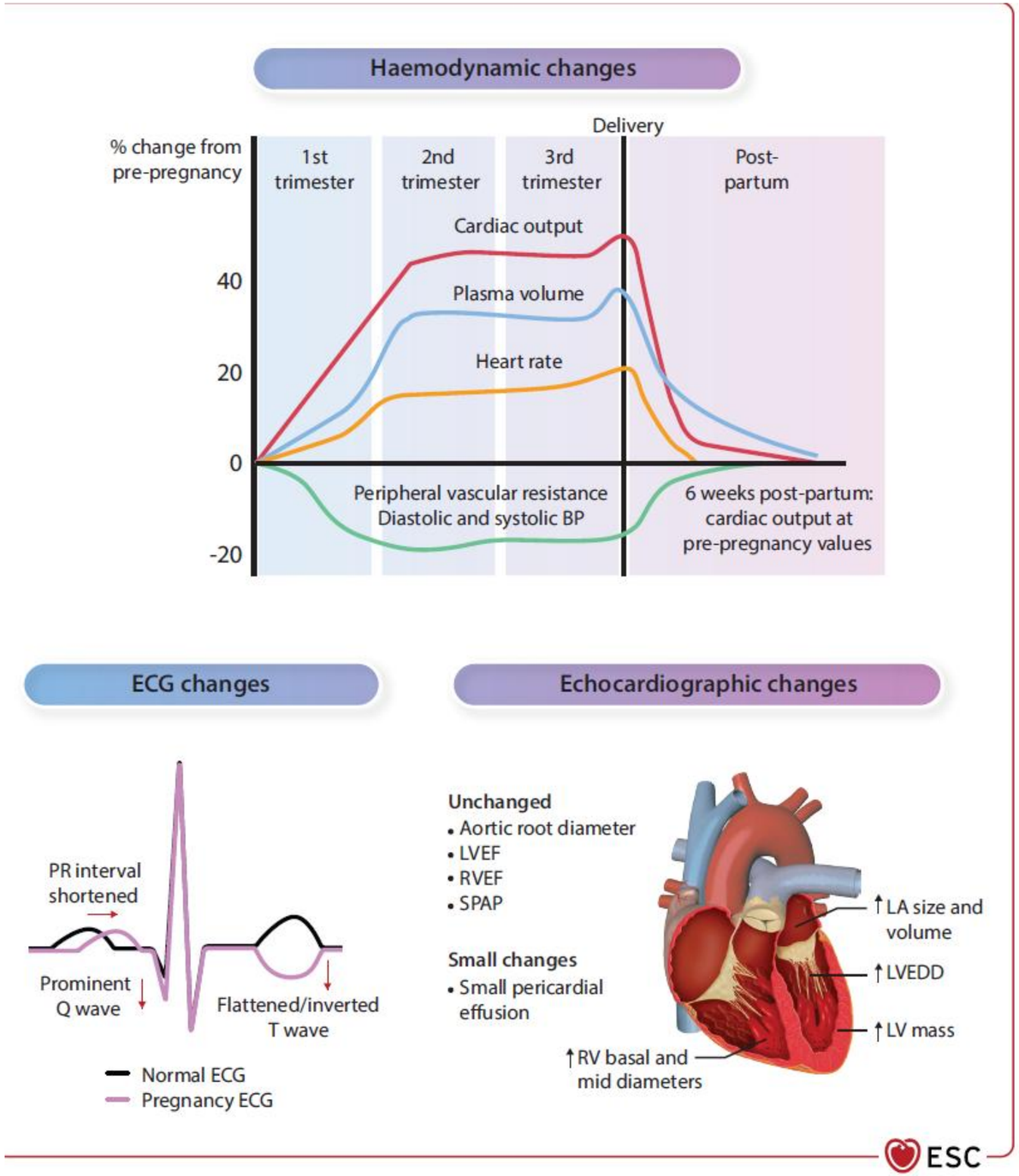
Eur Heart J 2024;45:3912-4018

Fyziologické změny v těhotenství



Eur Heart J 2024;45:3912-4018

Léky v těhotenství a v období laktace
Obecné principy

1. Farmakokinetika a farmakodynamika

- Fyziologická adaptace mateřských orgánů na těhotenství ovlivňuje farmakokinetiku a farmakodynamiku teoreticky všech léků včetně kardiovaskulárních
  - Zvýšená aktivita GIT- metabolismu v játrech, jaterní enzymy, GFR
  - Změna vazby proteinů
  - Pokles albumin v séru

Drugs in pregnancy and during lactation

General principles

2. Pharmacogenetics

- CYP2D6 polymorphism is associated with different phenotypes (extensive, ultrarapid or poor metabolizer).
- Poor and ultrarapid metabolizers may experience extreme variations in drug plasma levels and bioavailability, and thus in their effects.

Drugs in pregnancy and during lactation

General principles

3. Newborn drug exposure in breast milk

- Given as a percentage value, calculated as the dose taken by the infant compared either to the therapeutic dose of the same drug (often unknown for newborns) or the maternal weight-adjusted dose.
- The ‘relative infant dose’ (RID) depends on the relative amount of a drug secreted in the milk (milk-to-plasma concentration ratio) and the quantity of milk intake (the standard is 150 mL/kg/day) on a body weight basis.
- RID of 5-10% is generally considered safe.

Betablokátory v těhotenství

- BB v časné fázi těhotenství – nebylo prokázáno vyšší riziko kongenitálních malformací.
- Atenolol způsobuje růstovou retardaci, bradykardii a hypoglykemii, není proto v těhotenství doporučován.
- Labetalol and lipopofilní BB (metoprolol, propranolol, carvedilol) jsou upřednosňovány díky svému výraznému „first-pass“ účinku. Beta-1-selektivní BB (bisoprolol, metoprolol) *snižují riziko hypoglykemie a IUGR.*
- Propranolol, metoprolol a labetalol mají nejnižší riziko rozvoje bradykardie u novorozenců v období laktace.

Hypertenze v těhotenství

- Nejčastější komplikace v těhotenství
- Výskyt ~10 % těhotenství:

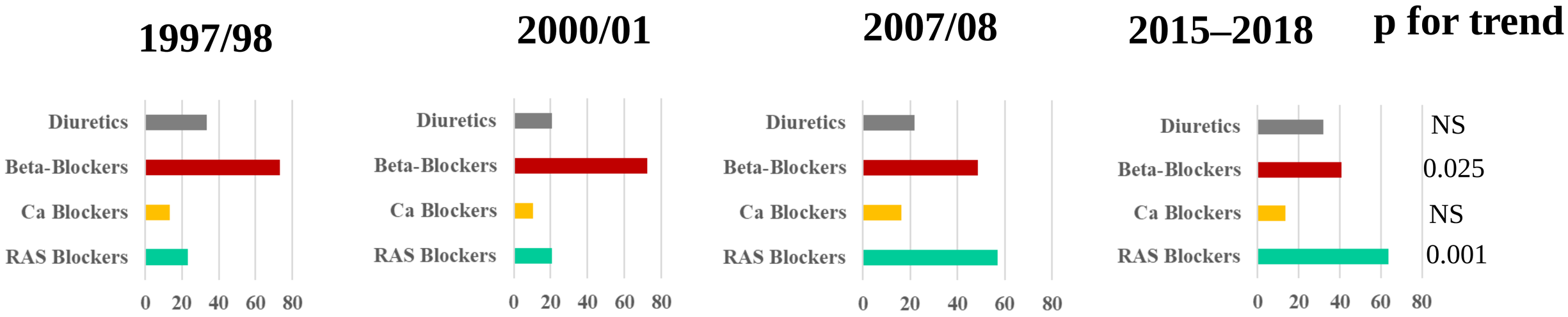
  1-5 % preexistující hypertenze
  5-6 % gestační hypertenze
  1-4 % preeklampsie

Prekoncepční poradenství

- **Beta-blokátory mohou navodit bradykardii plodu, růstovou retardaci a hypoglykémii, jsou méně účinné než blokátory kalciových kanálů**

Antihypertensive medication in women of reproductive age

Czech MONICA and post-MONICA



Atenolol in essential hypertension during pregnancy

Lucy Butters, Susan Kennedy, Peter C Rubin

Abstract

Objective—To determine the effect of atenolol on the outcome of pregnancy in women with essential hypertension.

Design—Prospective, randomised, double blind, placebo controlled study.

Setting—Hospital clinic.

Patients—33 Women with mild essential hypertension (systolic blood pressure 140-170 mm Hg or diastolic pressure 90-110 mm Hg on two occasions at least 24 hours apart) consecutively referred to two obstetric medical clinics. Four patients in the placebo group were withdrawn from the study: control of blood pressure was inadequate in two, one developed breathlessness, and one changed her mind about participating. The mean gestation in the 29 remaining women on entry to the study was 15·9 weeks.

Main outcome measures—Blood pressure and birth weight.

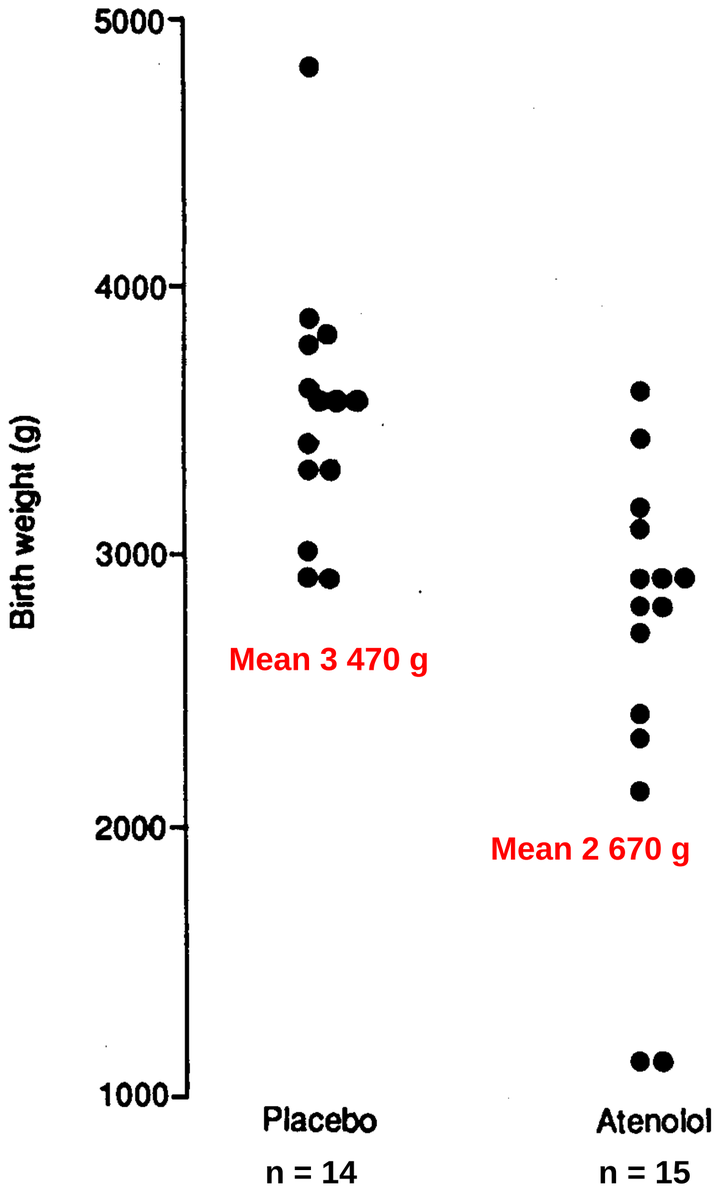
Intervention—14 Women received placebo. 15 Women received atenolol 50 mg daily initially, increasing until either the blood pressure was <140/90 mm Hg or a dose of 200 μg daily was reached.

Results—The mean blood pressure on entry was 148/86 mm Hg in the group given atenolol and 144/86 mm Hg in the group given placebo. During treatment the mean diastolic pressure was significantly reduced by atenolol compared with placebo (to 74 *v* 81 mm Hg; difference in means (95% confidence interval) 7·0 (2·9 to 10·0) mm Hg) but the effect on systolic pressure was marginal (132 *v* 136 mm Hg; 4·0 (−1·4 to 8·6) mm Hg). Babies in the atenolol group had a significantly lower birth weight than those in the placebo group (2620 g *v* 3530 g; 910 (440 to 1380) g).

Conclusion—Atenolol given from the end of the first trimester in patients with mild hypertension is associated with intrauterine growth retardation. When taken in conjunction with the results of a previous study in which methyldopa was given these findings indicate that benefit is unlikely to result from treating mild essential hypertension in pregnancy.

BMJ 1990;301:587-9

Birth weights of babies in atenolol and placebo groups



BMJ 1990;301:587-9

Effect of *Atenolol* on Birth Weight

Gregory Y.H. Lip, MD, Michèle Beevers, SRN, David Churchill, MD, Lara M. Shaffer, MB, and D. Gareth Beevers, MD

A previous small, prospective study from Glasgow reported that babies born to women treated with atenolol in early pregnancy had significantly lower birth weights than those in the placebo group.[1] Beta blockers, while safe in the third trimester of pregnancy, are also considered to cause significant growth restriction when used for longer periods.[2] An antenatal hypertension clinic has been in operation at City Hospital, Birmingham since 1980, where pregnant women with hypertension undergo careful follow-up jointly by an obstetrician and a physician with a special interest in hypertension. Patients were referred to the clinic by obstetricians and general practitioners on the basis of previous hypertension, or raised blood pressures detected for the first time in pregnancy. In many, the blood pressure decreased with no therapy, and where possible antihypertensive drugs were discontinued. After the Glasgow study,[1] the use of atenolol in early pregnancy was discontinued and an audit was conducted of birth weights in relation to drug therapy.

• • •

We conducted an analysis of our own prospectively gathered and computerized database of all women attending our clinic between 1980 and 1995. Information on demographic data, presenting blood pressures, drug therapies, pregnancy complications, and pregnancy outcome were recorded. The mean termine significant predictors for birth weights. A p value <0.05 was considered statistically significant.

We reviewed data from the antenatal records of 398 consecutive pregnancies (137 white, 103 black, 158 Asian women; mean age 30 ± 6 years) attending our antenatal hypertension clinic between 1980 and 1995. Two hundred thirty-five women were not taking any therapy during the first 20 weeks of pregnancy, whereas atenolol was taken by 76 women, labetolol by 7, other β blockers by 12, calcium antagonists by 22, diuretics by 26, methyldopa by 17, and angiotensin-converting enzyme inhibitors by 7 women; 18 women were taking multiple drug combinations.

Blood pressures during antihypertensive therapy are summarized in Table I. When compared with untreated cases, there was a trend toward higher mean systolic (1-way ANOVA, $p = 0.064$) and diastolic blood pressures ($p <0.001$) in the first 20 weeks of pregnancy among women who were taking antihypertensive drugs (Table I). There were no significant differences in mean gestation period for each patient subgroup of treated and untreated women (1-way ANOVA, p = NS).

Mean birth weights, median placental weights, and ponderal index are also summarized in Table I. Babies born to women taking atenolol were significantly lighter (1-way ANOVA, $F = 5.3$, $p <0.001$)

AmJ Cardiol 1997;79:1436-1438

Effect of *Atenolol* on Birth Weight

Gregory Y.H. Lip, MD, Michèle Beevers, SRN, David Churchill, MD, Lara M. Shaffer, MB, and D. Gareth Beevers, MD

In conclusion, this survey suggests that atenolol use may be detrimental in early pregnancy and provides confirmatory data with previous small prospective randomized trials. Our findings suggest that atenolol should be avoided in women who are trying to conceive or who are in the early stages of pregnancy.

Am J Cardiol 1997;79:1436-1438

Prekoncepční poradenství

- **Beta-blokátory mohou navodit bradykardii plodu, růstovou retardaci a hypoglykémii, jsou méně účinné než blokátory kalciových kanálů**

- **Beta-blokátor a jeho dávka by měly být pečlivě voleny**
  - **nepříznivější data jsou pro labetalol**
  - **vyhnout se podávání atenololu**

Hypertension in pregnancy

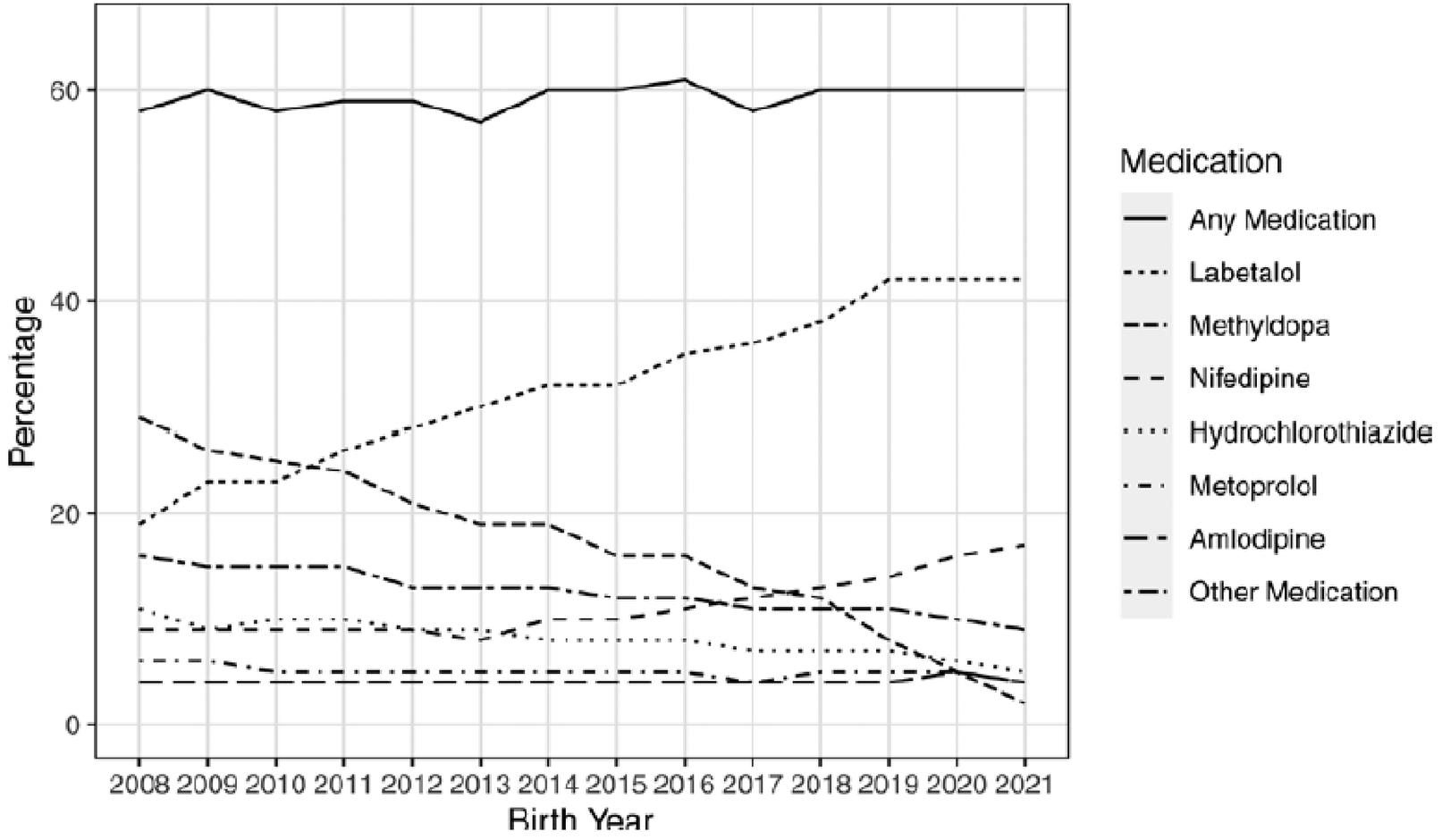
Labetalol[a] and α-methyl-DOPA are the first choice BP-lowering agents for hypertensive disorders in pregnancy unless contraindicated.	I	B
Extended-release nifedipine is recommended as an alternative BP-lowering agent during pregnancy.	I	B
Up-titration of monotherapy should precede any combination drug treatment.	II	C
Combination drug treatment between labetalol, extended-release nifedipine, or α-methyldopa may be reasonable to achieve the desirable BP target after the failure of up-titrated monotherapy.	II	C
ACE inhibitors, ARBs, or direct renin inhibitors are not recommended during pregnancy.	III	C

Antihypertensive drugs in pregnancy

Methyldopa is recommended for the treatment of hypertension in pregnancy.[623,624]	I	B
Labetalol, metoprolol, and dihydropyridine CCBs are recommended for the treatment of hypertension in pregnancy.[623]	I	C
In severe hypertension, drug treatment with i.v. labetalol, urapidil, nicardipine, or oral short acting nifedipine or methyldopa is recommended for acute reduction in blood pressure.[625,626] Intravenous hydralazine is a second-line option.	I	C
In pre-eclampsia associated with pulmonary oedema, nitroglycerine given as an i.v. infusion is recommended.[627]	I	C

Eur Heart J 2024;45:3912-4018

Antihypertenzní léčba v těhotenství , USA, 2008-2021



Hypertension 2024;81:1716-1723

Kojení

- TK nestoupá u kojících matek
- Všechna antihypertenziva užívaná kojícími matkami se vylučují do mateřského mléka; většina z nich je však přítomna v nízkých koncentracích vyjma propranololu a nifedipinu, jejichž koncentrace je podobná jako v mateřské plazmě

Maternal antihypertensive medications usually compatible with breastfeeding

- Diuretics (furosemide, hydrochlorothiazide, and spironolactone) may reduce milk production.
- **Metoprolol is classified as compatible with breastfeeding**, although it is concentrated in human milk.
- Acebutolol and atenolol should not be used in nursing mothers.

Pediatrics 2001;108:776-789

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European Society of Cardiology
European Heart Journal - Cardiovascular Pharmacotherapy
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POSITION PAPER
Hypertension

Peripartum management of hypertension: a position paper of the ESC Council on Hypertension and the European Society of Hypertension

Renata Cífková[1,2]*, Mark R. Johnson[3], Thomas Kahan[4], Jana Brguljan[5], Bryan Williams[6], Antonio Coca[7], Athanasios Manolis[8], Costas Thomopoulos[9], Claudio Borghi[10], Costas Tsioufis[11], Gianfranco Parati[12,13], Isabella Sudano[14], Richard J. McManus[15], Bert-Jan H. van den Born[16], Vera Regitz-Zagrosek[17], and Giovanni de Simone[18]

Eur Heart J Cardiovasc Pharmacother. 2019 Dec 16: doi: 10.1093/ehjcvp/pvz082.

Další indikace podávání betablokátorů v těhotenství

- **Kardiomyopatie**

  Léčba BB má pokračovat v těhotenství za těsné monitorace růstu plodu, atenolol má být nahražen před početím.
  U HKMP má být léčba BB zahájena v případě nových symptomů (obstrukce LVOT). IC

- **Sy dlouhého QT**

Beta-blockers[c], with pre-pregnancy dose and with nadolol and propranolol as drugs of choice, are recommended during pregnancy in women with LQTS.[312–316,335]	I	B
It is recommended to continue beta-blocker therapy during lactation in women with LQTS to reduce arrhythmic risk.[148,336]	I	B
Pre-pregnancy beta-blocker dose of nadolol or propranolol, is recommended in women with LQT2, particularly in the post-partum period, which represents a high-risk period for life-threatening arrhythmias.[148,313,315]	I	B

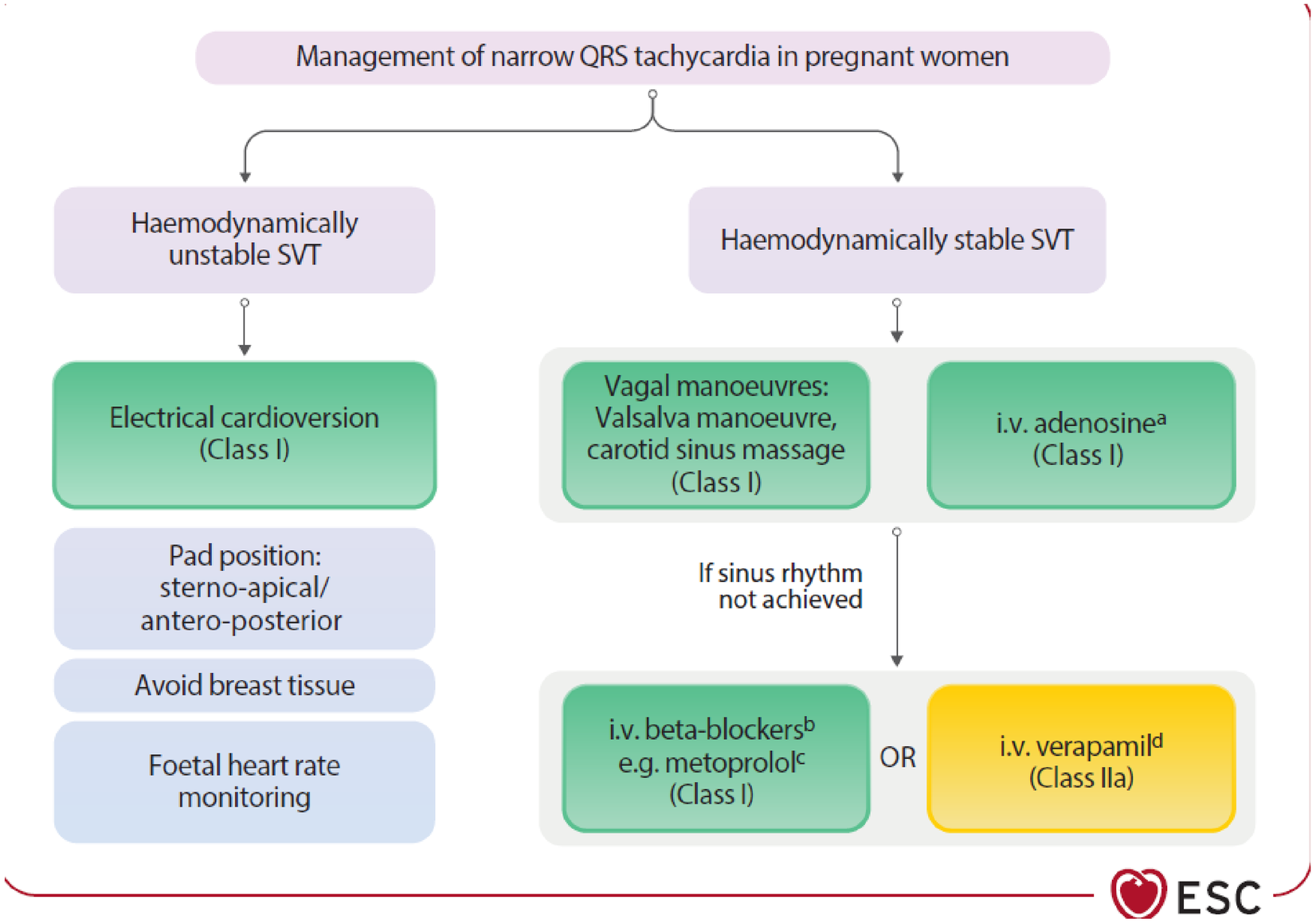
Další indikace podávání betablokátorů v těhotenství

- **Geneticky podmíněná onemocnění aorty**

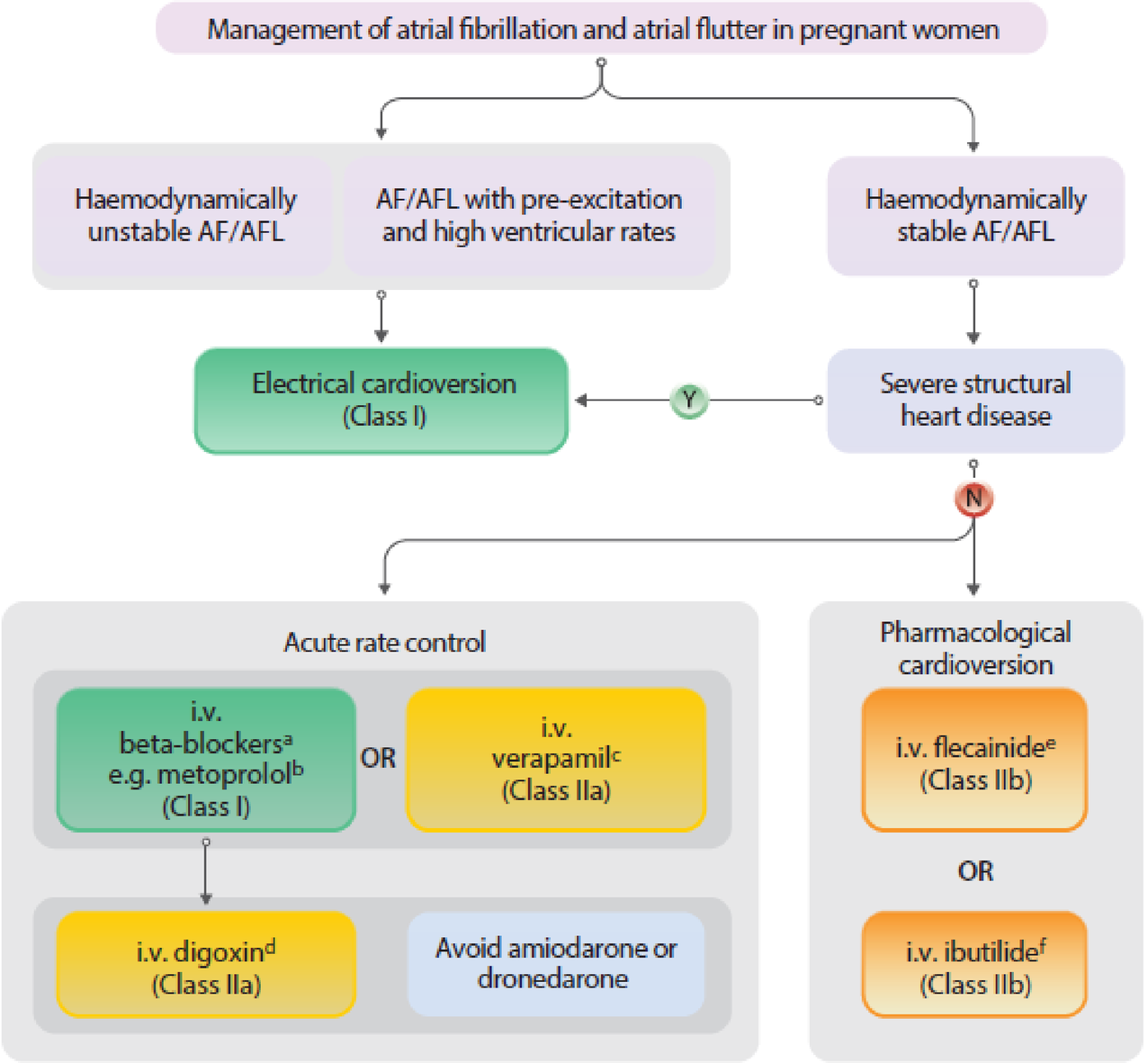
  Cílová hodnota STK 120-129 mm Hg, zvážit léčbu BB za těsné monitorace růstu plodu

- **ICHS**
- **Arytmie**

Léčba tachykardie s úzkým QRS komplexem



Léčba fibrilace síní a flutteru u těhotných



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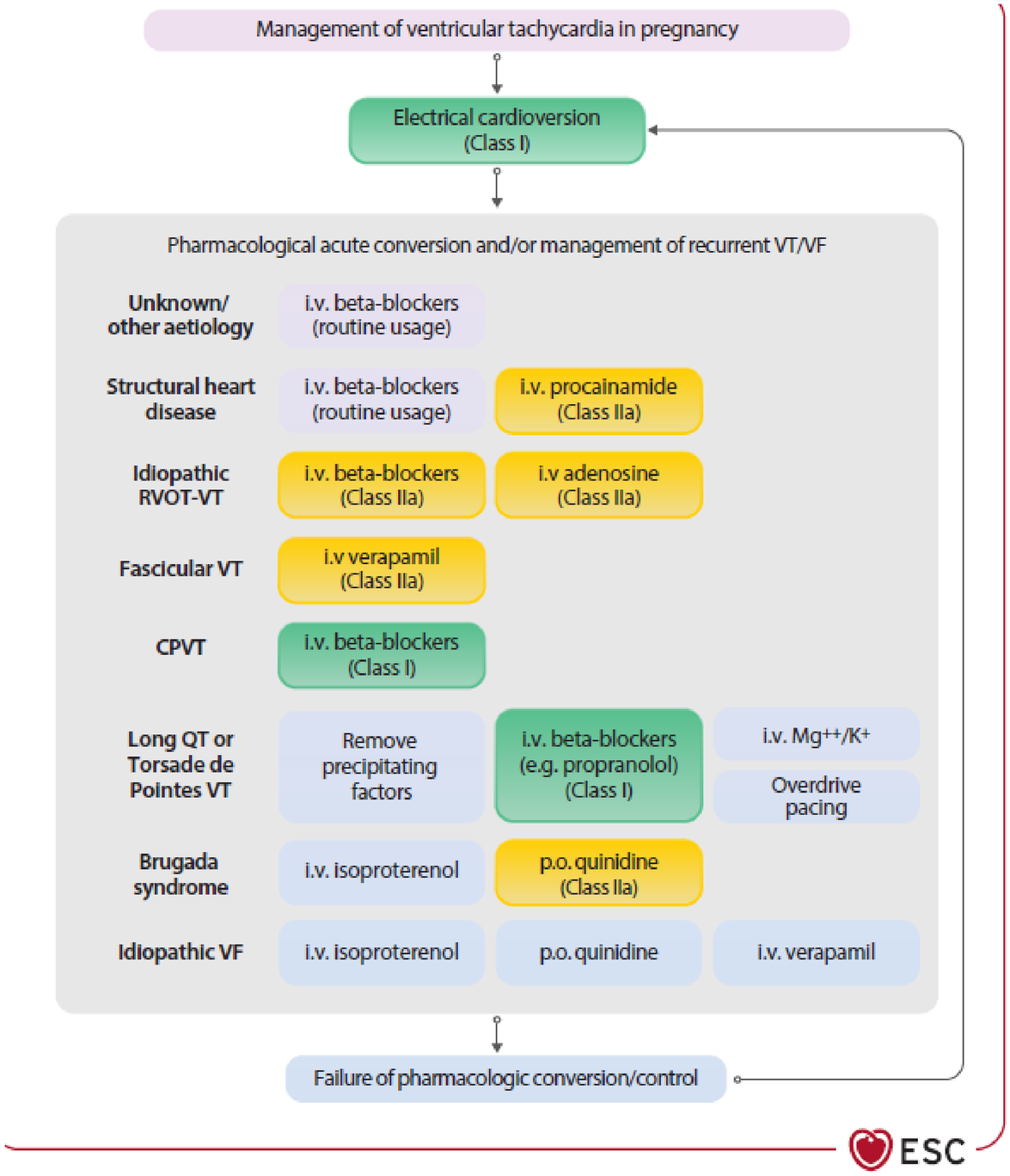
Léčba komorových arytmií v těhotenství



Nepřiměřená sinusová tachykardie

(inappropriate sinus tachycardia)

Inappropriate Sinus Tachycardia: Etiology, Pathophysiology, and Management

JACC Review Topic of the Week

Adnan Ahmed, MD,[a] Naga Venkata K. Pothineni, MD,[a] Rishi Charate, MD,[a] Jalaj Garg, MD,[b] Mehmet Elbey, MD,[a] Carlo de Asmundis, MD,[c] Mark LaMeir, MD,[c] Ahmed Romeya, MD,[a] Poojita Shivamurthy, MD,[a] Brian Olshansky, MD,[d] Andrea Russo, MD,[e] Rakesh Gopinathannair, MD,[a] Dhanunjaya Lakkireddy, MD[a]

ABSTRACT

Inappropriate sinus tachycardia (IST) is a clinical syndrome that generally affects young patients and is associated with distressing symptoms. Although the most common symptom is palpitations, it can be accompanied by a myriad of symptoms, including anxiety, dizziness, presyncope, and syncope. The pathogenesis of IST is not well understood and considered multifactorial, with autonomic dysfunction being the central abnormality. IST is a diagnosis of exclusion. Management presents a clinical challenge. The overall efficacy of lifestyle modifications and medical therapy may be limited. Recent advances in catheter and surgical sinus node sparing ablation techniques have led to improvement in outcomes. In addition, increased focus has led to development of multimodality team-based interventions to improve outcomes in this group of patients. In this review, we discuss the mechanistic basis of IST, review current approaches to diagnosis, and outline contemporary therapeutic approaches. (J Am Coll Cardiol 2022;79:2450–2462)
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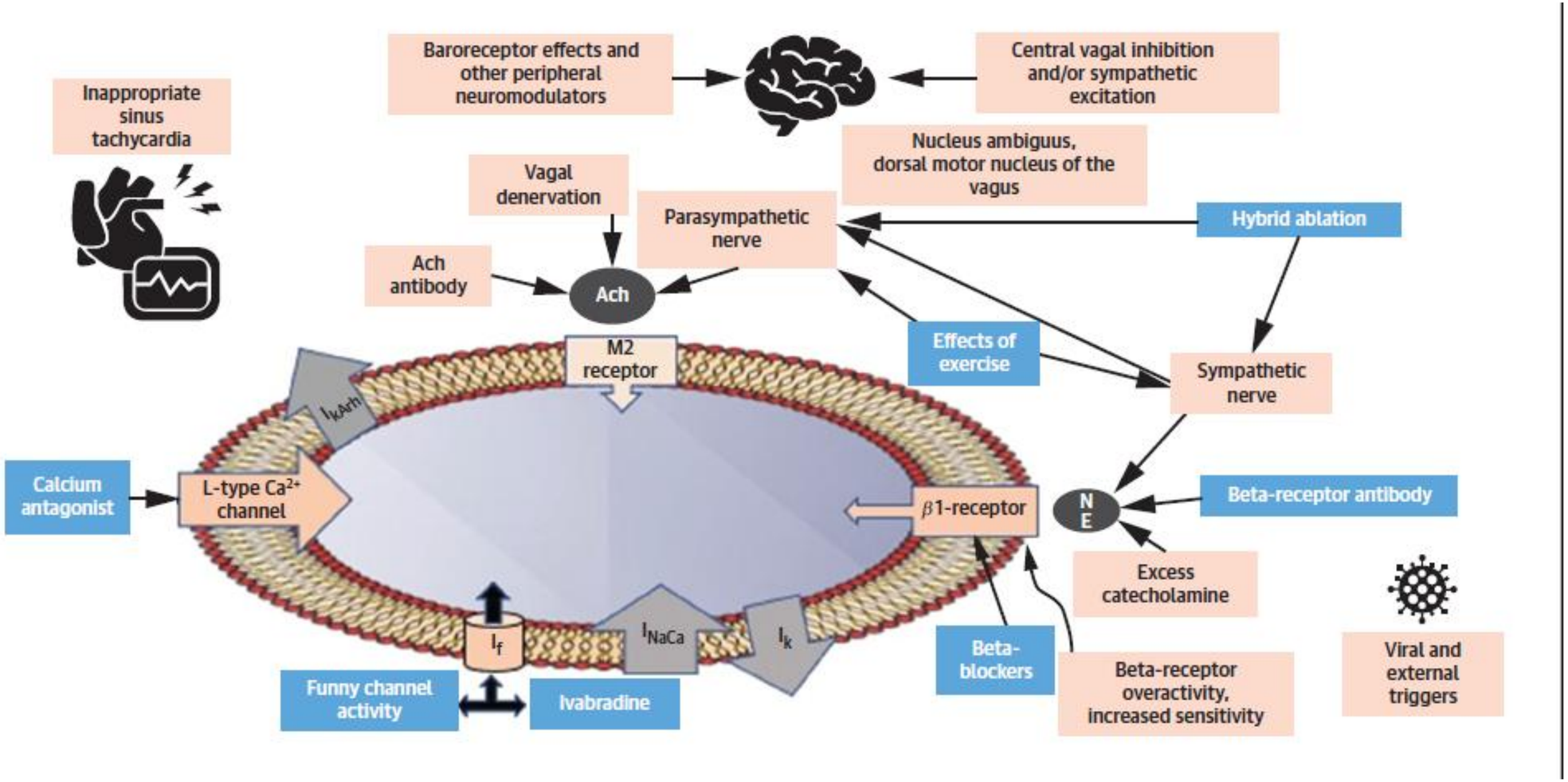
JACC 2022;79:2450-2462

Patofyziologie nepřiměřené sinusové tachykardie



JACC 2022;79:2450-2462

Možné příčiny sinusové tachykardie

Physiological	Medications or Substance Abuse	Medical Problems
Dehydration	Alcohol	Anemia
Emotional	Beta-blocker withdrawal	Cardiac disorders–cardiomyopathy, pericarditis, valvular regurgitation, cardiogenic shock
Exercise	Caffeine	Cushing's disease
Fever	Decongestants	Hyperthyroidism
Hypoglycemia	Illicit drug abuse–cocaine	Infection
Pain	Sympathomimetics	Pheochromocytoma
Pregnancy	Theophylline	Pneumothorax
	Thyroid hormone supplements	Psychiatric (panic disorder, depression, anxiety, schizophrenia)
	Tobacco	Pulmonary embolism
		Orthostatic hypotension

JACC 2022;79:2450-2462

V.F.

24-letá primigravida ve 23. týdnu těhotenství

Odeslána PL pro TF 100-115/min.

Echo: LK normální velikosti, bez hyperterofie stěn, bez ložiskové poruchy kinetiky, EF 60-65 %

24-hod. monitorace ekg: SR se sklonem k tachykardii o prům. f 109/min.

Závěry

- Podávání všech léků v těhotenství má být pečlivě zvažováno, stejně jako výběr jednotlivých účinných látek.
- Betablokátory jsou indikovány u řady KVO v těhotenství.
- Nebylo prokázáno vyšší riziko kongenitálních malformací při podávání BB v časné fázi těhotenství.
- Betablokátory jsou heterogenní léková skupina, liší účinností i bezpečnostním profilem.
- Atenolol způsobuje výraznou růstovou retardaci, bradykardii a hypoglykemii, není proto v těhotenství doporučován.
- Upřednostňuje se labetalol a lipofilní BB (metoprolol – nižší riziko hyperglykemie, IUGR a bradykardie u novorozenců – vhodný v období laktace)

Choice of medication

Hypertension

Pregnancy	Lactation and breastfeading
++ Methyldopa, nifedipine, labetalol, propranolol, metoprolol, amlodipine	++ Amlodipine, labetalol, ACE-I
+- Hydralazine, hydrochlorothiazide, indapamide	+- Hydralazine, hydrochlorothiazide, indapamide, methyldopa (depression), candesartan
x ACE-I, ARB, aliskiren, atenolol	x Aliskiren, clonidine, ARB[a]

Choice of medication

Hypertension

Pregnancy	Lactation and breastfeading
++ Methyldopa, nifedipine, labetalol, propranolol, metoprolol, amlodipine	++ Amlodipine, labetalol, ACE-I
+- Hydralazine, hydrochlorothiazide, indapamide	+- Hydralazine, hydrochlorothiazide, indapamide, methyldopa (depression), candesartan
x ACE-I, ARB, aliskiren, atenolol	x Aliskiren, clonidine, ARB[a]

Take-Home Message

- **Careful selection of drugs in pregnancy and during lactation**