

EVALUATION

Heart failure: ivabradine is no better than optimised beta-blocker therapy

● In a double-blind randomised placebo-controlled trial including about 6500 heart failure patients, *ivabradine* did not reduce overall mortality or cardiovascular mortality. *Ivabradine* reduced mortality due to heart failure, but not in the subgroup of patients receiving at least half the recommended dose of a beta-blocker.

● In a double-blind randomised placebo-controlled trial in about 10 000 patients with coronary artery disease and heart failure, *ivabradine* had no tangible efficacy.

● Treatment withdrawals were more frequent with *ivabradine* than in the placebo arms of these trials. Adverse effects included bradycardia and visual disorders.

● In practice, beta-blockers used at optimal doses have documented efficacy in heart failure patients. This is not the case for *ivabradine*, and its adverse effects have been confirmed.

The first-choice treatment for heart failure is based on an angiotensin-converting-enzyme inhibitor (ACE inhibitor) plus a diuretic (1). Adding a beta-blocker (*bisoprolol*, *carvedilol* or *metoprolol*) reduces overall mortality (1).

Ivabradine, a heart-rate-lowering drug derived from *verapamil*, has a negative harm-benefit balance in stable angina, mainly because of its visual and cardiac adverse effects (2,3). Two recent trials provide useful information on the harms and benefits of *ivabradine* in heart failure.

No decrease in overall mortality or cardiovascular mortality (Shift study). A double-blind randomised placebo-controlled trial (Shift) examined the effects of *ivabradine*, added to the usual treatment for heart failure, in 6558 patients (4,5). Heart failure was defined as a systolic ejection fraction below 35% and at least one hospitalisation for worsening heart failure in the

12 months prior to inclusion. The patients also had to have a resting heart rate above 70 beats per minute, no cardiac rhythm disorders or severe valve disease, no history of myocardial infarction or coronary revascularisation within the previous 2 months, and no history of stroke within the previous 4 weeks (5).

About half of the patients had class II heart failure according to the New York Heart Association (NYHA) classification, while the other half had class III heart failure (4). Median follow-up was about 23 months (4).

Ivabradine had no effect on overall mortality (about 17% overall) or on cardiovascular mortality (about 15%) (4).

Ivabradine reduced the frequency of the primary outcome, which combined cardiovascular mortality and hospitalisation for worsening heart failure (24% in the *ivabradine* group, versus 29% in the placebo group; $p < 0.0001$) (4). This difference was mainly due to fewer hospitalisations for heart failure.

In the subgroup of patients receiving at least half the recommended maximum dose of a beta-blocker (56% of the patients included in the trial), there was no statistically significant difference between the *ivabradine* and placebo arms in terms of either overall mortality or the primary outcome (a) (4).

The results for the subgroup of patients receiving less than 50% of the recommended dose of a beta-blocker were not reported in detail (4).

No tangible benefit for patients with coronary heart disease and heart failure (Beautiful study). The Beautiful double-blind randomised trial compared *ivabradine* versus placebo, in addition to the usual treatment, in 10 917 patients with coronary heart disease and heart failure (systolic ejection fraction below 40%) (6).

The results showed that *ivabradine* provided no tangible benefit, even in the 1430 patients who were not taking a beta-blocker (3,6).

Treatment withdrawals, bradycardia and visual disorders. Treatment withdrawals were more frequent with *ivabradine* than with placebo.

In the Shift study, 21% of patients on *ivabradine* discontinued the medication, versus 19% of patients on placebo ($p = 0.017$) (4). In the Beautiful study, 28% of patients on *ivabradine* discontinued the medication, versus

16% of patients on placebo ($p < 0.001$, our calculations) (6).

As expected, bradycardia was more frequent with *ivabradine* than with placebo. In the Shift study, respectively 11% and 2% of patients in the *ivabradine* and placebo arms developed bradycardia (4). Bradycardia was symptomatic in half of the cases and led to treatment cessation in 1 out of 5 cases (4). In the Beautiful study, respectively 13% and 2% of patients in the *ivabradine* and placebo groups had bradycardia that led to treatment cessation (6).

Visual adverse effects (phosphenes or visual disorders) were observed in initial trials of *ivabradine* in angina (b) (2). In the Shift study, 3% of patients in the *ivabradine* group had phosphenes. The outcome of this adverse effect and its impact on vision were not specified (4). In the Beautiful study, visual disorders were reported in 0.5% of patients in the *ivabradine* group versus 0.2% of patients in the placebo group. In patients who stopped the treatment because of these disorders (0.3% of patients), the symptoms disappeared (6).

In practice: optimise beta-blocker therapy. For heart failure patients in whom beta-blockers are tolerated and not contraindicated because of clinical status and heart rate, a beta-blocker (*bisoprolol*, *carvedilol* or *metoprolol*) used at an optimal dose has documented efficacy in reducing mortality. For patients in whom beta-blocker dose optimisation is not possible, there is no firm evidence that *ivabradine* has a positive harm-benefit balance.

The visual and cardiac adverse effects of *ivabradine* call for caution.

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a- For heart failure patients, the generally recommended doses of beta-blockers are *bisoprolol* 10 mg/day, *carvedilol* 50 mg/day, and *metoprolol succinate* 200 mg/day (ref 7).
b- Phosphenes are transient flashes of light in part of the visual field (ref 2).

Selected references from Prescrire's literature search.

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MINI-REVIEW

Retinal vein occlusion

- **Retinal vein occlusion can provoke a sudden loss of visual acuity. It is generally unilateral. Risk factors include ageing, arterial hypertension, diabetes and elevated intraocular pressure.**
- **Neovascularisation of the retina or iris can occur in patients with macular ischaemia, creating a risk of glaucoma.**
- **If macular oedema develops, recovery of visual acuity occurs spontaneously but slowly.**
- **Patients must be monitored in order to detect and treat neovascularisation as early as possible. Treatments for macular oedema are disappointing.**

In adults, retinal vein occlusion can lead to a loss of visual acuity, usually in one eye. Australian authors have estimated that retinal vein occlusion affects between 0.7% and 1.6% of individuals over 50 years of age (1,2). It usually occurs after the age of 65 (2).

The decline in visual acuity depends mainly on the type of occlusion (central or branch retinal vein) and the occurrence of macular oedema or other complications (2). Branch retinal vein occlusion is more common than central vein occlusion (2).

Risk factors. Risk factors for retinal vein occlusion include ageing, arterial hypertension and diabetes (1,3,4). Increased intraocular pressure associated with open-angle glaucoma is another important risk factor (4). There

is also weak evidence of a link with lipid disorders and rare clotting disorders such as protein S, protein C, or antithrombin III deficiency (2-5). Screening for these disorders is recommended in young patients with retinal vein occlusion and in all patients with bilateral occlusion.

The other eye is affected later in about 10% of cases (2).

Generally unilateral loss of visual acuity. Retinal vein occlusion leads to a variable loss of visual acuity in one eye. It is painless and may occur abruptly when the central retinal vein is affected (2,4,5). Diagnosis is based on ophthalmologic examination: retinal examination shows retinal haemorrhage, tortuous and dilated veins, and cotton wool spots (2,5).

Venous occlusion, especially of the central vein, sometimes leads to retinal ischaemia (ischaemic form), with a loss of visual acuity that depends on the extent of macular involvement: more than 90% of these patients have a visual acuity of 2/20 at best (2,4). Neovascularisation of the iris and retina occurs in about 35% of patients with ischaemic forms, with a risk of neovascular glaucoma (without retinal photocoagulation therapy) and vitreous haemorrhage (2).

Macular oedema is a frequent complication of retinal vein occlusion (5). It resolves spontaneously in about half of the patients, with recovery of visual acuity after 3 to 6 months (4). Most patients regained visual acuity of at least 10/20 (3).

Retinal vein occlusion does not seem to be associated with an increase in cardiovascular mortality (4).

Treatment: prevent aggravation. There is currently no curative treatment for retinal vein occlusion (2). Management is based on diagnosis and treatment of precipitating factors. Ophthalmologic monitoring, every 1 to 3 months, is necessary to detect neovascularisation and possible complications (3).

Laser photocoagulation is not effective in macular oedema secondary to venous occlusion (1,5). It may be beneficial if neovascularisation occurs, for prevention of neovascular glaucoma and vitreous haemorrhage (2-4).

If macular oedema persists, with a visual acuity between 2/20 and 10/20 after 3 to 6 months, laser photocoagulation around the macula may be used to reduce the oedema (3,4). Photoco-

agulation seems to have little efficacy when visual acuity is less than 2/20 (3).

Intravitreal steroid injections and *dexamethasone* intravitreal implants have transient efficacy on macular oedema but not on long-term visual acuity. However, they carry a risk of serious adverse effects, especially an increase in intraocular pressure and cataracts (5).

Antiplatelet drugs and growth factor inhibitors (*pegaptanib*, *ranibizumab*, *bevacizumab*) do not have a positive harm-benefit balance in this setting (3,4), nor does haemodilution (a) (2-4).

Surgical approaches have not been shown to prevent the loss of visual acuity, or to restore visual acuity (6).

In practice. Patients with documented retinal vein occlusion should receive ophthalmologic monitoring to prevent complications.

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a- Haemodilution consists of replacing a volume of blood by an equivalent volume of fluid in order to reduce the red cell count and to increase fluidity (ref 2).

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