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# First-Line Antiarrhythmic Transplacental Treatment for Fetal Tachyarrhythmia: A Systematic Review and Meta-Analysis

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***Background*—**There is no consensus on the most effective and best tolerated first-line antiarrhythmic treatment for fetal tachyarrhythmia. The purpose of this systematic review and meta-analysis was to compare the efficacy, safety, and fetal–maternal tolerance of first-line monotherapies for fetal supraventricular tachycardia and atrial flutter.

***Methods and Results*—**A comprehensive search of several databases was conducted through January 2017. Only studies that made a direct comparison between first-line treatments of fetal tachyarrhythmia were included. Outcomes of interest were termination of fetal tachyarrhythmia, fetal demise, and maternal complications. Ten studies met inclusion criteria, with 537 patients. Overall, 291 patients were treated with digoxin, 137 with flecainide, 102 with sotalol, and 7 with amiodarone. Digoxin achieved a lower rate of supraventricular tachycardia termination compared with flecainide (odds ratio [OR]: 0.773; 95% confidence interval [CI], 0.605–0.987; $I^2$=34%). In fetuses with hydrops fetalis, digoxin had lower rates of tachycardia termination compared with flecainide (OR: 0.412; 95% CI, 0.268–0.632; $I^2$=0%). There was no significant difference in the incidence of maternal side effects between digoxin and flecainide groups (OR: 1.134; 95% CI, 0.129–9.935; $I^2$=80.79%). The incidence of maternal side effects was higher in patients treated with digoxin compared with sotalol (OR: 3.148; 95% CI, 1.468–6.751; $I^2$=0%). There was no difference in fetal demise between flecainide and digoxin (OR: 0.767; 95% CI, 0.140–4.197; $I^2$=44%).

***Conclusions*—**Flecainide may be more effective treatment than digoxin as a first-line treatment for fetal supraventricular tachycardia. **(*J Am Heart Assoc*. 2017;6:e007164. DOI: 10.1161/JAHA.117.007164.)**

**Key Words:** arrhythmia • arrhythmia (heart rhythm disorders) • pediatrics

Fetal arrhythmias are encountered in 1% of pregnancies. The majority of fetal arrhythmias are benign intermittent premature atrial contractions that require no intervention.[1–3] Sustained fetal tachyarrhythmias (FTs) are less common, ≈1 in 1000 pregnancies, but are associated with significant morbidity and mortality.[4] If untreated, sustained FT causes increased central venous pressure and decreased cardiac output. This may result in fetal hemodynamic compromise and development of nonimmune hydrops fetalis that can lead to fetal demise. Hydrops fetalis occurs in about half of these cases, with fetal demise occurring in 9% of untreated FT cases.[2,5,6]

Supraventricular tachycardia (SVT) along with atrial flutter (AF) are the most common types of sustained FT. Fetal rhythm control and conversion to sinus rhythm via transplacental medical interventions was reported nearly 40 years ago.[7] Digoxin, sotalol, flecainide, amiodarone, and other antiarrhythmic agents have been described as successful interventions to treat fetal SVT and AF in multiple studies. These studies were mostly single-center studies, and had small sample sizes.[8–11] Secondary to this gap in the literature, recent statements from the American Heart Association acknowledged the lack of consensus on the most effective and best tolerated first-line agent for fetal SVT or AF.[12]

The objective of this systematic review and meta-analysis was to compare the efficacy, safety, and fetal–maternal tolerance of first-line monotherapies for fetal SVT and AF to provide comparative effectiveness inferences about the preferred first-line therapy.

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An accompanying Figure S1 is available at http://jaha.ahajournals.org/content/6/12/007164/DC1/embed/inline-supplementary-material-1.pdf

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## Clinical Perspective

### What Is New?

- This study is a systematic review of the literature for first-line treatment of fetal supraventricular tachycardia.
- Flecainide was superior to digoxin in terminating fetal supraventricular tachycardia in patients with and without hydrops fetalis.
- Flecainide was not associated with increased side effects or risk of fetal demise compared with digoxin.

### What Are the Clinical Implications?

- Flecainide is more effective than digoxin and may be used as a first-line treatment in fetal supraventricular tachycardia.
- Even in nonhydropic fetuses, flecainide is more effective than digoxin in terminating fetal supraventricular tachycardia.
- Flecainide seems to be a safe treatment without significant increase in maternal side effects or fetal demise and thus can be used as a first-line treatment.

## Methods and Evidence Acquisition

This systematic review was reported according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement.[13] The review followed a registered protocol that was a priori developed and registered (PROSPERO 2017:CRD42017054382).

## Data Sources and Search Strategy

A comprehensive search of several databases was conducted from each database's inception to January 10, 2017, including any language. The databases included Ovid Medline In-Process and Other Non-Indexed Citations, Ovid Medline, PubMed, Ovid Embase, Ovid Cochrane Central Register of Controlled Trials, Ovid Cochrane Database of Systematic Reviews, and Scopus. The search strategy was designed and conducted by an experienced librarian with input from the study's principal investigator. Controlled vocabulary supplemented with keywords was used to search for studies comparing the efficacy of digoxin, amiodarone, flecainide, or sotalol for FT. The actual strategy is in the appendix.

## Selection of Studies

Initial screening of the identified studies was performed by 3 independent reviewers working in duplicate based on the titles and abstracts, taking into consideration the inclusion criteria. After removing irrelevant and nonoriginal studies, full-text screening was performed to assess eligibility for final inclusion. Discrepancies were resolved through discussion and consensus.

We used a list of inclusion criteria set a priori for the initial and full article screening. We sought studies that evaluated the medical management of fetal arrhythmia as first-line therapy. Sustained FT was defined as fetal heart rate >180 beats/min for >50% of the fetal scan time. Only studies that made a direct comparison between different medication options as first-line treatment of fetal arrhythmia were included. Main outcomes of interest were termination of FT, fetal demise, and maternal complications of medications used. We included comparative original studies (randomized or observational) and excluded single-arm studies.

## Data Extraction

Reviewers extracted data independently from the included studies in duplicate, using a standardized, piloted, Web-based form that was developed based on the protocol. Data extracted included demographics of participants, patient inclusion criteria, study design, intervention details, and outcomes of interest. For all outcomes, we extracted dichotomous data whenever available, including number of patients with outcome and total numbers in each arm. Outcome data were extracted at the last follow-up reported. All disagreements or differences in extracted data were resolved by consensus.

## Methodological Quality and Risk of Bias Assessment

We found no randomized trials.[14] Observational studies were evaluated using the Newcastle-Ottawa tool.[15] This tool included assessment of how the participants represented the population of interest, how the comparative group was selected, and how outcome was assessed, as well as length and adequacy of follow-up when applicable. All discrepancies were resolved by a third reviewer.

## Statistical Analyses

The reviewers extracted the contingency table data from the included studies to calculate the relative risks. We conducted a meta-analysis to pool relative risks using the random-effects model to account for heterogeneity between studies and within-study variability. We used the $I^2$ statistic to estimate the percentage of total between-study variation due to heterogeneity rather than chance (ranging from 0% to 100%).[16,17] $I^2$ values of 25%, 50%, and 75% are thought to represent low, moderate, and high heterogeneity, respectively. Given the small number of studies, the analysis was repeated using a fixed-effects model. Statistical analyses were

conducted through OpenMeta.[18] All values are 2-tailed, and $P<0.05$ was set as the threshold for statistical significance.

Because first-line treatment of fetal tachycardia may differ between atrial flutter and SVT, a subgroup analysis was performed. The effect of hydrops fetalis on the choice of medication was evaluated. Fetal hydrops was defined by the presence of 2 of the following: subcutaneous edema, ascites, or pleuropericardial fluid. Finally, we analyzed the side effects associated with antiarrhythmic medications and the incidence of fetal demise.

## Results

Ten studies met the inclusion criteria (Figure 1). These encompassed a total of 537 patients. The average gestational age at diagnosis was 30.3 weeks (Table 1). The average heart rate at diagnosis was 238 beats/min. Once started, the antiarrhythmic medications were continued until delivery. The following 4 medications were used as a first-line therapy for fetal arrhythmia: digoxin, sotalol, flecainide, and amiodarone. Of the 537 patients, 291 (54%) patients were treated with digoxin, 137 (26%) were treated with flecainide, 102 (19%) were treated with sotalol, and 7 (1%) were treated with amiodarone. The dosing and route of administration of the medications are reported in Table 2. Amiodarone was not included in the analysis given the small number of patients reported in the literature. The studies included in the meta-analysis are summarized in Table 3.[19,20]

## Termination of SVT and AF

In patients with SVT, digoxin achieved a lower rate of SVT termination compared with flecainide (odds ratio [OR]: 0.773; 95% confidence interval [CI], 0.605–0.987; $I^2$=34%; Figure 2A). There was no difference between digoxin and sotalol (OR: 1.009; 95% CI, 0.515–1.976; $I^2$=68%; Figure 2B) or between flecainide and sotalol (OR: 1.451; 95% CI, 0.996–2.114; $I^2$=0%; Figure 2C).

In patients with AF, only 2 studies compared the efficacy of medications. There was no statistically significant difference between digoxin and sotalol (OR: 0.658; 95% CI, 0.240–1.803;

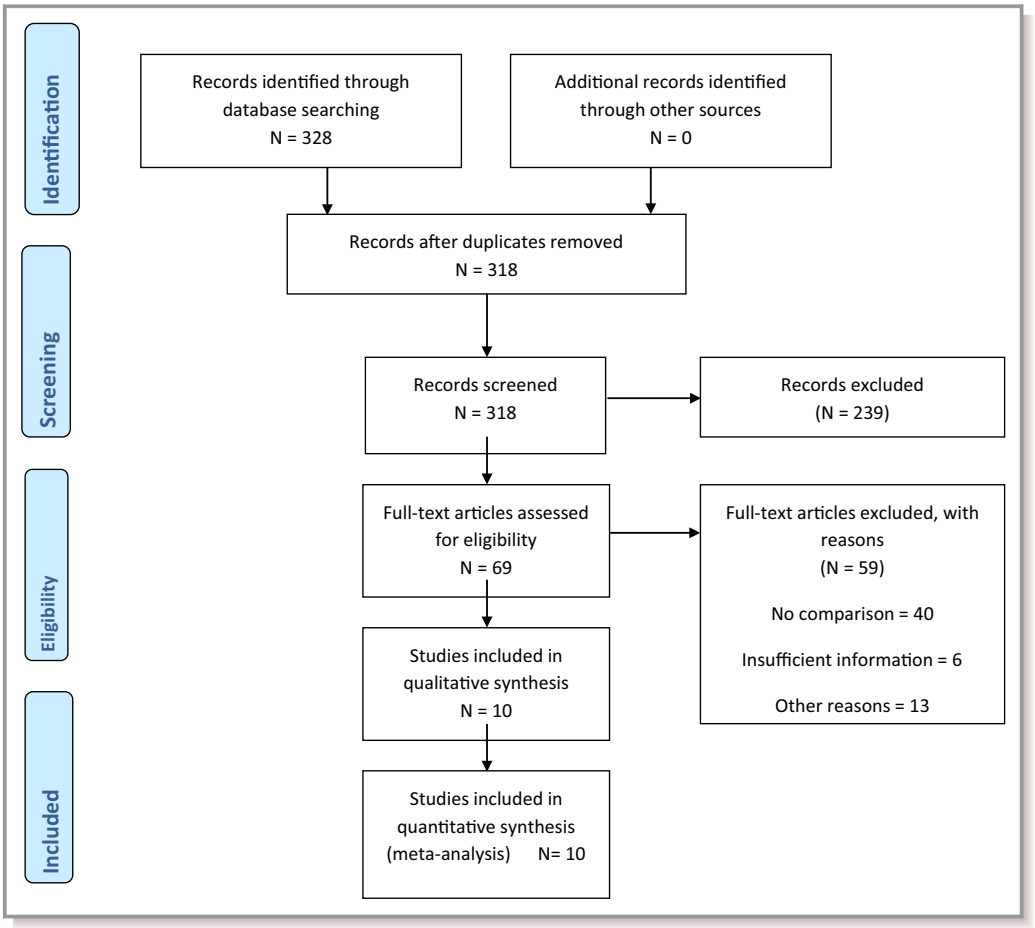


**Figure 1.** PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) 2009 flow diagram for study selection.

**Table 1.** Characteristics of Treated Fetuses by Medication Group

| | Digoxin | Flecainide | Sotalol | Amiodarone |
|---|---|---|---|---|
| Total number of fetuses | 393 | 202 | 102 | 7 |
| Gestational age at diagnosis, wk | 30.8 | 30 | 30 | |
| Fetal hydrops, n | 66 | 60 | 32 | 2 |
| Heart rate, beats/min | 235 | 240 | 236 | |
| Atrial flutter, n | 40 | 14 | 26 | 2 |

$I^2$=48.3%; Figure 3). Data were not adequate to compare digoxin and flecainide regarding termination of AF.

## Effect of Hydrops Fetalis on Arrhythmia Termination

In patients without hydrops fetalis, digoxin had a lower rate of tachycardia termination compared to flecainide (OR: 0.657; 95% CI, 0.447–0.965; $I^2$=53%; Figure 4A). There was no difference between digoxin and sotalol (Figure 4B). As expected in fetuses with hydrops fetalis, digoxin had lower rates of tachycardia termination compared with flecainide (OR: 0.412; 95% CI, 0.268–0.632; $I^2$=0%; Figure 4C).

## Maternal Side Effects and Fetal Demise

Few studies reported maternal side effects during FT treatment. These studies showed no significant difference in the incidence of maternal side effects between digoxin and flecainide groups, and the analysis was limited by high heterogeneity (OR: 1.134; 95% CI, 0.129–9.935; $I^2$=80.79%; Figure 5A). The incidence of maternal side effects was higher in cases treated with digoxin compared with sotalol, and the studies had less heterogeneity (OR: 3.148; 95% CI, 1.468–6.751; $I^2$=0%; Figure 5B). The side effects of the flecainide were nausea, dizziness, visual disturbances, heightened alertness, Brugada pattern on ECG, and headache, whereas the side effects of digoxin were nausea, dizziness, visual disturbances, and first-degree atrioventricular block.[4,21] The side effects of sotalol were nausea, dizziness, and bradycardia.[9] The majority of the maternal side effects were minor and did not require drug changes. Significant maternal side effects requiring decrease in dosage or discontinuation were mostly limited to digoxin. There was no difference in fetal demise between flecainide and digoxin with significant heterogeneity in the analysis (OR: 0.767; 95% CI, 0.140–4.197; $I^2$=44%; Figure 5C). We could not evaluate the effect of these medications on birth weight or gestational age at birth because data were insufficient.

## Risk of Bias Assessment

The risk of bias in the included studies is summarized in Figure 6 and Table 4. All 10 included studies were retrospective and nonrandomized studies. The risk of bias was assessed as low in most of the studies. Poor comparability of interventional groups because of the presence or absence of hydrops and poor selection of patients by combining SVT and AF were concerning regarding bias.

## Discussion

In this systematic review and meta-analysis, we compared efficacy and safety of different agents used as first-line therapy for sustained FT. Flecainide was found to be superior to digoxin in cases of fetal SVT, and its superiority to digoxin was more notable in cases of hydropic fetal SVT. Fetal SVT termination rates were higher in the patients treated with flecainide compared with sotalol. There was no difference between sotalol and digoxin in AF termination. There was also no difference in fetal demise or incidence of maternal side effects between digoxin and flecainide. Digoxin has higher

**Table 2.** Medication Dose and Route of Administration

| | Digoxin | Flecainide | Sotalol | Amiodarone |
|---|---|---|---|---|
| Dose | Start: loading with 1.5–2 mg over 24–48 h. Maintenance: 0.375–1 mg/day, target maternal drug levels in the upper therapeutic range (1–2.5 ng/mL). | Start: 200–300 mg divided BID or TID. Maintenance: can be increased to 450 mg/day if no response. When monitored, maternal serum drug concentrations of 0.2–1 μ/mL were targeted. | Start: 160–320 mg divided BID. Maintenance: can be increased in a few days to 480 mg/day. | Start: loading dose 1600–2400 mg/day 2–4 times daily, usually halved every 24 h. Maintenance dose 200–400 mg/day BID. |
| Route | PO or IV loading followed by PO | PO | PO | PO or IV |

BID indicates twice daily; IV, intravenous; PO, by mouth; TID, three times daily.

**Table 3.** Summary of Included Studies

| Reference | Trial Period | Country | Study Drug | SVT | AF | Gestation, wk | Heart Rate, beats/min | Hydrops | Study Design |
|---|---|---|---|---|---|---|---|---|---|
| Sridharan et al[4] | 1987–2011 | UK, Czech Republic | Digoxin, flecainide | 84 | 0 | 30.5 | 235 | 28 | Retrospective |
| Jouannic et al[19] | 1990–2000 | France | Digoxin, sotalol, amiodarone | 40 | 12 | 29 | 245 | 0 | Retrospective |
| van Engelen et al[6] | 1985–1992 | USA, Netherlands | Digoxin, flecainide | 34 | 15 | NR | NR | 15 | Retrospective |
| Strizek et al[21] | 2002–2014 | Germany | Digoxin, flecainide | 36 | 2 | 29 | 235 | 18 | Retrospective |
| Simpson and Sharland[26] | 1980–1996 | UK | Digoxin, flecainide | 83 | 12 | 32 | 240 | 32 | Retrospective |
| Pezard et al[20] | 1986–2007 | France | Digoxin, flecainide, amiodarone | 16 | 7 | 30.1 | 240 | 7 | Retrospective |
| Jaeggi et al[9] | 1998–2008 | Canada | Digoxin, flecainide, sotalol | 75 | 36 | 30.2 | 240 | 33 | Retrospective |
| Hahurij et al[8] | 1990–2005 | Netherlands | Digoxin, flecainide, sotalol | 7 | 1 | NR | NR | 1 | Retrospective |
| Frohn-Mulder et al[11] | 1982–1993 | Netherlands | Digoxin, flecainide | 21 | 14 | NR | NR | 13 | Retrospective |
| Ekman-Joelsson et al[24] | 1990–2012 | Sweden | Digoxin, flecainide, sotalol | 63 | 23 | 31.4 | 231 | 35 | Retrospective |

AF indicates atrial flutter; NR, not reported; SVT, supraventricular tachycardia.

incidence of side effects and less tolerance compared with sotalol.

## SVT Termination

Digoxin has been commonly considered the first-line agent in treating patients with fetal SVT.[9] Digoxin has been used for other types of arrhythmia for years and has a positive inotropic effect that makes it attractive in cases of depressed systolic function.[4] In neonates with atrioventricular reentry tachycardia, digoxin was used to prevent recurrence, although flecainide was found to be a more effective agent.[22] Although it is logical to use the most effective agent for neonates to treat fetuses with tachycardia, there has been some

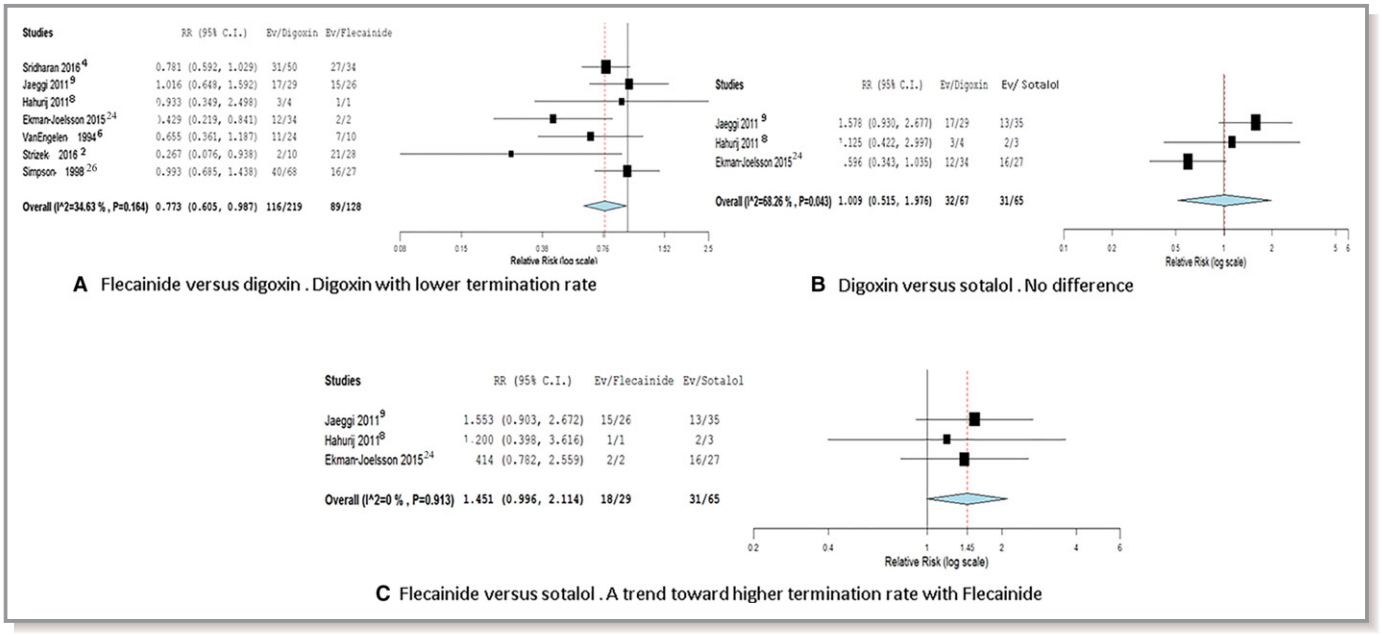


**Figure 2.** A, Flecainide vs digoxin in termination of supraventricular tachycardia.[4,6,8,9,21,24,26] B, Digoxin vs sotalol in termination of supraventricular tachycardia.[8,9,24] C, Flecainide vs sotalol in termination of supraventricular tachycardia.[8,9,24] CI indicates confidence interval; RR, relative risk.

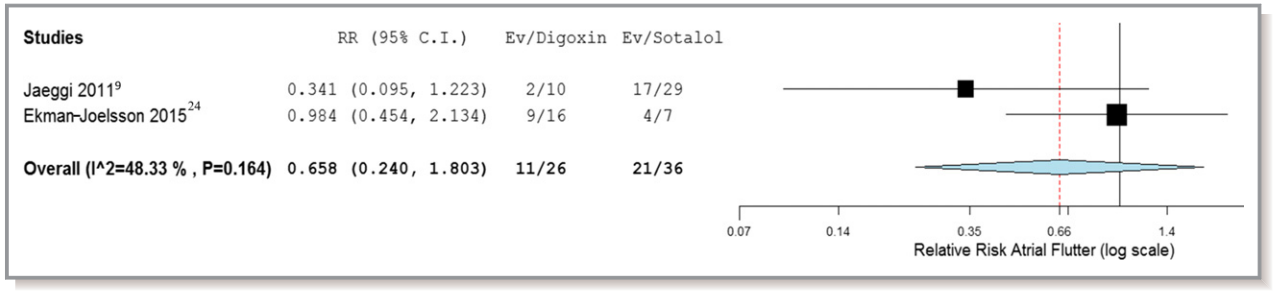


**Figure 3.** Sotalol vs digoxin in the termination of atrial flutter.[9,24] CI indicates confidence interval; RR, relative risk.

hesitation in the use of flecainide, mainly because of safety concerns.[9] After myocardial infarction in adults, flecainide was used to treat ventricular arrhythmia and was associated with increased mortality, likely due to the arrhythmogenic effect of flecainide on the recently infarcted ventricle.[23] There was some reports about increased risks of fetal demise.[4] These concerns are discussed below.

## Atrial Flutter

Only 2 studies compared the efficacy of different medications used for AF because AF is less common than SVT.[9,24] One study showed that sotalol has higher rate of conversion to sinus rhythm in cases of AF compared with digoxin.[9] The other study showed no difference in the rate of conversion between the 2 medications.[24] Meta-analysis of the 2 studies showed no significant difference. Of note, the duration of treatment required to convert to sinus rhythm is longer in AF compared with SVT, and it is possible that patients treated with digoxin were switched to another therapy, resulting in an increased rate of "digoxin failure" in these patients.[9,24] Further studies are needed to evaluate the best first-line agent in AF.

## Effect of Hydrops

In cases of sustained FT, elevated ventricular end-diastolic pressure may lead to increased central venous pressure leading to hydrops fetalis and decreased cardiac output.[4] Hydrops fetalis is associated with a high mortality rate (one fifth to one half) in this patient population.[4] When hydrops is present, the bioavailability of digoxin decreases, leading to lower blood concentration of digoxin compared with nonhydropic fetuses. Flecainide has excellent bioavailability in hydropic fetuses and thus achieves a higher rate of arrhythmia control, which, in some cases, results in hydrops resolution and less mortality.[4] This was shown in all studies that we evaluated, and the effect of flecainide was not

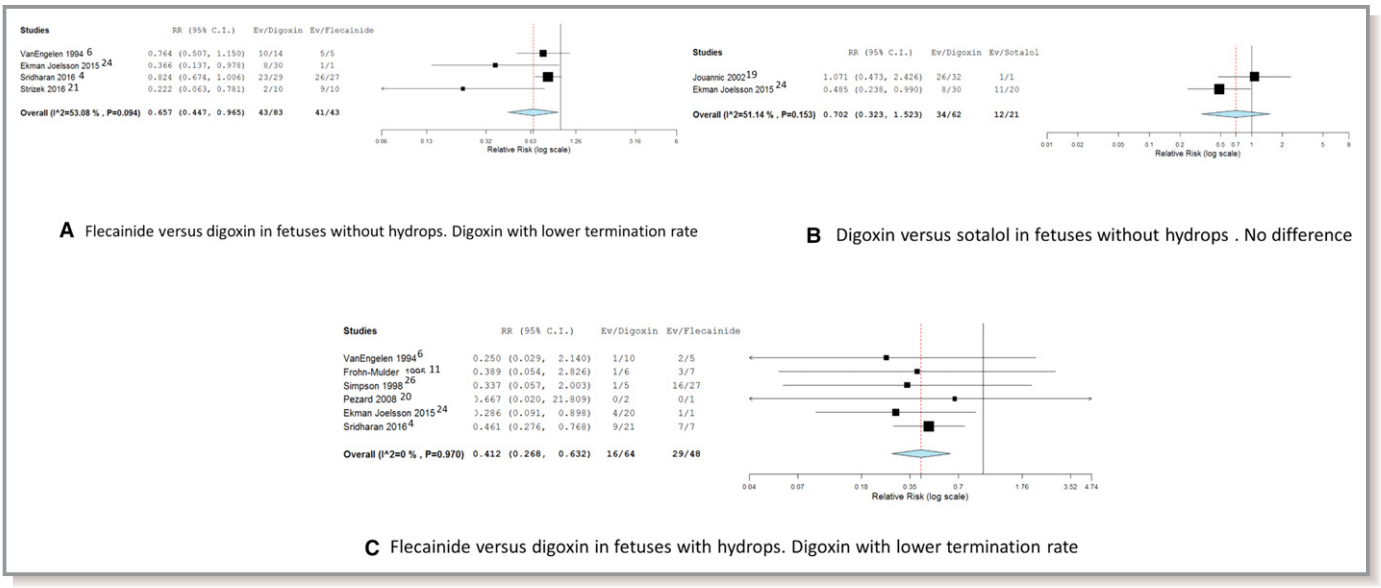


**Figure 4.** A, Digoxin vs flecainide in termination of supraventricular tachycardia in nonhydropic fetuses.[4,6,21,24] B, Digoxin vs sotalol in termination of supraventricular tachycardia in nonhydropic fetuses.[19,24] C, Flecainide vs digoxin in termination of supraventricular tachycardia in hydropic fetuses.[4,6,9,21,26] CI indicates confidence interval; RR, relative risk.

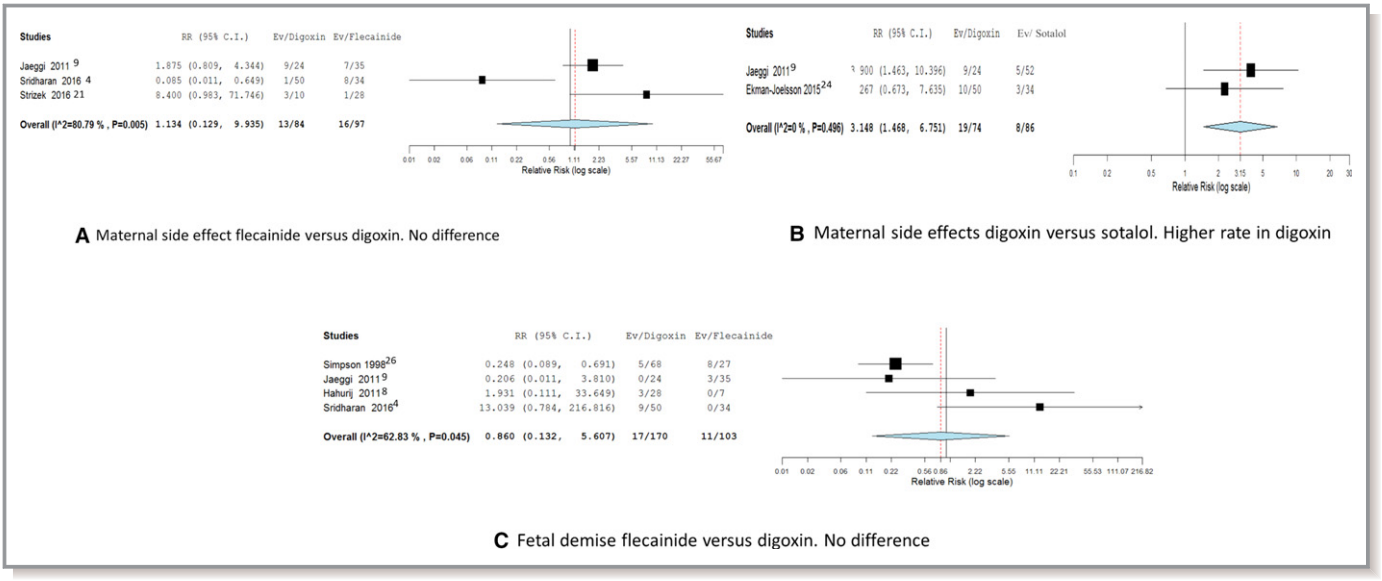


**Figure 5.** A, Maternal side effects during treatment with digoxin vs flecainide.[4,9,21] B, Maternal side effects during treatment with digoxin vs sotalol.[9,24] C, Fetal demise during treatment with digoxin vs flecainide.[4,8,9,26] CI indicates confidence interval; RR, relative risk.

surprisingly superior to digoxin in these fetuses. Our systematic review, however, showed that flecainide is superior to digoxin in nonhydropic fetuses as well, although we noticed more heterogeneity between studies. It is possible that time to conversion to sinus rhythm is longer with digoxin compared with flecainide and may result in switching to another agents in patients treated with digoxin.[9,25] We did not find sufficient data to compare the time to conversion to sinus rhythm across different medications, and this remains an important question for future studies. Furthermore, there was some concern about possibly higher rates of fetal demise in earlier studies with flecainide; however, similar findings were not confirmed in more recent studies. A theoretical reason for the association of flecainide with higher fetal mortality could be related to the preferential use of flecainide in fetuses with hydrops fetalis, who inherently have much higher risk of fetal demise.[4,21,26]

## Maternal Side Effects and Fetal Demise

Maternal intolerance to medications can be a limiting factor to appropriate treatment of fetal arrhythmias. Only a limited number of studies reported on maternal side effects in our analysis. Although minor maternal side effects appeared to be common events during treatment of FT, these were well tolerated. Drug levels were monitored in several studies included in this analysis, but there was paucity of data regarding their use in monitoring for maternal side effects. Given the limited number of patients with major side effects requiring decrease or cessation of medications, we were

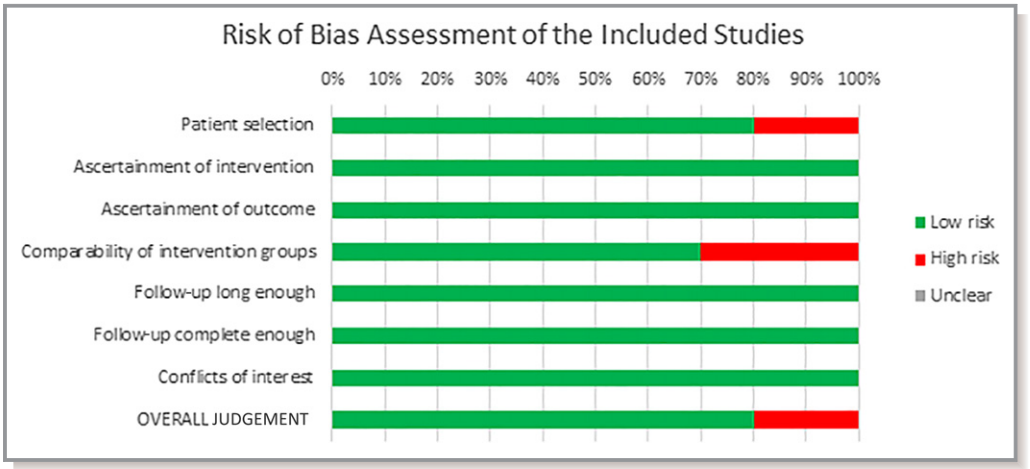


**Figure 6.** Risk of bias assessment of the included studies.

**Table 4.** Risk of Bias Assessment

| Reference | Year | Selection of Patients | Ascertainment of Intervention | Ascertainment of Outcome | Ascertainment of Outcome Based on the Presence or Absence of Hydrops | Comparability of Intervention Groups | Follow-up Long Enough for All Outcomes | Follow-up Long Enough for Termination of Arrhythmia to Occur | Adequacy of Follow-up | Conflict of Interest | Overall Judgment |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Sridharan et al[4] | 2016 | Low | Low | Low | Low | Low | Low | Low | Low | Low | Low |
| Jouannic et al[19] | 2002 | Low | Low | Low | Low | Low | Low | Low | Low | Low | Low |
| van Engelen et al[6] | 1994 | High | Low | Low | Low | Low | Low | Low | Low | Low | Low |
| Strizek et al[21] | 2016 | Low | Low | Low | Low | Low | Low | Low | Low | Low | Low |
| Simpson and Sharland[26] | 1998 | Low | Low | Low | Low | High | Low | Low | Low | Low | Low |
| Pezard et al[20] | 2008 | Low | Low | Low | Low | Low | Low | Low | Low | Low | Low |
| Jaeggi et al[9] | 2011 | Low | Low | Low | Low | Low | Low | Low | Low | Low | Low |
| Hahurij et al[8] | 2011 | Low | Low | Low | Low | High | Low | Low | Low | Low | High |
| Frohn-Mulder et al[11] | 1995 | High | Low | Low | Low | High | Low | Low | Low | Low | High |
| Ekman-Joelsson et al[24] | 2015 | Low | Low | Low | Low | Low | Low | Low | Low | Low | Low |

unable to compare this risk between medications. Flecainide can be associated with prolonged QRS interval; however, data evaluating the QRS interval were not reported in any included studies. A previous study that used flecainide to treat 20 fetuses with SVT reported no incidence of maternal prolongation of QRS interval.[27] Notably, side effects leading to changing the dose or discontinuing the medication were limited to digoxin treatment only, suggesting that flecainide was well tolerated. Fetal demise was more common among those with hydrops and was usually secondary to drug refractory arrhythmias. Although 1 study noted 3 intrauterine deaths within 24 hours of initiation of flecainide, our meta-analysis showed no significant difference in the risk of fetal demise with digoxin or flecainide.[26] Furthermore, there was some concern about possibly higher rates of fetal demise in earlier studies with flecainide; however, similar findings were not confirmed in more recent studies. A theoretical reason for the association of flecainide with higher fetal mortality could be related to the preferential use of flecainide in fetuses with hydrops fetalis, who inherently have much higher risk of fetal demise.[4,21,26] Given its safety, some studies reported outpatient management with flecainide either from the beginning or after conversion to sinus rhythm.[4,21] Using the current data, the cost effectiveness of each treatment could not be compared.

## Limitations

All of the included studies were observational and nonrandomized. In addition, because all studies were retrospective and drug choice was provider dependent, selection bias is likely. Insufficient data were available for important outcomes, including rate control, rate of prematurity, time to arrhythmia termination, fetal growth restriction, and neonatal mortality, although we found no study that reported important differences between agents in these outcomes. Some analyses were imprecise (small number of events), and some demonstrated statistical heterogeneity. Because the number of included studies was small given the scarcity of eligible data in the literature, another limitation is the potentially limited generalizability of the results to a wider population. We provided a sensitivity analysis by using both analyses with random- and fixed-effects models for the main outcome. It is worth noting that the results did not change (Figure S1).

We were unable to evaluate publication bias because of the small number of studies.[28] Despite these limitations, we believe that this meta-analysis provides valid insights into effectiveness and safety of flecainide as first-line therapy for patients with fetal SVT. Given the rarity of the disease and the relatively small sample sizes in all studies evaluated, a multicenter prospective study will be essential to evaluate the

best treatment approach to FT, taking into consideration effectiveness, safety, and cost of each strategy.

## Conclusion

Flecainide may be a more effective as a first-line treatment for fetal supraventricular tachycardia than digoxin. The maternal side effects and the rate of fetal demise were not increased in the flecainide group. The benefit of flecainide was more pronounced in fetuses with hydrops fetalis. We found no difference in AF termination rate between sotalol and digoxin, although sotalol seems to have fewer side effects compared with digoxin.

## Disclosures

None.

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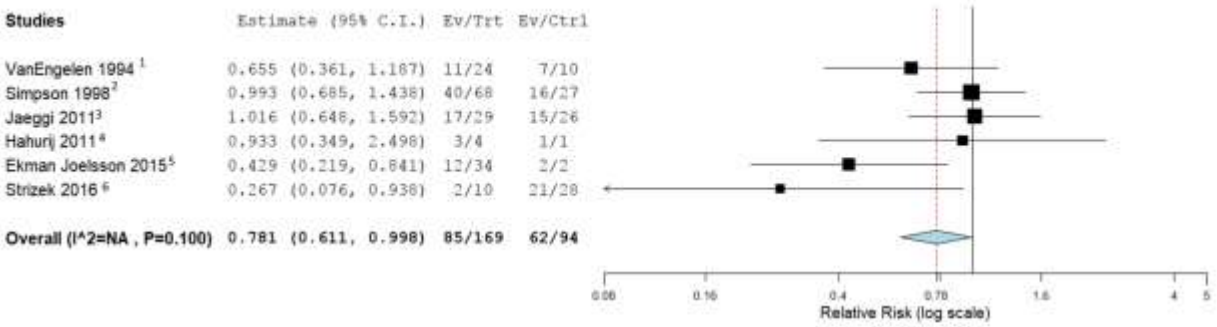
# SUPPLEMENTAL MATERIAL

**Figure S1.** Termination of supraventricular tachycardia using fixed effect model.




Flecainide versus digoxin in termination of Supraventricular Tachycardia using fixed effect model.[1-6]

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