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From VICTORIA to VICTOR: Where Vericiguat Fits in HFrEF Care

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ABSTRACT

Background. Vericiguat, an oral soluble guanylate cyclase stimulator, augments impaired NO-sGC-cGMP signaling in heart failure with reduced ejection fraction (HFrEF). The pivotal VICTORIA trial enrolled high-risk patients with recent worsening heart failure (WHF) and showed a reduction in the composite of cardiovascular (CV) death or first HF hospitalization, whereas the subsequent VICTOR trial tested ambulatory, clinically stable HFrEF without recent WHF and did not meet its primary endpoint.

Objective. To synthesize contemporary evidence on vericiguat after VICTORIA and VICTOR, clarify patient selection and optimal timing and position the drug within guideline-directed medical therapy.

Methods. Narrative review of randomized trials (VICTORIA, VICTOR), prespecified and post-hoc subgroup and pooled patient-level analyses, pharmacology studies, drug-label information, and major guideline documents, covering literature through September 13, 2025. Outcomes of interest were CV death, HF hospitalization (first and recurrent), safety/tolerability and practical implementation.

Results. In VICTORIA (n≈5,050), vericiguat reduced the primary composite of CV death or first HF hospitalization versus placebo on top of contemporary therapy with acceptable safety and small increases in hypotension and anemia. VICTOR (n≈6,100) did not meet its primary composite in stable ambulatory HFrEF without recent WHF, secondary analyses signaled lower CV and all-cause mortality. A pooled patient-level analysis across VICTORIA+VICTOR (≈11,000 patients) suggested a significant reduction in the composite outcome across a broader risk spectrum. Guidelines continue to recommend vericiguat primarily after recent WHF despite optimized foundational therapy.

Conclusion. Vericiguat remains most compelling for high-risk HFrEF after recent worsening, in stable ambulatory patients, evidence indicates a possible mortality signal but the overall effect on the composite outcome is uncertain and may depend on baseline risk. Careful selection (recent WHF, SBP ≥100 mmHg, on quadruple therapy), dose uptitration with food, and attention to anemia, hypotension, pregnancy risk, and PDE-5 interactions optimize real-world value.

Keywords. vericiguat; HFrEF; worsening heart failure; VICTORIA; VICTOR; soluble guanylate cyclase; cGMP; cardiovascular death.

Słowa kluczowe. vericiguat; niewydolność serca z obniżoną frakcją wyrzutową (HFrEF); pogorszenie HF; VICTORIA; VICTOR; stymulator sGC; cGMP; śmiertelność sercowo-naczyniowa.

INTRODUCTION

Despite major advances, many patients with HFrEF continue to experience recurrent hospitalization and premature death, especially in the months following a recent worsening heart-failure event (WHF). This residual risk reflects, in part, endothelial dysfunction and impairment of the NO-sGC-cGMP pathway - biology not directly targeted by the four foundational drug classes (ARNI/ACEi/ARB, β-blockers, MRAs, SGLT2 inhibitors) [5–7]. Guidelines therefore highlight therapies that complement GDMT by addressing alternative mechanisms, including sGC stimulation.

Vericiguat is the first oral sGC stimulator approved for adults with symptomatic chronic HFrEF following a recent WHF event. The VICTORIA trial established clinical benefit for vericiguat in high-risk patients soon after WHF [1]. The subsequent VICTOR trial enrolled stable ambulatory HFrEF without recent WHF and was neutral on its primary composite, though secondary analyses indicated lower CV and all-cause mortality with vericiguat [3]. A pooled individual-participant analysis across VICTORIA and VICTOR suggests reduction in CV death or HF hospitalization across ≈11,155 patients [3,4]. This review synthesizes these data to guide patient selection, timing, and expectations for vericiguat in practice.

This narrative review summarizes the clinical evidence, clarifies patient selection and timing, and briefly outlines the mechanistic basis for sGC stimulation in HFrEF with practical implications for integration alongside foundational therapy.

MATERIALS AND METHODS

Search Strategy

A structured literature search was conducted in PubMed, Embase, and the Cochrane Library for publications from January 2015 through September 13, 2025. Search strings combined keywords and MeSH/Emtree terms related to the intervention and disease area, including: *vericiguat*, *soluble guanylate cyclase*, *sGC stimulator*, *cyclic GMP*, *nitric oxide*, *heart failure with reduced ejection fraction*, *HFrEF*, *worsening heart failure*, and trial identifiers (*VICTORIA*, *VICTOR*, *SOCRATES-REDUCED*). Boolean operators AND/OR were used; filters limited results to human studies and English-language publications. Conference

abstracts and society press communications were screened to capture late-breaking trial readouts; such sources were treated as supportive signals and described with cautious language (e.g., *signal*, *suggests*, *indicates*), not as definitive proof.

Inclusion Criteria

Study designs: randomized controlled trials (phase 2/3), pooled individual-participant analyses, prespecified/post-hoc subgroup/secondary analyses, pharmacology/chemistry and PK/PD papers, major guidelines/consensus, real-world eligibility/uptake studies, and health-economic evaluations.

Population: adults with HFrEF; for context, we allowed related sGC or HF phenotypes when informative (e.g., preserved EF program) provided the link to clinical positioning was explicit.

Intervention: vericiguat on top of guideline-directed medical therapy.

Outcomes: cardiovascular death, heart-failure hospitalization (first and recurrent), composite outcomes, safety/tolerability (e.g., hypotension, anemia), and implementation/value endpoints.

Exclusion Criteria

- Animal or in-vitro work; pediatric populations.
- Case reports/series, editorials, or commentaries without original data.
- Studies lacking relevant clinical endpoints or with inaccessible full text in English.
- Preprints or congress materials without peer-review were not used for firm estimates; when cited, findings are labeled as exploratory signals.

Study Selection Process

1. **Identification**: database searches and citation chaining identified records meeting the strategy above.
2. **Deduplication**: duplicate entries were removed.
3. **Screening**: two reviewers independently screened titles/abstracts for relevance to vericiguat in HFrEF.
4. **Eligibility**: full texts were assessed against inclusion/exclusion criteria; disagreements were resolved by consensus.
5. **Inclusion**: 25 sources were included in the qualitative synthesis (matching the reference list), spanning: randomized trials (n=3), pooled IPD (n=1), subgroup/secondary analyses (≈n=6), guidelines/consensus (n=3), pharmacology/chemistry (≈n=3), real-world eligibility/uptake (≈n=3), health-economic modeling (n=1), and additional context articles related to the sGC class or phenotype (≈n=5).

Data Extraction

Two reviewers independently extracted: study design, setting, population criteria, background therapy, endpoints (CV death, HF hospitalization - first and **recurrent**), effect estimates (e.g., HRs with 95% CIs), safety outcomes (hypotension, anemia, renal parameters) and implementation/value signals. For pharmacology/chemistry, we collected mechanism and PK/PD features relevant to clinical use. Differences in extraction were reconciled by discussion.

Quality Assessment

Randomized trials: assessed with Cochrane RoB 2 domains (randomization, deviations from intended interventions, missing data, outcome measurement, reporting).

Observational/real-world studies: assessed with the Newcastle–Ottawa Scale.

Guidelines/consensus and economic evaluations: appraised for methodological transparency and consistency with source data (e.g., CHEERS elements for economic models).

Certainty of evidence: key clinical outcomes were summarized using GRADE concepts (high/moderate/low/very low). Findings from congress press releases or late-breaking presentations were explicitly labeled as exploratory and interpreted as signals rather than definitive evidence.

MECHANISM OF ACTION

Endothelial dysfunction and oxidative stress in HFrEF reduce nitric-oxide (NO) bioavailability and desensitize/oxidize the heme of sGC, lowering intracellular cGMP and impairing protein kinase G (PKG) signaling. Vericiguat binds and directly stimulates sGC while increasing its sensitivity to endogenous NO, restoring cGMP generation. This is distinct from PDE-5 inhibition, which slows cGMP degradation. Downstream, enhanced cGMP–PKG signaling promotes vasodilation/afterload reduction, improves lusitropy, and may counteract adverse remodeling - complementing foundational therapies [8,9,24].

Table 1. The NO-sGC-cGMP pathway in HFrEF and the role of vericiguat

Problem in HFrEF	Biological change	What vericiguat does	Why this matters	Evidence
Endothelial dysfunction and oxidative stress	↓ NO bioavailability; heme-oxidized sGC → low cGMP	Direct sGC stimulation and NO sensitization → more cGMP	Improves vascular tone and myocardial relaxation; may counter remodeling	Mechanistic/translational, discovery chemistry, clinical PK/PD.
Residual risk after WHF	High near-term risk despite GDMT	Targets a non-RAAS, non-sympatholytic pathway	Complements foundational therapy	Guideline positioning as add-on in selected patients.
Safety considerations	Vasodilators may lower BP; small Hb drops reported	Monitor for symptomatic hypotension and mild anemia	Generally well tolerated in trials	VICTORIA safety and focused analyses.

CLINICAL EVIDENCE

Phase 2: SOCRATES-REDUCED

In stabilized patients within weeks of WHF, SOCRATES-REDUCED (n=456) was overall neutral for 12-week NT-proBNP change but showed dose-response signals and acceptable tolerability, informing risk-enriched phase-3 design [2].

VICTORIA: high-risk HFrEF after recent WHF

VICTORIA randomized 5,050 patients with HFrEF (LVEF <45%) and recent WHF (HF hospitalization or outpatient IV diuretics) to vericiguat or placebo on top of contemporary care [1]. Over ≈11 months, vericiguat reduced CV death or first HF hospitalization (HR 0.90, 95% CI 0.83–0.98). Absolute benefit was greatest in those at highest baseline risk, symptomatic hypotension and anemia were slightly more frequent than with placebo [1,10–16,18].

Subgroup/secondary insights (VICTORIA).

• NT-proBNP: attenuation at the very highest levels; strongest proportional benefit at "high but not extreme" concentrations [11,16]

• Diabetes: relative effects were similar regardless of type-2 diabetes [13].

• Recurrent events: benefits extended to recurrent HF hospitalizations [14].

• Safety: small average BP effects; mild hemoglobin reductions without progressive decline [10,18].

VICTOR: stable ambulatory HFrEF without recent WHF

VICTOR enrolled 6,105 ambulatory, clinically stable HFrEF patients on robust GDMT and no recent WHF [3]. The primary composite of CV death or HF hospitalization was neutral (HR 0.93, 95% CI 0.83–1.04). Secondary analyses signaled lower CV death (HR 0.83, 95% CI 0.71–0.97) and all-cause death (HR 0.84, 95% CI 0.74–0.97) with vericiguat, safety was consistent with VICTORIA [3].

Pooled individual-participant analysis: VICTORIA + VICTOR

Across ≈11,155 participants spanning recent-WHF to stable ambulatory HFrEF, pooled IPD analysis indicates a statistically significant reduction in CV death or HF hospitalization (HR 0.91, 95% CI 0.85–0.98), While statistically significant, these findings should be viewed as supportive signals that align with VICTORIA and the mortality signal from VICTOR rather than stand-alone proof of efficacy outside the post-WHF setting. [4].

Table 2. Pivotal trials of vericiguat in HFrEF

Trial	**Population**	**N**	**Primary endpoint**	**Key results (HR, 95% CI)**	**Notes**
SOCRATES-REDUCED (2015)	Stabilized HFrEF within 4 wks of WHF	456	NT-proBNP change	Neutral overall; dose-response signals	Informed dose/risk enrichment
VICTORIA (2020)	HFrEF with recent WHF	5,050	CV death or first HF hospitalization	0.90 (0.83–0.98)	Greatest absolute benefit in higher-risk pts; small ↑ hypotension/anemia
VICTOR (2025)	Stable ambulatory HFrEF, no recent WHF	6,105	CV death or HF hospitalization	0.93 (0.83–1.04) (neutral); CV death 0.83 (0.71–0.97); all-cause death 0.84 (0.74–0.97)	Safety consistent with VICTORIA
Pooled IPD (2025)	Broad HFrEF spectrum	≈11,155	CV death or HF	0.91 (0.85–0.98)	Benefit across spectrum; largest yield post-WHF

			hospitalization		

SAFETY AND TOLERABILITY

Across trials, vericiguat was generally well tolerated. Symptomatic hypotension and anemia were more frequent than with placebo but rarely led to discontinuation, hemoglobin changes were modest without progressive decline [1,10,18]. Caution is warranted with concomitant vasodilators and conditions predisposing to low blood pressure. Pregnancy is contraindicated (embryo-fetal risk) [6,17].

PLACE IN THERAPY AND GUIDELINES

Guidelines position vericiguat as an add-on for symptomatic HFrEF after recent WHF on optimized GDMT (class of recommendation varies by document and context) [5–7]. In stable ambulatory HFrEF without recent WHF, the neutral primary outcome in VICTOR supports selective, individualized use in high-risk profiles, acknowledging that the mortality and pooled-analysis findings are signals rather than definitive proof. [3,4]. Health-economic analyses suggest intermediate value that improves with higher baseline risk, consistent with the VICTORIA phenotype [25].

PRACTICAL IMPLICATIONS

Best-fit patients now: those with recent WHF at elevated risk despite foundational GDMT - often with high (but not extreme) NT-proBNP, recurrent hospitalizations and adequate blood pressure [1,5–7,11,14–16].

Stable ambulatory patients: consider selectively in high-risk individuals after shared decision-making that explicitly discusses VICTOR's neutral primary endpoint and the supportive mortality/pooling signals [3,4].

Monitoring: focus on blood pressure, symptoms of hypotension, and hemoglobin during early follow-up [1,10,18].

HEALTH-ECONOMIC CONSIDERATIONS

Modeling based on VICTORIA suggests that vericiguat delivers intermediate value overall, becoming more attractive as baseline risk and event rates rise - precisely the post-WHF context where absolute risk reduction is greatest [25]. Budget-impact and equity considerations will vary by health-system pricing and GDMT penetration.

LIMITATIONS

This review summarizes published trials and high-quality analyses, but several boundaries apply. Evidence is strongest after a recent WHF event (VICTORIA, median follow-up ≈11 months), applicability to lower-risk stable outpatients is less certain because VICTOR was neutral for its primary composite [1,3]. Treatment effect appears risk-dependent and may attenuate at very high NT-proBNP levels [11,16]. Trials did not start therapy at SBP <100 mmHg, excluded pregnancy and prohibited PDE-5 inhibitors/other sGC stimulators, limiting generalizability in those settings [6,17]. Subgroup findings are exploratory and the mortality signal in VICTOR needs confirmation with longer follow-up and across health systems [3]. Finally, cost-effectiveness is sensitive on baseline risk, event rates and local pricing [25].

CONCLUSIONS

Vericiguat provides a mechanistically distinct means to reduce clinical events in HFrEF by restoring NO-sGC-cGMP signaling. The most robust evidence comes from VICTORIA in patients after recent WHF, where the drug reduced the composite of CV death or first HF hospitalization on top of contemporary therapy [1]. In stable ambulatory HFrEF, VICTOR was neutral for the primary composite but signaled lower CV and all-cause mortality. Taken together with the pooled IPD indicates a reduction in the composite across the broader spectrum, yet these findings should be considered supportive rather than definitive [3,4].

In practice, vericiguat is best positioned as an add-on to four-pillar GDMT for patients recently worsened or otherwise at elevated risk, implemented within structured post-discharge pathways and monitored for symptomatic hypotension and mild anemia [5–7,10,18 Its value is maximized when patient selection is deliberate, expectations are calibrated to risk and follow-up targets blood pressure, hemoglobin, and clinical status - helping clinicians deploy this therapy precisely and equitably across the HFrEF spectrum. [1–7,10–16,18–22,25].

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